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Proteinases of the Blood Coagulation System and Fibrinolysis as Cell Regulators

The contemporary concept of blood coagulation is based on the enzymatic theory of A. A. Schmidt (1872) and a model considering the blood coagulation process as a cascade of consecutive proteolytic reactions. The blood coagulation cascade proceeds through an external coagulation pathway, which is induced by tissue factor or through an internal pathway, which is triggered by the activation of the contact phase of the coagulation (Davie and Ratnoff (1964); McFarlan (1964)). This sequence of processes results in the formation of the key enzyme of blood coagulation—thrombin.

There is strong evidence for a leading role of a subendothelial tissue factor in the initiation of the blood coagulation process. An endothelial injury caused by bacterial toxins, virus infections, cytokines, or oxidized lipoproteins results in exposure of the tissue factor to the surface of endothelial cells and also in activation of monocytes. These processes stimulate blood coagulation and cause an inflammatory response. In the course of the inflammatory response, the transmembrane tissue factor (representative of class II cytokine receptors) binds the blood coagulation factor VIIa, this triggering the sequence of intracellular reactions resulting in phosphorylation of myogen activated protein kinases (MAP-kinases). The phosphorylation of MAP-kinases leads to proliferation, adhesion, and migration of cells.

In recent times, the traditional view on the role of such serine proteinases as thrombin, blood coagulation factor Xa, factor VIIa (as a complex with tissue factor), active protein C, and urokinase has significantly changed. These proteins were shown to exhibit properties of cell regulators affecting embryogenesis, angiogenesis, inflammation, wound healing, thrombosis, atherogenesis, and tumor genesis. These serine proteinases serve as signal molecules controlling cell functions through specific membrane receptors. New proteinase activated receptors (PARs) have been discovered and cloned. All PAR representatives fall into a superfamily of integral G-protein coupled membrane receptors, which have seven transmembrane domains. Thrombin and a number of other serine proteinases control cell activity by cleaving a single peptide bond in the extracellular domain of the PAR, resulting in the appearance of a new N-terminal site of the receptor, which serves as its agonist.

Although to date only four representatives of the PAR family have been cloned (PAR-1, -3, and -4, the thrombin receptors, and PAR-2, the receptor of the blood coagulation factor Xa, factor VIIa with tissue factor, trypsin, mast cell tryptase, and membrane type serine proteinase 1 (MT-SP-1)), the family is expected to comprise a great number of receptors and their agonists.

It is noteworthy that a single proteinase can interact with receptors of several types. For example, there is information concerning at least two receptors of factor Xa on endothelial cells—the non-cleaving endothelial proteinase receptor (EPR-1) and PAR-2. A new cascade mechanism of cell activation by factor Xa includes complementary binding of the enzyme to the EPR-1 receptor and then a local proteolysis of the PAR-2 receptor.

Expression of PARs increases at sites of vascular injury, inflammation, atherogenesis, tissue reparation, and in the microenvironment of a tumor. The activation of PARs initiates a number of signal transmission mechanisms, which result in the activation of transcription factors controlling the expression of tissue factor, adhesive proteins, growth factors, cytokines, and other ligands involved in the processes of inflammation and the migration and proliferation of cells. Thus, the proteinases of the blood coagulation system and fibrinolysis, binding to the membrane receptors and activating the signal systems, play an important role in such processes as embryogenesis, angiogenesis, inflammation, wound healing, atherogenesis, and growth and metastatic spread of tumors.

The articles included in the present issue are prepared by highly skilled specialists in the field of hemostasis and reflect the modern trends in the biochemistry of blood coagulation and fibrinolysis. In the beginning, reviews are presented devoted to general problems of blood coagulation, i.e., the role of tissue factor in the initiation of thrombinogenesis (S. Butenas and K. G. Mann), functions of the contact coagulation phase factors (G. A. Yarovaya, T. B. Blokhina, and A. E. Neshkova), cell effects of tissue factor, factor X, and factor VII in embryogenesis (M. Aasrum and H. Prydz), and genetic mechanisms of hereditary disorders in hemostasis (L. I. Patrushev). Then reviews are presented considering mechanisms of thrombin interaction with cells involved in blood coagulation (F. A. Ofosu), inflammation, vascu-

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lar injury, and tumor genesis (C. K. Derian, B. P. Damiano, M. R. D'Andrea, and P. Andrade-Gordon), mechanisms of the relation between the processes of blood coagulation and inflammation (T. N. Dugina, E. V. Kiseleva, I. V. Chistov, B. A. Umarova, and S. M. Strukova), and mechanisms of the thrombin induced permeability of endothelium (N. B. Bogacheva, J. G. N. Garsia, and A. D. Verin). These reviews are logically connected with the review by J. Fenton et al., where the antithrombic action of statins is explained by the suppression of the expression of tissue factor, PAR-1, and the plasminogen activator inhibitor (PAI-1). In conclusion, the issue presents reviews discussing catalytic mechanisms of proteinases involved in fibrinolysis: regulation of the activity and physiological functions of the main components of fibrinolysis (A. B. Dobrovol'skii and E. V. Titaeva), urokinase as an activator of receptor systems regulating the adhesion and migration of cells (V. V. Stepanova and V. A. Tkachuk), a role of plasminogen activators in vessel remodeling and angiogenesis (Ye. V. Parfyonova, O. S. Plekhanova, and V. A. Tkachuk), molecular interactions between matrix metalloproteinases and fibrinolysis system components affecting cellular fibrinolysis (G. R. Lainen), and two reviews devoted to regulators of hemostasis in bloodsucking (L. L. Zavalova, A. V. Basanova, and I. P. Baskova).

The articles presented demonstrate that receptors, enzymes, and their protein regulators, which are usually considered as components of the systems of blood coagulation and fibrinolysis, are involved in a wider spectrum of physiological processes. They control activity of various blood and vessel cells, affect tissue morphogenesis, and take part in the development of various pathological processes, in particular, malignant growth. We hope that the detailed discussion of the main recent achievements in the field of structure, functions, and mechanisms of action of proteins involved in the systems of blood coagulation and fibrinolysis will allow better understanding of the relationship between the systems of hemostasis, immunity, and morphogenesis in the human body and stimulate the appearance of new ideas and attract new scientists to this field of research.

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