Vascular Endothelial Growth Factor (VEGF) and Lipopolysaccharide (LPS) and Kidney 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: 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. Vascular endothelial growth factor (VEGF) is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate. Serum concentration of VEGF is high in many diseases such as bronchial asthma and diabetes mellitus, etc. VEGF's normal function is to create new blood vessels during embryonic development, new blood vessels after injury, muscle following exercise, and new vessels to bypass blocked vessels. Overexpression of VEGF can cause disease. Solid cancers cannot grow beyond a limited size without an adequate blood supply, but are able to grow and metastasize with the overexpression of VEGF. Overexpression of VEGF can cause vascular disease in the retina of the eye and other parts of the body, and drugs such as bevacizumab and ranibizumab can inhibit VEGF and control or slow these diseases. Endotoxin lipopolysaccharide (LPS) is a structural component of membranes of gram-negative bacteria and a potent proinflammatory agent. Epidemiologic reports indicate that exposure to endotoxin can cause inflammatory airway diseases in agricultural workers and can exacerbate reactive airway disease in those with asthma and in wheezing children.

[Ma H, Young M, Yang Y. **Vascular Endothelial Growth Factor (VEGF) and Lipopolysaccharide (LPS) and Kidney Literatures.** *Researcher* 2015;7(5):19-27]. (ISSN: 1553-9865). http://www.sciencepub.net/researcher. 4

Key words: vascular endothelial growth factor (VEGF); lipopolysaccharide (LPS); kidney

1. Introduction

Vascular endothelial growth factor (VEGF) is a signal protein produced by animal cells that stimulates vasculogenesis and angiogenesis, which is a part of the system that restores the oxygen supply to tissues when blood circulation is inadequate. VEGF's normal function is to create new blood vessels during embryonic development or after injury, etc. Serum concentration of VEGF is higher than normal in many diseases such as bronchial asthma and diabetes mellitus, etc. VEGF Overexpression can cause disease. Normally the cancers cannot grow beyond a limited size without an adequate blood supply, but the cancers are able to grow and metastasize with a VEGF overexpression. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors on the cell surface that causes the VEGFs to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region and an intracellular portion containing a split tyrosine-kinase domain.

VEGF is a sub-family of the platelet-derived growth factor family in both vasculogenesis and angiogenesis. The VEGF family comprises 5 members in mammals: VEGF-A, VEGF-B, VEGF-C, VEGF-D and placenta growth factor (PGF). VEGF-A stimulates endothelial cell mitogenesis and cell migration, and it is also a vasodilator and increases microvascular permeability and was originally referred to as vascular permeability factor. There are multiple isoforms of VEGF-A from alternative mRNA splicing of a single, 8-exon VEGF-A gene, which are classified into 2: the proximal splice site or distal splice site. VEGF-C is an important inducer of neurogenesis.

VEGF-A production can be induced in cells that are not receiving enough oxygen. Cell will produce hypoxia-inducible factor (HIF) when they are deficient in oxygen, and HIF stimulates VEGF-A release. VEGF-A binds with VEGF receptors on endothelial cells and triggers a tyrosine kinase pathway causing angiogenesis. The endothelial cell will be death and vascular will be regression if the expression of angiopoietin-2 in the absence of VEGF. HIF1-alpha and HIF1-beta are constantly being produced. When the cell becomes hypoxic, HIF1-alpha persists and the HIF1alpha/beta complex stimulates VEGF release. The overexpression of VEGF-A may be an early step in the process of tumor

metastasis.

VEGF-A is released in rheumatoid arthritis in response to TNF-α, increasing endothelial permeability and swelling and also stimulating angiogenesis. VEGF-A is also important in diabetic retinopathy (DR). The microcirculatory problems in the retina of people with diabetes can cause retinal ischaemia, which results in the release of VEGF-A and a switch in the balance of pro-angiogenic VEGF isoforms over the normally expressed VEGF isoforms. VEGF causes the creation of new blood vessels in the retina in eye, and VEGF-A plays a role in the disease pathology of the wet form age-related macular degeneration (AMD). The vascular pathology of AMD shares certain similarities with diabetic retinopathy, although the cause of disease and the typical source of neovascularization differs between the two diseases. Patients suffering from pulmonary emphysema have been found to have decreased levels of VEGF in the pulmonary arteries. In the kidney, increased expression of VEGF-A in glomeruli directly causes the glomerular hypertrophy that is associated with proteinuria. Anti-VEGF therapies are important in the treatment of certain cancers and in age-related macular degeneration. They can involve monoclonal antibodies such as bevacizumab (Avastin), antibody derivatives such as ranibizumab (Lucentis), or orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF: lapatinib (Tykerb), sunitinib (Sutent), sorafenib (Nexavar), axitinib, and pazopanib. THC and cannabidiol both inhibit VEGF and slow Glioma growth. Both antibody-based compounds are commercialized. The first three orally available compounds are commercialized, as well. Bergers and Hanahan concluded in 2008 that anti-VEGF drugs can show therapeutic efficacy in mouse models of cancer and in an increasing number of human cancers. VEGF is also inhibited by thiazolidinediones (used for diabetes mellitus type 2 and related disease), and this effect on granulosa cells gives the potential of thiazolidinediones to be used in ovarian hyperstimulation syndrome. Ranibizumab, a monoclonal antibody fragment (Fab) derived from bevacizumab, has been developed by Genetech for intraocular use.

Endotoxin lipopolysaccharide (LPS) is a structural component of membranes of gram-negative bacteria and a potent proinflammatory agent. Epidemiologic reports indicate that exposure to endotoxin can cause inflammatory airway diseases in agricultural workers and can exacerbate reactive airway disease in those with asthma and in wheezing children. Experimental investigations of humans and mice are consistent with these epidemiologic data and further show that a single exposure to aerosolized LPS can induce airflow obstruction that commences within minutes of challenge and persists for up to 48 hours. In addition to airflow obstruction, inhaled LPS also leads to neutrophil recruitment and the release of proinflammatory molecules, including interleukin (IL), tumor necrosis factor (TNF), and the chemokines macrophage inflammatory protein-2, keratinocyte-derived chemokine. Like LPS, inhalation of coarse, ambient particulate matter may also contribute to the exacerbation of reactive airways disease (Hollingsworth, et al, 2004). Pretreatment with toll-like receptor 4 (TLR4) antagonist inhibits LPS-induced preterm uterine contractility, cytokines, and prostaglandins in rhesus monkeys (Adams Waldorf et al.). Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system. Members of the TLR family are detected on glia, neurons and on neural progenitor cells in which they regulate cell-fate decision.

The immune system is a biological structures and processes within an organism to protect the orgnism from disease. Pathogens can rapidly evolve and adapt, and thereby avoid detection and neutralization by the immune system. Disorders of the immune system can result in autoimmune diseases, inflammatory diseases and cancer, etc. The immune system protects organisms from infection with layered defenses of increasing specificity and physical barriers prevent pathogens such as bacteria and viruses from entering the organism. Both innate and adaptive immunity depend on the ability of the immune system to distinguish between self and non-self molecules.

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

Araujo, I. M., S. C. Abreu, et al. "Bone marrow-derived mononuclear cell therapy in experimental pulmonary and extrapulmonary acute lung injury." Crit Care Med. 2010 Aug;38(8):1733-41. doi: 10.1097/CCM.0b013e3181e796d2.

To hypothesize that bone marrow-derived mononuclear cell (BMDMC) therapy might act differently on lung and distal organs in models of pulmonary or extrapulmonary acute lung injury with similar mechanical compromises. The pathophysiology of acute lung injury differs according to the type of primary insult. DESIGN: Prospective, randomized, controlled, experimental study. SETTING: University research laboratory. BMDMC therapy was effective at modulating the inflammatory and fibrogenic processes in both acute lung injury models; however, survival and lung mechanics and histology improved more in ALIexp. These changes may be attributed to paracrine effects balancing pro- and anti-inflammatory cytokines and growth factors,

because a small degree of pulmonary BMDMC engraftment was observed.

Botero, T. M., C. E. Shelburne, et al. "TLR4 mediates LPS-induced VEGF expression in odontoblasts." J Endod. 2006 Oct;32(10):951-5. Epub 2006 Jul 26.

Lipopolysaccharide (LPS) from gram-negative bacteria cell walls such as Prevotella intermedia and Escherichia coli induce vascular endothelial growth factor (VEGF) expression in odontoblasts, but not in undifferentiated dental pulp cells. CD14 and TLR4 are responsible for LPS signaling in macrophages, but their expression levels and function in dental pulp cells are unknown. We showed here that murine odontoblast-like cells (MDPC-23) express CD14 and TLR4 by immunohistochemistry and flow cytometry. In contrast, undifferentiated dental pulp cells (OD-21) presented low or no expression of these two receptors. MDPC-23 cells showed CD14 and TLR4 up-regulation upon exposure to LPS, as determined by real time PCR. Dominant negative murine TLR4 (DN-mTLR4) transfected MDPC-23 cells did not show upregulated VEGF expression in response to LPS stimulation.

Carlini, R. G., E. J. Alonzo, et al. "Effect of recombinant human erythropoietin on endothelial cell apoptosis." Kidney Int. 1999 Feb;55(2):546-53.

Recombinant human erythropoietin (rHuEPO) induces endothelial cell growth and angiogenesis in vitro. The mechanisms are unknown. Because an increase in endothelial cell survival could play a role in this process, we examined the effect of rHuEPO on lipopolysaccharide (LPS)-induced apoptosis in bovine pulmonary artery endothelial cells (BPAECs). The results suggest that rHuEPO prevents LPS-induced apoptosis in endothelial cells. This protective effect could be an important factor in the action of rHuEPO on vascular endothelium.

Cejudo-Martin, P., J. Ros, et al. "Increased production of vascular endothelial growth factor in peritoneal macrophages of cirrhotic patients with spontaneous bacterial peritonitis." Hepatology. 2001 Sep;34(3):487-93.

Spontaneous bacterial peritonitis (SBP) is a common complication of cirrhotic patients with ascites that usually results in renal failure and death despite the efficacy of the current antibiotic therapy. The pathogenesis of these phenomena is poorly known but it has been related to the production of vasoactive cell mediators locally acting on the splanchnic vasculature. The results, therefore, are consistent with the concept that locally released macrophage-derived VEGF may result in increased vascular permeability and plasma leakage in the peritoneal vessels of cirrhotic patients with SBP.

Gazzaniga, S., L. Gonzalez, et al. "Isolation and molecular characterization of a mouse renal microvascular endothelial cell line." In Vitro Cell Dev Biol Anim. 2004 Mar-Apr;40(3-4):82-8.

Murine endothelial cells (ECs) have proven difficult to obtain and maintain in culture. Long-term maintenance of normal ECs remains a difficult task. In this article we report the establishment of the first cellular line of renal microvascular endothelium obtained from normal tissue. Cells were isolated, cloned, and maintained by serial passages for longer than 24 mo, using endothelial cell growth supplement (ECGS) and gelatin-coated plates. Their morphology and ultrastructure, expression of von Willebrand factor, presence of smooth muscle alpha-actin, vimentin, cytokeratin filaments, capillary structures formed on Matrigel, and some typical ECs surface molecules were the criteria used to characterize cultured ECs. When examined for responsiveness to Shiga toxin-1, 13-20% of cytotoxicity was observed when coincubated with lipopolysaccharides. This cytotoxicity was not observed for normal lung ECs (1G11). Consequently, REC-A4 line retains characteristics of resting microvascular ECs and represents a useful in vitro model to study biological and physiopathological properties of renal endothelium.

Giblin, S. P. and K. S. Midwood "Tenascin-C: Form versus function." Cell Adh Migr. 2015 Jan 2;9(1-2):48-82. doi: 10.4161/19336918.2014.987587.

Tenascin-C is a large, multimodular, extracellular matrix glycoprotein that exhibits a very restricted pattern of expression but an enormously diverse range of functions. Here, we discuss the importance of deciphering the expression pattern of, and effects mediated by, different forms of this molecule in order to fully understand tenascin-C biology. We focus on both post transcriptional and post translational events such as splicing, glycosylation, assembly into a 3D matrix and proteolytic cleavage, highlighting how these modifications are key to defining tenascin-C function.

Harrison, L. M., C. van den Hoogen, et al. "Chemokine expression in the monocytic cell line THP-1 in response to purified shiga toxin 1 and/or lipopolysaccharides." Infect Immun. 2005 Jan;73(1):403-12.

Infections with Shiga toxin (Stx)-producing bacteria are associated with bloody diarrhea and postdiarrheal sequelae, including hemolytic uremic syndrome and central nervous system (CNS)

abnormalities. Stx-induced intestinal, renal, and CNS vascular lesions may involve a localized production of proinflammatory cytokines in target organs, as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta) up-regulate Stx receptor globotriaosylceramide (Gb(3)) expression on vascular endothelial cells. The data suggest that in response to Stx1 and LPS, macrophages may be a source of chemokines that promote tissue damage through leukocyte recruitment and activation.

Jeong, S. J., S. H. Han, et al. "Anti-vascular endothelial growth factor antibody attenuates inflammation and decreases mortality in an experimental model of severe sepsis." Crit Care. 2013 May 27;17(3):R97. doi: 10.1186/cc12742.

Severe sepsis is associated with an unacceptably high rate of mortality. Recent studies revealed elevated levels of vascular endothelial growth factor (VEGF), a potent angiogenic and vascular permeability factor, in patients with sepsis. There was also an association between VEGF levels and sepsis severity. Here we investigate the effects of an anti-VEGF antibody (Bevacizumab, Bev) in an experimental model of sepsis. METHODS: Human umbilical vein endothelial cells (HUVECs), murine cecal ligation and puncture (CLP), and endotoxemia models of sepsis were used. HUVECs were treated with lipopolysaccharide (LPS) and/or Bev, harvested and cytokine mRNA levels determined using a semi-quantitative reverse transcription-polymerase chain reaction assay. Anti-VEGF antibody may be a promising therapeutic agent due to its beneficial effects on the survival of sepsis by decreasing inflammatory responses and endothelial permeability.

Kimura, Y. and M. Sumiyoshi "Anti-tumor and anti-metastatic actions of wogonin isolated from Scutellaria baicalensis roots through anti-lymphangiogenesis." Phytomedicine. 2013 Feb 15;20(3-4):328-36. doi: 10.1016/j.phymed.2012.10.016. Epub 2012 Dec 6.

Tumor growth and metastasis are associated with angiogenesis and lymphangiogenesis through the production of vascular endothelial growth factor (VEGF) or VEGF-C in tumors, and the phosphorylation of VEGF receptor (VEGFR)-2 or VEGFR-3 in vascular endothelial cells or lymphatic endothelial cells (LECs). Tumor-associated macrophages (TAMs) play an important role in tumor lymphangiogenesis, and consequently stimulate metastasis through the lymphatic system to lymph nodes. We examined the effects of wogonin isolated from Scutellaria baicalensis roots on tumor growth and metastasis using a highly metastatic model in osteosarcoma LM8-bearing mice. The anti-tumor and anti-metastatic actions of wogonin may be associated with the inhibition of VEGF-C-induced lymphangiogenesis through a reduction in VEGF-C-induced VEGFR-3 phosphorylation by the inhibition of COX-2 expression and IL-1beta production in TAMs.

Kitamura, S., Y. Maeshima, et al. "Transforming growth factor-beta 1 induces vascular endothelial growth factor expression in murine proximal tubular epithelial cells." Nephron Exp Nephrol. 2003;95(2):e79-86.

Vascular endothelial growth factor (VEGF) is a potent endothelial cell mitogen that promotes angiogenesis, vasculogenesis, and increases vascular permeability. VEGF is expressed in renal tubular epithelial cells and urinary VEGF excretion is increased in various glomerular disorders. However, the mechanisms underlying expression of VEGF in renal tubular epithelial cells have not been fully elucidated. In the present study, we attempted to define a predominant regulator of VEGF expression using a cultured murine renal proximal tubular epithelial cell line (mProx24). The regulatory mechanism may be associated with the progression of tubulointerstitial lesions in renal disorders.

Kobayashi, S. "Applications of LDL-apheresis in nephrology." Clin Exp Nephrol. 2008 Feb;12(1):9-15. doi: 10.1007/s10157-007-0003-8. Epub 2008 Jan 5.

LDL-apheresis (LA) was originally used for familial hyperlipidemia, and then in Japan extended to use for the treatment of patients with peripheral arterial disease (PAD) and nephrotic syndrome due to steroid-resistant focal glomerular sclerosis (FGS). The reason why this treatment is applicable for these disorders is due to the fact that LA exerts its favorable effects beyond the lipid-lowering effect. The main underlying mechanisms, for example, in the case of LA application in patients with PAD are: (1) improvement of hemorheology, (2) improvement of endothelial dysfunction, (3) elevations of serum levels of NO and bradykinin, (4) increase in serum levels of vascular endothelial growth factor, and (5) reduction of adhesion molecules on monocytes. Furthermore, we have reported that LA could have anti-inflammatory effects because LA reduces serum levels of P-selectin, which is known to play an important role in the development of atherosclerosis as well as a reduction of serum C-reactive protein levels as standard biomarker of atherosclerosis. Massive proteinuria is also an important challenge in nephrology.

Liu, J. Y., S. H. Park, et al. "Sorafenib has soluble epoxide hydrolase inhibitory activity, which contributes to its effect profile in vivo." Mol Cancer

Ther. 2009 Aug;8(8):2193-203. doi: 10.1158/1535-7163.MCT-09-0119. Epub 2009 Aug 11.

The advent of multikinase inhibitors targeting the vascular endothelial growth factor (VEGF) receptor has revolutionized the treatment of highly angiogenic malignancies such as renal cell carcinoma. Interestingly, several such inhibitors are commercially available, and they each possess diverse specific beneficial and adverse effect profiles. In examining the structure of sorafenib, it was hypothesized that this compound would possess inhibitory effects on the soluble epoxide hydrolase, an enzyme with pleiotropic effects on inflammation and vascular disease. We now show that sorafenib but not another VEGF receptor targeted inhibitor sunitinib is a potent inhibitor of the human soluble epoxide hydrolase in vitro (K(I) = 17 +/- 4 nmol/L). Furthermore, sorafenib causes the expected in vivo shift in oxylipid profile resulting from soluble epoxide hydrolase inhibition, evidence of a reduction in the acute inflammatory response. Lipopolysaccharide-induced hypotension was reversed with sorafenib but not sunitinib treatment, suggesting that soluble epoxide hydrolase inhibition accounts for at least part of the anti-inflammatory effect of sorafenib.

Messmer, U. K., V. A. Briner, et al. "Basic fibroblast growth factor selectively enhances TNF-alpha-induced apoptotic cell death in glomerular endothelial cells: effects on apoptotic signaling pathways." J Am Soc Nephrol. 2000 Dec;11(12):2199-211.

Endothelial cell damage of glomeruli and kidney arterioles seems to play a pivotal role in several pathologic situations, such as Gram-negative sepsis, glomerulonephritis, and acute renal failure. Bacterial lipopolysaccharide (LPS) and tumor necrosis factor-alpha (TNF-alpha) have been identified as potent inducers of apoptotic cell death in bovine glomerular endothelial cells. Both agents elicited apoptotic DNA laddering within 12 to 24 h. Basic fibroblast growth factor (bFGF) was generally described as a protective factor for endothelial cells against radiation-, TNF-alpha-, and UV-light-induced programmed cell death. Therefore, whether bFGF also affects apoptosis of microvascular endothelial cells was questioned. The results point to a selective bFGF-mediated enhancement of distinct proapoptotic pathways induced by TNF-alpha in glomerular endothelial cells.

Messmer, U. K., G. Winkel, et al. "Glucocorticoids potently block tumour necrosis factor-alpha- and lipopolysaccharide-induced apoptotic cell death in bovine glomerular endothelial cells upstream of caspase 3 activation." Br J Pharmacol. 1999 Aug;127(7):1633-40.

1. Endothelial cell damage in glomeruli and kidney arterioles appears to play a pivotal role in glomerular inflammatory diseases. Glomerular endothelial cells, a specialized microvascular cell type involved in the regulation of glomerular ultrafiltration, die by apoptosis in response to tumour necrosis factor-alpha (TNF-alpha), TNF-alpha/basic fibroblast growth factor (bFGF), TNF-alpha/cycloheximide, and bacterial lipopolysaccharide (LPS). Apoptotic cell death is characterized by extensive DNA cleavage, DNA ladder formation, and characteristic morphological alterations. 2. In search for apoptosis-preventing signals, we identified glucocorticoids as potent death preventing factors. Co-treatment of cells with 10 nM dexamethasone and TNF-alpha, TNF-alpha/bFGF, TNF-alpha/cycloheximide, or LPS blocked roughly 90% of apoptotic cell death in glomerular endothelial cells. 3. Similarly to dexamethasone (TNF-alpha- and LPS-induced apoptosis are prevented with IC50 values of 0.8 and 0.9 nM, respectively), other synthetic and natural forms of glucocorticoids, such as fluocinolone, prednisolone, hydrocortisone, and corticosterone potently inhibited cell death with IC50 values of 0.2, 6, 50 and 1000 nM, for TNF-alpha and 0.7, 8, 100 and 500 nM for LPS, respectively.

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. In order to clarify the role of vascular endothelial growth factor (VEGF) and angiopoietin 1 (Ang-1) in the renal recovery from HUS, we produced a model of mild HUS and examined the renal recovery process. METHODS: We investigated three groups of mice. Group 1 consisted of mice that received an injection of Shiga toxin 2 (Stx2) and lipopolysaccharide (LPS); group 2 consisted of mice that received an injection of low dose of Stx2 and LPS, and group 3 consisted of control mice. RESULTS: Serum Cr levels in group 1 were greater than those in group 2, and all mice in group 1 died, whereas all mice in group 2 remained alive. Endothelial injury at 24 h in group 1 was higher than in group 2. Electron-microscopic findings demonstrated that the endothelial cells formed immature capillary-like lumina from 7 to 28 days with increases in the expression of CD31-positive cells.

Ortega, A., A. Fernandez, et al. "Outcome of acute renal injury in diabetic mice with experimental endotoxemia: role of hypoxia-inducible factor-1

alpha." J Diabetes Res. 2013;2013:254529. doi: 10.1155/2013/254529. Epub 2013 Jul 31.

The role of diabetic nephropathy in the outcome of acute renal injury (AKI) is not well defined. Herein we evaluate the outcome of lipopolysaccharide- (LPS-) induced AKI in streptozotocin-induced diabetes, as well as the potential role of Hypoxia Inducible Factor (HIF-1 alpha) in this condition. Although 6 h after LPS injection all mice developed a decrease in renal function, proteinuric diabetic mice showed a better recovery of this parameter throughout the study (72 h). Both HIF-1 alpha and vascular endothelium growth factor (VEGF) were found to be upregulated in diabetic mice. After LPS injection, all animals showed an upregulation of these factors, although it was higher in the diabetic group. Glycated albumin (GA) was found to upregulate HIF-1 alpha in HK-2 cells, which resulted in increased production of VEGF. Interestingly, LPS cooperated with GA to induce HIF-1 alpha upregulation. In conclusion, diabetic mice display a better recovery of AKI after experimental endotoxemia. Moreover, these animals showed an increased expression of both HIF-1 alpha and VEGF that was reproduced by incubating renal cells with GA. Since VEGF is considered a survival factor for tubular cells, our findings suggest that diabetes displays HIF-1 alpha upregulation that might function as a "precondition state" offering protection from endotoxic AKI.

Ren, X. S., Y. Sato, et al. "Biliary infection may exacerbate biliary cystogenesis through the induction of VEGF in cholangiocytes of the polycystic kidney (PCK) rat." Am J Pathol. 2011 Dec;179(6):2845-54. doi: 10.1016/j.ajpath.2011.08.028. Epub 2011 Oct 18.

Cholangitis arising from biliary infection dominates the prognosis in Caroli's disease. To clarify the influences of bacterial infection on the biliary cystogenesis, in vivo and in vitro studies were performed using the polycystic kidney (PCK) rat as an animal model of Caroli's disease. Cholangitis became a frequent histological finding in aged PCK rats, and neovascularization around the bile ducts also increased in aged PCK rats. Immunohistochemistry revealed that expression of vascular endothelial growth factor (VEGF) was increased in PCK rat biliary epithelium. In vitro, PCK cholangiocytes overexpressed VEGF, and the supernatant of cultured PCK cholangiocytes significantly increased the proliferative activity, migration, and tube formation of cultured rat vascular endothelial cells. Stimulation with lipopolysaccharide (LPS) further induced VEGF expression in PCK cholangiocytes, which might be mediated by signaling pathways involving phosphatidylinositol 3-kinase (PI3K)-Akt and c-Jun N-terminal kinase (JNK). Both LPS and VEGF increased cell proliferative activity in PCK cholangiocytes, and siRNA against VEGF significantly reduced LPS-induced cell proliferation. Thus, LPS-induced overexpression of VEGF in the biliary epithelium may lead to hypervascularity around the bile ducts; concurrently, LPS and VEGF act as cell proliferation factors for cholangiocytes. Biliary infection may thus exacerbate biliary cystogenesis in PCK rats.

Schindler, R., C. A. Dinarello, et al. "Angiotensin-converting-enzyme inhibitors suppress synthesis of tumour necrosis factor and interleukin 1 by human peripheral blood mononuclear cells." Cytokine. 1995 Aug;7(6):526-33.

Administration of angiotensin-converting-enzyme (ACE) inhibitors reduce vascular proliferation following endothelial injury as well as progression of renal disease in various animal models. These effects might be due to interference with cytokines such as interleukin 1 (IL-1) or tumour necrosis factor alpha (TNF) since they have been implicated in regulating the effects of vascular cell growth factors such as fibroblast- and platelet-derived growth factors. We investigated the in vitro synthesis of IL-1 and TNF from human peripheral blood mononuclear cells (PBMC) in the presence of various ACE-inhibitors. Captopril dose-dependently suppressed the IL-1 beta-induced synthesis of TNF by 74% ($P < 0.01$) and the IL-1 beta-induced synthesis of IL-1 alpha by 60% ($P < 0.01$). Cytokine synthesis induced by lipopolysaccharide was less affected. At concentrations suppressing TNF and IL-1, captopril did not reduce the synthesis of complement C3 in the same cells. Enalapril and cilazapril also suppressed cytokine-induced cytokine synthesis. Ramipril, lisinopril, perindopril and spirapril had no significant effect on TNF synthesis suggesting that the effect was not related specifically to the inhibition of ACE. Accumulation of mRNA for IL-1 and TNF were not affected by captopril, suggesting a posttranscriptional effect. We conclude that certain ACE-inhibitors suppress IL-1 and TNF synthesis at a posttranscriptional level and might therefore influence cytokine-mediated cell growth.

Sundaram, J., S. Keshava, et al. "Factor VIIa binding to endothelial cell protein C receptor protects vascular barrier integrity in vivo." J Thromb Haemost. 2014 May;12(5):690-700.

BACKGROUND: Recent studies have shown that factor VIIa binds to endothelial cell protein C receptor(EPCR), a cellular receptor for protein C and activated protein C. At present, the physiologic significance of FVIIa interaction with EPCR in vivo

remains unclear. OBJECTIVE: To investigate whether exogenously administered FVIIa, by binding to EPCR, induces a barrier protective effect in vivo. METHODS: Lipopolysaccharide(LPS)-induced vascular leakage in the lung and kidney,and vascular endothelial growth factor (VEGF)-induced vascular leakage in the skin, were used to evaluate the FVIIa-induced barrier protective effect. Wild-type, EPCR-deficient, EPCR-overexpressing and hemophilia A mice were used in the studies. RESULTS: Administration ofFVIIa reduced LPS-induced vascular leakage in the lung and kidney; the FVIIa-induced barrier protective effect was attenuated in EPCR-deficient mice. The extent of VEGF-induced vascular leakage in the skin was highly dependent on EPCR expression levels. Therapeutic concentrations of FVIIa attenuated VEGF-induced vascular leakage in control mice but not in EPCR-deficient mice.Blockade of FVIIa binding to EPCR with a blocking mAb completely attenuated the FVIIa-induced barrier protective effect. Similarly, administration of protease activated receptor 1 antagonist blocked the FVIIa induced barrier protective effect. Hemophilic mice showed increased vascular permeability, and administration of therapeutic concentrations of FVIIa improved barrier integrity in these mice. CONCLUSIONS: This is the first study to demonstrate that FVIIa binding to EPCR leads to a barrier protective effect in vivo. This finding may have clinical relevance, as it indicates additional advantages of using FVIIa in treating hemophilic patients.

Tai, S. C., G. B. Robb, et al. "Endothelial nitric oxide synthase: a new paradigm for gene regulation in the injured blood vessel." Arterioscler Thromb Vasc Biol. 2004 Mar;24(3):405-12. Epub 2003 Dec 1.

Advances in our understanding of the molecular mechanisms involved in the constitutive and regulated expression of endothelial nitric oxide synthase (eNOS) mRNA expression present a new level of complexity to the study of endothelial gene regulation in health and disease. Recent studies highlight the contribution of both transcription and RNA stability to net steady-state mRNA levels of eNOS in vascular endothelium, introducing a new paradigm to gene regulation in the injured blood vessel. Constitutive eNOS expression is dependent on basal transcription machinery in the core promoter, involving positive and negative protein-protein and protein-DNA interactions. Chromatin-based mechanisms and epigenetic events also regulate expression of eNOS at the transcriptional level in a cell-restricted fashion. Although constitutively active, important physiological and pathophysiologic stimuli alter eNOS gene transcription rates. For instance, eNOS transcription rates increase in response to lysophosphatidylcholine, shear stress, and TGF-beta, among others. Under basal conditions, eNOS mRNA is extremely stable. Surprisingly, posttranscriptional mechanisms have emerged as important regulatory pathways in the observed decreases in eNOS expression in some settings. In models of inflammation, proliferation/injury, oxidized low-density lipoprotein treatment, and hypoxia, eNOS mRNA destabilization plays a significant role in the rapid downregulation of eNOS mRNA levels.

Trichonas, G., A. Manola, et al. "A novel nonradioactive method to evaluate vascular barrier breakdown and leakage." Invest Ophthalmol Vis Sci. 2010 Mar;51(3):1677-82. doi: 10.1167/iovs.09-4193. Epub 2009 Oct 29.

PURPOSE: To identify a novel, sensitive, nonradioactive leakage assay that can be used in the assessment of retinal vascular permeability in rats and mice. METHODS: Breakdown of the vascular barrier was induced by vascular endothelial growth factor (VEGF), lipopolysaccharide (LPS), or diabetes. Biotinylated bovine serum albumin (bBSA) was administered as a tracer. After perfusion with lactated Ringer's solution, extravasated bBSA was detected with immunoprecipitation and Western blot analysis or sandwich ELISA. The results were then normalized against the final bBSA plasma concentration, the circulation time, and the protein concentration of the tissue. RESULTS: Six hours after VEGF injection, BRB breakdown was quantified in the injected eye and was 2.5-fold higher than in the contralateral phosphate-buffered saline (PBS)-injected eye ($n = 6$ rats, $P < 0.01$). Intravitreal LPS injection induced severe inflammation in the directly injected eye and moderate inflammation in the contralateral untreated eye. Leakage was six- and threefold higher, respectively, compared with that in the untreated control animals ($n = 5$ rats, $P < 0.01$). Nine-month diabetic rats had a threefold increase in vascular leakage compared with age-matched control animals ($n = 6$ retinas, $P < 0.05$).

van Meurs, M., P. Castro, et al. "Adiponectin diminishes organ-specific microvascular endothelial cell activation associated with sepsis." Shock. 2012 Apr;37(4):392-8. doi: 10.1097/SHK.0b013e318248225e.

Experimental sepsis was induced in male C57BL/6j, adiponectin-deficient mice (ADPNKO), and wild-type littermates by i.p. injection of 16 mg/kg lipopolysaccharide or cecal ligation and puncture. Blood and tissue samples were harvested 24 h after model induction. Circulating adiponectin is reduced in mice with endotoxemic challenge and after cecal

ligation and puncture compared with healthy control mice. Quantitative reverse transcriptase-polymerase chain reaction for adiponectin reveals a pattern of response that is both model- and organ-specific. When challenged with sepsis, adiponectin deficiency results in increased expression of endothelial adhesion and coagulation molecules in the lung, liver, and kidney as quantified by reverse transcriptase-polymerase chain reaction, increased macrophage and neutrophil infiltration by immunohistochemistry, and vascular leakage in the liver and kidney. Adiponectin-deficient mice have reduced survival following cecal ligation and puncture and increased blood levels of interleukin 6, soluble vascular endothelial growth factor receptor 1, and soluble endothelial adhesion molecules E-selectin and intercellular adhesion molecule 1. Finally, ADPNKO promoted end-organ injury in the liver and kidney, whereas the lungs were not affected.

Xu, C., A. Chang, et al. "TNF-mediated damage to glomerular endothelium is an important determinant of acute kidney injury in sepsis." Kidney Int. 2014 Jan;85(1):72-81. doi: 10.1038/ki.2013.286. Epub 2013 Jul 31.

Severe sepsis is often accompanied by acute kidney injury (AKI) and albuminuria. Here we studied whether the AKI and albuminuria associated with lipopolysaccharide (LPS) treatment in mice reflects impairment of the glomerular endothelium with its associated endothelial surface layer. LPS treatment decreased the abundance of endothelial surface layer heparan sulfate proteoglycans and sialic acid, and led to albuminuria likely reflecting altered glomerular filtration permselectivity. LPS treatment decreased the glomerular filtration rate (GFR), while also causing significant ultrastructural alterations in the glomerular endothelium. The density of glomerular endothelial cell fenestrae was 5-fold lower, whereas the average fenestrae diameter was 3-fold higher in LPS-treated than in control mice. The effects of LPS on the glomerular endothelial surface layer, endothelial cell fenestrae, GFR, and albuminuria were diminished in TNF receptor 1 (TNFR1) knockout mice, suggesting that these LPS effects are mediated by TNF-alpha activation of TNFR1. Indeed, intravenous administration of TNF decreased GFR and led to loss of glomerular endothelial cell fenestrae, increased fenestrae diameter, and damage to the glomerular endothelial surface layer. LPS treatment decreased kidney expression of vascular endothelial growth factor (VEGF). Thus, our findings confirm the important role of glomerular endothelial injury, possibly by a decreased VEGF level, in the development and progression of AKI and albuminuria in the LPS model of sepsis in the mouse.

Yang, R. B., C. K. Ng, et al. "Identification of a novel family of cell-surface proteins expressed in human vascular endothelium." J Biol Chem. 2002 Nov 29;277(48):46364-73. Epub 2002 Sep 21.

Vascular endothelial cells (EC) play a key role in a variety of pathophysiologic processes, such as angiogenesis, inflammation, cancer metastasis, and vascular diseases. As part of a strategy to identify all genes expressed in human EC, a full-length cDNA encoding a potential secreted protein harboring 10 epidermal growth factor (EGF)-like domains and one CUB domain at the carboxyl terminus (termed, SCUBE1 for Signal peptide-CUB-EGF-like domain containing protein 1) was identified. SCUBE1 shares homology with several protein families, including members of the fibrillin and Notch families, and the anticoagulant proteins, thrombomodulin and protein C. SCUBE1 mRNA is found in several highly vascularized tissues such as liver, kidney, lung, spleen, and brain and is selectively expressed in EC by in situ hybridization. SCUBE1 is a secreted glycoprotein that can form oligomers and manifests a stable association with the cell surface. A second gene encoding a homologue (designated SCUBE2) was also identified and is expressed in EC as well as other cell types. SCUBE2 is also a cell-surface protein and can form a heteromeric complex with SCUBE1. Both SCUBE1 and SCUBE2 are rapidly down-regulated in EC after interleukin-1beta and tumor necrosis factor-alpha treatment in vitro and after lipopolysaccharide injection in vivo.

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References

1. Araujo, I. M., S. C. Abreu, et al. "Bone marrow-derived mononuclear cell therapy in experimental pulmonary and extrapulmonary acute lung injury." Crit Care Med. 2010 Aug;38(8):1733-41. doi: 10.1097/CCM.0b013e3181e796d2.
2. Botero, T. M., C. E. Shelburne, et al. "TLR4 mediates LPS-induced VEGF expression in odontoblasts." J Endod. 2006 Oct;32(10):951-5. Epub 2006 Jul 26.
3. Carlini, R. G., E. J. Alonzo, et al. "Effect of recombinant human erythropoietin on endothelial cell apoptosis." Kidney Int. 1999 Feb;55(2):546-53.
4. Cejudo-Martin, P., J. Ros, et al. "Increased production of vascular endothelial growth factor in peritoneal macrophages of cirrhotic patients with spontaneous bacterial peritonitis." Hepatology. 2001 Sep;34(3):487-93.
5. Gazzaniga, S., L. Gonzalez, et al. "Isolation and molecular characterization of a mouse renal microvascular endothelial cell line." In Vitro Cell Dev Biol Anim. 2004 Mar-Apr;40(3-4):82-8.

6. Giblin, S. P. and K. S. Midwood "Tenascin-C: Form versus function." Cell Adh Migr. 2015 Jan 2;9(1-2):48-82. doi: 10.4161/19336918.2014.987587.
7. Harrison, L. M., C. van den Hoogen, et al. "Chemokine expression in the monocytic cell line THP-1 in response to purified shiga toxin 1 and/or lipopolysaccharides." Infect Immun. 2005 Jan;73(1):403-12.
8. Jeong, S. J., S. H. Han, et al. "Anti-vascular endothelial growth factor antibody attenuates inflammation and decreases mortality in an experimental model of severe sepsis." Crit Care. 2013 May 27;17(3):R97. doi: 10.1186/cc12742.
9. Kimura, Y. and M. Sumiyoshi "Anti-tumor and anti-metastatic actions of wogonin isolated from Scutellaria baicalensis roots through anti-lymphangiogenesis." Phytomedicine. 2013 Feb 15;20(3-4):328-36. doi: 10.1016/j.phymed.2012.10.016. Epub 2012 Dec 6.
10. Kitamura, S., Y. Maeshima, et al. "Transforming growth factor-beta 1 induces vascular endothelial growth factor expression in murine proximal tubular epithelial cells." Nephron Exp Nephrol. 2003;95(2):e79-86.
11. Kobayashi, S. "Applications of LDL-apheresis in nephrology." Clin Exp Nephrol. 2008 Feb;12(1):9-15. doi: 10.1007/s10157-007-0003-8. Epub 2008 Jan 5.
12. Liu, J. Y., S. H. Park, et al. "Sorafenib has soluble epoxide hydrolase inhibitory activity, which contributes to its effect profile in vivo." Mol Cancer Ther. 2009 Aug;8(8):2193-203. doi: 10.1158/1535-7163.MCT-09-0119. Epub 2009 Aug 11.
13. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
14. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
15. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7 - 15.
16. 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.
17. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11.Nature and science 2007;5(1):81-96.
18. Messmer, U. K., G. Winkel, et al. "Glucocorticoids potently block tumour necrosis factor-alpha- and lipopolysaccharide-induced apoptotic cell death in bovine glomerular endothelial cells upstream of caspase 3 activation." Br J Pharmacol. 1999 Aug;127(7):1633-40.
19. Messmer, U. K., V. A. Briner, et al. "Basic fibroblast growth factor selectively enhances TNF-alpha-induced apoptotic cell death in glomerular endothelial cells: effects on apoptotic signaling pathways." J Am Soc Nephrol. 2000 Dec;11(12):2199-211.
20. National Center for Biotechnology Information, U.S. National Library of Medicine**.** http://www.ncbi.nlm.nih.gov/pubmed. 2015.
21. 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.
22. Ortega, A., A. Fernandez, et al. "Outcome of acute renal injury in diabetic mice with experimental endotoxemia: role of hypoxia-inducible factor-1 alpha." J Diabetes Res. 2013;2013:254529. doi: 10.1155/2013/254529. Epub 2013 Jul 31.
23. Ren, X. S., Y. Sato, et al. "Biliary infection may exacerbate biliary cystogenesis through the induction of VEGF in cholangiocytes of the polycystic kidney (PCK) rat." Am J Pathol. 2011 Dec;179(6):2845-54. doi: 10.1016/j.ajpath.2011.08.028. Epub 2011 Oct 18.
24. Schindler, R., C. A. Dinarello, et al. "Angiotensin-converting-enzyme inhibitors suppress synthesis of tumour necrosis factor and interleukin 1 by human peripheral blood mononuclear cells." Cytokine. 1995 Aug;7(6):526-33.
25. Sundaram, J., S. Keshava, et al. "Factor VIIa binding to endothelial cell protein C receptor protects vascular barrier integrity in vivo." J Thromb Haemost. 2014 May;12(5):690-700.
26. Tai, S. C., G. B. Robb, et al. "Endothelial nitric oxide synthase: a new paradigm for gene regulation in the injured blood vessel." Arterioscler Thromb Vasc Biol. 2004 Mar;24(3):405-12. Epub 2003 Dec 1.
27. Trichonas, G., A. Manola, et al. "A novel nonradioactive method to evaluate vascular barrier breakdown and leakage." Invest Ophthalmol Vis Sci. 2010 Mar;51(3):1677-82. doi: 10.1167/iovs.09-4193. Epub 2009 Oct 29.
28. van Meurs, M., P. Castro, et al. "Adiponectin diminishes organ-specific microvascular endothelial cell activation associated with sepsis." Shock. 2012 Apr;37(4):392-8. doi: 10.1097/SHK.0b013e318248225e.
29. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2015.
30. Xu, C., A. Chang, et al. "TNF-mediated damage to glomerular endothelium is an important determinant of acute kidney injury in sepsis." Kidney Int. 2014 Jan;85(1):72-81. doi: 10.1038/ki.2013.286. Epub 2013 Jul 31.
31. Yang, R. B., C. K. Ng, et al. "Identification of a novel family of cell-surface proteins expressed in human vascular endothelium." J Biol Chem. 2002 Nov 29;277(48):46364-73. Epub 2002 Sep 21.