Novel Platelet Functions Beyond Haemostasis

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Platelets play a number of important roles in thrombosis and haemostasis, and its functions have long been considered to be related to these realms. However, recent findings suggest novel functions of platelets beyond the conventional concept of this tiny cell: platelets are required for liver regeneration. Platelets are important in defence against various pathogens. Platelets are related to tumor growth and metastasis. We recently identified a platelet-specific protein, CLEC-2 which plays a critical role in vein-lymphatic vessel separation.

Rhodocytin, purified from snake toxins of *Calloselasma rhodostoma* was found to activate platelets with a pattern similar to that of collagen. Through a series of studies, we found that rhodocytin binds an as-yet unidentified protein leading to platelet activation. We used rhodocytin affinity chromotography and TOF-MASS spectrometry and identified a novel class of platelet activation receptor, c-type lectin-like receptor 2 (CLEC-2), which belongs to c-type lectin superfamily. Although its physiological ligand had not been identified, CLEC-2 attracted attention of researchers as a novel target of anti-platelet drugs because of its ability to stimulate powerful platelet aggregation and its specific expression in platelets and megakaryocytes. We subsequently revealed that the physiological ligand of CLEC-2 is podoplanin, which is a sialoglycoprotein present in renal podocytes and lymphatic endothelial cells. It is also present on the surface of certain tumar cells and is involved in tumor cell induced platelet aggregation and tumar metastasis. Using antibodies against podoplanin or CLEC-2, we demonstrated that platelets serve to facilitate tumor metastasis by way of CLEC-2 and podoplanin interactions.

In order to better understand the role of CLEC-2, we produced CLEC-2 knockout mice, which were lethal at the fetal stage. It had edema, lymphatic vessel dilation, and the presence of blood cells in lymphatic vessels. Thus, CLEC-2 knockout mice have the phenotype of blood vessel-lymphatic vessel mal-separation. We found that growth, migration, and tube formation of lymphatic endothelial cells is inhibited by releasates from platelets activated by the interaction between CLEC-2 on the platelet membrane and podoplanin on lymphatic endothelial cells interactions, and recently found that f BMP-9 which belongs to the family of TGF-, is the major factor in platelet releasates which is responsible for blood vessel-lymphatic vessel separation.

Keywords platelets, metastasis, lymphatics

Conflict of interest No