S4

Extravascular Fibrinolysis in Cancer Invasion, Inflammation and Wound Healing

Masugi Maruyama, MD., PhD.

Department of Physiology, Miyazaki Medical College, Miyazaki, Japan

In closed blood vessel system, like our circulatory system, bleeding is the most dangerous phenomenon. To prevent bleeding, very complex mechanism has been developed in a long long history of evolution. Once the blood vessel is injured and the blood components encounter the subendothelial structure or surrounding tissue, rapid and strong hemostatic mechanism will be initiated. Platelets and blood coagulation system are major players in this mechanism, forming firm thrombus in the injured area. The reaction involves positive feedback mechanism and tends to produce excessive thrombus in the injured area. The excessive thrombus may cause vascular obstruction such as myocardial infarction and cerebral infarction. To counterbalance this thrombotic tendency, fibrinolytic system plays a critical role in the end phase of thrombus formation.

As soon as coagulation system is activated, fibrinolytic system is simultaneously activated, releasing tissue-type plasminogen activator(tPA) from surrounding intact vascular endothelial cells. Released tPA is adsorbed in fibrin network of thrombus, then converts proenzyme, plasminogen, to a broad spectrum protease, plasmin. Plasmin hydrolysis excessive fibrin clot into fibrin-degradation-products(FDP), forming an appropriate sized thrombus to stop bleeding or cover the injured area.

Fibrinolytic system also plays important roles in extravascular space, regulating cell movement and adhesion. Since mid 80s, the mechanism has

been well researched in cancer cell invasion and metastasis. In this extravascular fibrinolysis, major components are urokinase-type plasminogen activator (uPA) and it's cell surface receptor, uPA receptor(uPAR). Along the advancing tip of cancer cell surface, uPAR is upregulated and uPA secreted in both autocrine and paracrine manner binds to uPAR. The bound uPA then converts plasminogen into plasmin. Plasmin is a key enzyme to degrade extracellular matrix proteins in the very close proximity of advancing cancer cell, forming some space for the cell moves in.

Recently, it has been found that extravascular fibrinolysis is also important for inflammation and wound healing. Inflammation and wound healing are very complex phenomenon, involving a number of processes. The processes include migration and proliferation of various cells, such as inflammatory cells, parenchymal cells and connective tissue cells. Accumulated evidences indicate the significant role of fibrinolytic system in not only matrix degradation but also cell proliferation, adhesion and migration.

In this presentation, I would like to summarize recent findings of so-called extravascular fibrinolysis in cancer invasion, inflammation and wound healing.