Renal and sterol regulatory element binding protein (SREBP) research literatures

Ma Hongbao [1], Margaret Ma [2], Yang Yan [1]

[1] Brookdale Hospital, Brooklyn, New York 11212, USA; [2] Cambridge, MA 02138, USA
ma8080@gmail.com

Abstract: Sterol regulatory element-binding proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. Mammalian SREBPs are encoded by the genes SREBF1 and SREBF2. SREBPs belong to the basic-helix-loop-helix leucine zipper class of transcription factors. Unactivated SREBPs are attached to the nuclear envelope and endoplasmic reticulum membranes. In cells with low levels of sterols, SREBPs are cleaved to a water-soluble N-terminal domain that is translocated to the nucleus. These activated SREBPs then bind to specific sterol regulatory element DNA sequences, thus upregulating the synthesis of enzymes involved in sterol biosynthesis. Sterols in turn inhibit the cleavage of SREBPs and therefore synthesis of additional sterols is reduced through a negative feed back loop
[Ma H, Young M, Yang Y. **Renal and sterol regulatory element binding protein (SREBP) research literatures.** *Rep Opinion* 2015;7(10):71-100]. (ISSN: 1553-9873). http://www.sciencepub.net/report. 8

Key words: renal; sterol regulatory element binding protein (SREBP); research; literatures; life; cell

1. Introduction

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. Mammalian SREBPs are encoded by the genes SREBF1 and SREBF2. SREBPs belong to the basic-helix-loop-helix leucine zipper class of transcription factors. Unactivated SREBPs are attached to the nuclear envelope and endoplasmic reticulum membranes. In cells with low levels of sterols, SREBPs are cleaved to a water-soluble N-terminal domain that is translocated to the nucleus. These activated SREBPs then bind to specific sterol regulatory element DNA sequences, thus upregulating the synthesis of enzymes involved in sterol biosynthesis. Sterols in turn inhibit the cleavage of SREBPs and therefore synthesis of additional sterols is reduced through a negative feed back loop (Wikipedia-The free encyclopedia, 2015).

The following introduces recent reports as references in the related studies.

Bai, Q., X. Zhang, et al. "Oxysterol sulfation by cytosolic sulfotransferase suppresses liver X receptor/sterol regulatory element binding protein-1c signaling pathway and reduces serum and hepatic lipids in mouse models of nonalcoholic fatty liver disease." Metabolism. 2012 Jun;61(6):836-45. doi: 10.1016/j.metabol.2011.11.014. Epub 2012 Jan 5.

Cytosolic sulfotransferase (SULT2B1b) catalyzes oxysterol sulfation. 5-Cholesten-3beta-25-diol-3-sulfate (25HC3S), one product of this reaction, decreases intracellular lipids in vitro by suppressing liver X receptor/sterol regulatory element binding protein (SREBP)-1c signaling, with regulatory properties opposite to those of its precursor 25-hydroxycholesterol. Upregulation of SULT2B1b may be an effective strategy to treat hyperlipidemia and hepatic steatosis. The objective of the study was to explore the effect and mechanism of oxysterol sulfation by SULT2B1b on lipid metabolism in vivo. C57BL/6 and LDLR(-/-) mice were fed with high-cholesterol diet or high-fat diet for 10 weeks and infected with adenovirus encoding SULT2B1b. SULT2B1b expressions in different tissues were determined by immunohistochemistry and Western blot. Sulfated oxysterols in liver were analyzed by high-pressure liquid chromatography. Serum and hepatic lipid levels were determined by kit reagents and hematoxylin and eosin staining. Gene expressions were determined by real-time reverse transcriptase polymerase chain reaction and Western Blot. Following infection, SULT2B1b was successfully overexpressed in the liver, aorta, and lung tissues, but not in the heart or kidney. SULT2B1b overexpression, combined with administration of 25-hydroxycholesterol, significantly increased the formation of 25HC3S in liver tissue and significantly decreased serum and hepatic lipid levels, including triglycerides, total cholesterol, free cholesterol, and free fatty acids, as compared with controls in both C57BL/6 and LDLR(-/-) mice. Gene expression analysis showed that increases in SULT2B1b expression were accompanied by reduction in key regulators and enzymes involved in lipid metabolism, including liver X receptor alpha, SREBP-1, SREBP-2, acetyl-CoA carboxylase-1, and fatty acid synthase. These findings support the hypothesis that 25HC3S is an important endogenous regulator of lipid biosynthesis.

Bakker, P. J., L. M. Butter, et al. "Nlrp3 is a key modulator of diet-induced nephropathy and renal cholesterol accumulation." Kidney Int. 2014 May;85(5):1112-22. doi: 10.1038/ki.2013.503. Epub 2013 Dec 18.

Metabolic syndrome (MetSyn) is a major health concern and associates with the development of kidney disease. The mechanisms linking MetSyn to renal disease have not been fully elucidated but are known to involve hyperuricemia, inflammation, and fibrosis. Since the innate immune receptor Nlrp3 is an important mediator of obesity and inflammation, we sought to determine whether Nlrp3 is involved in the development of MetSyn-associated nephropathy by giving wild-type or Nlrp3-knockout mice a Western-style compared to a normal diet or water without or with fructose. A plausible driver of pathology, the Nlrp3-dependent cytokine IL-1beta was not increased in the kidney. Interestingly, Nlrp3-dependent renal cholesterol accumulation, another well-known driver of renal pathology, was enhanced during MetSyn. We also determined the role of Nlrp3 and fructose-fortified water on the development of MetSyn and kidney function since fructose is an important driver of obesity and kidney disease. Surprisingly, fructose did not induce MetSyn but, irrespective of this, did induce Nlrp3-dependent renal inflammation. The presence of Nlrp3 was crucial for the development of Western-style diet-induced renal pathology as reflected by the prevention of renal inflammation, fibrosis, steatosis, microalbuminuria, and hyperuricemia in the Nlrp3-knockout mice. Thus, Nlrp3 may mediate renal pathology in the context of diet-induced MetSyn.

Briggs, M. R., C. Yokoyama, et al. "Nuclear protein that binds sterol regulatory element of low density lipoprotein receptor promoter. I. Identification of the protein and delineation of its target nucleotide sequence." J Biol Chem. 1993 Jul 5;268(19):14490-6.

The current paper reports the identification of a protein in rat liver nuclei that binds to the sterol regulatory element (SRE-1) in the promoter of the gene for the low density lipoprotein receptor. The 10-base pair SRE-1 is embedded within a 16-base pair sequence designated Repeat 2 located immediately upstream of a related sequence designated Repeat 3. To confirm that DNA recognition by the SRE-1 binding protein (SREBP) correlates with sterol-regulated transcription, we synthesized an artificial promoter that contains two copies of wild-type or mutant Repeat 2 + 3 sequences immediately upstream of a TATA box from adenovirus. The synthetic promoters were inserted upstream of a reporter gene and tested for transcriptional activity in the absence and presence of sterols after transient transfection into monkey CV-1 cells. The reporter gene with two copies of the wild-type Repeat 2 + 3 sequence was transcribed actively in sterol-deprived cells and was repressed by more than 80% when sterols were present. Binding of SREBP to the SRE-1 sequence, assessed by gel mobility shift assays, correlated precisely on a nucleotide-by-nucleotide basis with the transcriptional activity of each of 16 synthetic promoters with point mutations in Repeat 2. The SREBP bound to the nine mutant promoters that were positive for sterol-regulated transcription, and it did not bind to any of the nine point mutants that abolished transcription. We conclude that SREBP is a DNA binding protein that mediates sterol-regulated transcription of the low density lipoprotein receptor gene.

Buga, G. M., J. S. Frank, et al. "D-4F reduces EO6 immunoreactivity, SREBP-1c mRNA levels, and renal inflammation in LDL receptor-null mice fed a Western diet." J Lipid Res. 2008 Jan;49(1):192-205. Epub 2007 Oct 9.

LDL receptor-null (LDLR(-/-)) mice on a Western diet (WD) develop endothelial dysfunction and atherosclerosis, which are improved by the apolipoprotein A-I (apoA-I) mimetic peptide D-4F. Focusing on the kidney, LDLR(-/-)mice were fed a WD with D-4F or the inactive control peptide scrambled D-4F (ScD-4F) added to their drinking water. The control mice (ScD-4F) developed glomerular changes, increased immunostaining for MCP-1/CCL2 chemokine, increased macrophage CD68 and F4/80 antigens, and increased oxidized phospholipids recognized by the EO6 monoclonal antibody in both glomerular and tublo-interstitial areas. All of these parameters were significantly reduced by D-4F treatment, approaching levels found in wild-type C57BL/6J or LDLR(-/-) mice fed a chow diet. Sterol-regulatory element binding protein-1c (SREBP-1c) mRNA levels and triglyceride levels were elevated in the kidneys of the control mice (ScD-4F) fed the WD compared with C57BL/6J and LDLR(-/-) mice on chow ($P < 0.001$ and $P < 0.001$, respectively) and compared with D-4F-treated mice on the WD ($P < 0.01$). There was no significant difference in plasma lipids, lipoproteins, glucose, blood pressure, or renal apoB levels between D-4F- and ScD-4F-treated mice. We conclude that D-4F reduced renal oxidized phospholipids, resulting in lower expression of SREBP-1c, which, in turn, resulted in lower triglyceride content and reduced renal inflammation.

Carmona-Antonanzas, G., D. R. Tocher, et al. "Conservation of lipid metabolic gene transcriptional regulatory networks in fish and mammals." Gene. 2014 Jan 15;534(1):1-9. doi: 10.1016/j.gene.2013.10.040. Epub 2013 Oct 28.

Lipid content and composition in aquafeeds have changed rapidly as a result of the recent drive to replace ecologically limited marine ingredients, fishmeal and fish oil (FO). Terrestrial plant products are the most economic and sustainable alternative; however, plant meals and oils are devoid of physiologically important cholesterol and long-chain polyunsaturated fatty acids (LC-PUFA), eicosapentaenoic (EPA), docosahexaenoic (DHA) and arachidonic (ARA) acids. Although replacement of dietary FO with vegetable oil (VO) has little effect on growth in Atlantic salmon (Salmo salar), several studies have shown major effects on the activity and expression of genes involved in lipid homeostasis. In vertebrates, sterols and LC-PUFA play crucial roles in lipid metabolism by direct interaction with lipid-sensing transcription factors (TFs) and consequent regulation of target genes. The primary aim of the present study was to elucidate the role of key TFs in the transcriptional regulation of lipid metabolism in fish by transfection and overexpression of TFs. The results show that the expression of genes of LC-PUFA biosynthesis (elovl and fads2) and cholesterol metabolism (abca1) are regulated by Lxr and Srebp TFs in salmon, indicating highly conserved regulatory mechanism across vertebrates. In addition, srebp1 and srebp2 mRNA respond to replacement of dietary FO with VO. Thus, Atlantic salmon adjust lipid metabolism in response to dietary lipid composition through the transcriptional regulation of gene expression. It may be possible to further increase efficient and effective use of sustainable alternatives to marine products in aquaculture by considering these important molecular interactions when formulating diets.

Castoreno, A. B., Y. Wang, et al. "Transcriptional regulation of phagocytosis-induced membrane biogenesis by sterol regulatory element binding proteins." Proc Natl Acad Sci U S A. 2005 Sep 13;102(37):13129-34. Epub 2005 Sep 2.

In the process of membrane biogenesis several dozen proteins must operate in precise concert to generate approximately 100 lipids at appropriate concentrations. To study the regulation of bilayer assembly in a cell cycle-independent manner, we have exploited the fact that phagocytes replenish membranes expended during particle engulfment in a rapid phase of lipid synthesis. In response to phagocytosis of latex beads, human embryonic kidney 293 cells synthesized cholesterol and phospholipids at amounts equivalent to the surface area of the internalized particles. Lipid synthesis was accompanied by increased transcription of several lipogenic proteins, including the low-density lipoprotein receptor, enzymes required for cholesterol synthesis (3-hydroxy-3-methylglutaryl CoA synthase, 3-hydroxy-3-methylglutaryl CoA reductase), and fatty acid synthase. Phagocytosis triggered the proteolytic activation of two lipogenic transcription factors, sterol regulatory element binding protein-1a (SREBP-1a) and SREBP-2. Proteolysis of SREBPs coincided with the appearance of their transcriptionally active N termini in the nucleus and 3-fold activation of an SREBP-specific reporter gene. In previous studies with cultured cells, proteolytic activation of SREBP-1a and SREBP-2 has been observed in response to selective starvation of cells for cholesterol and unsaturated fatty acids. However, under the current conditions, SREBP-1a and SREBP-2 are induced without lipid deprivation. SREBP activation is inhibited by high levels of the SREBP-interacting proteins Insig1 or the cytosolic domain of SREBP cleavage-activating protein. Upon overexpression of these proteins, phagocytosis-induced transcription and lipid synthesis were blocked. These results identify SREBPs as essential regulators of membrane biogenesis and provide a useful system for further studies on membrane homeostasis.

Chechi, K., N. Yasui, et al. "Flax oil-mediated activation of PPAR-gamma correlates with reduction of hepatic lipid accumulation in obese spontaneously hypertensive/NDmcr-cp rats, a model of the metabolic syndrome." Br J Nutr. 2010 Nov;104(9):1313-21. doi: 10.1017/S0007114510002187. Epub 2010 Jun 15.

Flax oil feeding has been proposed to have beneficial effects on the outcome of the metabolic syndrome due to the high n-3 fatty acid content of flax oil; however, the mechanisms of its action remain largely unknown. We investigated the effects of flax oil feeding on hyperlipidaemia, hyperglycaemia, hepatic steatosis and oxidative stress in the spontaneously hypertensive (SHR)/NDmcr-cp rats, a genetic model of the metabolic syndrome. Hepatic gene expression of PPAR-alpha, PPAR-gamma and sterol-regulatory element-binding protein-1c was also assessed in order to investigate the possible underlying mechanisms. Obese and lean SHR/NDmcr-cp rats were fed high-fat diets enriched with either lard or flax oil for a period of 4 weeks. Obese rats exhibited higher body weight, liver weight and mesenteric fat-, epididymal fat- and renal fat-pad weights, and also TAG and cholesterol concentrations in serum and VLDL, LDL and HDL fractions, when compared with the lean rats ($P < 0.001$), irrespective of the diets. Concentrations of fasting serum insulin and urinary thiobarbituric acid reactive substances were lower in flax oil-fed obese (FO) rats compared with the lard-fed obese (LO) rats ($P < 0.01$). Flax oil feeding also revealed a significant reduction in hepatic TAG and cholesterol concentrations in obese rats compared with

the LO rats (P < 0.05). In addition, FO rats exhibited significantly higher hepatic mRNA expression of PPAR-gamma, which negatively correlated (r - 0.98, P < 0.05) with their hepatic lipid levels. These findings suggest that flax oil feeding may activate PPAR-gamma-dependent pathways to alter the hepatic lipid metabolism and to increase insulin sensitivity in the obese SHR/NDmcr-cp rats.

Chen, I. B., V. K. Rathi, et al. "Association of genes with physiological functions by comparative analysis of pooled expression microarray data." Physiol Genomics. 2013 Jan 15;45(2):69-78. doi: 10.1152/physiolgenomics.00116.2012. Epub 2012 Nov 20.

The physiological functions of a tissue in the body are carried out by its complement of expressed genes. Genes that execute a particular function should be more specifically expressed in tissues that perform the function. Given this premise, we mined public microarray expression data to build a database of genes ranked by their specificity of expression in multiple organs. The database permitted the accurate identification of genes and functions known to be specific to individual organs. Next, we used the database to predict transcriptional regulators of brown adipose tissue (BAT) and validated two candidate genes. Based upon hypotheses regarding pathways shared between combinations of BAT or white adipose tissue (WAT) and other organs, we identified genes that met threshold criteria for specific or counterspecific expression in each tissue. By contrasting WAT to the heart and BAT, the two most mitochondria-rich tissues in the body, we discovered a novel function for the transcription factor ESRRG in the induction of BAT genes in white adipocytes. Because the heart and other estrogen-related receptor gamma (ESRRG)-rich tissues do not express BAT markers, we hypothesized that an adipocyte co-regulator acts with ESRRG. By comparing WAT and BAT to the heart, brain, kidney and skeletal muscle, we discovered that an isoform of the transcription factor sterol regulatory element binding transcription factor 1 (SREBF1) induces BAT markers in C2C12 myocytes in the presence of ESRRG. The results demonstrate a straightforward bioinformatic strategy to associate genes with functions. The database upon which the strategy is based is provided so that investigators can perform their own screens.

Chen, Y., L. Zhao, et al. "Inflammatory stress reduces the effectiveness of statins in the kidney by disrupting HMGCoA reductase feedback regulation." Nephrol Dial Transplant. 2014 Oct;29(10):1864-78. doi: 10.1093/ndt/gfu203. Epub 2014 Jun 3.

BACKGROUND: Patients with chronic kidney disease (CKD) are unlikely to gain the same benefit from conventional doses of statins as do patients with cardiovascular disease alone. This study investigated whether inflammation accompanying CKD causes statin resistance. METHODS: Inflammatory stress was induced by adding cytokines and lipopolysaccharide (LPS) to human mesangial cells (HMCs) in vitro, and in vivo by subcutaneous casein injection in apolipoprotein E, scavenger receptors class A and CD36 triple knockout mice. RESULTS: Inflammatory stress exacerbated cholesterol accumulation and was accompanied in vitro and in vivo by increased HMGCoA reductase (HMGCoA-R) mRNA and protein expression mediated via activation of the sterol regulatory element-binding protein cleavage-activating protein (SCAP)/sterol regulatory element-binding protein 2 pathway. Atorvastatin reduced HMGCoA-R enzymatic activity and intracellular cholesterol synthesis in vitro; however, inflammatory stress weakened these suppressive effects. Atorvastatin at concentrations of 15 microM inhibited HMGCoA-R activity by 50% (IC50) in HMCs, but the same concentration in the presence of interleukin (IL)-1beta resulted in only 30% inhibition of HMGCoA-R activity in HMCs. Knocking down SCAP prevented statin resistance induced by IL-1beta, and overexpression of SCAP-induced statin resistance even without inflammatory stress. In vivo, the amount of atorvastatin required to lower serum cholesterol and decrease kidney lipid accumulation rose from 2 to 10 mg/kg/day in the presence of inflammatory stress. CONCLUSIONS: Inflammatory stress can disrupt HMGCoA-R-mediated cholesterol synthesis resulting in intracellular lipid accumulation and statin resistance.

Chin, H. J., Y. Y. Fu, et al. "Omacor, n-3 polyunsaturated fatty acid, attenuated albuminuria and renal dysfunction with decrease of SREBP-1 expression and triglyceride amount in the kidney of type II diabetic animals." Nephrol Dial Transplant. 2010 May;25(5):1450-7. doi: 10.1093/ndt/gfp695. Epub 2009 Dec 29.

BACKGROUND: We assumed that n-3 polyunsaturated fatty acid (n-3 PUFA) would attenuate the tissue dyslipidemic condition through suppression of sterol regulatory element-binding protein (SREBP-1) in the kidney and would prevent renal progression in diabetic animals. METHODS: We gavaged Omacor, composed of docosahexaenoic acid and eicosapentaenoic acid, to db/db mice for 2 weeks (0.2 g/100 g/day). We measured the markers of renal function, triglyceride amount and expressions of SREBP-1, liver X-activated receptor alpha (LXRalpha), collagen IV and TGFbeta-1 in kidney

lysate, and performed immunohistochemical staining for SREBP-1, desmin and WT-1 in the renal sections. We measured collagen IV in primary mesangial cells cultured with high glucose media (25 mM), both with and without a transient transfection of small interfering RNA (siRNA) SREBP-1. RESULTS: Omacor decreased the concentration of serum free fatty acid, and the amount of renal triglyceride, which was associated with decreased expression of SREBP-1 in the kidney, albuminuria and renal dysfunction in db/db mice. Omacor attenuated the expansion of mesangial matrix and the expression of desmin, preserved the WT-1 positive cells, and inhibited the phosphorylation of nuclear factor kappaB in renal tissue. In mesangial cells cultured in high glucose media, the suppression of SREBP-1 expression decreased the collagen IV in the cells. CONCLUSIONS: Our study results demonstrated that n-3 PUFA prevented renal progression with attenuation of SREBP-1 and reduction of triglyceride in the diabetic kidney. This suggests that the regulation of dyslipidemic signals in the kidney could be a possible mechanism by which PUFA preserves renal function in the diabetic condition.

Chmielewski, M. and B. Rutkowski Mechanisms of dyslipidemia in chronic kidney disease, Am J Physiol Renal Physiol. 2009 Sep;297(3):F835. doi: 10.1152/ajprenal.00269.2009.

Chmielewski, M., E. Sucajtys-Szulc, et al. "Feedback inhibition of cholesterol biosynthesis by dietary cholesterol in experimental chronic renal failure." J Ren Nutr. 2008 Sep;18(5):448-55. doi: 10.1053/j.jrn.2008.04.005.

OBJECTIVE: Enhanced liver cholesterol synthesis is present in experimental chronic renal failure (CRF), even though cholesterol concentrations in blood and liver are increased, suggesting that CRF results in disturbed cholesterolegenesis feedback regulation. DESIGN: This study sought to elucidate whether dietary cholesterol exerts inhibitory effects on liver cholesterologenesis in CRF rats. METHODS: Male Wistar rats were used. Experimental CRF was achieved by a 5/6 nephrectomy model. Cholesterologenesis was measured (1) in vivo by tritiated water incorporation into cholesterol, and (2) in vitro (using liver slices) by [(14)C]-acetate and [(3)H]-mevalonate incorporation into cholesterol. In addition, the mRNA abundance of 3-hydroxy-3-methylglutaryl-CoA reductase, a rate-limiting enzyme in cholesterologenesis pathway, as well as its activity, was determined. Finally, the mRNA level of liver sterol regulatory element-binding protein-2, a nuclear transcription factor engaged in intracellular cholesterol homeostasis, was measured. RESULTS: Experimental CRF was associated with significantly increased concentrations of serum and liver cholesterol. In vitro and in vivo cholesterologenesis was enhanced in CRF rats. A cholesterol-enriched diet resulted in a significant decrease in (1) in vivo and in vitro cholesterol synthesis, (2) 3-hydroxy-3-methylglutaryl-CoA reductase gene expression, and (3) the level of liver sterol regulatory element-binding protein-2 mRNA in CRF rats. CONCLUSIONS: Despite elevated plasma and liver cholesterol concentrations, cholesterologenesis is increased in CRF rats. It is, however, inhibited by dietary cholesterol. These results suggest that a feedback inhibition of cholesterologenesis by dietary cholesterol is preserved in experimental CRF.

Chmielewski, M., E. Sucajtys-Szulc, et al. "Increased gene expression of liver SREBP-2 in experimental chronic renal failure." Atherosclerosis. 2007 Apr;191(2):326-32. Epub 2006 Jun 30.

Sterol regulatory element-binding protein-2 (SREBP-2) is a transcription factor regarded as the main regulator of cholesterol homeostasis. Therefore, increased level of SREBP-2 could be responsible for hypercholesterolemia, which is observed in experimental chronic renal failure (CRF). This study was designed primary to evaluate the impact of experimental CRF (5/6 nephrectomy model) on rat liver SREBP-2 gene expression. In CRF rats, a twofold increase in SREBP-2 mRNA level, as well as in mature SREBP-2 protein abundance was found, when compared to control animals. It was associated with enhanced activity and mRNA abundance of liver HMG-CoA reductase, a rate-limiting enzyme for cholesterol biosynthesis. A twofold increase in liver cholesterologenesis rate was also noted. We conclude that experimental CRF is associated with increased liver SREBP-2 gene expression. This is probably the cause for enhanced HMG-CoA reductase gene expression and, consequently, for increase in liver cholesterol synthesis in CRF rats. Despite increased SREBP-2 gene expression we found LDL-receptor mRNA level to be lower than in controls, suggesting SREBP-2 independent mechanisms of LDL-receptor transcriptional regulation in CRF rats. Enhanced cholesterol synthesis and decreased LDL-receptor mRNA level are probably responsible for an almost fourfold increase in serum cholesterol concentration in CRF rats.

Cho, H. K., H. J. Kong, et al. "Characterization of Paralichthys olivaceus peroxisome proliferator-activated receptor-alpha gene as a master regulator of flounder lipid metabolism." Gen Comp Endocrinol. 2012 Jan 1;175(1):39-47. doi: 10.1016/j.ygcen.2011.08.026. Epub 2011 Oct 25.

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that play key roles in lipid and energy homeostasis. Paralichthys olivaceus PPARalpha (PoPPARalpha) cDNA was isolated by initial reverse transcription-polymerase chain reaction (RT-PCR) using conserved region among fish species and rapid amplification of cDNA ends (RACE). The full-length of PoPPARalpha cDNA is 2040-bp long encoding a polypeptide with 505 amino acids and containing a DNA binding domain (C4-type zinc finger) and a ligand-binding domain. PoPPARalpha was detected from 1 day post-hatch and was highly expressed in the stomach, liver, and intestine of continuously fed flounder, approximately 16 cm in size. PoPPARalpha mRNA expression was down-regulated in the kidney, stomach, and liver of the 4.5-month-old flounder after a 30 day food-deprivation period. PoPPARalpha activates the PPAR response element (PPRE)-driven reporter, and treatment with Wy14643, a PPARalpha agonist, augmented PoPPARalpha-stimulated peroxisome proliferator response element activity in HINAE and HepG2 cells. PoPPARalpha activated the expression of fatty acid beta-oxidation related genes such as carnitine palmitoyltransferase 1A, medium chain acyl-CoA dehydrogenase, and acyl-CoA oxidase 1 and inhibited the expression of sterol regulatory element binding protein and fatty acid synthase by competitively inhibiting LXR/RXR heterodimer formation. These results suggest that PoPPARalpha plays an important role in lipid metabolism of olive flounder and that it is functionally and evolutionarily conserved in olive flounder and mammals.

Choi, Y. J., H. S. Shin, et al. "Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes." Lab Invest. 2014 Oct;94(10):1114-25. doi: 10.1038/labinvest.2014.98. Epub 2014 Aug 11.

Non-alcoholic fatty liver disease (NAFLD) is currently one of the most common types of chronic liver injury. Elevated serum uric acid is a strong predictor of the development of fatty liver as well as metabolic syndrome. Here we demonstrate that uric acid induces triglyceride accumulation by SREBP-1c activation via induction of endoplasmic reticulum (ER) stress in hepatocytes. Uric acid-induced ER stress resulted in an increase of glucose-regulated protein (GRP78/94), splicing of the X-box-binding protein-1 (XBP-1), the phosphorylation of protein kinase RNA-like ER kinase (PERK), and eukaryotic translation initiation factor-2alpha (eIF-2alpha) in cultured hepatocytes. Uric acid promoted hepatic lipogenesis through overexpression of the lipogenic enzyme, acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FAS), and stearoyl-CoA desaturase 1 (SCD1) via activation of SREBP-1c, which was blocked by probenecid, an organic anion transport blocker in HepG2 cells and primary hepatocytes. A blocker of ER stress, tauroursodeoxycholic acid (TUDCA), and an inhibitor of SREBP-1c, metformin, blocked hepatic fat accumulation, suggesting that uric acid promoted fat synthesis in hepatocytes via ER stress-induced activation of SREBP-1c. Uric acid-induced activation of NADPH oxidase preceded ER stress, which further induced mitochondrial ROS production in hepatocytes. These studies provide new insights into the mechanisms by which uric acid stimulates fat accumulation in the liver.

Chow, J. D., M. E. Jones, et al. "A selective estrogen receptor alpha agonist ameliorates hepatic steatosis in the male aromatase knockout mouse." J Endocrinol. 2011 Sep;210(3):323-34. doi: 10.1530/JOE-10-0462. Epub 2011 Jun 24.

Male aromatase knockout mice (ArKO; an estrogen-deficient model) present with male-specific hepatic steatosis that is reversible upon 17beta-estradiol replacement. This study aims to elucidate which estrogen receptor (ER) subtype, ERalpha or ERbeta, is involved in the regulation of triglyceride (TG) homeostasis in the liver. Nine-month-old male ArKO mice were treated with vehicle, ERalpha- or ERbeta-specific agonists via s.c. injection, daily for 6 weeks. Male ArKO mice treated with ERalpha agonist had normal liver histology and TG contents compared with vehicle-treated ArKO; omental (gonadal) and infra-renal (visceral) fat pad weights were normalized to those of vehicle-treated wild-type (WT). In contrast, ERbeta agonist treatment did not result in the similar reversal of these ArKO phenotypes. In vehicle-treated ArKO mice, hepatic transcript expression of fatty acid synthase (Fasn) and stearoyl-coenzyme A desaturase 1 (key enzymes in de novo FA synthesis) were significantly elevated compared with vehicle-treated WT, but only Fasn expression was lowered to WT level after ERalpha agonist treatment. There were no significant changes in the transcript levels of carnitine palmitoyl transferase 1 (required for transfer of FA residues into the mitochondria for beta-oxidation) and sterol regulatory element-binding factor 1c (the upstream regulator of de novo FA synthesis). We also confirmed by RT-PCR that only ERalpha is expressed in the mouse liver. There were no changes in hepatic androgen receptor transcript level across all treatment groups. Our data suggest that estrogens act via ERalpha to regulate TG homeostasis in the ArKO liver. Since the liver, adipose tissue and arcuate nucleus express mainly ERalpha, estrogens could regulate hepatic functions via peripheral and central pathways.

David-Silva, A., H. S. Freitas, et al. "Hepatocyte nuclear factors 1alpha/4alpha and forkhead box A2 regulate the solute carrier 2A2 (Slc2a2) gene expression in the liver and kidney of diabetic rats." Life Sci. 2013 Nov 19;93(22):805-13. doi: 10.1016/j.lfs.2013.10.011. Epub 2013 Oct 21.

AIMS: Solute carrier 2a2 (Slc2a2) gene codifies the glucose transporter GLUT2, a key protein for glucose flux in hepatocytes and renal epithelial cells of proximal tubule. In diabetes mellitus, hepatic and tubular glucose output has been related to Slc2a2/GLUT2 overexpression; and controlling the expression of this gene may be an important adjuvant way to improve glycemic homeostasis. Thus, the present study investigated transcriptional mechanisms involved in the diabetes-induced overexpression of the Slc2a2 gene. MAIN METHODS: Hepatocyte nuclear factors 1alpha and 4alpha (HNF-1alpha and HNF-4alpha), forkhead box A2 (FOXA2), sterol regulatory element binding protein-1c (SREBP-1c) and the CCAAT-enhancer-binding protein (C/EBPbeta) mRNA expression (RT-PCR) and binding activity into the Slc2a2 promoter (electrophoretic mobility assay) were analyzed in the liver and kidney of diabetic and 6-day insulin-treated diabetic rats. KEY FINDINGS: Slc2a2/GLUT2 expression increased by more than 50% ($P<0.001$) in the liver and kidney of diabetic rats, and 6-day insulin treatment restores these values to those observed in non-diabetic animals. Similarly, the mRNA expression and the binding activity of HNF-1alpha, HNF-4alpha and FOXA2 increased by 50 to 100% ($P<0.05$ to $P<0.001$), also returning to values of non-diabetic rats after insulin treatment. Neither the Srebf1 and Cebpb mRNA expression, nor the SREBP-1c and C/EBP-beta binding activity was altered in diabetic rats. SIGNIFICANCE: HNF-1alpha, HNF-4alpha and FOXA2 transcriptional factors are involved in diabetes-induced overexpression of Slc2a2 gene in the liver and kidney. These data point out that these transcriptional factors are important targets to control GLUT2 expression in these tissues, which can contribute to glycemic homeostasis in diabetes.

Dif, N., V. Euthine, et al. "Insulin activates human sterol-regulatory-element-binding protein-1c (SREBP-1c) promoter through SRE motifs." Biochem J. 2006 Nov 15;400(1):179-88.

In the present study, we aimed to decipher the mechanisms involved in the transcriptional effect of insulin on the SREBP-1c specific promoter of the human srebf-1 gene. Using luciferase reporter gene constructs in HEK-293 cells (human embryonic kidney cells), we demonstrated that the full effect of insulin requires the presence of SREs (sterol response elements) in the proximal region of the promoter. Furthermore, insulin increases the binding of SREBP-1 (sterol-regulatory-element-binding protein-1) to this promoter region in chromatin immunoprecipitation assay. We also found that the nuclear receptors LXRs (liver X receptors) strongly activate SREBP-1c gene expression and identified the LXRE (LXR-response element) involved in this effect. However, our results suggested that these LXREs do not play a major role in the response to insulin. Finally, using expression vectors and adenoviruses allowing ectopic overexpressions of the human mature forms of SREBP-1a or SREBP-1c, we demonstrated the direct role of SREBP-1 in the control of SREBP-1c gene expression in human skeletal-muscle cells. Altogether, these results strongly suggest that the SREBP-1 transcription factors are the main mediators of insulin action on SREBP-1c expression in human tissues.

Drabkin, H. A. and R. M. Gemmill "Obesity, cholesterol, and clear-cell renal cell carcinoma (RCC)." Adv Cancer Res. 2010;107:39-56. doi: 10.1016/S0065-230X(10)07002-8.

Multiple epidemiologic studies have linked the development of renal cancer to obesity. In this chapter, we begin with a review of selected population studies, followed by recent mechanistic discoveries that further link lipid deregulation to the RCC development. The upregulation of leptin and downregulation of adiponectin pathways in obesity fit well with our molecular understanding of RCC pathogenesis. In addition, two forms of hereditary RCC involve proteins, Folliculin and TRC8, that are positioned to coordinately regulate lipid and protein biosynthesis. Both of these biosynthetic pathways have important downstream consequences on HIF-1/2alpha levels and angiogenesis, key aspects in the disease pathogenesis. The role of lipid biology and its interface with protein translation regulation represents a new dimension in RCC research with potential therapeutic implications.

Feramisco, J. D., J. L. Goldstein, et al. "Membrane topology of human insig-1, a protein regulator of lipid synthesis." J Biol Chem. 2004 Feb 27;279(9):8487-96. Epub 2003 Dec 5.

Insig-1 is an intrinsic protein of the endoplasmic reticulum (ER) that regulates the proteolytic processing of membrane-bound sterol regulatory element-binding proteins (SREBPs), transcription factors that activate the synthesis of cholesterol and fatty acids in mammalian cells. When cellular levels of sterols rise, Insig-1 binds to the membranous sterol-sensing domain of SREBP cleavage-activating protein (SCAP), retaining the SCAP/SREBP complex in the ER and preventing it from moving to the Golgi for proteolytic processing. Under conditions of sterol excess, Insig-1 also binds to

the ER enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, facilitating its ubiquitination and proteasomal degradation. Here, we use protease protection, glycosylation site mapping, and cysteine derivitization to define the topology of the 277-amino acid human Insig-1. The data indicate that short segments at the N and C termini of Insig-1 face the cytosol. Most of the protein is buried within the membrane, forming six transmembrane segments separated by five short luminal and cytosolic loops that range from approximately 5 to 16 amino acids. The membranous nature of Insig-1 is consistent with its sterol-dependent binding to hydrophobic sterol-sensing domains in SCAP and HMG CoA reductase.

Foley, D. L. and A. Mackinnon "A systematic review of antipsychotic drug effects on human gene expression related to risk factors for cardiovascular disease." Pharmacogenomics J. 2014 Oct;14(5):446-51. doi: 10.1038/tpj.2014.8. Epub 2014 Mar 11.

Psychosis is associated with an elevated risk for cardiovascular disease. We reviewed evidence for a causal association between experimentally controlled antipsychotic drug exposure and a change in the expression of genes relevant to cardiovascular disease in human cell lines. Reports from SCOPUS - V.4 (Elsevier) and MEDLINE (ISI) were assessed for global or candidate gene expression analysis, tissue and cell type, tissue source or cell line, antipsychotic drug and dosage, length of drug exposure and statistically significant fold change in gene expression after drug exposure; 29 eligible studies analysed gene expression in the brain, eye (as a model of neuronal cells), heart, kidney (as a model of any cell), liver, pancreas or skin. Antipsychotic drugs alter the expression of numerous genes related to cardiovascular health, including genes under the control of the sterol regulatory element binding protein transcription factors that control lipid and fatty acid biosynthesis.

Hannah, V. C., J. Ou, et al. "Unsaturated fatty acids down-regulate srebp isoforms 1a and 1c by two mechanisms in HEK-293 cells." J Biol Chem. 2001 Feb 9;276(6):4365-72. Epub 2000 Nov 20.

Sterol regulatory element-binding proteins (SREBPs) are membrane-bound transcription factors that increase the synthesis of fatty acids as well as cholesterol in animal cells. All three SREBP isoforms (SREBP-1a, -1c, and -2) are subject to feedback regulation by cholesterol, which blocks their proteolytic release from membranes. Previous data indicate that the SREBPs are also negatively regulated by unsaturated fatty acids, but the mechanism is uncertain. In the current experiments, unsaturated fatty acids decreased the nuclear content of SREBP-1, but not SREBP-2, in cultured human embryonic kidney (HEK)-293 cells. The potency of unsaturated fatty acids increased with increasing chain length and degree of unsaturation. Oleate, linoleate, and arachidonate were all effective, but the saturated fatty acids palmitate and stearate were not effective. Down-regulation occurred at two levels. The mRNAs encoding SREBP-1a and SREBP-1c were markedly reduced, and the proteolytic processing of these SREBPs was inhibited. When SREBP-1a was produced by a cDNA expressed from an independent promoter, unsaturated fatty acids reduced nuclear SREBP-1a without affecting the mRNA level. There was no effect when the cDNA encoded a truncated version that was not membrane-bound. When administered together, sterols and unsaturated fatty acids potentiated each other in reducing nuclear SREBP-1. In the absence of fatty acids, sterols did not cause a sustained reduction of nuclear SREBP-1, but they did reduce nuclear SREBP-2. We conclude that unsaturated fatty acids, as well as sterols, can down-regulate nuclear SREBPs and that unsaturated fatty acids have their greatest inhibitory effects on SREBP-1a and SREBP-1c, whereas sterols have their greatest inhibitory effects on SREBP-2.

Hao, J., S. Liu, et al. "PI3K/Akt pathway mediates high glucose-induced lipogenesis and extracellular matrix accumulation in HKC cells through regulation of SREBP-1 and TGF-beta1." Histochem Cell Biol. 2011 Feb;135(2):173-81. doi: 10.1007/s00418-011-0777-3. Epub 2011 Jan 15.

Previous studies have shown that high glucose stimulates renal SREBP-1 gene expression and increases renal tubular cells lipid metabolism, however, the mechanisms remain elusive. In the present study we demonstrated that PI3K/Akt pathway was activated in human renal proximal tubular cell line (HKC) exposed to high glucose accompanied with up-regulation of SREBP-1, TGF-beta1, lipid droplets deposits and extracellular matrix production. Inhibition of PI3K/Akt pathway by chemical LY294002 or specific short hairpin RNA (shRNA) vector prevented SREBP-1 and TGF-beta1 up-regulation, as well as ameliorated HKC cells lipogenesis and extracellular matrix accumulation. These findings indicate that PI3K/Akt pathway potentially mediates high glucose-induced lipogenesis and extracellular matrix accumulation in HKC cells.

Hao, J., S. X. Liu, et al. "[High fat diet induced the expression of SREBP-1, TGF-beta1 and alpha-SMA in renal tubular cells and extracellular matrix accumulation in Wistar rats]." Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2010 Aug;26(3):307-11.

OBJECTIVE: To explore the effect of high fat diet on the expression of sterol regulatory element binding protein-1 (SREBP-1), transforming growth factor-beta1 (TGF-beta1) and alpha-smooth muscle actin (alpha-SMA) in renal tubular cells and extracellular matrix accumulation in Wistar rats. METHODS: The Wistar rats were treated with high fat diet for 12 weeks and renal lipid deposit was detected by the method of Oil Red O staining. The immunohistochemistry and Western blot were used to investigate the expression of SREBP-1, TGF-beta1, alpha-SMA and fibronectin (FN) protein. The expression of SREBP-1 mRNA was determined with in situ hybridization. Masson staining was for the detection of extracellular matrix (ECM) accumulation. RESULTS: The weight of rats raised by high fat diet increased, in company with the high serum glucose, serum triglyceride and serum insulin. The Oil Red O staining revealed that the renal proximal tubular epithelial cells showed significant lipid droplet in high fat diet rats. SREBP-1 protein and mRNA were located in the renal tubular cells and the expressions of high fat diet rats were higher than those of normal control rats. They were respectively 1.88 times and 1.85 times than those of normal control group. TGF-beta1 and alpha-SMA protein were also located in renal tubular cells and high fat diet up-regulated the expression of them. ECM accumulation was detected with Masson staining and the result showed that high fat diet treatment increased interstitial ECM product and FN protein was found high expression. CONCLUSION: High fat diet may induce lipid droplet deposit in renal tubular cells by up-regulation of the expression of SREBP-1, which causes ECM accumulation by increasing the expression of TGF-beta1 and alpha-SMA.

Hashimoto, K., M. Yamada, et al. "Mouse sterol response element binding protein-1c gene expression is negatively regulated by thyroid hormone." Endocrinology. 2006 Sep;147(9):4292-302. Epub 2006 Jun 22.

Sterol regulatory element-binding protein (SREBP)-1c is a key regulator of fatty acid metabolism and plays a pivotal role in the transcriptional regulation of different lipogenic genes mediating lipid synthesis. In previous studies, the regulation of SREBP-1c mRNA levels by thyroid hormone has remained controversial. In this study, we examined whether T3 regulates the mouse SREBP-1c mRNA expression. We found that T3 negatively regulates the mouse SREBP-1c gene expression in the liver, as shown by ribonuclease protection assays and real-time quantitative RT-PCR. Promoter analysis with luciferase assays using HepG2 and Hepa1-6 cells revealed that T3 negatively regulates the mouse SREBP-1c gene promoter (-574 to +42) and that Site2 (GCCTGACAGGTGAAATCGGC) located around the transcriptional start site is responsible for the negative regulation by T3. Gel shift assays showed that retinoid X receptor-alpha/thyroid hormone receptor-beta heterodimer bound to Site2, but retinoid X receptor-alpha/liver X receptor- heterodimer could not bind to the site. In vivo chromatin immunoprecipitation assays demonstrated that T3 induced thyroid hormone receptor-beta recruitment to Site2. Thus, we demonstrated that mouse SREBP-1c mRNA is down-regulated by T3 in vivo and that T3 negatively regulates mouse SREBP-1c gene transcription via a novel negative thyroid hormone response element: Site2.

Hawkins, J. L., M. D. Robbins, et al. "Pharmacologic inhibition of site 1 protease activity inhibits sterol regulatory element-binding protein processing and reduces lipogenic enzyme gene expression and lipid synthesis in cultured cells and experimental animals." J Pharmacol Exp Ther. 2008 Sep;326(3):801-8. doi: 10.1124/jpet.108.139626. Epub 2008 Jun 24.

Sterol regulatory element-binding proteins (SREBPs) are major transcriptional regulators of cholesterol, fatty acid, and glucose metabolism. Genetic disruption of SREBP activity reduces plasma and liver levels of cholesterol and triglycerides and insulin-stimulated lipogenesis, suggesting that SREBP is a viable target for pharmacological intervention. The proprotein convertase SREBP site 1 protease (S1P) is an important posttranscriptional regulator of SREBP activation. This report demonstrates that 10 microM PF-429242 (Bioorg Med Chem Lett 17:4411-4414, 2007), a recently described reversible, competitive aminopyrrolidineamide inhibitor of S1P, inhibits endogenous SREBP processing in Chinese hamster ovary cells. The same compound also down-regulates the signal from an SRE-luciferase reporter gene in human embryonic kidney 293 cells and the expression of endogenous SREBP target genes in cultured HepG2 cells. In HepG2 cells, PF-429242 inhibited cholesterol synthesis, with an IC(50) of 0.5 microM. In mice treated with PF-429242 for 24 h, the expression of hepatic SREBP target genes was suppressed, and the hepatic rates of cholesterol and fatty acid synthesis were reduced. Taken together, these data establish that small-molecule S1P inhibitors are capable of reducing cholesterol and fatty acid synthesis in vivo and, therefore, represent a potential new class of therapeutic agents for dyslipidemia and for a variety of cardiometabolic risk factors associated with diabetes, obesity, and the metabolic syndrome.

Herman-Edelstein, M., P. Scherzer, et al. "Altered renal lipid metabolism and renal lipid accumulation in

human diabetic nephropathy." J Lipid Res. 2014 Mar;55(3):561-72. doi: 10.1194/jlr.P040501. Epub 2013 Dec 26.

Animal models link ectopic lipid accumulation to renal dysfunction, but whether this process occurs in the human kidney is uncertain. To this end, we investigated whether altered renal TG and cholesterol metabolism results in lipid accumulation in human diabetic nephropathy (DN). Lipid staining and the expression of lipid metabolism genes were studied in kidney biopsies of patients with diagnosed DN (n = 34), and compared with normal kidneys (n = 12). We observed heavy lipid deposition and increased intracellular lipid droplets. Lipid deposition was associated with dysregulation of lipid metabolism genes. Fatty acid beta-oxidation pathways including PPAR-alpha, carnitine palmitoyltransferase 1, acyl-CoA oxidase, and L-FABP were downregulated. Downregulation of renal lipoprotein lipase, which hydrolyzes circulating TGs, was associated with increased expression of angiopoietin-like protein 4. Cholesterol uptake receptor expression, including LDL receptors, oxidized LDL receptors, and acetylated LDL receptors, was significantly increased, while there was downregulation of genes effecting cholesterol efflux, including ABCA1, ABCG1, and apoE. There was a highly significant correlation between glomerular filtration rate, inflammation, and lipid metabolism genes, supporting a possible role of abnormal lipid metabolism in the pathogenesis of DN. These data suggest that renal lipid metabolism may serve as a target for specific therapies aimed at slowing the progression of glomerulosclerosis.

Hitkova, I., G. Yuan, et al. "Caveolin-1 protects B6129 mice against Helicobacter pylori gastritis." PLoS Pathog. 2013;9(4):e1003251. doi: 10.1371/journal.ppat.1003251. Epub 2013 Apr 11.

Caveolin-1 (Cav1) is a scaffold protein and pathogen receptor in the mucosa of the gastrointestinal tract. Chronic infection of gastric epithelial cells by Helicobacter pylori (H. pylori) is a major risk factor for human gastric cancer (GC) where Cav1 is frequently down-regulated. However, the function of Cav1 in H. pylori infection and pathogenesis of GC remained unknown. We show here that Cav1-deficient mice, infected for 11 months with the CagA-delivery deficient H. pylori strain SS1, developed more severe gastritis and tissue damage, including loss of parietal cells and foveolar hyperplasia, and displayed lower colonisation of the gastric mucosa than wild-type B6129 littermates. Cav1-null mice showed enhanced infiltration of macrophages and B-cells and secretion of chemokines (RANTES) but had reduced levels of CD25+ regulatory T-cells. Cav1-deficient human GC cells (AGS), infected with the CagA-delivery proficient H. pylori strain G27, were more sensitive to CagA-related cytoskeletal stress morphologies ("humming bird") compared to AGS cells stably transfected with Cav1 (AGS/Cav1). Infection of AGS/Cav1 cells triggered the recruitment of p120 RhoGTPase-activating protein/deleted in liver cancer-1 (p120RhoGAP/DLC1) to Cav1 and counteracted CagA-induced cytoskeletal rearrangements. In human GC cell lines (MKN45, N87) and mouse stomach tissue, H. pylori down-regulated endogenous expression of Cav1 independently of CagA. Mechanistically, H. pylori activated sterol-responsive element-binding protein-1 (SREBP1) to repress transcription of the human Cav1 gene from sterol-responsive elements (SREs) in the proximal Cav1 promoter. These data suggested a protective role of Cav1 against H. pylori-induced inflammation and tissue damage. We propose that H. pylori exploits down-regulation of Cav1 to subvert the host's immune response and to promote signalling of its virulence factors in host cells.

Huq, M. D., N. P. Tsai, et al. "Regulation of retinal dehydrogenases and retinoic acid synthesis by cholesterol metabolites." EMBO J. 2006 Jul 12;25(13):3203-13. Epub 2006 Jun 8.

Retinoic acid (RA) constitutes the major active ingredient of vitamin A and is required for various biological processes. The tissue RA level is maintained through a cascade of metabolic reactions where retinal dehydrogenases (RALDHs) catalyze the terminal reaction of RA biosynthesis from retinal, a rate-limiting step. We showed that dietary supplement of cholesterol enhanced the expression of RALDH1 and 2 genes and the cellular RA content in vital organs such as brain, kidney, liver and heart. Consistently, the cholesterol-lowering agent (pravastatin sodium) downregulated the expression of RALDH1 and 2 genes in several organs especially the liver and in cultured liver cells. Further, cholesterol metabolites, predominantly the oxysterols, the natural ligands for liver X receptor (LXR), induced these genes via upregulation of sterol regulatory element binding protein-1c (SREBP-1c) that bound to the regulatory regions of these genes. Knockdown of LXRalpha/beta or SREBP-1c downregulated the expression of RALDH genes, which could be rescued by re-expressing SREBP-1c, suggesting SREBP-1c as a direct positive regulator for these genes. This study uncovered a novel crosstalk between cholesterol and RA biosynthesis.

Im, S. S., S. Y. Kang, et al. "Glucose-stimulated upregulation of GLUT2 gene is mediated by sterol response element-binding protein-1c in the hepatocytes." Diabetes. 2005 Jun;54(6):1684-91.

GLUT2 is mainly expressed in the liver, beta-cells of the pancreas, and the basolateral membrane of kidney proximal tubules and plays an important role in glucose homeostasis in living organisms. The transcription of the GLUT2 gene is known to be upregulated in the liver during postprandial hyperglycemic states or in type 2 diabetes. However, a molecular mechanism by which glucose activates GLUT2 gene expression is not known. In this study, we report evidence that sterol response element-binding protein (SREBP)-1c plays a key role in glucose-stimulated GLUT2 gene expression. The GLUT2 promoter reporter is activated by SREBP-1c, and the activation is inhibited by a dominant-negative form of SREBP-1c (SREBP-1c DN). Adenoviral expression of SREBP-1c DN suppressed glucose-stimulated GLUT2 mRNA level in primary hepatocytes. An electrophoretic mobility shift assay and mutational analysis of the GLUT2 promoter revealed that SREBP-1c binds to the -84/-76 region of the GLUT2 promoter. Chromatin immunoprecipitation revealed that the binding of SREBP-1c to the -84/-76 region was increased by glucose concentration in a dose-dependent manner. These results indicate that SREBP-1c mediates glucose-stimulated GLUT2 gene expression in hepatocytes.

Irisawa, M., J. Inoue, et al. "The sterol-sensing endoplasmic reticulum (ER) membrane protein TRC8 hampers ER to Golgi transport of sterol regulatory element-binding protein-2 (SREBP-2)/SREBP cleavage-activated protein and reduces SREBP-2 cleavage." J Biol Chem. 2009 Oct 16;284(42):28995-9004. doi: 10.1074/jbc.M109.041376. Epub 2009 Aug 25.

TRC8 (translocation in renal cancer from chromosome 8) is an intrinsic protein of the endoplasmic reticulum that contains a sterol-sensing domain and a RING finger motif encoding an E3 ubiquitin ligase. Here we show that TRC8 overexpression hinders sterol regulatory element-binding protein-2 (SREBP-2) processing, thereby reducing SREBP-2 target gene expression, TRC8 depletion has the opposite effect. Mutation analyses of TRC8 reveal that the ubiquitin ligase activity is dispensable for these effects. Activating transcription factor 6 (ATF6) is also processed in the Golgi by the same two proteases as those for SREBP, but ATF6 processing is not affected by TRC8. TRC8 is capable of binding both SREBP-2 and SREBP cleavage-activated protein (SCAP), thereby forming a TRC8.SREBP-2.SCAP complex. This complex formation hampers the interaction between SCAP and Sec24, one of the COPII proteins that are involved in SREBP-2 transport to the Golgi, thereby reducing SREBP-2 cleavage. TRC8 conjugated by ubiquitin is unstable, whereas the mutant TRC8, lacking the E3 ubiquitin ligase activity and only slightly modified by ubiquitin, is quite stable. TRC8 becomes stable when cells are cultured with a proteasome inhibitor or under a lipoprotein-depleted condition. Lipoprotein depletion impairs ubiquitination of TRC8. Taken together, TRC8 is a novel sterol-sensing endoplasmic reticulum membrane protein that hinders SREBP-2 processing through interaction with SREBP-2 and SCAP, regulating its own turnover rate by means of its E3 ubiquitin ligase activity.

Ishigaki, N., T. Yamamoto, et al. "Involvement of glomerular SREBP-1c in diabetic nephropathy." Biochem Biophys Res Commun. 2007 Dec 21;364(3):502-8. Epub 2007 Oct 16.

The role of glomerular SREBP-1c in diabetic nephropathy was investigated. PEPCK-promoter transgenic mice overexpressing nuclear SREBP-1c exhibited enhancement of proteinuria with mesangial proliferation and matrix accumulation, mimicking diabetic nephropathy, despite the absence of hyperglycemia or hyperlipidemia. Isolated transgenic glomeruli had higher expression of TGFbeta-1, fibronectin, and SPARC in the absence of marked lipid accumulation. Gene expression of P47phox, p67phox, and PU.1 were also activated, accompanying increased 8-OHdG in urine and kidney, demonstrating that glomerular SREBP-1c could directly cause oxidative stress through induced NADPH oxidase. Similar changes were observed in STZ-treated diabetic mice with activation of endogenous SREBP-1c. Finally, diabetic proteinuria and oxidative stress were ameliorated in SREBP-1-null mice. Adenoviral overexpression of active and dominant-negative SREBP-1c caused consistent reciprocal changes in expression of both profibrotic and oxidative stress genes in MES13 mesangial cells. These data suggest that activation of glomerular SREBP-1c could contribute to emergence and/or progression of diabetic nephropathy.

Jeon, B. N., Y. S. Kim, et al. "Kr-pok increases FASN expression by modulating the DNA binding of SREBP-1c and Sp1 at the proximal promoter." J Lipid Res. 2012 Apr;53(4):755-66. doi: 10.1194/jlr.M022178. Epub 2012 Feb 13.

Kr-pok (kidney cancer-related POZ domain and Kruppel-like protein) is a new proto-oncogenic POZ-domain transcription factor. Fatty acid synthase gene (FASN) encodes one of the key enzymes in fatty acids synthesis and is the only enzyme that synthesizes fatty acids in cancer cells. Sp1 and SREBP-1c are the two major transcription activators of FASN. We investigated whether Kr-pok modulates transcription of the FASN. FASN expression is significantly

decreased in Kr-pok knockout murine embryonic fibroblasts. Coimmunoprecipitation, GST fusion protein pull-down, and immunocytochemistry assays show that the zinc-finger domain of Kr-pok interacts directly with the bZIP DNA binding domain of SREBP-1. Electrophoretic mobility shift assay, oligonucleotide pull-down, and chromatin immunoprecipitation assays showed that Kr-pok changes the transcription factor binding dynamics of Sp1 and SREBP-1c to the SRE/E-box elements of the proximal promoter. We found that Kr-pok expression increased during 3T3-L1 preadipocyte differentiation and that FASN expression is decreased by the knockdown of Kr-pok. Kr-pok facilitates the SREBP-1c-mediated preadipocyte differentiation and/or fatty acid synthesis. Kr-pok may act as an important regulator of fatty acid synthesis and may induce rapid cancer cell proliferation by increasing palmitate synthesis.

Korczynska, J., E. Stelmanska, et al. "Upregulation of lipogenic enzymes genes expression in white adipose tissue of rats with chronic renal failure is associated with higher level of sterol regulatory element binding protein-1." Metabolism. 2004 Aug;53(8):1060-5.

Chronic renal failure (CRF) frequently results in hypertriglyceridemia and elevated plasma concentration of very-low-density lipoprotein (VLDL). These abnormalities are thought to be primarily due to depressed lipoprotein lipase and hepatic lipase activities, as well as impaired clearance of plasma lipoproteins. Some results suggest that not only lipoproteins catabolism but also their overproduction might contribute to hypertriglyceridemia in CRF. Because sterol regulatory element binding protein (SREBP) plays an important role in the regulation of lipid homeostasis, increased level of this transcription factor might be involved in modulating lipid metabolism in CRF. The purpose of the present study is to determine whether there is an altered regulation of the SREBP-1 in CRF rats and whether the altered regulation of SREBP-1 is associated with the upregulation of lipogenic enzymes genes expression in CRF rats. In the white adipose tissue (WAT) of CRF rats, marked increases in the microsomal (precursor) and nuclear (mature) forms of SREBP-1 have been found. The increase in SREBP-1 was associated with an increased level of lipogenic enzymes (acetyl-coenzyme A [CoA] carboxylase [ACC], adenosine triphosphate-citrate lyase [ACL], fatty acid synthase [FAS], glucose 6-phosphate dehydrogenase [G6PDH], 6-phosphogluconate dehydrogenase [6PGDH], and malic enzyme [ME]) genes expression. In turn, this was associated with an increased rate of fatty acids synthesis in WAT and a significant increase in plasma triacylglycerol (TAG) and VLDL concentration. Our study indicates that WAT SREBP-1 expression is increased in CRF rats and that SREBP-1 may play an important role in the increased fatty acid synthesis. These results reveal another facet of disturbed lipid metabolism in CRF.

Kovacs, W. J., K. N. Charles, et al. "Peroxisome deficiency-induced ER stress and SREBP-2 pathway activation in the liver of newborn PEX2 knock-out mice." Biochim Biophys Acta. 2012 Jun;1821(6):895-907. doi: 10.1016/j.bbalip.2012.02.011. Epub 2012 Mar 13.

Disruption of the Pex2 gene leads to peroxisome deficiency and widespread metabolic dysfunction. We previously demonstrated that peroxisomes are critical for maintaining cholesterol homeostasis, using peroxisome-deficient Pex2(-/-) mice on a hybrid Swiss Websterx129S6/SvEv (SW/129) genetic background. Peroxisome deficiency activates hepatic endoplasmic reticulum (ER) stress pathways, leading to dysregulation of the endogenous sterol response mechanism. Herein, we demonstrate a more profound dysregulation of cholesterol homeostasis in newborn Pex2(-/-) mice congenic on a 129S6/SvEv (129) genetic background, and substantial differences between newborn versus postnatal Pex2(-/-) mice in factors that activate ER stress. These differences extend to relationships between activation of genes regulated by SREBP-2 versus PPARalpha. The SREBP-2 pathway is induced in neonatal Pex2(-/-) livers from 129 and SW/129 strains, despite normal hepatic cholesterol levels. ER stress markers are increased in newborn 129 Pex2(-/-) livers, which occurs in the absence of hepatic steatosis or accumulation of peroxins in the ER. Moreover, the induction of SREBP-2 and ER stress pathways is independent of PPARalpha activation in livers of newborn 129 and SW/129 Pex2(-/-) mice. Two-week-old wild-type mice treated with the peroxisome proliferator WY-14,643 show strong induction of PPARalpha-regulated genes and decreased expression of SREBP-2 and its target genes, further demonstrating that SREBP-2 pathway induction is not dependent on PPARalpha activation. Lastly, there is no activation of either SREBP-2 or ER stress pathways in kidney and lung of newborn Pex2(-/-) mice, suggesting a parallel induction of these pathways in peroxisome-deficient mice. These findings establish novel associations between SREBP-2, ER stress and PPARalpha pathway inductions.

Lhotak, S., S. Sood, et al. "ER stress contributes to renal proximal tubule injury by increasing SREBP-2-mediated lipid accumulation and apoptotic cell death." Am J Physiol Renal Physiol. 2012 Jul 15;303(2):F266-

78. doi: 10.1152/ajprenal.00482.2011. Epub 2012 May 9.

Renal proximal tubule injury is induced by agents/conditions known to cause endoplasmic reticulum (ER) stress, including cyclosporine A (CsA), an immunosuppressant drug with nephrotoxic effects. However, the underlying mechanism by which ER stress contributes to proximal tubule cell injury is not well understood. In this study, we report lipid accumulation, sterol regulatory element-binding protein-2 (SREBP-2) expression, and ER stress in proximal tubules of kidneys from mice treated with the classic ER stressor tunicamycin (Tm) or in human renal biopsy specimens showing CsA-induced nephrotoxicity. Colocalization of ER stress markers [78-kDa glucose regulated protein (GRP78), CHOP] with SREBP-2 expression and lipid accumulation was prominent within the proximal tubule cells exposed to Tm or CsA. Prolonged ER stress resulted in increased apoptotic cell death of lipid-enriched proximal tubule cells with colocalization of GRP78, SREBP-2, and Ca(2+)-independent phospholipase A(2) (iPLA(2)beta), an SREBP-2 inducible gene with proapoptotic characteristics. In cultured HK-2 human proximal tubule cells, CsA- and Tm-induced ER stress caused lipid accumulation and SREBP-2 activation. Furthermore, overexpression of SREBP-2 or activation of endogenous SREBP-2 in HK-2 cells stimulated apoptosis. Inhibition of SREBP-2 activation with the site-1-serine protease inhibitor AEBSF prevented ER stress-induced lipid accumulation and apoptosis. Overexpression of the ER-resident chaperone GRP78 attenuated ER stress and inhibited CsA-induced SREBP-2 expression and lipid accumulation. In summary, our findings suggest that ER stress-induced SREBP-2 activation contributes to renal proximal tubule cell injury by dysregulating lipid homeostasis.

Marcil, V., E. Seidman, et al. "Modification in oxidative stress, inflammation, and lipoprotein assembly in response to hepatocyte nuclear factor 4alpha knockdown in intestinal epithelial cells." J Biol Chem. 2010 Dec 24;285(52):40448-60. doi: 10.1074/jbc.M110.155358. Epub 2010 Sep 24.

Hepatocyte nuclear factor 4alpha (HNF4alpha) is a nuclear transcription factor mainly expressed in the liver, intestine, kidney, and pancreas. Many of its hepatic and pancreatic functions have been described, but limited information is available on its role in the gastrointestinal tract. The objectives of this study were to evaluate the anti-inflammatory and antioxidant functions of HNF4alpha as well as its implication in intestinal lipid transport and metabolism. To this end, the HNF4A gene was knocked down by transfecting Caco-2 cells with a pGFP-V-RS lentiviral vector containing an shRNA against HNF4alpha. Inactivation of HNF4alpha in Caco-2 cells resulted in the following: (a) an increase in oxidative stress as demonstrated by the levels of malondialdehyde and conjugated dienes; (b) a reduction in secondary endogenous antioxidants (catalase, glutathione peroxidase, and heme oxygenase-1); (c) a lower protein expression of nuclear factor erythroid 2-related factor that controls the antioxidant response elements-regulated antioxidant enzymes; (d) an accentuation of cellular inflammatory activation as shown by levels of nuclear factor-kappaB, interleukin-6, interleukin-8, and leukotriene B4; (e) a decrease in the output of high density lipoproteins and of their anti-inflammatory and anti-oxidative components apolipoproteins (apo) A-I and A-IV; (f) a diminution in cellular lipid transport revealed by a lower cellular secretion of chylomicrons and their apoB-48 moiety; and (g) alterations in the transcription factors sterol regulatory element-binding protein 2, peroxisome proliferator-activated receptor alpha, and liver X receptor alpha and beta. In conclusion, HNF4alpha appears to play a key role in intestinal lipid metabolism as well as intestinal anti-oxidative and anti-inflammatory defense mechanisms.

Mason, M. M., Y. He, et al. "Regulation of leptin promoter function by Sp1, C/EBP, and a novel factor." Endocrinology. 1998 Mar;139(3):1013-22.

Leptin is a hormone produced in adipose cells that regulates energy expenditure, food intake, and adiposity. To understand leptin's transcriptional regulation, we are studying its promoter. Four conserved and functional regions were identified. Mutations in the C/EBP and TATA motifs each caused an approximately 10-fold decrease in promoter activity. The C/EBP motif bound recombinant C/EBP alpha and mediated trans-activation by C/EBP alpha, -beta, and -delta. Mutation of a consensus Sp1 site reduced promoter activity 2.5-fold and abolished binding of Sp1. Mutation of a fourth factor-binding site, denoted LP1, abolished protein binding and reduced promoter activity 2-fold. Factor binding to the LP1 motif was observed with adipocyte, but not with nonadipocyte extracts. Adipocytes from fa/fa Zucker rats transcribed the reporter plasmids more efficiently than did control adipocytes. No effect on the transient expression of leptin was noted upon treatment with a thiazolidinedione, BRL49653, or upon cotransfection with peroxisome proliferator-activated receptor-gamma/retinoid X receptor-alpha or sterol response element-binding protein-1. Mutations of the Sp1, LP1, and C/EBP sites in pairwise combinations diminished promoter activity to the extent predicted assuming these motifs contribute independently to leptin promoter function. Our identification of motifs regulating leptin transcription is an important step in

the elucidation of the mechanisms underlying hormonal and metabolic regulation of this gene.

Matsumoto, M., W. Ogawa, et al. "PKClambda in liver mediates insulin-induced SREBP-1c expression and determines both hepatic lipid content and overall insulin sensitivity." J Clin Invest. 2003 Sep;112(6):935-44.

PKClambda is implicated as a downstream effector of PI3K in insulin action. We show here that mice that lack PKClambda specifically in the liver (L-lambdaKO mice), produced with the use of the Cre-loxP system, exhibit increased insulin sensitivity as well as a decreased triglyceride content and reduced expression of the sterol regulatory element-binding protein-1c (SREBP-1c) gene in the liver. Induction of the hepatic expression of Srebp1c and of its target genes involved in fatty acid/triglyceride synthesis by fasting and refeeding or by hepatic expression of an active form of PI3K was inhibited in L-lambdaKO mice compared with that in control animals. Expression of Srebp1c induced by insulin or by active PI3K in primary cultured rat hepatocytes was inhibited by a dominant-negative form of PKClambda and was mimicked by overexpression of WT PKClambda. Restoration of PKClambda expression in the liver of L-lambdaKO mice with the use of adenovirus-mediated gene transfer corrected the metabolic abnormalities of these animals. Hepatic PKClambda is thus a determinant of hepatic lipid content and whole-body insulin sensitivity.

Matsumoto, M., W. Ogawa, et al. "Role of the insulin receptor substrate 1 and phosphatidylinositol 3-kinase signaling pathway in insulin-induced expression of sterol regulatory element binding protein 1c and glucokinase genes in rat hepatocytes." Diabetes. 2002 Jun;51(6):1672-80.

The mechanism by which insulin induces the expression of the sterol regulatory element binding protein 1c (SREBP-1c) and glucokinase genes was investigated in cultured rat hepatocytes. Overexpression of an NH(2)-terminal fragment of IRS-1 that contains the pleckstrin homology and phosphotyrosine binding domains (insulin receptor substrate-1 NH(2)-terminal fragment [IRS-1N]) inhibited insulin-induced tyrosine phosphorylation of IRS-1 as well as the association of IRS-1 with phosphatidylinositol (PI) 3-kinase activity, whereas the tyrosine phosphorylation of IRS-2 and its association with PI 3-kinase activity were slightly enhanced. The equivalent fragment of IRS-2 (IRS-2N) prevented insulin-induced tyrosine phosphorylation of both IRS-1 and IRS-2, although that of IRS-1 was inhibited more efficiently. The insulin-induced increases in the abundance of SREBP-1c and glucokinase mRNAs, both of which were sensitive to a dominant-negative mutant of PI 3-kinase, were blocked in cells in which the insulin-induced tyrosine phosphorylation of IRS-1 was inhibited by IRS-1N or IRS-2N. A dominant-negative mutant of Akt enhanced insulin-induced tyrosine phosphorylation of IRS-1 (but not that of IRS-2) and its association with PI 3-kinase activity, suggesting that Akt contributes to negative feedback regulation of IRS-1. The Akt mutant also promoted the effects of insulin on the accumulation of SREBP-1c and glucokinase mRNAs. These results suggest that the IRS-1-PI 3-kinase pathway is essential for insulin-induced expression of SREBP-1c and glucokinase genes.

Mesotten, D., J. V. Swinnen, et al. "Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy." J Clin Endocrinol Metab. 2004 Jan;89(1):219-26.

Compared with the conventional approach, which recommended only insulin therapy when blood glucose levels exceeded 12 mmol/liter, strict maintenance of blood glucose levels less than 6.1 mmol/liter with intensive insulin therapy has shown to reduce intensive care mortality, acute renal failure, critical illness polyneuropathy, and bloodstream infections in critically ill patients by about 40%. This study of 363 patients, requiring intensive care for more than 7 d and randomly assigned to either conventional or intensive insulin therapy, examines the effects of intensive insulin therapy on glucose and lipid homeostasis and their respective impact on the improved outcome. Intensive insulin therapy effectively normalized blood glucose levels within 24 h, both in survivors and nonsurvivors. Intensive insulin therapy also increased serum levels of low-density lipoprotein ($P = 0.007$) and high-density lipoprotein ($P = 0.005$), whereas it suppressed the elevated serum triglyceride concentrations ($P < 0.0001$). Multivariate logistic regression analysis, corrected for baseline univariate risk factors and the effect on inflammation, indicated that lipid rather than glucose control independently determined the beneficial effects of intensive insulin therapy on morbidity and mortality. In postmortem biopsies obtained from 74 patients who died in the intensive care unit, intensive insulin therapy increased mRNA levels of skeletal muscle glucose transporter 4 ($P = 0.02$) and hexokinase ($P = 0.03$), unlike those of hepatic glucokinase. In conclusion, our data suggest that intensive insulin therapy normalizes blood glucose levels through stimulation of peripheral glucose uptake and concomitantly partially restores the abnormalities in the serum lipid profile, which may have contributed

significantly to the improved outcome of protracted critical illness.

Miserez, A. R., P. Y. Muller, et al. "Sterol-regulatory element-binding protein (SREBP)-2 contributes to polygenic hypercholesterolaemia." Atherosclerosis. 2002 Sep;164(1):15-26.

Sterol-regulatory element-binding protein (SREBP)-2 is a key regulator of cholesterol. When cells are deprived of cholesterol, proteolytic cleavage releases the NH(2)-terminal domain of SREBP-2 that binds and activates the promoters of SREBP-2-regulated genes including the genes encoding the low-density lipoprotein (LDL) receptor, 3-hydroxymethyl-3-glutaryl-(HMG-)CoA-synthase, and HMG-CoA-reductase. Thus, SREPB-2 gene activation leads to enhanced cholesterol uptake and biosynthesis. A novel protein polymorphism (SREBP-2-595A/G) discovered in the regulatory domain of human SREBP-2 was investigated regarding its impact on cholesterol homeostasis. In human embryonic kidney (HEK)-293-cells, the cleavage-rate of the SREBP-2-595A-isoform was slightly decreased compared to that of the SREBP-2-595G-isoform. Since cleavage of SREBP-2 activates the LDL receptor-mediated uptake of plasma cholesterol, we hypothesized the LDL receptor-mediated uptake to be decreased in homozygous SREBP-2-595A-carriers and thus, plasma total cholesterol (TC) to be higher than in SREBP-2-595G-carriers. Multiple linear regression analysis of population samples from Switzerland (N=1334) and Israel (N=923) demonstrated a significant positive, gene dose-dependent association of the SREBP-2-595A-isoform with higher plasma TC (P=0.001). This cholesterol-modulating effect was present in hypercholesterolaemic (DeltaTC=1.05 mmol/l, 14.4%; P=0.002; N=477), but absent in normocholesterolaemic subjects (DeltaTC=0.06 mmol/l, 1.4%; P=0.334; N=1780). In summary, a slightly but constantly decreased cleavage-rate of the SREBP-2-595A-isoform compared to that of the SREBP-2-595G-isoform may lead to a reduced transcriptional activation of the LDL receptor-gene weakening the SREBP-mediated compensation mechanisms, and may, therefore, be a critical factor in the development of polygenic hypercholesterolaemia.

Nakahara, M., H. Fujii, et al. "Bile acids enhance low density lipoprotein receptor gene expression via a MAPK cascade-mediated stabilization of mRNA." J Biol Chem. 2002 Oct 4;277(40):37229-34. Epub 2002 Jul 30.

Recent studies have indicated that bile acids regulate the expression of several genes involved in bile acid and lipid metabolism as ligands for the farnesoid X receptor (FXR). We report here that bile acids are directly able to govern cholesterol metabolism by a novel mechanism. We show that chenodeoxycholic acid (CDCA) enhances low density lipoprotein (LDL) receptor gene expression in human cultured cell lines (HeLa, Hep G2, and Caco-2). The proteolytic activation of sterol regulatory element-binding protein-2 (SREBP-2), a major regulator for LDL receptor gene expression, is not affected by CDCA. Both deoxycholic acid and lithocholic acid as well as CDCA, but not ursodeoxycholic acid, increase the mRNA level for the LDL receptor, even when Hep G2 cells are cultured with 25-hydroxycholesterol, a potent suppressor of gene expression for the LDL receptor. Although it seems possible that FXR might be involved in genetic regulation, both reporter assays with a reporter gene containing the LDL receptor promoter as well as Northern blot analysis reveal that FXR is not involved in the process. On the other hand, inhibition of mitogen-activated protein (MAP) kinase activities, which are found to be induced by CDCA, abolishes the CDCA-mediated up-regulation of LDL receptor gene expression. We further demonstrate that CDCA stabilizes LDL receptor mRNA and that the MAP kinase inhibitors accelerate its turnover. Taken together, these results indicate that bile acids increase LDL uptake and the intracellular cholesterol levels through the activation of MAP kinase cascades in conjunction with a down-regulation of bile acid biosynthesis by FXR. This work opens up a new avenue for developing pharmaceutical interventions that lower plasma LDL by stabilizing LDL receptor mRNA.

Narita, I., S. Goto, et al. "Interaction between ACE and ADD1 gene polymorphisms in the progression of IgA nephropathy in Japanese patients." Hypertension. 2003 Sep;42(3):304-9. Epub 2003 Jul 28.

An interaction effect between the angiotensin-converting enzyme insertion/deletion (ACE I/D) and alpha-adducin (ADD1) Gly460Trp polymorphisms (G460W) on blood pressure regulation has recently been suggested, although its significance in the prognosis of renal function in IgA nephropathy (IgAN) has not been fully investigated. Therefore, we evaluated the clinical manifestations and renal prognosis in 276 Japanese patients with histologically proven IgAN with respect to their ACE I/D and ADD1 G460W polymorphisms. The prognosis of renal function was analyzed by Kaplan-Meier survival curves and multivariate Cox proportional-hazards regression models. Baseline data, including blood pressures, proteinuria, renal function, and incidence of hypertension, were similar for the different genotypes of ACE and ADD1. The individual genotypes taken alone were not associated with the progression of renal dysfunction. However, renal survival of patients with

the 460WW polymorphism of ADD1 was significantly worse within the group with the II genotype of ACE (Kaplan-Meier, log rank test; chi2=6.062, P=0.0138) but not for those with other ACE genotypes. In the Cox proportional-hazards regression model with adjustment for clinical risk factors, including hypertension, proteinuria, and no administration of an angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, the 460WW variant of ADD1 was a highly significant and independent risk factor only for patients with the ACE II genotype, with a hazard ratio of 3.65 (P=0.0016), but not for those with other ACE genotypes (hazard ratio=0.65, P=0.2902). These findings suggest an interaction between ACE and ADD1 polymorphisms not only on blood pressure regulation but also on the progression of renal dysfunction in patients with IgAN.

Oberkofler, H., E. Schraml, et al. "Restoration of sterol-regulatory-element-binding protein-1c gene expression in HepG2 cells by peroxisome-proliferator-activated receptor-gamma co-activator-1alpha." Biochem J. 2004 Jul 15;381(Pt 2):357-63.

The expression of SREBP-1 (sterol-regulatory-element-binding protein-1) isoforms differs between tissues and cultured cell lines in that SREBP-1a is the major isoform in established cell lines, whereas SREBP-1c predominates in liver and most other human tissues. SREBP-1c is transcriptionally less active than SREBP-1a, but is a main mediator of hepatic insulin action and is selectively up-regulated by LXR (liver X receptor) agonists. LXR-mediated transactivation is co-activated by PGC-1alpha (peroxisome-proliferator-activated receptor-gamma co-activator-1alpha), which displays deficient expression in skeletal-muscle-derived cell lines. In the present paper, we show that PGC-1alpha expression is also deficient in HepG2 cells and in a human brown adipocyte cell line (PAZ6). In transient transfection studies, PGC-1alpha selectively amplified the LXR-mediated transcription from the human SREBP-1c promoter in HepG2 and PAZ6 cells via two LXR-response elements with extensive similarity to the respective murine sequence. Mutational analysis showed that the human LXR-response element-1 (hLXRE-1) was essential for co-activation of LXR-mediated SREBP-1c gene transcription by PGC-1alpha. Ectopic overexpression of PGC-1alpha in HepG2 cells enhanced basal SREBP-1c and, to a lesser extent, -1a mRNA expression, but only SREBP-1c expression was augmented further in an LXR/RXR (retinoic X receptor)-dependent fashion, thereby inducing mRNA abundance levels of SREBP-1c target genes, fatty acid synthase and acetyl-CoA carboxylase. These results indicate that PGC-1alpha contributes to the regulation of SREBP-1 gene expression, and can restore the SREBP-1 isoform expression pattern of HepG2 cells to that of human liver.

Park, C. H., J. S. Noh, et al. "Effects of morroniside isolated from Corni Fructus on renal lipids and inflammation in type 2 diabetic mice." J Pharm Pharmacol. 2010 Mar;62(3):374-80. doi: 10.1211/jpp.62.03.0013.

OBJECTIVES: The effects of morroniside isolated from Corni Fructus on renal lipids and inflammation provoked by hyperglycaemia were investigated using type 2 diabetic mice. METHODS: Morroniside was administered orally to db/db mice at 20 or 100 mg/kg daily for 8 weeks, and its effects were compared with those in vehicle-treated db/db and m/m (non-diabetic) mice. Serum and renal biochemical factors and protein expression related to lipid homeostasis and inflammation were measured. KEY FINDINGS: Morroniside produced significant dose-dependent reductions in serum triglyceride and renal glucose and lipid levels. Morroniside altered the abnormal protein expression of sterol regulatory element binding proteins (SREBP-1 and SREBP-2). In addition, the formation of reactive oxygen species and lipid peroxidation were inhibited in the morroniside-treated db/db mouse group, and the ratio of reduced glutathione to the oxidised form was significantly elevated. These results suggest that morroniside alleviated oxidative stress in the kidneys of db/db mice. Furthermore, 100 mg/kg morroniside down-regulated the expression of nuclear factor-kappaBp65, cyclooxygenase-2 and inducible nitric oxide synthase augmented in db/db mice. CONCLUSIONS: Morroniside may inhibit abnormal lipid metabolism and inflammation due to reactive oxygen species in the kidneys in type 2 diabetes.

Pawar, A., D. Botolin, et al. "The role of liver X receptor-alpha in the fatty acid regulation of hepatic gene expression." J Biol Chem. 2003 Oct 17;278(42):40736-43. Epub 2003 Aug 13.

Liver X receptors (LXR) alpha and beta play an important role in regulating the expression of genes involved in hepatic bile and fatty acid synthesis, glucose metabolism, as well as sterol efflux. Studies with human embryonic kidney 293 cells indicate that unsaturated fatty acids interfere with oxysterols binding to LXR and antagonize oxysterol-induced LXRalpha activity. In this report, we evaluated the effects of unsaturated fatty acids on LXR-regulated hepatic gene expression. The LXR agonist, T1317, induced mRNAs encoding sterol regulatory element-binding protein 1c (SREBP-1c) and two SREBP-1c-regulated lipogenic genes, e.g. fatty-acid synthase and the S14 protein in primary hepatocytes. Treatment of hepatocytes with eicosapentaenoic acid (20:5n-3)

suppressed these mRNAs in the absence and presence of T1317. The cis-regulatory elements targeted by T1317 were not required for fatty-acid suppression of FAS or S14 promoter activity. In contrast to SREBP-1-regulated lipogenic genes, 20:5n-3 had no effect on the T1317 induction of ABCG5 or ABCG8 in the rat hepatoma cell line, FTO-2B. These two genes require LXR but not SREBP-1c for their expression. Feeding rats a diet supplemented with fish oil suppressed hepatic SREBP-1c-regulated genes and induced PPARalpha-regulated genes but had no effect on the LXR-regulated transcripts, CYP7A1, ABCG5, or ABCG8. Transfection studies, using either full-length hLXRalpha or a chimera containing only the LXRalpha ligand binding domain, indicate that a wide array of unsaturated fatty acids had little effect on LXRalpha activity in primary hepatocytes or FTO-2B. These studies suggest that LXRalpha is not a target for unsaturated fatty acid regulation in primary rat hepatocytes or in liver. Thus, oxysterol/LXR-mediated regulation of transcripts involved in bile acid synthesis or sterol efflux appear insensitive to dietary unsaturated fatty acids. The unsaturated fatty acid suppression of SREBP-1 and its targeted lipogenic genes is independent of LXRalpha

Proctor, G., T. Jiang, et al. "Regulation of renal fatty acid and cholesterol metabolism, inflammation, and fibrosis in Akita and OVE26 mice with type 1 diabetes." Diabetes. 2006 Sep;55(9):2502-9.

In Akita and OVE26 mice, two genetic models of type 1 diabetes, diabetic nephropathy is characterized by mesangial expansion and loss of podocytes, resulting in glomerulosclerosis and proteinuria, and is associated with increased expression of profibrotic growth factors, proinflammatory cytokines, and increased oxidative stress. We have also found significant increases in renal triglyceride and cholesterol content. The increase in renal triglyceride content is associated with 1) increased expression of sterol regulatory element-binding protein (SREBP)-1c and carbohydrate response element-binding protein (ChREBP), which collectively results in increased fatty acid synthesis, 2) decreased expression of peroxisome proliferator-activated receptor (PPAR)-alpha and -delta, which results in decreased fatty acid oxidation, and 3) decreased expression of farnesoid X receptor (FXR) and small heterodimer partner (SHP). The increase in cholesterol content is associated with 1) increased expression of SREBP-2 and 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, which results in increased cholesterol synthesis, and 2) decreased expression of liver X receptor (LXR)-alpha, LXR-beta, and ATP-binding cassette transporter-1, which results in decreased cholesterol efflux. Our results indicate that in type 1 diabetes, there is altered renal lipid metabolism favoring net accumulation of triglycerides and cholesterol, which are driven by increases in SREBP-1, ChREBP, and SREBP-2 and decreases in FXR, LXR-alpha, and LXR-beta, which may also play a role in the increased expression of profibrotic growth hormones, proinflammatory cytokines, and oxidative stress.

Rae, F. K., G. Martinez, et al. "Anlaysis of complementary expression profiles following WT1 induction versus repression reveals the cholesterol/fatty acid synthetic pathways as a possible major target of WT1." Oncogene. 2004 Apr 15;23(17):3067-79.

The Wilms' tumour suppressor gene, WT1, encodes a zinc-finger protein that is mutated in Wilms' tumours and other malignancies. WT1 is one of the earliest genes expressed during kidney development. WT1 proteins can activate and repress putative target genes in vitro, although the in vivo relevance of such target genes often remains unverified. To better understand the role of WT1 in tumorigenesis and kidney development, we need to identify downstream target genes. In this study, we have expression profiled human embryonic kidney 293 cells stably transfected to allow inducible WT1 expression and mouse mesonephric M15 cells transfected with a WT1 antisense construct to abolish endogenous expression of all WT1 isoforms to identify WT1-responsive genes. The complementary overlap between the two cell lines revealed a pronounced repression of genes involved in cholesterol biosynthesis by WT1. This pathway is transcriptionally regulated by the sterol responsive element-binding proteins (SREBPs). Here, we provide evidence that the C-terminal end of the WT1 protein can directly interact with SREBP, suggesting that WT1 may modify the transcriptional function of SREBPs via a direct protein-protein interaction. Therefore, the tumour suppressor activities of WT1 may be achieved by repressing the mevalonate pathway, thereby controlling cellular proliferation and promoting terminal differentiation.

Ruan, X. Z., Z. Varghese, et al. "Dysregulation of LDL receptor under the influence of inflammatory cytokines: a new pathway for foam cell formation." Kidney Int. 2001 Nov;60(5):1716-25.

BACKGROUND: Lipid-mediated renal injury is an important component of glomerulosclerosis and its similarity to atherosclerosis is well described. This study focused on the relationship between lipid-mediated injury and inflammation by examining the role of inflammatory cytokines in the regulation of human mesangial cell low-density lipoprotein (LDL) receptors. METHODS:

A human mesangial cell line (HMCL) was used to study the effects of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta) on the regulation of LDL receptor mRNA and protein in the presence of a high concentration of native LDL (250 microg/mL). RESULTS: Native LDL caused foam cell formation in HMCL in the presence of antioxidants, TNF-alpha and IL-1beta. Both cytokines overrode LDL receptor suppression induced by a high concentration of LDL and increased LDL uptake by enhancing receptor expression. These cytokines also caused increased expression of SCAP [sterol responsive element binding protein (SREBP) cleavage activation protein], and an increase in the nuclear translocation of SREBP, which induces LDL receptor expression. CONCLUSION: These observations demonstrate that inflammatory cytokines can modify cholesterol-mediated LDL receptor regulation in mesangial cells, permitting unregulated intracellular accumulation of unmodified LDL and causing foam cell formation. These findings suggest that inflammatory cytokines contribute to lipid-mediated renal damage, and also may have wider implications for the study of inflammation in the atherosclerotic process.

Saito, K., N. Ishizaka, et al. "Lipid accumulation and transforming growth factor-beta upregulation in the kidneys of rats administered angiotensin II." Hypertension. 2005 Nov;46(5):1180-5. Epub 2005 Oct 3.

Abnormal lipid metabolism may play a role in progressive renal failure. We studied whether lipid accumulation occurs and whether lipid deposits are colocalized with transforming growth factor-beta1 (TGF-beta1) in the kidney of angiotensin II-infused animals. Oil red O staining showed marked lipid deposition in the tubular epithelial and vascular wall cells of angiotensin II-treated but not in norepinephrine-treated rats. Histological analyses showed that increased amounts of superoxide and intense TGF-beta1 mRNA expression were present in lipid-positive tubular epithelial cells in angiotensin II-infused animals. Protein expression of sterol regulatory element-binding protein 1 (SREBP-1) and mRNA expression of fatty acid synthase in the kidney were &3 times and 1.5 times, respectively, higher in angiotensin II-treated rats than in controls. Treatment of angiotensin II-infused animals with an iron chelator, deferoxamine, attenuated the angiotensin II-induced increases in renal expression of SREBP-1 and fatty acid synthase and normalized the lipid content in the renal cortical tissues. Abnormal lipid metabolism may be associated with upregulation of TGF-beta1 expression and aberrant iron homeostasis in the kidneys of angiotensin II-infused animals.

Sakai, J., E. A. Duncan, et al. "Sterol-regulated release of SREBP-2 from cell membranes requires two sequential cleavages, one within a transmembrane segment." Cell. 1996 Jun 28;85(7):1037-46.

Sterol regulatory element binding proteins (SREBPs) are transcription factors attached to the endoplasmic reticulum. The NH2-segment, which activates transcription, is connected to membranes by a hairpin anchor formed by two transmembrane sequences and a short lumenal loop. Using H-Ras-SREBP-2 fusion proteins, we show that the NH2-segment is released from membranes by two sequential cleavages. The first, regulated by sterols, occurs in the lumenal loop. The second, not regulated by sterols, occurs within the first transmembrane domain. The liberated NH2-segment enters the nucleus and activates genes controlling cholesterol synthesis and uptake. Certain mutant Chinese hamster ovary cells are auxotrophic for cholesterol because they fail to carry out the second cleavage; the NH2-segment remains membrane-bound and transcription is not activated.

Schmidt, R. J., J. V. Ficorilli, et al. "A 15-ketosterol is a liver X receptor ligand that suppresses sterol-responsive element binding protein-2 activity." J Lipid Res. 2006 May;47(5):1037-44. Epub 2006 Jan 13.

Hypercholesterolemia is a major risk factor for coronary artery disease. Oxysterols are known to inhibit cholesterol biosynthesis and have been explored as potential antihypercholesterolemic agents. The ability of 3beta-hydroxy-5alpha-cholest-8(14)-en-15-one (15-ketosterol) to lower non-HDL cholesterol has been demonstrated in rodent and primate models, but the mechanisms of action remain poorly understood. Here we show in a coactivator recruitment assay and cotransfection assays that the 15-ketosterol is a partial agonist for liver X receptor-alpha and -beta (LXRalpha and LXRbeta). The binding affinity for the LXRs was comparable to those of native oxysterols. In a macrophage cell line of human origin, the 15-ketosterol elevated ATP binding cassette transporter ABCA1 mRNA in a concentration-dependent fashion with a potency similar to those of other oxysterols. We further found that in human embryonic kidney HEK 293 cells, the 15-ketosterol suppressed sterol-responsive element binding protein processing activity and thus inhibited mRNA expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, LDL receptor, and PCSK9. Our data thus provide a molecular basis for the hypocholesterolemic activity of the 15-ketosterol and further suggest its potential antiatherosclerotic benefit as an LXR agonist.

Seishima, M. "[Disturbance of lipid metabolism]." Rinsho Byori. 2002 Mar;50(3):219-25.

The disturbance of lipid metabolism is seen in some inherited diseases and also in patients with some kinds of underlying diseases. The presence of its disturbance can be detected by measuring the concentrations of cholesterol and triglyceride in serum. Although hyperlipidemia or hypolipidemia is the result of abnormal lipid metabolism, hyperlipidemia is of more concern to physicians because of the close association with atherosclerosis. Responsible genes for some primary (or hereditary) hyperlipidemic diseases have been confirmed as follows; LPL or apo C-II for primary chylomicronemia, LDL receptor for familial hypercholesterolemia and apo B-100 for familial defective apo B-100. However, the responsible gene remains controversial for familial combined hyperlipidemia, though AI/CIII/AIV cluster is one of the possible candidate genes. Secondary hyperlipidemia is caused by various diseases such as diabetes mellitus, renal diseases and cholestasis. This type of hyperlipidemia is improved by therapy for the underlying diseases.

Sharma, A. K., S. Bharti, et al. "Up-regulation of PPARgamma, heat shock protein-27 and -72 by naringin attenuates insulin resistance, beta-cell dysfunction, hepatic steatosis and kidney damage in a rat model of type 2 diabetes." Br J Nutr. 2011 Dec;106(11):1713-23. doi: 10.1017/S000711451100225X. Epub 2011 Jun 21.

Naringin, a bioflavonoid isolated from grapefruit, is well known to possess lipid-lowering and insulin-like properties. Therefore, we assessed whether naringin treatment ameliorates insulin resistance (IR), beta-cell dysfunction, hepatic steatosis and kidney damage in high-fat diet (HFD)-streptozotocin (STZ)-induced type 2 diabetic rats. Wistar albino male rats were fed a HFD (55 % energy from fat and 2 % cholesterol) to develop IR and on the 10th day injected with a low dose of streptozotocin (40 mg/kg, intraperitoneal (ip)) to induce type 2 diabetes. After confirmation of hyperglycaemia (>13.89 mmol/l) on the 14th day, different doses of naringin (25, 50 and 100 mg/kg per d) and rosiglitazone (5 mg/kg per d) were administered orally for the next 28 d while being maintained on the HFD. Naringin significantly decreased IR, hyperinsulinaemia, hyperglycaemia, dyslipidaemia, TNF-alpha, IL-6, C-reactive protein and concomitantly increased adiponectin and beta-cell function in a dose-dependent manner. Increased thiobarbituric acid-reactive substances and decreased antioxidant enzyme activities in the serum and tissues of diabetic rats were also normalised. Moreover, naringin robustly increased PPARgamma expression in liver and kidney; phosphorylated tyrosine insulin receptor substrate 1 in liver; and stress proteins heat shock protein (HSP)-27 and HSP-72 in pancreas, liver and kidney. In contrast, NF-kappaB expression in these tissues along with sterol regulatory element binding protein-1c and liver X receptor- expressions in liver were significantly diminished.

Shimano, H., I. Shimomura, et al. "Elevated levels of SREBP-2 and cholesterol synthesis in livers of mice homozygous for a targeted disruption of the SREBP-1 gene." J Clin Invest. 1997 Oct 15;100(8):2115-24.

The synthesis of cholesterol and its uptake from plasma LDL are regulated by two membrane-bound transcription factors, designated sterol regulatory element binding protein-1 and -2 (SREBP-1 and SREBP-2). Here, we used the technique of homologous recombination to generate mice with disruptions in the gene encoding the two isoforms of SREBP-1, termed SREBP-1a and SREBP-1c. Heterozygous gene-disrupted mice were phenotypically normal, but 50- 85% of the homozygous (-/-) mice died in utero at embryonic day 11. The surviving -/- mice appeared normal at birth and throughout life. Their livers expressed no functional SREBP-1. There was a 1.5-fold upregulation of SREBP-2 at the level of mRNA and a two- to threefold increase in the amount of mature SREBP-2 in liver nuclei. Previous studies showed that SREBP-2 is much more potent than SREBP-1c, the predominant hepatic isoform of SREBP-1, in activating transcription of genes encoding enzymes of cholesterol synthesis. Consistent with this observation, the SREBP-1 -/- animals manifested elevated levels of mRNAs for 3-hydroxy-3-methylglutaryl coenzyme A synthase and reductase, farnesyl diphosphate synthase, and squalene synthase. Cholesterol synthesis, as measured by the incorporation of [3H]water, was elevated threefold in livers of the -/- mice, and hepatic cholesterol content was increased by 50%. Fatty acid synthesis was decreased in livers of the -/- mice. The amount of white adipose tissue was not significantly decreased, and the levels of mRNAs for lipogenic enzymes, adipocyte lipid binding protein, lipoprotein lipase, and leptin were normal in the -/- mice. We conclude from these studies that SREBP-2 can replace SREBP-1 in regulating cholesterol synthesis in livers of mice and that the higher potency of SREBP-2 relative to SREBP-1c leads to excessive hepatic cholesterol synthesis in these animals.

Soccio, R. E., R. M. Adams, et al. "The cholesterol-regulated StarD4 gene encodes a StAR-related lipid transfer protein with two closely related homologues, StarD5 and StarD6." Proc Natl Acad Sci U S A. 2002 May 14;99(10):6943-8.

Using cDNA microarrays, we identified StarD4 as a gene whose expression decreased more than 2-fold in the livers of mice fed a high-cholesterol diet. StarD4 expression in cultured 3T3 cells was also sterol-regulated, and known sterol regulatory element binding protein (SREBP)-target genes showed coordinate regulation. The closest homologues to StarD4 were two other StAR-related lipid transfer (START) proteins named StarD5 and StarD6. StarD4, StarD5, and StarD6 are 205- to 233-aa proteins consisting almost entirely of START domains. These three constitute a subfamily among START proteins, sharing approximately 30% amino acid identity with one another, approximately 20% identity with the cholesterol-binding START domains of StAR and MLN64, and less than 15% identity with phosphatidylcholine transfer protein (PCTP) and other START domains. StarD4 and StarD5 were expressed in most tissues, with highest levels in liver and kidney, whereas StarD6 was expressed exclusively in the testis. In contrast to StarD4, expression of StarD5 and MLN64 was not sterol-regulated. StarD4, StarD5, and StarD6 may be involved in the intracellular transport of sterols or other lipids.

Soetikno, V., F. R. Sari, et al. "Curcumin decreases renal triglyceride accumulation through AMPK-SREBP signaling pathway in streptozotocin-induced type 1 diabetic rats." J Nutr Biochem. 2013 May;24(5):796-802. doi: 10.1016/j.jnutbio.2012.04.013. Epub 2012 Aug 13.

Diabetic kidney disease has been associated with the presence of lipid deposits. We assumed that curcumin, a polyphenol, would attenuate the tissue dyslipidemic condition through activation of 5' adenosine monophosphate (AMP)-activated protein kinase (AMPK) phosphorylation and suppression of sterol regulatory element-binding protein (SREBP)-1c in the kidney and would prevent renal progression in experimental type 1 diabetic rats. Diabetes was induced with streptozotocin (STZ) (55 mg/kg) by intraperitoneal injection in male Sprague-Dawley rats. Three weeks after STZ injection, rats were divided into three groups, namely, control, diabetic and diabetic treated with curcumin (100 mg/kg/day) by gavage for 8 weeks. We found that curcumin decreased plasma triglyceride and the amount of renal triglyceride significantly. Furthermore, treatment of diabetic rats with curcumin increased the phosphorylation of AMPK and prevented the increased renal expression of SREBP-1c and, as a result, decreased the expression of acetyl CoA carboxylase and fatty acid synthase as well as adipose differentiation-related protein, a marker of cytoplasmic droplets. We also demonstrate that curcumin significantly suppressed the increased expression of transforming growth factor beta, vascular endothelial growth factor and extracellular matrix proteins such as type IV collagen and fibronectin. In addition, curcumin treatment increased nephrin expression to near-normal levels in diabetic rats. These results demonstrated that curcumin protects against the development of diabetic nephropathy through the AMPK-SREBP pathway and the reduction of renal triglyceride accumulation which could be a possible mechanism by which curcumin preserves renal function in diabetes.

Stelmanska, E., J. Korczynska, et al. "Tissue-specific effect of refeeding after short- and long-term caloric restriction on malic enzyme gene expression in rat tissues." Acta Biochim Pol. 2004;51(3):805-14.

Restricting food intake to a level below that consumed voluntarily (85%, 70% and 50% of the ad libitum energy intake for 3 or 30 days) and re-feeding ad libitum for 48 h results in an increase of malic enzyme (ME) gene expression in rat white adipose tissue. The increase of ME gene expression was much more pronounced in rats maintained on restricted diet for 30 days than for 3 days. The changes in ME gene expression resembled the changes in the content of SREBP-1 in white adipose tissue. A similar increase of serum insulin concentration was observed in all groups at different degrees of caloric restriction and refed ad libitum for 48 h. Caloric restriction and refeeding caused on increase of ME activity also in brown adipose tissue (BAT) and liver. However, in liver a significant increase of ME activity was found only in rats maintained on the restricted diet for 30 days. No significant changes after caloric restriction and refeeding were found in heart, skeletal muscle, kidney cortex, and brain. These data indicate that the increase of ME gene expression after caloric restriction/refeeding occurs only in lipogenic tissues. Thus, one can conclude that caloric restriction/refeeding increases the enzymatic capacity for fatty acid biosynthesis.

Szolkiewicz, M., M. Chmielewski, et al. "The potential role of sterol regulatory element binding protein transcription factors in renal injury." J Ren Nutr. 2007 Jan;17(1):62-5.

The disturbed lipid metabolism is a permanent finding in renal failure. It is supposed to be a main reason for the accelerated atherosclerosis and high cardiovascular and cerebrovascular mortality of patients with renal failure. Sterol regulatory element binding proteins (SREBPs) are the transcription factors involved in the regulation of lipid homeostasis. They are responsible for the transcription activation of genes associated with the synthesis of fatty acids, triglycerides, and cholesterol. SREBP-1 gene

expression in adipose tissue and SREBP-2 in liver are significantly elevated in renal failure. This is accompanied with the up-regulation of genes encoding enzymes of both fatty acids and cholesterol synthesis and significant serum lipid enhancement. Moreover, it has been shown that a destructive accumulation of lipids in the kidney structures is associated with enhanced kidney SREBP gene expression and increased lipid production. This was found even in the absence of any abnormalities in serum lipids. One may suppose that SREBP transcription factors play an important role in disturbed lipid metabolism in renal failure.

Szolkiewicz, M., E. Sucajtys, et al. "Mechanisms of enhanced carbohydrate and lipid metabolism in adipose tissue in uremia." J Ren Nutr. 2005 Jan;15(1):166-72.

OBJECTIVE: Hyperlipidemia is a permanent finding in advanced renal failure. It is supposed to be responsible for the accelerated arteriosclerosis and cardiovascular complications observed in patients with that disease. The background is partially determined, however, our knowledge in this matter is not yet satisfactory. METHODS: This study is based on the experimental rat model of chronic renal failure (CRF). Considering white adipose tissue (WAT) lipogenesis upregulation in CRF, along with the determination of acetyl coenzyme A carboxylase (ACC) and fatty acid synthase (FAS) genes expression, we have measured WAT gene expression for sterol regulatory binding protein 1 (SREBP-1) at the level of protein mass and mRNA abundance. Furthermore, we have determined glucose uptake, glucose-to-CO 2 conversion rate, and glucose translocator (GLUT-4) gene expression in WAT. RESULTS: Upregulation of both FAS and ACC gene expression was found in WAT of CRF rats. It was accompanied by WAT SREBP-1 gene overexpression. Moreover, we have observed the increased glucose uptake, glucose to CO 2 conversion rate, and GLUT-4 gene expression in WAT of CRF rats in comparison with controls. CONCLUSION: SREBP-1 gene overexpression may contribute to enhanced lipogenesis upregulation in WAT of CRF rats. It is not excluded that the increased WAT glucose metabolism activity is also induced by this mechanism, although there is no evidence currently to that end. We hypothesize that the increased WAT lipogenesis capacity could be a part of mechanism(s) leading to CRF-induced hyperlipidemia.

Torres, N., I. Torre-Villalvazo, et al. "Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders." J Nutr Biochem. 2006 Jun;17(6):365-73. Epub 2005 Dec 5.

Soybeans have a high-quality protein that has been consumed for approximately 5000 years in Oriental countries. The awareness that soy products are healthy has increased their consumption in Western countries. Substantial data from epidemiological surveys and nutritional interventions in humans and animals indicate that soy protein reduces serum total and low-density lipoprotein (LDL) cholesterol and triglycerides as well as hepatic cholesterol and triglycerides. This review examines the evidence on the possible mechanisms for which soy protein has beneficial effects in diabetes, obesity and some forms of chronic renal disease. Consumption of soy protein due to low methionine content reduces serum homocysteine concentration, decreasing the risk of acquiring a cardiovascular disease. On the other hand, soy protein reduces the insulin/glucagon ratio, which in turn down-regulates the expression of the hepatic transcription factor sterol regulatory element binding protein (SREBP)-1. The reduction of this factor decreases the expression of several lipogenic enzymes, decreasing in this way serum and hepatic triglycerides as well as LDL cholesterol and very LDL triglycerides in diabetes and obesity, reducing lipotoxicity in the liver. Soy protein intake also reduces hepatic lipotoxicity by maintaining the number of functional adipocytes, preventing the transfer of fatty acids to extra adipose tissues.

Tovar, A. R., F. Murguia, et al. "A soy protein diet alters hepatic lipid metabolism gene expression and reduces serum lipids and renal fibrogenic cytokines in rats with chronic nephrotic syndrome." J Nutr. 2002 Sep;132(9):2562-9.

Nephrotic syndrome (NS) is characterized by the presence of proteinuria and hyperlipidemia. However, ingestion of soy protein has a hypolipidemic effect. The present study was designed to determine whether the ingestion of a 20% soy protein diet regulates the expression of hepatic sterol regulatory element binding protein (SREBP)-1, fatty acid synthase (FAS), malic enzyme, beta-hydroxy-beta-methylglutaryl-CoA (HMG-CoA) reductase (r) and synthase (s), and LDL receptor (r), and to assess whether soy protein improves lipid and renal abnormalities in rats with chronic NS. Male Wistar rats were injected with vehicle or with puromycin aminonucleoside to induce NS and were fed either 20% casein or soy protein diets for 64 d. NS rats fed 20% soy protein had improved creatinine clearance and reduced proteinuria, hypercholesterolemia, hypertriglyceridemia, as well as VLDL-triglycerides and LDL cholesterol compared with NS rats fed the 20% casein diet. In addition, the soy protein diet decreased the incidence of glomerular sclerosis, and proinflammatory cytokines in kidney. Ingestion of the

soy protein diet by control rats reduced the gene expression of SREBP-1, malic enzyme, FAS and increased HMG-CoAr, HMG-CoAs and LDLr. However, NS rats fed either casein or soy protein diets had low insulin concentrations with reductions in SREBP-1, FAS and malic enzyme expression compared with control rats fed the casein diet. NS rats fed the soy diet also had lower HMG-CoAr and LDLr mRNA levels than NS rats fed casein. In conclusion, the beneficial effects of soy protein on lipid metabolism are modulated in part by SREBP-1. However, in NS rats, the benefit may be through a direct effect of this protein on kidney rather than mediated by changes in expression of hepatic lipid metabolism genes.

Tovar-Palacio, C., A. R. Tovar, et al. "Proinflammatory gene expression and renal lipogenesis are modulated by dietary protein content in obese Zucker fa/fa rats." Am J Physiol Renal Physiol. 2011 Jan;300(1):F263-71. doi: 10.1152/ajprenal.00171.2010. Epub 2010 Oct 20.

Obesity is a risk factor for the development of chronic kidney disease (CKD) and end-stage renal disease. It is not clear whether the adoption of a high-protein diet in obese patients affects renal lipid metabolism or kidney function. Thus the aims of this study were to assess in obese Zuckerfa/fa rats the effects of different types and amounts of dietary protein on the expression of lipogenic and inflammatory genes, as well as renal lipid concentration and biochemical parameters of kidney function. Rats were fed different concentrations of soy protein or casein (20, 30, 45%) for 2 mo. Independent of the type of protein ingested, higher dietary protein intake led to higher serum triglycerides (TG) than rats fed adequate concentrations of protein. Additionally, the soy protein diet significantly increased serum TG compared with the casein diet. However, rats fed soy protein had significantly decreased serum cholesterol concentrations compared with those fed a casein diet. No significant differences in renal TG and cholesterol concentrations were observed between rats fed with either protein diets. Renal expression of sterol-regulatory element binding protein 2 (SREBP-2) and its target gene HMG-CoA reductase was significantly increased as the concentration of dietary protein increased. The highest protein diets were associated with greater expression of proinflammatory cytokines in the kidney, independent of the type of dietary protein. These results indicate that high soy or casein protein diets upregulate the expression of lipogenic and proinflammatory genes in the kidney.

Treguier, M., C. Doucet, et al. "Transcription factor sterol regulatory element binding protein 2 regulates scavenger receptor Cla-1 gene expression." Arterioscler Thromb Vasc Biol. 2004 Dec;24(12):2358-64. Epub 2004 Oct 14.

OBJECTIVE: The human scavenger receptor class B type I (Cla-1) plays a key role in cellular cholesterol movement in facilitating transport of cholesterol between cells and lipoproteins. Indirect evidence has suggested that Cla-1 gene expression is under the feedback control of cellular cholesterol content. To define the molecular mechanisms underlying such putative regulation, we evaluated whether Cla-1 is a target gene of the sterol regulatory element binding protein (SREBP) transcription factor family. METHODS AND RESULTS: Transient transfections demonstrated that SREBP factors induce Cla-1 promoter activity and that SREBP-2 is a more potent inducer than the SREBP-1a isoform. The 5'-deletion analysis of 3 kb of the 5'-flanking sequence of the Cla-1 gene, combined with site-directed mutagenesis and electrophoretic mobility shift assay, allowed identification of a unique sterol responsive element. SREBP-mediated Cla-1 regulation was confirmed in stably transfected human embryonic kidney 293 cells expressing the active form of SREBP-2 at incremental levels. In these cell lines, Cla-1 mRNA and protein levels were increased in direct proportion to the level of SREBP-2 expression. CONCLUSIONS: These findings provide evidence that SREBP-2, a key regulator of cellular cholesterol uptake through modulation of the expression of the low-density lipoprotein receptor gene, may influence cellular cholesterol homeostasis via regulation of Cla-1 gene expression.

Uttarwar, L., B. Gao, et al. "SREBP-1 activation by glucose mediates TGF-beta upregulation in mesangial cells." Am J Physiol Renal Physiol. 2012 Feb 1;302(3):F329-41. doi: 10.1152/ajprenal.00136.2011. Epub 2011 Oct 26.

Glomerular matrix accumulation is a hallmark of diabetic nephropathy. Recent studies showed that overexpression of the transcription factor sterol-responsive element-binding protein (SREBP)-1 induces pathology reminiscent of diabetic nephropathy, and SREBP-1 upregulation was observed in diabetic kidneys. We thus studied whether SREBP-1 is activated by high glucose (HG) and mediates its profibrogenic responses. In primary rat mesangial cells, HG activated SREBP-1 by 30 min, seen by the appearance of its cleaved nuclear form (nSREBP-1), EMSA, and by activation of an SREBP-1 response element (SRE)-driven green fluorescent protein construct. Activation was dose dependent and not induced by an osmotic control. Site 1 protease was required, since its inhibition by AEBSF prevented SREBP-1 activation. SCAP, the ER-associated

chaperone for SREBP-1, was also necessary since its inhibitor fatostatin also blocked SREBP-1 activation. Signaling through the EGFR/phosphatidylinositol 3-kinase (PI3K) pathway, which we previously showed mediates HG-induced TGF-beta1 upregulation, and through RhoA, were upstream of SREBP-1 activation (Wu D, Peng F, Zhang B, Ingram AJ, Gao B, Krepinsky JC. Diabetologia 50: 2008-2018, 2007; Wu D, Peng F, Zhang B, Ingram AJ, Kelly DJ, Gilbert RE, Gao B, Krepinsky JC. J Am Soc Nephrol 20: 554-566, 2009). Fatostatin and AEBSF prevented HG-induced TGF-beta1 upregulation by Northern blot analysis, and HG-induced TGF-beta1 promoter activation was inhibited by both fatostatin and dominant negative SREBP-1a. Chromatin immunoprecipitation analysis confirmed that HG led to SREBP-1 binding to the TGF-beta1 promoter in a region containing a putative SREBP-1 binding site (SRE). Thus HG-induced SREBP-1 activation requires EGFR/PI3K/RhoA signaling and SCAP-mediated transport to the Golgi for its proteolytic cleavage. Activated SREBP-1 binds to the TGF-beta promoter, resulting in TGF-beta1 upregulation in response to HG. SREBP-1 thus provides a potential novel therapeutic target for the treatment of diabetic nephropathy.

Wilentz, R. E., L. A. Witters, et al. "Lipogenic enzymes fatty acid synthase and acetyl-coenzyme A carboxylase are coexpressed with sterol regulatory element binding protein and Ki-67 in fetal tissues." Pediatr Dev Pathol. 2000 Nov-Dec;3(6):525-31.

Endogenous fatty acid synthesis has been observed in some rapidly proliferating cells and tissues, both normal and neoplastic, and probably supports membrane synthesis. Sterol regulatory element binding proteins (SREBPs) are transcription factors that regulate the expression of genes for both cholesterol and fatty acid synthesis. The inactive precursor form resides in cytoplasmic membranes. Intracellular lipid depletion triggers proteolytic cleavage of SREBP, allowing the amino terminus to enter the nucleus and activate the expression of enzymes, including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), major biosynthetic enzymes for fatty acid synthesis. The expression patterns of ACC, FAS, SREBP, and Ki-67 in fetal tissues were compared to determine whether SREBP is likely to participate in the regulation of proliferation-associated fatty acid synthesis during fetal growth. Tissues from 22 fetuses, 12 first-trimester and 10 second-trimester (range 7.0 to 21.6 weeks), were studied. Serial 5-microm sections were stained with antibodies to ACC, FAS, SREBP, and Ki-67 and were compared. ACC, FAS, SREBP, and Ki-67 were coexpressed in the proliferative compartments of the intestines, skin, and kidney. ACC, FAS, and Ki-67 were coexpressed with little SREBP in lung and cytotrophoblast. SREBP, ACC, and FAS were coexpressed without Ki-67 in hepatocytes, ganglion cells, and intermediate trophoblast. The close linkage of SREBP, ACC, FAS, and Ki-67 in some proliferating fetal tissues suggests that in these tissues SREBP participates in the transcriptional regulation of lipogenic genes during proliferation. SREBP, ACC, and FAS coexpression without Ki-67 occurs in differentiated tissues that may synthesize fatty acids for other functions.

Willemarck, N., E. Rysman, et al. "Aberrant activation of fatty acid synthesis suppresses primary cilium formation and distorts tissue development." Cancer Res. 2010 Nov 15;70(22):9453-62. doi: 10.1158/0008-5472.CAN-10-2324. Epub 2010 Oct 1.

Aberrant activation of fatty acid synthesis is a key feature of many advanced human cancers. Unlike in classical lipogenic tissues, this process has been implicated in membrane production required for rapid cell proliferation. Here, to gain further insight into the consequences of tumor-associated fatty acid synthesis, we have mimicked the lipogenic phenotype of cancer cells in Xenopus embryos by microinjection of RNA encoding the lipogenic transcription factor sterol regulatory element binding protein 1c (SREBP1c). Dramatic morphologic changes were observed that could be linked to alterations in Wnt and Hedgehog signaling, and ultimately to a distortion of the primary cilium. This is a sophisticated microtubular sensory organelle that is expressed on the surface of nearly every cell type and that is lost in many cancers. SREBP1c-induced loss of the primary cilium could be confirmed in mammalian Madin-Darby canine kidney (MDCK) cells and was mediated by changes in the supply of fatty acids. Conversely, inhibition of fatty acid synthesis in highly lipogenic human prostate cancer cells restored the formation of the primary cilium. Lipid-induced ciliary loss was associated with mislocalization of apical proteins, distortion of cell polarization, and aberrant epithelial tissue development as revealed in three-dimensional cultures of MDCK cells and in the developing mouse prostate. These data imply that tumor-associated lipogenesis, in addition to rendering cells more autonomous in terms of lipid supply, disturbs cilium formation and contributes to impaired environmental sensing, aberrant signaling, and distortion of polarized tissue architecture, which are all hallmarks of cancer.

Xu, Z. E., Y. Chen, et al. "Inflammatory stress exacerbates lipid-mediated renal injury in ApoE/CD36/SRA triple knockout mice." Am J Physiol Renal Physiol. 2011 Oct;301(4):F713-22. doi: 10.1152/ajprenal.00341.2010. Epub 2011 Jul 27.

Both lipids and inflammation play important roles in the progression of kidney disease. This study was designed to investigate whether inflammation exacerbates lipid accumulation via LDL receptors (LDLr), thereby causing renal injury in C57BL/6J mice, apolipoprotein E (ApoE) knockout (KO) mice, and ApoE/CD36/scavenger receptor A triple KO mice. The mice were given a subcutaneous casein injection to induce inflammatory stress. After 14 wk, terminal blood samples were taken for renal function, lipid profiles, amyloid A (SAA), and IL-6 assays. Lipid accumulation in kidneys was visualized by oil red O staining. Fibrogenic molecule expression in kidneys was examined. There was a significant increase in serum SAA and IL-6 in the all casein-injected mice compared with respective controls. Casein injection reduced serum total cholesterol, LDL cholesterol, and HDL cholesterol and caused lipid accumulation in kidneys from three types of mice. The expression of LDLr and its regulatory proteins sterol-responsive element-binding protein (SREBP) 2 and SREBP cleavage-activating protein (SCAP) were upregulated in inflamed mice compared with controls. Casein injection induced renal fibrosis accompanied by increased expression of fibrogenic molecules in the triple KO mice. These data imply that inflammation exacerbates lipid accumulation in the kidney by diverting lipid from the plasma to the kidney via the SCAP-SREBP2-LDLr pathway and causing renal injury. Low blood cholesterol levels, resulting from inflammation, may be associated with high risk for chronic renal fibrosis.

Yamabe, N., K. S. Kang, et al. "Matcha, a powdered green tea, ameliorates the progression of renal and hepatic damage in type 2 diabetic OLETF rats." J Med Food. 2009 Aug;12(4):714-21. doi: 10.1089/jmf.2008.1282.

Matcha, a powdered green tea produced by grinding with a stone mill, has been popularly used in the traditional tea ceremony and foods in Japan. Matcha is well known to be richer in some nutritional elements and epigallocatechin 3-O-gallate than other green teas. In our previous study, epigallocatechin 3-O-gallate exhibited protective effects against renal damage in a rat model of diabetic nephropathy. In the present study, we investigated the preventive effects of Matcha (50, 100, or 200 mg/kg/day) on the progression of hepatic and renal damage in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. OLETF rats were orally administered Matcha for 16 weeks, and we assessed biochemical parameters in the serum, liver, and kidney and expression levels of major products of advanced glycation end products (AGEs), N(6)-(carboxylmethyl)lysine (CML) and N(6)-(carboxylethyl)lysine (CEL), receptor for AGE (RAGE), and sterol regulatory element binding proteins (SREBPs)-1 and -2. Serum total protein levels were significantly increased by Matcha administration, whereas the serum albumin and glycosylated protein levels as well as the renal glucose and triglyceride levels were only slightly or not at all affected. However, Matcha treatment significantly lowered the glucose, triglyceride, and total cholesterol levels in the serum and liver, renal AGE levels, and the serum thiobarbituric acid-reactive substances levels.

Yamabe, N., J. S. Noh, et al. "Evaluation of loganin, iridoid glycoside from Corni Fructus, on hepatic and renal glucolipotoxicity and inflammation in type 2 diabetic db/db mice." Eur J Pharmacol. 2010 Dec 1;648(1-3):179-87. doi: 10.1016/j.ejphar.2010.08.044. Epub 2010 Sep 15.

Previously, we have reported that Corni Fructus possessed hypoglycemic and hypocholesterolemic effects in streptozotocin-induced type 1 diabetic rats and diet-induced hypercholesterolemic rats. Herein, we have focused on the effect and mechanism of loganin, a major iridoid glycoside of Corni Fructus, on the type 2 diabetic db/db mice. Loganin was orally administered to db/db mice at a dose of 20 or 100 mg/kg body weight daily for 8 weeks. The biochemical factors and expressions of protein and mRNA related to lipid metabolism, inflammation, advanced glycation endproducts, and its receptor were measured. In loganin-treated db/db mice, hyperglycemia and dyslipidemia were ameliorated in both the serum and hepatic tissue; however, in the kidney, only triglyceride was reduced. The enhanced oxidative stress was alleviated by loganin through a decrease in thiobarbituric acid-reactive substances (liver and kidney) and reactive oxygen species (serum, liver, and kidney), as well as augmentation of the oxidized to reduced glutathione ratio (liver and kidney). The marked lipid-regulatory effect of loganin was exerted in the liver of type 2 diabetic mice via suppressing mRNA expressions related to lipid synthesis and adjusting the abnormal expression of peroxisome proliferator-activated receptor alpha and sterol regulatory-element binding protein in the nucleus. Furthermore, loganin inhibited advanced glycation endproduct formation and the expression of its receptor, and nuclear factor-kappa B-induced inflammation in the hepatic tissue of db/db mice. Loganin exhibits protective effects against hepatic injury and other diabetic complications associated with abnormal metabolic states and inflammation caused by oxidative stress and advanced glycation endproduct formation.

Yokoyama, M., K. Tanigawa, et al. "Dietary polyunsaturated fatty acids slow the progression of diabetic nephropathy in streptozotocin-induced diabetic rats." Nutr Res. 2010 Mar;30(3):217-25. doi: 10.1016/j.nutres.2010.03.002.

Diabetic nephropathy is associated with lipid deposits in the kidney. We hypothesized that a diet containing polyunsaturated fatty acids (PUFAs) could ameliorate pathogenesis of diabetic kidney diseases associated with lipid depositions in the kidneys. We examined if the pathogenesis and progression of diabetic nephropathy are affected by the type of dietary fat using streptozotocin (45 mg/kg body weight, intravenous)-induced diabetic rats (5-week-old male Sprague-Dawley rats). Streptozotocin-induced diabetic rats were fed a lard diet containing saturated fatty acids or a rapeseed oil diet containing PUFAs (DML and DMR, respectively) for 11 days. Similarly, streptozotocin-nontreated rats were fed a lard diet or a rapeseed oil diet (NL and NR, respectively) for 11 days. Hyperglycemia was induced in DML and DMR, compared with NL and NR groups. The levels of plasma ketone, total cholesterol, and triglyceride (TG) were significantly increased in the DML group. Moreover, albuminuria and renal TG content were enhanced in the DML group. The renal TG content correlated positively with urinary albumin excretion ($P < .001$). Oil-Red O staining of kidney sections indicated a marked accumulation of neutral lipids in both glomerular and tubular cells in the DML group. In addition, a renal sterol regulatory element-binding protein-1 mature protein increment was induced in the DML group. Conversely, sterol regulatory element-binding protein-1 expression in the kidney was maintained at normal levels in the DMR group. These results suggest that dietary PUFAs may slow the progression of diabetic nephropathy associated with lipid depositions in the kidney.

Yoshikawa, T., T. Ide, et al. "Cross-talk between peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. I. PPARs suppress sterol regulatory element binding protein-1c promoter through inhibition of LXR signaling." Mol Endocrinol. 2003 Jul;17(7):1240-54. Epub 2003 May 1.

Liver X receptors (LXRs) and peroxisome proliferator-activated receptors (PPARs) are members of nuclear receptors that form obligate heterodimers with retinoid X receptors (RXRs). These nuclear receptors play crucial roles in the regulation of fatty acid metabolism: LXRs activate expression of sterol regulatory element-binding protein 1c (SREBP-1c), a dominant lipogenic gene regulator, whereas PPARalpha promotes fatty acid beta-oxidation genes. In the current study, effects of PPARs on the LXR-SREBP-1c pathway were investigated. Luciferase assays in human embryonic kidney 293 cells showed that overexpression of PPARalpha and gamma dose-dependently inhibited SREBP-1c promoter activity induced by LXR. Deletion and mutation studies demonstrated that the two LXR response elements (LXREs) in the SREBP-1c promoter region are responsible for this inhibitory effect of PPARs. Gel shift assays indicated that PPARs reduce binding of LXR/RXR to LXRE. PPARalpha-selective agonist enhanced these inhibitory effects. Supplementation with RXR attenuated these inhibitions by PPARs in luciferase and gel shift assays, implicating receptor interaction among LXR, PPAR, and RXR as a plausible mechanism. Competition of PPARalpha ligand with LXR ligand was observed in LXR/RXR binding to LXRE in gel shift assay, in LXR/RXR formation in nuclear extracts by coimmunoprecipitation, and in gene expression of SREBP-1c by Northern blot analysis of rat primary hepatocytes and mouse liver RNA. These data suggest that PPARalpha activation can suppress LXR-SREBP-1c pathway through reduction of LXR/RXR formation, proposing a novel transcription factor cross-talk between LXR and PPARalpha in hepatic lipid homeostasis.

Zager, R. A., V. O. Shah, et al. "The mevalonate pathway during acute tubular injury: selected determinants and consequences." Am J Pathol. 2002 Aug;161(2):681-92.

Renal injury evokes tubular cholesterol accumulation, mediated in part by increased HMG CoA reductase (HMGCR) levels. The present study was undertaken to define potential molecular determinants of these changes and to ascertain the relative importance of increased cholesterol production versus mevalonate pathway-driven protein prenylation, on the emergence of the so-called postrenal injury "cytoresistant state." Cultured proximal tubule (HK-2) cells were subjected to Fe or ATP depletion injury, followed 1 to 24 hours later by assessments of: 1) sterol transcription factor expression (SREBP)-1 and -2); 2) HMGCR mRNA levels; and 3) Ras/Rho prenylation. HMGCR mRNA and Ras/Rho prenylation were also assessed after in vivo ischemic and Fe-mediated renal damage. Using specific inhibitors, the relative importance of protein prenylation versus terminal cholesterol synthesis on HK-2 cell susceptibility to injury was also assessed. Acute injury induced HK-2 cell SREBP disruption and reductions in HMGCR mRNA. Renal cortical HMGCR mRNA also fell in response to either in vivo ischemic or Fe-mediated oxidant damage. At 24 hours after in vitro/in vivo injury, a time of cholesterol buildup, no increase in Ras/Rho prenylation was observed. Prenylation

inhibitors did not sensitize HK-2 cells to injury. Conversely, squalene synthase (terminal cholesterol synthesis) blockade sensitized HK-2 cells to both Fe and ATP depletion attack. We concluded that: 1) acute tubular cell injury can destroy SREBPs and lower HMGCR mRNA. This suggests that posttranscriptional/translational events are responsible for HMGCR enzyme and cholesterol accumulation after renal damage. 2) Injury-induced cholesterol accumulation appears dissociated from increased protein prenylation. 3) Cholesterol accumulation, per se, seems to be the dominant mechanism by which the mevalonate pathway contributes to the postrenal injury cytoresistant state.

Zelenski, N. G., R. B. Rawson, et al. "Membrane topology of S2P, a protein required for intramembranous cleavage of sterol regulatory element-binding proteins." J Biol Chem. 1999 Jul 30;274(31):21973-80.

In sterol-depleted mammalian cells, a two-step proteolytic process releases the NH(2)-terminal domains of sterol regulatory element-binding proteins (SREBPs) from membranes of the endoplasmic reticulum (ER). These domains translocate into the nucleus, where they activate genes of cholesterol and fatty acid biosynthesis. The SREBPs are oriented in the membrane in a hairpin fashion, with the NH(2)- and COOH-terminal domains facing the cytosol and a single hydrophilic loop projecting into the lumen. The first cleavage occurs at Site-1 within the ER lumen to generate an intermediate that is subsequently released from the membrane by cleavage at Site-2, which lies within the first transmembrane domain. A membrane protein, designated S2P, a putative zinc metalloprotease, is required for this cleavage. Here, we use protease protection and glycosylation site mapping to define the topology of S2P in ER membranes. Both the NH(2) and COOH termini of S2P face the cytosol. Most of S2P is hydrophobic and appears to be buried in the membrane. All three of the long hydrophilic sequences of S2P can be glycosylated, indicating that they all project into the lumen. The HEIGH sequence of S2P, which contains two potential zinc-coordinating residues, is contained within a long hydrophobic segment. Aspartic acid 467, located approximately 300 residues away from the HEIGH sequence, appears to provide the third coordinating residue for the active site zinc. This residue, too, is located in a hydrophobic sequence. The hydrophobicity of these sequences suggests that the active site of S2P is located within the membrane in an ideal position to cleave its target, a Leu-Cys bond in the first transmembrane helix of SREBPs.

Zulkifli, R. M., T. Parr, et al. "Regulation of ovine and porcine stearoyl coenzyme A desaturase gene promoters by fatty acids and sterols." J Anim Sci. 2010 Aug;88(8):2565-75. doi: 10.2527/jas.2009-2603. Epub 2010 Apr 9.

Stearoyl CoA desaturase (SCD) is responsible for converting SFA into MUFA and plays an important role in regulating the fatty acid composition of tissues. Although the number of SCD isoforms differs among species, SCD-1 is the predominant isoform expressed in the major lipogenic tissues of all species studied. The SCD-1 gene promoter region has been cloned for several species, including the human, mouse, pig, and recently, the cow. In this study, we cloned and partially characterized the ovine SCD promoter region. Sequence alignment showed a high degree of similarity with published bovine (94%) and porcine (92%) sequences. This included a highly conserved PUFA response region, which was also similar to that found in the human SCD and mouse SCD-1 promoters. Previous studies have indicated that there may be species differences in the regulation of SCD promoter activity by fatty acids. Using promoter-reporter gene (luciferase) constructs transfected into both HEK 293 and McA-RH7777 cells (kidney- and liver-derived cell lines, respectively), we showed the activity of the SCD promoter from 4 different species (mouse, human, pig, and sheep) to be reduced in a dose-dependent manner by addition of unsaturated fatty acids to the media, with linoleic acid being more potent than oleic acid after a 24-h treatment at 60 microM. This effect was dependent on the presence of the PUFA response region. In each of the species studied, the PUFA response region of the SCD promoter was shown to have an active sterol response element, which responded to treatment of cells with sterol or overexpression of the truncated active form of sterol regulatory element binding protein-1c. Thus, any species differences in previously reported regulation of SCD expression by fatty acids are not due to differences in promoter structure between species, but are more likely to depend on the cell type being studied or the relative concentrations and distribution of sterol regulatory element binding proteins or other transcription factors.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

1. Bai, Q., X. Zhang, et al. "Oxysterol sulfation by cytosolic sulfotransferase suppresses liver X receptor/sterol regulatory element binding protein-1c signaling pathway and reduces serum

and hepatic lipids in mouse models of nonalcoholic fatty liver disease." Metabolism. 2012 Jun;61(6):836-45. doi: 10.1016/j.metabol.2011.11.014. Epub 2012 Jan 5.

2. Bakker, P. J., L. M. Butter, et al. "Nlrp3 is a key modulator of diet-induced nephropathy and renal cholesterol accumulation." Kidney Int. 2014 May;85(5):1112-22. doi: 10.1038/ki.2013.503. Epub 2013 Dec 18.
3. Briggs, M. R., C. Yokoyama, et al. "Nuclear protein that binds sterol regulatory element of low density lipoprotein receptor promoter. I. Identification of the protein and delineation of its target nucleotide sequence." J Biol Chem. 1993 Jul 5;268(19):14490-6.
4. Buga, G. M., J. S. Frank, et al. "D-4F reduces EO6 immunoreactivity, SREBP-1c mRNA levels, and renal inflammation in LDL receptor-null mice fed a Western diet." J Lipid Res. 2008 Jan;49(1):192-205. Epub 2007 Oct 9.
5. Carmona-Antonanzas, G., D. R. Tocher, et al. "Conservation of lipid metabolic gene transcriptional regulatory networks in fish and mammals." Gene. 2014 Jan 15;534(1):1-9. doi: 10.1016/j.gene.2013.10.040. Epub 2013 Oct 28.
6. Castoreno, A. B., Y. Wang, et al. "Transcriptional regulation of phagocytosis-induced membrane biogenesis by sterol regulatory element binding proteins." Proc Natl Acad Sci U S A. 2005 Sep 13;102(37):13129-34. Epub 2005 Sep 2.
7. Chechi, K., N. Yasui, et al. "Flax oil-mediated activation of PPAR-gamma correlates with reduction of hepatic lipid accumulation in obese spontaneously hypertensive/NDmcr-cp rats, a model of the metabolic syndrome." Br J Nutr. 2010 Nov;104(9):1313-21. doi: 10.1017/S0007114510002187. Epub 2010 Jun 15.
8. Chen, I. B., V. K. Rathi, et al. "Association of genes with physiological functions by comparative analysis of pooled expression microarray data." Physiol Genomics. 2013 Jan 15;45(2):69-78. doi: 10.1152/physiolgenomics.00116.2012. Epub 2012 Nov 20.
9. Chen, Y., L. Zhao, et al. "Inflammatory stress reduces the effectiveness of statins in the kidney by disrupting HMGCoA reductase feedback regulation." Nephrol Dial Transplant. 2014 Oct;29(10):1864-78. doi: 10.1093/ndt/gfu203. Epub 2014 Jun 3.
10. Chin, H. J., Y. Y. Fu, et al. "Omacor, n-3 polyunsaturated fatty acid, attenuated albuminuria and renal dysfunction with decrease of SREBP-1 expression and triglyceride amount in the kidney of type II diabetic animals." Nephrol Dial Transplant. 2010 May;25(5):1450-7. doi: 10.1093/ndt/gfp695. Epub 2009 Dec 29.
11. Chmielewski, M. and B. Rutkowski Mechanisms of dyslipidemia in chronic kidney disease, Am J Physiol Renal Physiol. 2009 Sep;297(3):F835. doi: 10.1152/ajprenal.00269.2009.
12. Chmielewski, M., E. Sucajtys-Szulc, et al. "Feedback inhibition of cholesterol biosynthesis by dietary cholesterol in experimental chronic renal failure." J Ren Nutr. 2008 Sep;18(5):448-55. doi: 10.1053/j.jrn.2008.04.005.
13. Chmielewski, M., E. Sucajtys-Szulc, et al. "Increased gene expression of liver SREBP-2 in experimental chronic renal failure." Atherosclerosis. 2007 Apr;191(2):326-32. Epub 2006 Jun 30.
14. Cho, H. K., H. J. Kong, et al. "Characterization of Paralichthys olivaceus peroxisome proliferator-activated receptor-alpha gene as a master regulator of flounder lipid metabolism." Gen Comp Endocrinol. 2012 Jan 1;175(1):39-47. doi: 10.1016/j.ygcen.2011.08.026. Epub 2011 Oct 25.
15. Choi, Y. J., H. S. Shin, et al. "Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes." Lab Invest. 2014 Oct;94(10):1114-25. doi: 10.1038/labinvest.2014.98. Epub 2014 Aug 11.
16. Chow, J. D., M. E. Jones, et al. "A selective estrogen receptor alpha agonist ameliorates hepatic steatosis in the male aromatase knockout mouse." J Endocrinol. 2011 Sep;210(3):323-34. doi: 10.1530/JOE-10-0462. Epub 2011 Jun 24.
17. David-Silva, A., H. S. Freitas, et al. "Hepatocyte nuclear factors 1alpha/4alpha and forkhead box A2 regulate the solute carrier 2A2 (Slc2a2) gene expression in the liver and kidney of diabetic rats." Life Sci. 2013 Nov 19;93(22):805-13. doi: 10.1016/j.lfs.2013.10.011. Epub 2013 Oct 21.
18. Dif, N., V. Euthine, et al. "Insulin activates human sterol-regulatory-element-binding protein-1c (SREBP-1c) promoter through SRE motifs." Biochem J. 2006 Nov 15;400(1):179-88.
19. Drabkin, H. A. and R. M. Gemmill "Obesity, cholesterol, and clear-cell renal cell carcinoma (RCC)." Adv Cancer Res. 2010;107:39-56. doi: 10.1016/S0065-230X(10)07002-8.
20. Feramisco, J. D., J. L. Goldstein, et al. "Membrane topology of human insig-1, a protein regulator of lipid synthesis." J Biol Chem. 2004 Feb 27;279(9):8487-96. Epub 2003 Dec 5.
21. Foley, D. L. and A. Mackinnon "A systematic review of antipsychotic drug effects on human

gene expression related to risk factors for cardiovascular disease." Pharmacogenomics J. 2014 Oct;14(5):446-51. doi: 10.1038/tpj.2014.8. Epub 2014 Mar 11.
22. Hannah, V. C., J. Ou, et al. "Unsaturated fatty acids down-regulate srebp isoforms 1a and 1c by two mechanisms in HEK-293 cells." J Biol Chem. 2001 Feb 9;276(6):4365-72. Epub 2000 Nov 20.
23. Hao, J., S. Liu, et al. "PI3K/Akt pathway mediates high glucose-induced lipogenesis and extracellular matrix accumulation in HKC cells through regulation of SREBP-1 and TGF-beta1." Histochem Cell Biol. 2011 Feb;135(2):173-81. doi: 10.1007/s00418-011-0777-3. Epub 2011 Jan 15.
24. Hao, J., S. X. Liu, et al. "[High fat diet induced the expression of SREBP-1, TGF-beta1 and alpha-SMA in renal tubular cells and extracellular matrix accumulation in Wistar rats]." Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2010 Aug;26(3):307-11.
25. Hashimoto, K., M. Yamada, et al. "Mouse sterol response element binding protein-1c gene expression is negatively regulated by thyroid hormone." Endocrinology. 2006 Sep;147(9):4292-302. Epub 2006 Jun 22.
26. Hawkins, J. L., M. D. Robbins, et al. "Pharmacologic inhibition of site 1 protease activity inhibits sterol regulatory element-binding protein processing and reduces lipogenic enzyme gene expression and lipid synthesis in cultured cells and experimental animals." J Pharmacol Exp Ther. 2008 Sep;326(3):801-8. doi: 10.1124/jpet.108.139626. Epub 2008 Jun 24.
27. Herman-Edelstein, M., P. Scherzer, et al. "Altered renal lipid metabolism and renal lipid accumulation in human diabetic nephropathy." J Lipid Res. 2014 Mar;55(3):561-72. doi: 10.1194/jlr.P040501. Epub 2013 Dec 26.
28. Hitkova, I., G. Yuan, et al. "Caveolin-1 protects B6129 mice against Helicobacter pylori gastritis." PLoS Pathog. 2013;9(4):e1003251. doi: 10.1371/journal.ppat.1003251. Epub 2013 Apr 11.
29. Huq, M. D., N. P. Tsai, et al. "Regulation of retinal dehydrogenases and retinoic acid synthesis by cholesterol metabolites." EMBO J. 2006 Jul 12;25(13):3203-13. Epub 2006 Jun 8.
30. Im, S. S., S. Y. Kang, et al. "Glucose-stimulated upregulation of GLUT2 gene is mediated by sterol response element-binding protein-1c in the hepatocytes." Diabetes. 2005 Jun;54(6):1684-91.
31. Irisawa, M., J. Inoue, et al. "The sterol-sensing endoplasmic reticulum (ER) membrane protein TRC8 hampers ER to Golgi transport of sterol regulatory element-binding protein-2 (SREBP-2)/SREBP cleavage-activated protein and reduces SREBP-2 cleavage." J Biol Chem. 2009 Oct 16;284(42):28995-9004. doi: 10.1074/jbc.M109.041376. Epub 2009 Aug 25.
32. Ishigaki, N., T. Yamamoto, et al. "Involvement of glomerular SREBP-1c in diabetic nephropathy." Biochem Biophys Res Commun. 2007 Dec 21;364(3):502-8. Epub 2007 Oct 16.
33. Jeon, B. N., Y. S. Kim, et al. "Kr-pok increases FASN expression by modulating the DNA binding of SREBP-1c and Sp1 at the proximal promoter." J Lipid Res. 2012 Apr;53(4):755-66. doi: 10.1194/jlr.M022178. Epub 2012 Feb 13.
34. Korczynska, J., E. Stelmanska, et al. "Upregulation of lipogenic enzymes genes expression in white adipose tissue of rats with chronic renal failure is associated with higher level of sterol regulatory element binding protein-1." Metabolism. 2004 Aug;53(8):1060-5.
35. Kovacs, W. J., K. N. Charles, et al. "Peroxisome deficiency-induced ER stress and SREBP-2 pathway activation in the liver of newborn PEX2 knock-out mice." Biochim Biophys Acta. 2012 Jun;1821(6):895-907. doi: 10.1016/j.bbalip.2012.02.011. Epub 2012 Mar 13.
36. Lhotak, S., S. Sood, et al. "ER stress contributes to renal proximal tubule injury by increasing SREBP-2-mediated lipid accumulation and apoptotic cell death." Am J Physiol Renal Physiol. 2012 Jul 15;303(2):F266-78. doi: 10.1152/ajprenal.00482.2011. Epub 2012 May 9.
37. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
38. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
39. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7 - 15.
40. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
41. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11.Nature and science 2007;5(1):81-96.
42. Marcil, V., E. Seidman, et al. "Modification in oxidative stress, inflammation, and lipoprotein assembly in response to hepatocyte nuclear factor 4alpha knockdown in intestinal epithelial cells." J Biol Chem. 2010 Dec 24;285(52):40448-60. doi: 10.1074/jbc.M110.155358. Epub 2010 Sep 24.
43. Mason, M. M., Y. He, et al. "Regulation of leptin promoter function by Sp1, C/EBP, and a novel factor." Endocrinology. 1998 Mar;139(3):1013-22.

44. Matsumoto, M., W. Ogawa, et al. "PKClambda in liver mediates insulin-induced SREBP-1c expression and determines both hepatic lipid content and overall insulin sensitivity." J Clin Invest. 2003 Sep;112(6):935-44.
45. Matsumoto, M., W. Ogawa, et al. "Role of the insulin receptor substrate 1 and phosphatidylinositol 3-kinase signaling pathway in insulin-induced expression of sterol regulatory element binding protein 1c and glucokinase genes in rat hepatocytes." Diabetes. 2002 Jun;51(6):1672-80.
46. Mesotten, D., J. V. Swinnen, et al. "Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy." J Clin Endocrinol Metab. 2004 Jan;89(1):219-26.
47. Miserez, A. R., P. Y. Muller, et al. "Sterol-regulatory element-binding protein (SREBP)-2 contributes to polygenic hypercholesterolaemia." Atherosclerosis. 2002 Sep;164(1):15-26.
48. Nakahara, M., H. Fujii, et al. "Bile acids enhance low density lipoprotein receptor gene expression via a MAPK cascade-mediated stabilization of mRNA." J Biol Chem. 2002 Oct 4;277(40):37229-34. Epub 2002 Jul 30.
49. Narita, I., S. Goto, et al. "Interaction between ACE and ADD1 gene polymorphisms in the progression of IgA nephropathy in Japanese patients." Hypertension. 2003 Sep;42(3):304-9. Epub 2003 Jul 28.
50. National Center for Biotechnology Information, U.S. National Library of Medicine**.** http://www.ncbi.nlm.nih.gov/pubmed. 2015.
51. Oberkofler, H., E. Schraml, et al. "Restoration of sterol-regulatory-element-binding protein-1c gene expression in HepG2 cells by peroxisome-proliferator-activated receptor-gamma co-activator-1alpha." Biochem J. 2004 Jul 15;381(Pt 2):357-63.
52. Park, C. H., J. S. Noh, et al. "Effects of morroniside isolated from Corni Fructus on renal lipids and inflammation in type 2 diabetic mice." J Pharm Pharmacol. 2010 Mar;62(3):374-80. doi: 10.1211/jpp.62.03.0013.
53. Pawar, A., D. Botolin, et al. "The role of liver X receptor-alpha in the fatty acid regulation of hepatic gene expression." J Biol Chem. 2003 Oct 17;278(42):40736-43. Epub 2003 Aug 13.
54. Proctor, G., T. Jiang, et al. "Regulation of renal fatty acid and cholesterol metabolism, inflammation, and fibrosis in Akita and OVE26 mice with type 1 diabetes." Diabetes. 2006 Sep;55(9):2502-9.
55. Rae, F. K., G. Martinez, et al. "Anlaysis of complementary expression profiles following WT1 induction versus repression reveals the cholesterol/fatty acid synthetic pathways as a possible major target of WT1." Oncogene. 2004 Apr 15;23(17):3067-79.
56. Ruan, X. Z., Z. Varghese, et al. "Dysregulation of LDL receptor under the influence of inflammatory cytokines: a new pathway for foam cell formation." Kidney Int. 2001 Nov;60(5):1716-25.
57. Saito, K., N. Ishizaka, et al. "Lipid accumulation and transforming growth factor-beta upregulation in the kidneys of rats administered angiotensin II." Hypertension. 2005 Nov;46(5):1180-5. Epub 2005 Oct 3.
58. Sakai, J., E. A. Duncan, et al. "Sterol-regulated release of SREBP-2 from cell membranes requires two sequential cleavages, one within a transmembrane segment." Cell. 1996 Jun 28;85(7):1037-46.
59. Schmidt, R. J., J. V. Ficorilli, et al. "A 15-ketosterol is a liver X receptor ligand that suppresses sterol-responsive element binding protein-2 activity." J Lipid Res. 2006 May;47(5):1037-44. Epub 2006 Jan 13.
60. Seishima, M. "[Disturbance of lipid metabolism]." Rinsho Byori. 2002 Mar;50(3):219-25.
61. Sharma, A. K., S. Bharti, et al. "Up-regulation of PPARgamma, heat shock protein-27 and -72 by naringin attenuates insulin resistance, beta-cell dysfunction, hepatic steatosis and kidney damage in a rat model of type 2 diabetes." Br J Nutr. 2011 Dec;106(11):1713-23. doi: 10.1017/S000711451100225X. Epub 2011 Jun 21.
62. Shimano, H., I. Shimomura, et al. "Elevated levels of SREBP-2 and cholesterol synthesis in livers of mice homozygous for a targeted disruption of the SREBP-1 gene." J Clin Invest. 1997 Oct 15;100(8):2115-24.
63. Soccio, R. E., R. M. Adams, et al. "The cholesterol-regulated StarD4 gene encodes a StAR-related lipid transfer protein with two closely related homologues, StarD5 and StarD6." Proc Natl Acad Sci U S A. 2002 May 14;99(10):6943-8.
64. Soetikno, V., F. R. Sari, et al. "Curcumin decreases renal triglyceride accumulation through AMPK-SREBP signaling pathway in streptozotocin-induced type 1 diabetic rats." J Nutr Biochem. 2013 May;24(5):796-802. doi: 10.1016/j.jnutbio.2012.04.013. Epub 2012 Aug 13.
65. Stelmanska, E., J. Korczynska, et al. "Tissue-specific effect of refeeding after short- and long-term caloric restriction on malic enzyme gene

expression in rat tissues." Acta Biochim Pol. 2004;51(3):805-14.
66. Szolkiewicz, M., E. Sucajtys, et al. "Mechanisms of enhanced carbohydrate and lipid metabolism in adipose tissue in uremia." J Ren Nutr. 2005 Jan;15(1):166-72.
67. Szolkiewicz, M., M. Chmielewski, et al. "The potential role of sterol regulatory element binding protein transcription factors in renal injury." J Ren Nutr. 2007 Jan;17(1):62-5.
68. Torres, N., I. Torre-Villalvazo, et al. "Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders." J Nutr Biochem. 2006 Jun;17(6):365-73. Epub 2005 Dec 5.
69. Tovar, A. R., F. Murguia, et al. "A soy protein diet alters hepatic lipid metabolism gene expression and reduces serum lipids and renal fibrogenic cytokines in rats with chronic nephrotic syndrome." J Nutr. 2002 Sep;132(9):2562-9.
70. Tovar-Palacio, C., A. R. Tovar, et al. "Proinflammatory gene expression and renal lipogenesis are modulated by dietary protein content in obese Zucker fa/fa rats." Am J Physiol Renal Physiol. 2011 Jan;300(1):F263-71. doi: 10.1152/ajprenal.00171.2010. Epub 2010 Oct 20.
71. Treguier, M., C. Doucet, et al. "Transcription factor sterol regulatory element binding protein 2 regulates scavenger receptor Cla-1 gene expression." Arterioscler Thromb Vasc Biol. 2004 Dec;24(12):2358-64. Epub 2004 Oct 14.
72. Uttarwar, L., B. Gao, et al. "SREBP-1 activation by glucose mediates TGF-beta upregulation in mesangial cells." Am J Physiol Renal Physiol. 2012 Feb 1;302(3):F329-41. doi: 10.1152/ajprenal.00136.2011. Epub 2011 Oct 26.
73. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2015.
74. Wilentz, R. E., L. A. Witters, et al. "Lipogenic enzymes fatty acid synthase and acetyl-coenzyme A carboxylase are coexpressed with sterol regulatory element binding protein and Ki-67 in fetal tissues." Pediatr Dev Pathol. 2000 Nov-Dec;3(6):525-31.
75. Willemarck, N., E. Rysman, et al. "Aberrant activation of fatty acid synthesis suppresses primary cilium formation and distorts tissue development." Cancer Res. 2010 Nov 15;70(22):9453-62. doi: 10.1158/0008-5472.CAN-10-2324. Epub 2010 Oct 1.
76. Xu, Z. E., Y. Chen, et al. "Inflammatory stress exacerbates lipid-mediated renal injury in ApoE/CD36/SRA triple knockout mice." Am J Physiol Renal Physiol. 2011 Oct;301(4):F713-22. doi: 10.1152/ajprenal.00341.2010. Epub 2011 Jul 27.
77. Yamabe, N., J. S. Noh, et al. "Evaluation of loganin, iridoid glycoside from Corni Fructus, on hepatic and renal glucolipotoxicity and inflammation in type 2 diabetic db/db mice." Eur J Pharmacol. 2010 Dec 1;648(1-3):179-87. doi: 10.1016/j.ejphar.2010.08.044. Epub 2010 Sep 15.
78. Yamabe, N., K. S. Kang, et al. "Matcha, a powdered green tea, ameliorates the progression of renal and hepatic damage in type 2 diabetic OLETF rats." J Med Food. 2009 Aug;12(4):714-21. doi: 10.1089/jmf.2008.1282.
79. Yokoyama, M., K. Tanigawa, et al. "Dietary polyunsaturated fatty acids slow the progression of diabetic nephropathy in streptozotocin-induced diabetic rats." Nutr Res. 2010 Mar;30(3):217-25. doi: 10.1016/j.nutres.2010.03.002.
80. Yoshikawa, T., T. Ide, et al. "Cross-talk between peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. I. PPARs suppress sterol regulatory element binding protein-1c promoter through inhibition of LXR signaling." Mol Endocrinol. 2003 Jul;17(7):1240-54. Epub 2003 May 1.
81. Zager, R. A., V. O. Shah, et al. "The mevalonate pathway during acute tubular injury: selected determinants and consequences." Am J Pathol. 2002 Aug;161(2):681-92.
82. Zelenski, N. G., R. B. Rawson, et al. "Membrane topology of S2P, a protein required for intramembranous cleavage of sterol regulatory element-binding proteins." J Biol Chem. 1999 Jul 30;274(31):21973-80.
83. Zulkifli, R. M., T. Parr, et al. "Regulation of ovine and porcine stearoyl coenzyme A desaturase gene promoters by fatty acids and sterols." J Anim Sci. 2010 Aug;88(8):2565-75. doi: 10.2527/jas.2009-2603. Epub 2010 Apr 9.