Abstract

Originally, P-selectin played an important role in the vascular response to inflammation. In the first half of the nineties there were published papers demonstrated that P-selectin also played a significant role in blood coagulation and thrombosis. In these experiments anti-P-selectin antibodies blocked fibrin formation and suppressed the developing of thrombus. Shortly thereafter, P-selectin was shown to upregulate tissue factor (TF) generation on monocytes. The active role of P-selectin in hemostasis was supported also with our findings that overexpression of soluble P-selectin (sP-sel) can induce a procoagulant state in plasma/blood. I have focused in my postgraduate study on pathophysiology of sP-sel , its role in formation of microparicles (MPs) bearing TF.

In the detail study of sP-sel we found, that procoagulant state in plasma is due to procoagulant MPs, part of them contained TF. We confirmed that recently characterized "blood-borne" TF could be induced by sP-sel. Moreover, because the production of microparticles was suppressed by inhibiting antibody against PSGL-1 (receptor of P-selectin on leukocytes), we proposed the origin of MPs from leukocytes. Recruitment of TF-bearing MPs from monocytes I demonstrated later with FACS screening of presence of specific CD-markers. I realized that there might be instances where the procoagulant potential of sP-sel could be of benefit. This includes the bleeding disease hemophilia A caused by a deficiency of coagulation factor VIII. I treated transgenic mice with complete dysfunction of FVIII with sP-sel-Ig, which was known to increase coagulation potential in wild –type mice. In contrast to the infusion of control immunoglobin, within a few hours sP-sel-Ig improved clotting parameters tested. In blood from both hemophilia A mice and patients with hemophilia A treated with sP-sel-Ig *in vitro,* increases in microparticle production and TF activity were observed. I have also followed the purified MPs infused in *vivo* to mice. Their half-life shortened rapidly when an artificial injury was generated by calcium ionophore in microcirculation of *m.cremaster .* MPs were recruiting to the growing thrombus. They use the same mechanisms as platelets and leukocytes thus, interaction between P-SEL A PSGL-1.

The significantly increased levels of sP-sel have been documented in a variety of disease. It might serve also as a predictive risk factor for future cardiovascular events. Persistent higher level of sP-sel was one of reason for studying of procoagulant MPs and TF in patients with coronary syndromes. I found that amount of procoagulant MPs decreased according to the severity of the acute coronary syndrome. The result was surprising since one would expect higher level of MPs; however it correlated with pathophysiology of MPs to recruit rapidly to growing thrombus.

My work contributed to explanation of the role of sP-sel in hemostasis and inspired other projects that clarified sP-sel induced mechanism of formation of MPs from monocytes.