Lipopolysaccharide (LPS) and Toll-like Receptor (TLR) Research Literatures

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Abstract: Actins are cytoskeletal proteins that regulate cell motility. Cellular actins of various species have very similar immunological and physical properties. Actins are highly conserved proteins that are involved in cell motility, structure and integrity. Alpha actins are a major constituent of the contractile apparatus. Alpha-smooth muscle actin (α-SMA) is commonly used as a marker of myofibroblast formation. Lipopolysaccharides (LPS), also known as lipoglycans and endotoxin, are large molecules consisting of a lipid and a polysaccharide composed of O-antigen, outer core and inner core joined by a covalent bond. LPS is found in the outer membrane of Gram-negative bacteria, and elicit strong immune responses in animals.

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Introduction

Actins are cytoskeletal proteins that regulate cell motility. Cellular actins of various species have very similar immunological and physical properties. Actins are highly conserved proteins that are involved in cell motility, structure and integrity. Alpha actins are a major constituent of the contractile apparatus. Alpha-smooth muscle actin (α-SMA) is commonly used as a marker of myofibroblast formation.

Lipopolysaccharides (LPS), also known as lipoglycans and endotoxin, are large molecules consisting of a lipid and a polysaccharide composed of O-antigen, outer core and inner core joined by a covalent bond. LPS is found in the outer membrane of Gram-negative bacteria, and elicit strong immune responses in animals. The toxic activity of LPS was first discovered and termed endotoxin by Richard Friedrich Johannes Pfeiffer. LPS is secreted as part of the normal physiological activity of membrane vesicle trafficking in the form of bacterial outer membrane vesicles (OMVs), which may also contain other virulence factors and proteins. LPS is the major component of the outer membrane of gram-negative bacteria, contributing greatly to the structural integrity of the bacteria, and protecting the membrane from certain kinds of chemical attack. LPS also increases the negative charge of the cell membrane and helps stabilize the overall membrane structure. It is of crucial importance to gram-negative bacteria, whose death results if it is mutated or removed. LPS induces a strong response from normal animal immune systems. It has also been implicated in non-pathogenic aspects of bacterial ecology, including surface adhesion, bacteriophage sensitivity, and interactions with predators such as amoebae. The LPS Cores of many bacteria contain non-carbohydrate components, such as phosphate, amino acids, and ethanolamine substituents. The Lipid A moiety is a very conserved component of the LPS.

The making of LPS can be modified in order to present a specific sugar structure. Those can be recognised by either other LPS or glycosyltransferases that use those sugar structure to add more specific sugars. LPS acts as the prototypical endotoxin because it binds the CD14/TLR4/MD2 receptor complex in many cell types, but especially in monocytes, dendritic cells, macrophages and B cells, which promotes the secretion of pro-inflammatory cytokines, nitric oxide, and eicosanoids. Being of crucial importance to gram-negative bacteria, these molecules make candidate targets for new antimicrobial agents.

LPS also produces many types of mediators involved in septic shock. Humans are much more sensitive to LPS than other animals. A dose of 1 μg/kg induces shock in humans. LPS causes an IL-10-dependent inhibition of CD4 T-cell expansion and function by up-regulating PD-1 levels on monocytes which leads to IL-10 production by monocytes after binding of PD-1 by PD-L. Bruce Beutler was awarded a portion of the 2011 Nobel Prize in Physiology or Medicine for his work demonstrating that TLR4 is the LPS receptor. Toll-like receptors of the innate immune system recognize LPS and trigger an immune response. Lipid A may cause uncontrolled activation of mammalian immune systems with production of inflammatory mediators that may lead to septic shock. This inflammatory reaction is mediated by Toll-like receptor 4 which is responsible for immune system cell activation.

The presence of endotoxins in the blood is called endotoxemia. It can lead to septic shock, if the immune response is severely pronounced. Moreover,

endotoxemia of intestinal origin, especially, at the host-pathogen interface, is considered to be an important factor in the development of alcoholic hepatitis. Epidemiological studies have previously shown that increased endotoxin load, which can be a result of increased populations of endotoxin producing bacteria in the intestinal tract, is associated with certain obesity-related patient groups.

Obstructive uropathy is a condition in which the flow of urine is blocked. This causes the urine to back up and injure one or both kidneys. Obstructive uropathy occurs when urine cannot drain through a ureter. Urine backs up into the kidney and causes it to become hydronephrosis. It can occur suddenly, or be a long-term problem. If the blockage comes on suddenly, kidney damage is less likely if the problem is detected and treated promptly, and the damage to the kidneys goes away normally. Long-term damage to the kidneys may occur if the blockage has been present for a long time. If the problem is caused by a blockage in the bladder, the bladder may have long-term damage, which may lead to problems emptying the bladder or leakage of urine.

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

Brass, D. M., I. V. Yang, et al. "Fibroproliferation in LPS-induced airway remodeling and bleomycin-induced fibrosis share common patterns of gene expression." Immunogenetics. 2008 Jul;60(7):353-69. doi: 10.1007/s00251-008-0293-3. Epub 2008 Jun 13.

Chronic LPS inhalation causes submucosal thickening and airway narrowing. To address the hypothesis that environmental airway disease is, in part, a fibroproliferative lung disease, Brass et al exposed C57BL/6 mice daily to LPS by inhalation for up to 2 months followed by 1 month of recovery. C57BL/6 mice exposed to daily inhaled LPS had significantly enhanced mRNA expression of TGF-beta1, TIMP-1, fibronectin-1, and pro-collagen types I, III, and IV and show prominent submucosal expression of the myofibroblast markers desmin and alpha-SMA.

Castellano, G., A. Stasi, et al. "Endothelial dysfunction and renal fibrosis in endotoxemia-induced oliguric kidney injury: possible role of LPS-binding protein." Crit Care. 2014 Sep 27;18(5):520. doi: 10.1186/s13054-014-0520-2.

The pathophysiology of endotoxemia-induced acute kidney injury (AKI) is characterized by an intense activation of the host immune system and renal resident cells by lipopolysaccharide (LPS) and derived proinflammatory products. EC dysfunction might be pivotal in the acute development of tubulointerstitial fibrosis in LPS-induced AKI. Selective removal of the LPS adaptor protein LBP might represent a future therapeutic option to prevent EC dysfunction and tissue fibrosis in endotoxemia-induced AKI.

Chong, L. W., Y. C. Hsu, et al. "Antifibrotic effects of triptolide on hepatic stellate cells and dimethylnitrosamine-intoxicated rats." Phytother Res. 2011 Jul;25(7):990-9. doi: 10.1002/ptr.3381.

Triptolide (C(3)(8)H(4)(2)O(6)N(2), TP, a diterpene triepoxide derived from Tripterygium wilfordii Hook F.), is a potent immunosuppresive and antiinflammatory agent. TP exerted antifibrotic effects in both HSC-T6 cells and DMN rats.

Csak, T., A. Velayudham, et al. "Deficiency in myeloid differentiation factor-2 and toll-like receptor 4 expression attenuates nonalcoholic steatohepatitis and fibrosis in mice." Am J Physiol Gastrointest Liver Physiol. 2011 Mar;300(3):G433-41. doi: 10.1152/ajpgi.00163.2009. Epub 2011 Jan 13.

Toll-like receptor 4 (TLR4) and its coreceptor, myeloid differentiation factor-2 (MD-2), are key in recognition of lipopolysaccharide (LPS) and activation of proinflammatory pathways.

Davidson, D. J., F. M. Kilanowski, et al. "A primary culture model of differentiated murine tracheal epithelium." Am J Physiol Lung Cell Mol Physiol. 2000 Oct;279(4):L766-78.

When grown on semipermeable membranes at an air interface, dissociated murine tracheal epithelial cells formed confluent polarized epithelia with high transepithelial resistances (approximately 12 kOmega. cm(2)) that remained viable for up to 80 days. Immunohistochemistry and light and electron microscopy demonstrated that the cells were epithelial in nature (cytokeratin positive, vimentin and alpha-smooth muscle actin negative) and differentiated to form ciliated and secretory cells from day 8 after seeding onward. With RT-PCR, expression of the cystic fibrosis transmembrane conductance regulator (Cftr) and murine beta-defensin (Defb) genes was detected (Defb-1 was constitutively expressed, whereas Defb-2 expression was induced by exposure to lipopolysaccharide).

Eaton, A., E. Nagy, et al. "Cysteinyl leukotriene signaling through perinuclear CysLT(1) receptors on vascular smooth muscle cells transduces nuclear calcium signaling and alterations of gene expression." J Mol Med (Berl). 2012 Oct;90(10):1223-31. doi: 10.1007/s00109-012-0904-1. Epub 2012 Apr 20.

Leukotrienes are pro-inflammatory mediators that are locally produced in coronary atherosclerotic plaques. The response induced by cysteinyl

leukotrienes (CysLT) in human coronary arteries may be altered under pathological conditions, such as atherosclerosis.

Eskilsson, A., M. Tachikawa, et al. "Distribution of microsomal prostaglandin E synthase-1 in the mouse brain." J Comp Neurol. 2014 Oct 1;522(14):3229-44. doi: 10.1002/cne.23593. Epub 2014 Apr 8.

Previous studies in rats have demonstrated that microsomal prostaglandin E synthase-1 (mPGES-1) is induced in brain vascular cells that also express inducible cyclooxygenase-2, suggesting that such cells are the source of the increased PGE2 levels that are seen in the brain following peripheral immune stimulation, and that are associated with sickness responses such as fever, anorexia, and stress hormone release.

Esquenazi, S., J. He, et al. "Immunofluorescence of rabbit corneas after collagen cross-linking treatment with riboflavin and ultraviolet A." Cornea. 2010 Apr;29(4):412-7. doi: 10.1097/ICO.0b013e3181bdf1cc.

Collagen cross-linking results in early edema,keratocyte apoptosis, and necrosis, appearance of inflammatory cells in the surrounding area of treatment and transformation of surrounding keratocytes into myofibroblasts. Compaction of anterior stroma fibers, keratocyte loss, and displacement of cell nuclei including inflammatory cells may have clinical implications in the long-term risk of further corneal thinning in keratoconus and in the cross-linked corneal immune response.

Gobejishvili, L., S. Barve, et al. "Rolipram attenuates bile duct ligation-induced liver injury in rats: a potential pathogenic role of PDE4." J Pharmacol Exp Ther. 2013 Oct;347(1):80-90. doi: 10.1124/jpet.113.204933. Epub 2013 Jul 25.

Anti-inflammatory and antifibrotic effects of the broad spectrum phosphodiesterase (PDE) inhibitor pentoxifylline have suggested an important role for cyclic nucleotides in the pathogenesis of hepatic fibrosis; however, studies examining the role of specific PDEs are lacking. Endotoxemia and Toll-like receptor 4 (TLR4)-mediated inflammatory and profibrotic signaling play a major role in the development of hepatic fibrosis.

Gong, J. H., I. H. Cho, et al. "Inhibition of airway epithelial-to-mesenchymal transition and fibrosis by kaempferol in endotoxin-induced epithelial cells and ovalbumin-sensitized mice." Lab Invest. 2014 Mar;94(3):297-308. doi: 10.1038/labinvest.2013.137. Epub 2013 Dec 30.

Chronic airway remodeling is characterized by structural changes within the airway wall, including smooth muscle hypertrophy, submucosal fibrosis and epithelial shedding. The dietary kaempferol alleviated fibrotic airway remodeling via bronchial EMT by modulating PAR1 activation. Therefore, kaempferol may be a potential therapeutic agent targeting asthmatic airway constriction.

Greer, R. M., J. D. Miller, et al. "Epithelial-mesenchymal co-culture model for studying alveolar morphogenesis." Organogenesis. 2014 Oct 2;10(4):340-9. doi: 10.4161/org.29198. Epub 2014 Oct 31.

Division of large, immature alveolar structures into smaller, more numerous alveoli increases the surface area available for gas exchange. Alveolar division requires precise epithelial-mesenchymal interactions.

Groves, J., Z. Wang, et al. "Two distinct phenotypes of rat vascular smooth muscle cells: growth rate and Production of tumor necrosis factor-alpha." Am Surg. 2005 Jul;71(7):546-50; discussion 550-1.

The monoclonal theory of atherosclerosis postulates that a subpopulation of vascular smooth muscle cells (VSMCs) is selectively expanded in response to pathologic stimuli and accumulates in vascular intima. The purpose of this research was to clone VSMC, determine growth rates of the clones and their ability to release the mitogenic cytokine tumor necrosis factor-alpha (TNF-alpha).

He, Z., Y. Deng, et al. "Overexpression of PTEN suppresses lipopolysaccharide-induced lung fibroblast proliferation, differentiation and collagen secretion through inhibition of the PI3-K-Akt-GSK3beta pathway." Cell Biosci. 2014 Jan 6;4(1):2. doi: 10.1186/2045-3701-4-2.

Abnormal and uncontrolled proliferation of lung fibroblasts may contribute to pulmonary fibrosis. Lipopolysaccharide (LPS) can induce fibroblast proliferation and differentiation through activation of phosphoinositide3-Kinase (PI3-K) pathway. The expression and phosphatase activity of PTEN could be a potential therapeutic target for LPS-induced pulmonary fibrosis. Compared with PTEN expression level, phosphatase activity of PTEN is more crucial in affecting lung fibroblast proliferation, differentiation and collagen secretion.

He, Z., Y. Zhu, et al. "Inhibiting toll-like receptor 4 signaling ameliorates pulmonary fibrosis during acute lung injury induced by lipopolysaccharide: an experimental study." Respir Res. 2009 Dec 18;10:126. doi: 10.1186/1465-9921-10-126.

Toll-like receptor 4 (TLR4) is essential in lipopolysaccharide (LPS)-induced fibroblast activation and collagen secretion in vitro. However, its effects on the process of lung fibroblast activation and fibrosis initiation during LPS induced acute lung injury (ALI) remain unknown. Inhibiting TLR4 signaling could ameliorate fibrosis at the early stage of ALI induced by LPS.

He, Z., Y. Zhu, et al. "Toll-like receptor 4 mediates lipopolysaccharide-induced collagen secretion by phosphoinositide3-kinase-Akt pathway in fibroblasts during acute lung injury." J Recept Signal Transduct Res. 2009;29(2):119-25. doi: 10.1080/10799890902845690.

Gram-negative bacillus infection is an important risk factor of acute lung injury (ALI). Previous experiments have revealed that lipopolysaccharide (LPS), a primary component of endotoxin of gram-negative bacilli, stimulated the inflammatory reactions that contribute to ALI and pulmonary interstitial fibrosis, but the mechanisms were not well understood.

Hisada, S., K. Shimizu, et al. "Peroxisome proliferator-activated receptor gamma ligand prevents the development of chronic pancreatitis through modulating NF-kappaB-dependent proinflammatory cytokine production and pancreatic stellate cell activation." Rocz Akad Med Bialymst. 2005;50:142-7.

Thiazolidinedione derivatives (TZDs) are known to be ligands of peroxisome proliferator-activated receptor gamma (PPARgamma). Troglitazone prevented the progression of chronic pancreatitis via inhibition of ECM synthesis and proinflammatory cytokine production mediated by the inhibition of NF-kappaB activity.

Hui, Y., E. Ricciotti, et al. "Targeted deletions of cyclooxygenase-2 and atherogenesis in mice." Circulation. 2010 Jun 22;121(24):2654-60. doi: 10.1161/CIRCULATIONAHA.109.910687. Epub 2010 Jun 7.

Although the dominant product of vascular Cyclooxygenase-2 (COX-2), prostacyclin (PGI(2)), restrains atherogenesis, inhibition and deletion of COX-2 have yielded conflicting results in mouse models of atherosclerosis. TC COX-2 does not detectably influence TC development or function or atherogenesis in mice.

Isayama, F., I. N. Hines, et al. "LPS signaling enhances hepatic fibrogenesis caused by experimental cholestasis in mice." Am J Physiol Gastrointest Liver Physiol. 2006 Jun;290(6):G1318-28. Epub 2006 Jan 26.

Although it is clear that bile acid accumulation is the major initiator of fibrosis caused by cholestatic liver disease, endotoxemia is a common side effect. The endotoxin in a CD14-dependent manner exacerbates hepatic fibrogenesis and macrophage activation to produce oxidants and cytokines after bile duct ligation.

Kawasaki, H., T. Ohama, et al. "Establishment of mouse intestinal myofibroblast cell lines." World J Gastroenterol. 2013 May 7;19(17):2629-37. doi: 10.3748/wjg.v19.i17.2629.

To establish novel intestinal myofibroblast (IMF) cell lines from mouse colonic mucosa and investigate their biological characters.

Kitani, H., M. Yoshioka, et al. "Characterization of the liver-macrophages isolated from a mixed primary culture of neonatal swine hepatocytes." Results Immunol. 2014 Jan 23;4:1-7. doi: 10.1016/j.rinim.2014.01.001. eCollection 2014.

We recently developed a novel procedure to obtain liver-macrophages in sufficient number and purity using a mixed primary culture of rat and bovine hepatocytes. The isolated cells exhibited phagocytosis of polystyrene microbeads and a release of inflammatory cytokines upon lipopolysaccharide stimulation. This shaking and attachment method is applicable to the swine liver and provides a sufficient number of macrophages without any need of complex laboratory equipments.

Kono, K., Y. Kamijo, et al. "PPAR{alpha} attenuates the proinflammatory response in activated mesangial cells." Am J Physiol Renal Physiol. 2009 Feb;296(2):F328-36. doi: 10.1152/ajprenal.00484.2007. Epub 2008 Nov 26.

The activated mesangial cell is an important therapeutic target for the control of glomerulonephritis. The PPARalpha plays crucial roles in the attenuation of inflammatory response in activated mesangial cells. PPARalpha might be a novel therapeutic target against glomerular diseases.

Krebs, J., A. Kolz, et al. "Effects of lipopolysaccharide-induced inflammation on initial lung fibrosis during open-lung mechanical ventilation in rats." Respir Physiol Neurobiol. 2015 Apr 9. pii: S1569-9048(15)00077-4. doi: 10.1016/j.resp.2015.04.003.

This study aimed to assess the impact of pulmonary inflammation on early fibrotic response in rats challenged with increasing doses of lipopolysaccharide (LPS). In all LPS groups type I and III procollagen decreased compared to controls and there was a negative correlation between type III

procollagen-RNA expression and proinflammatory mediators.

Lee, S. J., J. H. Kang, et al. "PKCdelta as a regulator for TGFbeta1-induced alpha-SMA production in a murine nonalcoholic steatohepatitis model." PLoS One. 2013;8(2):e55979. doi: 10.1371/journal.pone.0055979. Epub 2013 Feb 18.

The precise mechanism of TGFbeta1 signaling in the progression of non-alcoholic steatohepatitis (NASH) has remained unclear.

Leimgruber, C., A. A. Quintar, et al. "Testosterone abrogates TLR4 activation in prostate smooth muscle cells contributing to the preservation of a differentiated phenotype." J Cell Physiol. 2013 Jul;228(7):1551-60. doi: 10.1002/jcp.24314.

Prostate smooth muscle cells (pSMCs) are capable of responding to inflammatory stimuli by secreting proinflammatory products, which causes pSMCs to undergo dedifferentiation. The testosterone might have a homeostatic role by contributing to preserve a contractile phenotype on pSMCs under inflammatory conditions.

Li, C., Y. Ren, et al. "Twist overexpression promoted epithelial-to-mesenchymal transition of human peritoneal mesothelial cells under high glucose." Nephrol Dial Transplant. 2012 Nov;27(11):4119-24. doi: 10.1093/ndt/gfs049. Epub 2012 Apr 11.

Long-term peritoneal dialysis (PD) results in functional and structural alterations of the peritoneal membrane. Previous studies have suggested that high glucose (HG) could induce transdifferentiation of peritoneal mesothelial cells into myofibroblasts, but the molecular mechanisms of HG-induced epithelial-to-mesenchymal transition (EMT) of human peritoneal mesothelial cells (HPMCs) are unclear. This study was undertaken to elucidate the effects and mechanisms of Twist on HG-induced EMT of HPMCs.

Liu, C., Q. Tao, et al. "Kupffer cells are associated with apoptosis, inflammation and fibrotic effects in hepatic fibrosis in rats." Lab Invest. 2010 Dec;90(12):1805-16. doi: 10.1038/labinvest.2010.123. Epub 2010 Oct 4.

Hepatocellular apoptosis, hepatic inflammation, and fibrosis are prominent features in chronic liver diseases. However, the linkage among these processes remains mechanistically unclear. The KCs are associated with hepatocellular apoptosis, inflammation, and fibrosis process in a liver fibrosis models.

Liu, J., L. Zeng, et al. "Selenium suppresses lipopolysaccharide-induced fibrosis in peritoneal mesothelial cells through inhibition of epithelial-to-mesenchymal transition." Biol Trace Elem Res. 2014 Nov;161(2):202-9. doi: 10.1007/s12011-014-0091-8. Epub 2014 Aug 10.

Peritoneal fibrosis resulting from long-term clinical peritoneal dialysis has been the main reason of dropout from peritoneal dialysis. Peritonitis as a common complication of peritoneal dialysis treatment may lead to the occurrences of peritoneal fibrosis.

Ma, F. Y., G. H. Tesch, et al. "ASK1/p38 signaling in renal tubular epithelial cells promotes renal fibrosis in the mouse obstructed kidney." Am J Physiol Renal Physiol. 2014 Dec 1;307(11):F1263-73. doi: 10.1152/ajprenal.00211.2014. Epub 2014 Oct 8.

Stress-activated kinases p38 MAPK and JNK promote renal fibrosis; however, how the pathways by which these kinases are activated in kidney disease remain poorly defined. Apoptosis signal-regulating kinase 1 (ASK1/MAPKKK5) is a member of the MAPKKK family that can induce activation of p38 and JNK. The ASK1 is an important upstream activator of p38 and JNK signaling in the obstructed kidney, and ASK1 is a potential therapeutic target in renal fibrosis.

Melgar-Lesmes, P., M. Pauta, et al. "Hypoxia and proinflammatory factors upregulate apelin receptor expression in human stellate cells and hepatocytes." Gut. 2011 Oct;60(10):1404-11. doi: 10.1136/gut.2010.234690. Epub 2011 Mar 29.

The activation of the apelin receptor (APJ) plays a major role in both angiogenic and fibrogenic response to chronic liver injury. However, the mechanisms that govern the induction of APJ expression have not been clarified so far. The hypoxia and inflammatory factors could play a major role in the activation of the hepatic apelin system leading to angiogenic and fibroproliferative response occurring in chronic liver disease.

Meng, X., J. M. Brown, et al. "Reduction of infarct size in the rat heart by LPS preconditioning is associated with expression of angiogenic growth factors and increased capillary density." Shock. 1999 Jul;12(1):25-31.

Inflammation induces the expression of angiogenic growth factors in tissues, which leads to microvascular growth. The LPS preconditioning induces cardiac bFGF and VEGF, and an increase in myocardial capillary density.

Mitchell, P. O., J. S. Jensen, et al. "Alcohol primes the airway for increased interleukin-13 signaling."

Alcohol Clin Exp Res. 2009 Mar;33(3):505-13. doi: 10.1111/j.1530-0277.2008.00863.x. Epub 2008 Dec 19.

Using an experimental model of airway fibrosis following lung transplantation, we recently showed that chronic alcohol ingestion by donor rats amplifies airway fibrosis in the recipient. The IL-13 and its receptors play a role in alcohol-mediated activation of pro-fibrotic pathways. Taken together, these data suggest that alcohol primes the airway for increased IL-13 signaling and subsequent tissue remodeling upon injury such as transplantation.

Morishita, K., K. Shimizu, et al. "Engulfment of gram-positive bacteria by pancreatic stellate cells in pancreatic fibrosis." Pancreas. 2010 Oct;39(7):1002-7. doi: 10.1097/MPA.0b013e3181d7ace1.

We previously reported the finding that pancreatic stellate cells (PSCs) have a phagocytic function. The aim of the present study was to investigate whether engulfment of gram-positive bacteria by PSCs plays any role in the pathogenesis of pancreatic fibrosis. The fibrogenic action of PSCs seems to be more strongly associated with activation of the toll-like receptor-dependent pathway than it is with phagocytosis of bacteria by PSCs.

Ohara, S., Y. Kawasaki, et al. "Role of vascular endothelial growth factor and angiopoietin 1 in renal injury in hemolytic uremic syndrome." Am J Nephrol. 2012;36(6):516-23. doi: 10.1159/000345142. Epub 2012 Nov 17.

The recovery process from renal injury in hemolytic uremic syndrome (HUS) remains obscure. The VEGF and Ang-1 play important roles in the recovery process, particularly in the regeneration of endothelial injury.

Pieper, C., J. J. Marek, et al. "Brain capillary pericytes contribute to the immune defense in response to cytokines or LPS in vitro." Brain Res. 2014 Mar 6;1550:1-8. doi: 10.1016/j.brainres.2014.01.004. Epub 2014 Jan 10.

The prevention of an inflammation in the brain is one of the most important goals the body has to achieve. Depending on the different specific pro-inflammatory factors pericytes changed the expression of alpha smooth muscle actin (alphaSMA), the most predominant pericyte marker. We conclude that the role of the pericytes within the immune system is regulated and fine-tuned by different cytokines strongly depending on the time when the cytokines are released and their concentration.

Qian, H., J. Shi, et al. "Sophocarpine attenuates liver fibrosis by inhibiting the TLR4 signaling pathway in rats." World J Gastroenterol. 2014 Feb 21;20(7):1822-32. doi: 10.3748/wjg.v20.i7.1822.

To explore the effect of sophocarpine on experimental liver fibrosis and the potential mechanism involved. Sophocarpine can alleviate liver fibrosis mainly by inhibiting the TLR4 pathway. Sophocarpine may be a potential chemotherapeutic agent for chronic liver diseases.

Rehan, V. K., S. K. Dargan-Batra, et al. "A paradoxical temporal response of the PTHrP/PPARgamma signaling pathway to lipopolysaccharide in an in vitro model of the developing rat lung." Am J Physiol Lung Cell Mol Physiol. 2007 Jul;293(1):L182-90. Epub 2007 Apr 13.

Chorioamnionitis alters lung development, resulting in a paradoxical decrease in the incidence of respiratory distress syndrome but an increase in the incidence of bronchopulmonary dysplasia (BPD).

Sakaida, I., S. Jinhua, et al. "Leptin receptor-deficient Zucker (fa/fa) rat retards the development of pig serum-induced liver fibrosis with Kupffer cell dysfunction." Life Sci. 2003 Sep 26;73(19):2491-501.

The aim of this study was to investigate the role of leptin in the development of liver fibrosis with Kupffer cell function using leptin receptor deficient rats. The leptin receptor deficiency retards the development of liver fibrosis due to the dysfunction of Kuppfer cells.

Sheng-Nan, P., Z. Hui-Hong, et al. "Protection of rhein on IgA nephropathy mediated by inhibition of fibronectin expression in rats." Indian J Pharmacol. 2013 Mar-Apr;45(2):174-9. doi: 10.4103/0253-7613.108309.

Twenty-eight female sprague dawley rats were divided randomly into four groups, namely control, IgAN, rhein-prevented and rhein-treated. The pathologic changes on renal tissue were observed by the H and E, staining and the amount of urinary red blood cells and 24-h urinary protein excretion were measured. These findings indicate that rhein prevents the development of glomerulosclerosis and halts the progression of IgAN via inhibition of FN and alpha-SMA expression.

Song, L., J. Xu, et al. "A therapeutic role for mesenchymal stem cells in acute lung injury independent of hypoxia-induced mitogenic factor." J Cell Mol Med. 2012 Feb;16(2):376-85. doi: 10.1111/j.1582-4934.2011.01326.x.

Bone marrow mesenchymal stem cells (BM-MSCs) have therapeutic potential in acute lung injury (ALI). Hypoxia-induced mitogenic factor (HIMF) is a

lung-specific growth factor that participates in a variety of lung diseases.

Su, L. J., C. C. Chang, et al. "Graptopetalum paraguayense ameliorates chemical-induced rat hepatic fibrosis in vivo and inactivates stellate cells and Kupffer cells in vitro." PLoS One. 2013;8(1):e53988. doi: 10.1371/journal.pone.0053988. Epub 2013 Jan 15.

Graptopetalum paraguayense (GP) is a folk herbal medicine with hepatoprotective effects that is used in Taiwan. The administration of MGP attenuated toxin-induced hepatic damage and fibrosis in vivo and inhibited HSC and Kupffer cell activation in vitro, suggesting that MGP might be a promising complementary or alternative therapeutic agent for liver inflammation and fibrosis.

Sun, X., T. N. Phan, et al. "LCB 03-0110, a novel pan-discoidin domain receptor/c-Src family tyrosine kinase inhibitor, suppresses scar formation by inhibiting fibroblast and macrophage activation." J Pharmacol Exp Ther. 2012 Mar;340(3):510-9. doi: 10.1124/jpet.111.187328. Epub 2011 Nov 29.

Wound healing generally induces an inflammatory response associated with tissue fibrosis in which activated macrophage and myofibroblast cells are primarily involved. Although this is known to be the underlying mechanism for scarring and various fibrotic pathologies, no effective intervention is currently available.

Sun, X., Y. Yang, et al. "Expression of Septin4 in human hepatic stellate cells LX-2 stimulated by LPS." Inflammation. 2013 Jun;36(3):539-48. doi: 10.1007/s10753-012-9575-x.

Septin4, a member of polymerizing GTP-binding proteins family, is reported to be involved in cytoskeletal organization in mitosis, apoptosis, fibrosis, and other cellular processes. The Septin4 may be involved in the process of activation of hepatic stellate cells by LPS stimulation. Further work would focus on the function of Septin4 in hepatic inflammatory injury and fibrosis.

Takabayashi, H., M. Shinohara, et al. "Anti-inflammatory activity of bone morphogenetic protein signaling pathways in stomachs of mice." Gastroenterology. 2014 Aug;147(2):396-406.e7. doi: 10.1053/j.gastro.2014.04.015. Epub 2014 Apr 18.

Bone morphogenetic protein (BMP)4 is a mesenchymal peptide that regulates cells of the gastric epithelium. The BMP signaling reduces inflammation and inhibits dysplastic changes in the gastric mucosa after infection of mice with H pylori or H felis.

Tiggelman, A. M., W. Boers, et al. "Interleukin-6 production by human liver (myo)fibroblasts in culture. Evidence for a regulatory role of LPS, IL-1 beta and TNF alpha." J Hepatol. 1995 Sep;23(3):295-306.

Interleukin-6 is a major trigger for the synthesis of acute phase proteins by liver parenchymal cells. Acute phase proteins may contribute to the regulation of liver fibrosis by inhibition of proteases (e.g. collagenase) and by binding of cytokines. The transformed fat-storing cells (VA cells) and fibroblasts (V cells) may function as a local source of interleukin-6 in the human liver. Since interleukin-6 plays a key role in the regulation of the production of acute phase proteins by liver parenchymal cells, we hypothesize that human liver (myo)fibroblasts may stimulate local production of acute phase proteins in the fibrotic liver, thus contributing to local regulation of inflammatory and fibrogenic reactions.

Tomita, K., M. Takashina, et al. "Cardiac fibroblasts: contributory role in septic cardiac dysfunction." J Surg Res. 2015 Feb;193(2):874-87. doi: 10.1016/j.jss.2014.09.012. Epub 2014 Sep 16.

Cardiac dysfunction is a frequent and severe complication of septic shock and contributes to the high mortality of sepsis. Although several mechanisms have been suspected to be responsible for sepsis-associated cardiac dysfunction, the precise cause(s) remains unclear to date. The cardiac fibroblasts are of pathogenetic importance in inflammation and fibrosis in the heart during sepsis, leading to cardiac dysfunction that would affect the outcome of sepsis syndrome.

Treiber, M., P. Neuhofer, et al. "Myeloid, but not pancreatic, RelA/p65 is required for fibrosis in a mouse model of chronic pancreatitis." Gastroenterology. 2011 Oct;141(4):1473-85, 1485.e1-7. doi: 10.1053/j.gastro.2011.06.087. Epub 2011 Jul 18.

Little is known about how transcription factors might regulate pathogenesis of chronic pancreatitis (CP). We analyzed the in vivo role of RelA/p65, a component of the transcription factor nuclear factor (NF)-kappaB, in different cell types during development of CP in mice. The RelA/p65 functions in myeloid cells to promote pathogenesis of CP. In acinar cells, RelA/p65 protects against chronic inflammation, whereas myeloid RelA/p65 promotes fibrogenesis. In macrophage, MMP-10 functions as a RelA/p65-dependent, potentially antifibrogenic factor during progression of CP.

Tsuchiya, K., S. Siddiqui, et al. "The presence of LPS in OVA inhalations affects airway inflammation and AHR but not remodeling in a rodent model of

asthma." Am J Physiol Lung Cell Mol Physiol. 2012 Jul 1;303(1):L54-63. doi: 10.1152/ajplung.00208.2011. Epub 2012 Apr 20.

Ovalbumin (OVA) is the most frequently used allergen in animal models of asthma. Lipopolysaccharide (LPS) contaminating commercial OVA may modulate the evoked airway inflammatory response to OVA.

Uemura, T. and C. R. Gandhi "Inhibition of DNA synthesis in cultured hepatocytes by endotoxin-conditioned medium of activated stellate cells is transforming growth factor-beta and nitric oxide-independent." Br J Pharmacol. 2001 Aug;133(7):1125-33.

Activated hepatic stellate cells play a major role in the pathophysiology of chronic liver disease. They can influence the metabolism of hepatocytes by producing a variety of cytokines and growth factors. The factors other than these cytokines produced by activated stellate cells upon stimulation with endotoxin or by hepatocytes challenged with endotoxin-conditioned stellate cell medium inhibit DNA synthesis in hepatocytes.

Vespasiani-Gentilucci, U., S. Carotti, et al. "Hepatic toll-like receptor 4 expression is associated with portal inflammation and fibrosis in patients with NAFLD." Liver Int. 2015 Feb;35(2):569-81. doi: 10.1111/liv.12531. Epub 2014 Apr 5.

Notwithstanding evidences implicating the lipopolysaccharides (LPS)/toll-like receptor-4 (TLR4) axis in the pathogenesis of NAFLD, there are no studies aimed to characterize hepatic TLR4 expression in NAFLD patients. We aimed to analyse hepatic TLR4 expression and to verify its relationship with disease activity/evolution in NAFLD patients. The TLR4 expression by regenerating and inflammatory cells at the porto-septal and interface level, favoured by increased LPS activity, is associated with activation of fibrogenic cells and the degree of fibrosis.

Vonlaufen, A., P. A. Phillips, et al. "Isolation of quiescent human pancreatic stellate cells: a promising in vitro tool for studies of human pancreatic stellate cell biology." Pancreatology. 2010;10(4):434-43. doi: 10.1159/000260900. Epub 2010 Aug 20.

BACKGROUND: Pancreatic stellate cells (PSCs) play a critical role in pancreatic fibrosis. To date, human PSC biology has been studied using cancer- or inflammation-associated (pre-activated) PSCs, but an in vitro model of quiescent normal human PSCs (NhPSCs) has been lacking.

Wan, Y., S. Jiang, et al. "Betulinic acid and betulin ameliorate acute ethanol-induced fatty liver via TLR4 and STAT3 in vivo and in vitro." Int Immunopharmacol. 2013 Oct;17(2):184-90. doi: 10.1016/j.intimp.2013.06.012. Epub 2013 Jun 28.

Ethanol consumption leads to many kinds of liver injury and suppresses innate immunity, but the molecular mechanisms have not been fully delineated.

Wang, F., S. Liu, et al. "NF-kappaB inhibition alleviates carbon tetrachloride-induced liver fibrosis via suppression of activated hepatic stellate cells." Exp Ther Med. 2014 Jul;8(1):95-99. Epub 2014 Apr 14.

An effective treatment for hepatic fibrosis is not available clinically. Nuclear factor (NF)-kappaB plays a central role in inflammation and fibrosis. The BAY attenuates liver fibrosis by blocking PI3K and Akt phosphorylation in activated HSCs. Thus, BAY demonstrates therapeutic potential as a treatment for hepatic fibrosis.

Wang, H. Y., L. Z. Yang, et al. "Hepatocyte growth factor-induced amelioration in chronic renal failure is associated with reduced expression of alpha-smooth muscle actin." Ren Fail. 2012;34(7):862-70. doi: 10.3109/0886022X.2012.687344. Epub 2012 Jun 8.

This study aimed to examine whether hepatocyte growth factor (HGF) can improve renal function in 5/6 nephrectomized rats and investigate whether this function is associated with a decrease in alpha-smooth muscle actin (alpha-SMA) expression in rat glomerulus mesangial cells and renal interstitium. The HGF can relieve chronic renal failure, and this protection is associated with the down-regulation of alpha-SMA expression in mesangial cells and renal interstitium.

Wei, J., M. Shi, et al. "IkappaB kinase-beta inhibitor attenuates hepatic fibrosis in mice." World J Gastroenterol. 2011 Dec 21;17(47):5203-13. doi: 10.3748/wjg.v17.i47.5203.

To investigate the anti-fibrosis effect of IkappaB kinase-beta inhibitor (IKK2 inhibitor IMD0354) in liver fibrosis. The IKK2 inhibitor IMD markedly improved non-alcoholic fatty liver disease in mice by lowering NF-kappaB activation, which could become a remedial target for liver fibrosis.

Wen, F. Q., K. Watanabe, et al. "Cytokines and lipopolysaccharide enhance basal and thrombin-stimulated production of PGI2 by cultured human pulmonary artery smooth muscle cells." Prostaglandins Leukot Essent Fatty Acids. 1997 Mar;56(3):185-92.

We evaluated the thrombin-stimulated production of prostacyclin (PGI2) by cultured human

pulmonary artery smooth muscle cells (HPASMC) that were pretreated with cytokines (IL-1 beta, TNF alpha) and lipopolysaccharide (LPS).

Weng, H. L., D. C. Feng, et al. "IFN-gamma inhibits liver progenitor cell proliferation in HBV-infected patients and in 3,5-diethoxycarbonyl-1,4-dihydrocollidine diet-fed mice." J Hepatol. 2013 Oct;59(4):738-45. doi: 10.1016/j.jhep.2013.05.041. Epub 2013 Jun 4.

Proliferation of liver progenitor cells (LPCs) is associated with inflammation and fibrosis in chronic liver diseases. However, how inflammation and fibrosis affect LPCs remains obscure.

Xing, L., L. Bai, et al. "[Effect of telmisartan on tubulointerstitial injury and expression of PPARgamma in rat renal tissue of IgA nephropathy model]." Zhonghua Yi Xue Za Zhi. 2010 Nov 2;90(40):2860-3.

To observe the effect of telmisartan on the expression of PPARgamma in rat renal tissue of IgA nephropathy model and clarify the possible mechanism of telmisartan in tubulointerstitial injury. Possibly through two separate passway of stimulating PPARgamma and preventing Angiotensin II receptor, telmisartan shows special protective function in tubulointerstitial injury.

Yamate, J., Y. Machida, et al. "Effects of lipopolysaccharide on the appearance of macrophage populations and fibrogenesis in cisplatin-induced rat renal injury." Exp Toxicol Pathol. 2004 Oct;56(1-2):13-24.

Macrophages play an important role in renal interstitial fibrosis via production of transforming growth factor-beta1 (TGF-beta1) and tumor necrosis factor-alpha (TNF-alpha); these fibrogenic factors mediate induction of myofibroblastic cells capable of producing extracellular matrices. We investigated the effects of lipopolysaccharide (LPS), a macrophage activator, on the appearance of macrophage populations and subsequent fibrogenesis in cisplatin (CDDP)-induced rat renal lesions. In keeping with the progression of interstitial fibrosis, alpha-smooth muscle actin (alpha-SMA)-immunopositive myofibroblastic cell number began to increase on day 4 and continued gradually until day 16 after CDDP injection.

Yamate, J., M. Maeda, et al. "Effects of lipopolysaccharide on a macrophage-like cell line (HS-P) from a rat histiocytic sarcoma." J Comp Pathol. 2001 Jul;125(1):15-24.

Lipopolysaccharide (LPS) is a major modulator of macrophage functions. To characterize a newly established rat histiocytic sarcoma-derived cell line (HS-P), immunophenotypic changes and cellular growth responses of HS-P cells exposed to LPS were investigated and compared with those of MT-9 cells isolated from a rat malignant fibrous histiocytoma. The study demonstrated that HS-P cells are highly LPS-responsive, indicating that they would be useful for studies of macrophage functions.

Yamate, J., M. Tajima, et al. "Phenotypic changes in lipopolysaccharide-treated cloned cells derived from transplantable rat malignant fibrous histiocytoma." J Vet Med Sci. 1996 Oct;58(10):1017-20.

To investigate a possible phenotypic modulation, MT-8L and MT-9L cells were induced by in vitro culture of undifferentiated MT-8 and fibrohistiocytic MT-9 cells, which had been established from a rat malignant fibrous histiocytoma (MFH), in the medium containing 10 micrograms lipopolysaccharide (LPS)/ml.

Yamate, J., H. Yasui, et al. "Characterization of newly established tumor lines from a spontaneous malignant schwannoma in F344 rats: nerve growth factor production, growth inhibition by transforming growth factor-beta1, and macrophage-like phenotype expression." Acta Neuropathol. 2003 Sep;106(3):221-33. Epub 2003 Jun 17.

Transplantable tumor (KE) and clone cell (KE-F11) lines were established from a spontaneous malignant schwannoma found in an aged F344 rat. The present study provides evidence that biological properties of malignant schwannoma-derived cells might be affected by exogenous factors such as TGF-beta1, LPS and laminin. These tumor lines may be useful for studies on pathobiological characteristics of Schwann cells.

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References

1. Brass, D. M., I. V. Yang, et al. "Fibroproliferation in LPS-induced airway remodeling and bleomycin-induced fibrosis share common patterns of gene expression." Immunogenetics. 2008 Jul;60(7):353-69. doi: 10.1007/s00251-008-0293-3. Epub 2008 Jun 13.
2. Castellano, G., A. Stasi, et al. "Endothelial dysfunction and renal fibrosis in endotoxemia-induced oliguric kidney injury: possible role of LPS-binding protein." Crit Care. 2014 Sep 27;18(5):520. doi: 10.1186/s13054-014-0520-2.
3. Chong, L. W., Y. C. Hsu, et al. "Antifibrotic effects of triptolide on hepatic stellate cells and dimethylnitrosamine-intoxicated rats." Phytother Res. 2011 Jul;25(7):990-9. doi: 10.1002/ptr.3381.
4. Csak, T., A. Velayudham, et al. "Deficiency in myeloid differentiation factor-2 and toll-like receptor 4 expression

attenuates nonalcoholic steatohepatitis and fibrosis in mice." Am J Physiol Gastrointest Liver Physiol. 2011 Mar;300(3):G433-41. doi: 10.1152/ajpgi.00163.2009. Epub 2011 Jan 13.
5. Davidson, D. J., F. M. Kilanowski, et al. "A primary culture model of differentiated murine tracheal epithelium." Am J Physiol Lung Cell Mol Physiol. 2000 Oct;279(4):L766-78.
6. Eaton, A., E. Nagy, et al. "Cysteinyl leukotriene signaling through perinuclear CysLT(1) receptors on vascular smooth muscle cells transduces nuclear calcium signaling and alterations of gene expression." J Mol Med (Berl). 2012 Oct;90(10):1223-31. doi: 10.1007/s00109-012-0904-1. Epub 2012 Apr 20.
7. Eskilsson, A., M. Tachikawa, et al. "Distribution of microsomal prostaglandin E synthase-1 in the mouse brain." J Comp Neurol. 2014 Oct 1;522(14):3229-44. doi: 10.1002/cne.23593. Epub 2014 Apr 8.
8. Esquenazi, S., J. He, et al. "Immunofluorescence of rabbit corneas after collagen cross-linking treatment with riboflavin and ultraviolet A." Cornea. 2010 Apr;29(4):412-7. doi: 10.1097/ICO.0b013e3181bdf1cc.
9. Gobejishvili, L., S. Barve, et al. "Rolipram attenuates bile duct ligation-induced liver injury in rats: a potential pathogenic role of PDE4." J Pharmacol Exp Ther. 2013 Oct;347(1):80-90. doi: 10.1124/jpet.113.204933. Epub 2013 Jul 25.
10. Gong, J. H., I. H. Cho, et al. "Inhibition of airway epithelial-to-mesenchymal transition and fibrosis by kaempferol in endotoxin-induced epithelial cells and ovalbumin-sensitized mice." Lab Invest. 2014 Mar;94(3):297-308. doi: 10.1038/labinvest.2013.137. Epub 2013 Dec 30.
11. Greer, R. M., J. D. Miller, et al. "Epithelial-mesenchymal co-culture model for studying alveolar morphogenesis." Organogenesis. 2014 Oct 2;10(4):340-9. doi: 10.4161/org.29198. Epub 2014 Oct 31.
12. Groves, J., Z. Wang, et al. "Two distinct phenotypes of rat vascular smooth muscle cells: growth rate and Production of tumor necrosis factor-alpha." Am Surg. 2005 Jul;71(7):546-50; discussion 550-1.
13. He, Z., Y. Deng, et al. "Overexpression of PTEN suppresses lipopolysaccharide-induced lung fibroblast proliferation, differentiation and collagen secretion through inhibition of the PI3-K-Akt-GSK3beta pathway." Cell Biosci. 2014 Jan 6;4(1):2. doi: 10.1186/2045-3701-4-2.
14. He, Z., Y. Zhu, et al. "Inhibiting toll-like receptor 4 signaling ameliorates pulmonary fibrosis during acute lung injury induced by lipopolysaccharide: an experimental study." Respir Res. 2009 Dec 18;10:126. doi: 10.1186/1465-9921-10-126.
15. He, Z., Y. Zhu, et al. "Toll-like receptor 4 mediates lipopolysaccharide-induced collagen secretion by phosphoinositide3-kinase-Akt pathway in fibroblasts during acute lung injury." J Recept Signal Transduct Res. 2009;29(2):119-25. doi: 10.1080/10799890902845690.
16. Hisada, S., K. Shimizu, et al. "Peroxisome proliferator-activated receptor gamma ligand prevents the development of chronic pancreatitis through modulating NF-kappaB-dependent proinflammatory cytokine production and pancreatic stellate cell activation." Rocz Akad Med Bialymst. 2005;50:142-7.
17. Hui, Y., E. Ricciotti, et al. "Targeted deletions of cyclooxygenase-2 and atherogenesis in mice." Circulation. 2010 Jun 22;121(24):2654-60. doi: 10.1161/CIRCULATIONAHA.109.910687. Epub 2010 Jun 7.
18. Isayama, F., I. N. Hines, et al. "LPS signaling enhances hepatic fibrogenesis caused by experimental cholestasis in mice." Am J Physiol Gastrointest Liver Physiol. 2006 Jun;290(6):G1318-28. Epub 2006 Jan 26.
19. Kawasaki, H., T. Ohama, et al. "Establishment of mouse intestinal myofibroblast cell lines." World J Gastroenterol. 2013 May 7;19(17):2629-37. doi: 10.3748/wjg.v19.i17.2629.
20. Kitani, H., M. Yoshioka, et al. "Characterization of the liver-macrophages isolated from a mixed primary culture of neonatal swine hepatocytes." Results Immunol. 2014 Jan 23;4:1-7. doi: 10.1016/j.rinim.2014.01.001. eCollection 2014.
21. Kono, K., Y. Kamijo, et al. "PPAR{alpha} attenuates the proinflammatory response in activated mesangial cells." Am J Physiol Renal Physiol. 2009 Feb;296(2):F328-36. doi: 10.1152/ajprenal.00484.2007. Epub 2008 Nov 26.
22. Krebs, J., A. Kolz, et al. "Effects of lipopolysaccharide-induced inflammation on initial lung fibrosis during open-lung mechanical ventilation in rats." Respir Physiol Neurobiol. 2015 Apr 9. pii: S1569-9048(15)00077-4. doi: 10.1016/j.resp.2015.04.003.
23. Lee, S. J., J. H. Kang, et al. "PKCdelta as a regulator for TGFbeta1-induced alpha-SMA production in a murine nonalcoholic steatohepatitis model." PLoS One. 2013;8(2):e55979. doi: 10.1371/journal.pone.0055979. Epub 2013 Feb 18.
24. Leimgruber, C., A. A. Quintar, et al. "Testosterone abrogates TLR4 activation in prostate smooth muscle cells contributing to the preservation of a differentiated phenotype." J Cell Physiol. 2013 Jul;228(7):1551-60. doi: 10.1002/jcp.24314.
25. Li, C., Y. Ren, et al. "Twist overexpression promoted epithelial-to-mesenchymal transition of human peritoneal mesothelial cells under high glucose." Nephrol Dial Transplant. 2012 Nov;27(11):4119-24. doi: 10.1093/ndt/gfs049. Epub 2012 Apr 11.
26. Liu, C., Q. Tao, et al. "Kupffer cells are associated with apoptosis, inflammation and fibrotic effects in hepatic fibrosis in rats." Lab Invest. 2010 Dec;90(12):1805-16. doi: 10.1038/labinvest.2010.123. Epub 2010 Oct 4.
27. Liu, J., L. Zeng, et al. "Selenium suppresses lipopolysaccharide-induced fibrosis in peritoneal mesothelial cells through inhibition of epithelial-to-mesenchymal transition." Biol Trace Elem Res. 2014 Nov;161(2):202-9. doi: 10.1007/s12011-014-0091-8. Epub 2014 Aug 10.
28. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
29. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
30. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7 - 15.
31. 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.
32. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11.Nature and science 2007;5(1):81-96.
33. Ma, F. Y., G. H. Tesch, et al. "ASK1/p38 signaling in renal tubular epithelial cells promotes renal fibrosis in the mouse obstructed kidney." Am J Physiol Renal Physiol. 2014 Dec 1;307(11):F1263-73. doi: 10.1152/ajprenal.00211.2014. Epub 2014 Oct 8.
34. Melgar-Lesmes, P., M. Pauta, et al. "Hypoxia and proinflammatory factors upregulate apelin receptor expression in human stellate cells and hepatocytes." Gut. 2011 Oct;60(10):1404-11. doi: 10.1136/gut.2010.234690. Epub 2011 Mar 29.
35. Meng, X., J. M. Brown, et al. "Reduction of infarct size in the rat heart by LPS preconditioning is associated with expression of angiogenic growth factors and increased capillary density." Shock. 1999 Jul;12(1):25-31.
36. Mitchell, P. O., J. S. Jensen, et al. "Alcohol primes the airway for increased interleukin-13 signaling." Alcohol Clin Exp Res. 2009 Mar;33(3):505-13. doi: 10.1111/j.1530-0277.2008.00863.x. Epub 2008 Dec 19.
37. Morishita, K., K. Shimizu, et al. "Engulfment of gram-positive bacteria by pancreatic stellate cells in pancreatic fibrosis." Pancreas. 2010 Oct;39(7):1002-7. doi: 10.1097/MPA.0b013e3181d7ace1.

38. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2015.
39. Ohara, S., Y. Kawasaki, et al. "Role of vascular endothelial growth factor and angiopoietin 1 in renal injury in hemolytic uremic syndrome." Am J Nephrol. 2012;36(6):516-23. doi: 10.1159/000345142. Epub 2012 Nov 17.
40. Pieper, C., J. J. Marek, et al. "Brain capillary pericytes contribute to the immune defense in response to cytokines or LPS in vitro." Brain Res. 2014 Mar 6;1550:1-8. doi: 10.1016/j.brainres.2014.01.004. Epub 2014 Jan 10.
41. Qian, H., J. Shi, et al. "Sophocarpine attenuates liver fibrosis by inhibiting the TLR4 signaling pathway in rats." World J Gastroenterol. 2014 Feb 21;20(7):1822-32. doi: 10.3748/wjg.v20.i7.1822.
42. Rehan, V. K., S. K. Dargan-Batra, et al. "A paradoxical temporal response of the PTHrP/PPARgamma signaling pathway to lipopolysaccharide in an in vitro model of the developing rat lung." Am J Physiol Lung Cell Mol Physiol. 2007 Jul;293(1):L182-90. Epub 2007 Apr 13.
43. Sakaida, I., S. Jinhua, et al. "Leptin receptor-deficient Zucker (fa/fa) rat retards the development of pig serum-induced liver fibrosis with Kupffer cell dysfunction." Life Sci. 2003 Sep 26;73(19):2491-501.
44. Sheng-Nan, P., Z. Hui-Hong, et al. "Protection of rhein on IgA nephropathy mediated by inhibition of fibronectin expression in rats." Indian J Pharmacol. 2013 Mar-Apr;45(2):174-9. doi: 10.4103/0253-7613.108309.
45. Song, L., J. Xu, et al. "A therapeutic role for mesenchymal stem cells in acute lung injury independent of hypoxia-induced mitogenic factor." J Cell Mol Med. 2012 Feb;16(2):376-85. doi: 10.1111/j.1582-4934.2011.01326.x.
46. Su, L. J., C. C. Chang, et al. "Graptopetalum paraguayense ameliorates chemical-induced rat hepatic fibrosis in vivo and inactivates stellate cells and Kupffer cells in vitro." PLoS One. 2013;8(1):e53988. doi: 10.1371/journal.pone.0053988. Epub 2013 Jan 15.
47. Sun, X., T. N. Phan, et al. "LCB 03-0110, a novel pan-discoidin domain receptor/c-Src family tyrosine kinase inhibitor, suppresses scar formation by inhibiting fibroblast and macrophage activation." J Pharmacol Exp Ther. 2012 Mar;340(3):510-9. doi: 10.1124/jpet.111.187328. Epub 2011 Nov 29.
48. Sun, X., Y. Yang, et al. "Expression of Septin4 in human hepatic stellate cells LX-2 stimulated by LPS." Inflammation. 2013 Jun;36(3):539-48. doi: 10.1007/s10753-012-9575-x.
49. Takabayashi, H., M. Shinohara, et al. "Anti-inflammatory activity of bone morphogenetic protein signaling pathways in stomachs of mice." Gastroenterology. 2014 Aug;147(2):396-406.e7. doi: 10.1053/j.gastro.2014.04.015. Epub 2014 Apr 18.
50. Tiggelman, A. M., W. Boers, et al. "Interleukin-6 production by human liver (myo)fibroblasts in culture. Evidence for a regulatory role of LPS, IL-1 beta and TNF alpha." J Hepatol. 1995 Sep;23(3):295-306.
51. Tomita, K., M. Takashina, et al. "Cardiac fibroblasts: contributory role in septic cardiac dysfunction." J Surg Res. 2015 Feb;193(2):874-87. doi: 10.1016/j.jss.2014.09.012. Epub 2014 Sep 16.
52. Treiber, M., P. Neuhofer, et al. "Myeloid, but not pancreatic, RelA/p65 is required for fibrosis in a mouse model of chronic pancreatitis." Gastroenterology. 2011 Oct;141(4):1473-85, 1485.e1-7. doi: 10.1053/j.gastro.2011.06.087. Epub 2011 Jul 18.
53. Tsuchiya, K., S. Siddiqui, et al. "The presence of LPS in OVA inhalations affects airway inflammation and AHR but not remodeling in a rodent model of asthma." Am J Physiol Lung Cell Mol Physiol. 2012 Jul 1;303(1):L54-63. doi: 10.1152/ajplung.00208.2011. Epub 2012 Apr 20.
54. Uemura, T. and C. R. Gandhi "Inhibition of DNA synthesis in cultured hepatocytes by endotoxin-conditioned medium of activated stellate cells is transforming growth factor-beta and nitric oxide-independent." Br J Pharmacol. 2001 Aug;133(7):1125-33.
55. Vespasiani-Gentilucci, U., S. Carotti, et al. "Hepatic toll-like receptor 4 expression is associated with portal inflammation and fibrosis in patients with NAFLD." Liver Int. 2015 Feb;35(2):569-81. doi: 10.1111/liv.12531. Epub 2014 Apr 5.
56. Vonlaufen, A., P. A. Phillips, et al. "Isolation of quiescent human pancreatic stellate cells: a promising in vitro tool for studies of human pancreatic stellate cell biology." Pancreatology. 2010;10(4):434-43. doi: 10.1159/000260900. Epub 2010 Aug 20.
57. Wan, Y., S. Jiang, et al. "Betulinic acid and betulin ameliorate acute ethanol-induced fatty liver via TLR4 and STAT3 in vivo and in vitro." Int Immunopharmacol. 2013 Oct;17(2):184-90. doi: 10.1016/j.intimp.2013.06.012. Epub 2013 Jun 28.
58. Wang, F., S. Liu, et al. "NF-kappaB inhibition alleviates carbon tetrachloride-induced liver fibrosis via suppression of activated hepatic stellate cells." Exp Ther Med. 2014 Jul;8(1):95-99. Epub 2014 Apr 14.
59. Wang, H. Y., L. Z. Yang, et al. "Hepatocyte growth factor-induced amelioration in chronic renal failure is associated with reduced expression of alpha-smooth muscle actin." Ren Fail. 2012;34(7):862-70. doi: 10.3109/0886022X.2012.687344. Epub 2012 Jun 8.
60. Wei, J., M. Shi, et al. "IkappaB kinase-beta inhibitor attenuates hepatic fibrosis in mice." World J Gastroenterol. 2011 Dec 21;17(47):5203-13. doi: 10.3748/wjg.v17.i47.5203.
61. Wen, F. Q., K. Watanabe, et al. "Cytokines and lipopolysaccharide enhance basal and thrombin-stimulated production of PGI2 by cultured human pulmonary artery smooth muscle cells." Prostaglandins Leukot Essent Fatty Acids. 1997 Mar;56(3):185-92.
62. Weng, H. L., D. C. Feng, et al. "IFN-gamma inhibits liver progenitor cell proliferation in HBV-infected patients and in 3,5-diethoxycarbonyl-1,4-dihydrocollidine diet-fed mice." J Hepatol. 2013 Oct;59(4):738-45. doi: 10.1016/j.jhep.2013.05.041. Epub 2013 Jun 4.
63. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2015.
64. Xing, L., L. Bai, et al. "[Effect of telmisartan on tubulointerstitial injury and expression of PPARgamma in rat renal tissue of IgA nephropathy model]." Zhonghua Yi Xue Za Zhi. 2010 Nov 2;90(40):2860-3.
65. Yamate, J., H. Yasui, et al. "Characterization of newly established tumor lines from a spontaneous malignant schwannoma in F344 rats: nerve growth factor production, growth inhibition by transforming growth factor-beta1, and macrophage-like phenotype expression." Acta Neuropathol. 2003 Sep;106(3):221-33. Epub 2003 Jun 17.
66. Yamate, J., M. Maeda, et al. "Effects of lipopolysaccharide on a macrophage-like cell line (HS-P) from a rat histiocytic sarcoma." J Comp Pathol. 2001 Jul;125(1):15-24.
67. Yamate, J., M. Tajima, et al. "Phenotypic changes in lipopolysaccharide-treated cloned cells derived from transplantable rat malignant fibrous histiocytoma." J Vet Med Sci. 1996 Oct;58(10):1017-20.
68. Yamate, J., Y. Machida, et al. "Effects of lipopolysaccharide on the appearance of macrophage populations and fibrogenesis in cisplatin-induced rat renal injury." Exp Toxicol Pathol. 2004 Oct;56(1-2):13-24.