There is growing evidence that the coagulation system co-evolved with the innate immune system. There is a remarkable degree of integration in their signaling pathways and regulatory circuits following tissue injury and microbial invasion: inflammatory mediators generate procoagulant signals and intravascular thrombosis activates multiple components of the innate immune system. The nexus between coagulation and inflammation is most obviously demonstrated by the successful use of recombinant activated protein C (APC) for the treatment of sepsis.

Blood coagulation is an important mechanism against bleeding. The formation of a platelet plug provides the initial occlusion of a vascular lesion. Blood coagulation is controlled by several coagulant and anticoagulant mechanisms essential to maintain the fluidity of the blood. The protein C anticoagulant pathway is an important anticoagulant mechanism, that also controls inflammatory responses and potentially decreases endothelial cell apoptosis in response to inflammatory cytokines and ischemia.

The essential components of this pathway are thrombin, thrombomodulin (TM), the endothelial cell protein C receptor (EPCR), protein C (PC) and proteins S (PS). Protein C is the key component of this pathway. It circulates as a proenzyme that is activated by thrombin bound to the endothelial membrane protein TM. When bound to TM, thrombin has reduced procoagulant activity. Activated protein C (APC) cleaves and inhibits several coagulation cofactors, hereby down-regulating the activity of the coagulation system. APC function is facilitated by its cofactor PS. APC also affects the fibrinolytic pathway by neutralizing the plasminogen activator inhibitor 1 (PAI-1).

Components of the protein C pathway have a wide range of biological effects other than those strictly referred to as being anticoagulant. For example, the lectin domain of TM has anti-inflammatory properties, down-regulating NF kappa-beta and the MAP kinase pathways and decreases leukocyte adhesion and extravasation. Both protein C and APC directly inhibit the adhesion of neutrophils to the endothelial cell surface and the trans-migration of neutrophils.

Furthermore, APC plays an important role in the inhibition of inflammation in the gastric mucosa in patients with Helicobacter pylori infection. APC protects the vasculature by blocking p53-mediated apoptosis in ischemic cerebral vasculature. TM regulates the anti-inflammatory capacities of APC. On its turn, TM has additional physiological functions such as regulation of fibrinolysis, cell adhesion, embryonic development, and tumor growth. Soluble TM released from endothelial cell surfaces can be detected in plasma and urine and high soluble TM levels indicate injury and/or enhanced turnover of the endothelium. TM is expressed on both the endothelium and tumor cells in several cancers and loss of TM expression correlates with a more malignant profile with poorer prognosis.

Inflammation has an important impact on the protein C pathway since both TM and EPCR gene transcription can be down regulated by inflammatory cytokines. Protein S function is also down regulated by inflammation. The cross talk between blood coagulation and inflammation is well studied in severe sepsis where blood coagulation is activated and protein C is consumed. The drop in the plasma level of protein C is a negative feedback loop initiated to limit the extent of blood coagulation.

Please visit our website for more information or to download previous issues of HycultScope.

www.hbt.nl
TECHNICAL NOTE

Oxidized phospholipids: Important mediators of chronic vascular inflammation

Oxidative stress and lipid peroxidation are characteristic features of atherosclerosis. Enzymatic or non-enzymatic oxidation of polyunsaturated fatty acids within phospholipid molecules generates oxidized phospholipids (OxPL) known to accumulate in vessel wall in vivo. OxPL demonstrate a variety of biological activities relevant to atherosclerosis such as stimulation of endothelial cells to bind monocytes but not neutrophils, which mimicks mononuclear cell specificity of atherosclerosis. OxPL stimulate induction of genes related to atherothrombosis, such as MCP-1, KC/IL-8, MIP-1alpha, MIP-1beta, RANTES and tissue factor both in vitro and in vivo. In addition, specific OxPL are ligands for scavenger receptor CD36 or mimick inflammatory and pro-aggregant effects of platelet-activating factor. OxPL seem to activate cells via receptor-mediated and non-receptor mechanisms leading to elevation of cAMP and cytosolic Ca2+ levels, activation of protein kinase C, ERK1/2 kinases, PI-3-kinase, c-Src, R-Ras, Rac and Cdc40-dependent pathways. Induction of specific protein synthesis by OxPL is mediated by several transcription factors, including EGR-1, NFAT, CREB, STAT3 and SREBP. These recent findings suggest that OxPL are not merely by-products but also important mediators of chronic vascular inflammation.

VN Bochkov, PhD, Department of Vascular Biology and Thrombosis Research, Vienna University, Vienna, Austria.

OXIDIZED APC
Cat. # Specificity  Quantity
HM2035 Oxidized APC (OxPAPC), 1 mg  Unique
HM2036 Oxidized APC (OxPAPC), 5 mg  Unique

Please inquire for other oxidized phospholipids and controls (PAPC and DMPC).

The protein C anticoagulant pathway: the nexus between coagulation and inflammation

Continued from page 1

protein C is considered to contribute to the development of micro-vascular thrombosis. In addition, the expression levels of TM and EPCR on endothelium decrease during sepsis. APC can counteract the deleterious effects associated with sepsis. A study using recombinant APC treatment of severe sepsis led to a 19% reduction in the relative risk of death and an absolute reduction of 6%.

The innate immune system and the blood coagulation system originate from a common ancestor which explains the cross-talk between these two systems. Ficolins, a group of proteins that are involved in the complement mediated host defense through nonself-recognition by vertebrates, are most probably intermediates in the evolution from invertebrate innate immunity to the vertebrate blood coagulation system. Further understanding and unraveling of the link between coagulation and innate immunity may help to gain more insight in the study and treatment of severe infections.

TGM Lauterslager, PhD, Hycult biotechnology, Uden, The Netherlands.

For more information and references, please visit our website.
The junctional adhesion molecule (JAM)-A is not only involved in maintenance of endothelial cell layer integrity via tight junctions, but is also involved in the mononuclear cell recruitment. The latter suggests a functional contribution of JAM-A to atherogenesis. JAMs are proteins of about 30-40 kDa and members of the immunoglobulin superfamily. JAMs are important for a variety of cellular processes, including tight junction assembly, leukocyte transmigration, platelet activation, angiogenesis and virus binding. JAM-A (also known as JAM, JAM-1 or F11 R) is expressed by endothelial and epithelial cells, platelets, neutrophils, monocytes, lymphocytes and erythrocytes. The extracellular domains of JAM-A molecules are involved in the homophilic interaction linking adjacent endothelial or epithelial cells and thereby stabilizing intracellular junctions, especially around tight junction strands. JAM-A was first discovered in platelets as the receptor of the platelet aggregation stimulatory monoclonal antibody F11. Binding of F11 to human platelets caused granule secretion, fibrinogen binding and platelet aggregation. Interestingly, autoantibodies against JAM-A have been detected in patients with thrombocytopenia. JAM-A also plays an important role in leukocyte transmigration. Leukocyte transmigration can be blocked by antibodies and by soluble JAM-A/Fc fusion proteins. However, the precise mechanisms of JAM-A action during leukocyte transmigration are not yet fully understood. Homophilic JAM-A interactions between leukocytes and the endothelium but also heterophilic interactions of JAM-A with the β2-integrin leukocyte function-associated antigen-1 (LFA-1) are considered to actively guide leukocytes during transmigration. Tumor necrosis factor is suggested to play an additional role by inducing disassembly of JAM-A from the junctions. This leads to junction loosening and redistribution of JAM-A to the apical surface of endothelial cells thereby becoming available for adhesive interactions with leukocyte LFA-1. Several studies imply a role of JAM-A in the initiation of atherosclerosis, since JAM-A is upregulated on early atherosclerotic endothelium and adhesion of activated platelets on activated endothelium is mediated by homophilic interactions of JAM-A. At atherosclerosis-prone sites, the intracellular adhesion molecule-1 (ICAM-1) is upregulated and inflammatory T lymphocytes are attracted. Soluble forms of JAM-A antagonize LFA-1/ICAM-1 interaction of LFA-1 expressing leukocytes to endothelial ICAM-1. Interestingly, JAM-A is also involved in neointimal lesion formation and monocyte infiltration after arterial injury in atherosclerosis-prone mice. In this context, hyperlipidemia upregulates JAM-A on atherosclerotic endothelium. Therefore, it would be very interesting to further investigate the role of JAM-A in blood vessel condition and to further elucidate the role of JAM-A in inflammatory thrombosis and atherogenesis.

For more information and references, please visit our website.
HycultScope is distributed by:

Cell Sciences, Inc.
480 Nponset Street, Building 12A
Canton, MA 02021
USA
T 888-769-1246 (Toll free)
T 781-828-6010
F 781-828-0342
E info@cellsciences.com
W www.cellsciences.com

For research purposes only. Not for drug, diagnostic or other use.