CBR

The Centre for Blood Research Seminar Series

Wednesday, November 4, 2015
LSC 3 - Life Sciences Centre
2350 Health Sciences Mall
12-1pm

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"The Platelet Release Reaction: Molecules and Mechanism (membrane trafficking in platelets)"

Activated platelets release hundreds of molecules that affect hemostasis, angiogenesis, inflammation, and wound healing. These molecules are stored in three granule types: dense, alpha, and lysosomes, and their release requires SNAREs (Soluble NSF Attachment Protein Receptors). v-SNAREs/VAMPs, on granules, pair with heterodimeric t-SNAREs (Syntaxins and SNAP-23/25s), on the plasma membrane, to mediate membrane fusion. Using platelets from knockout mice and from patients with Familial Hemophagocytic Lymphohistiocytosis (FHL), we are defining the platelet secretory machinery. Platelets from patients lacking Syntaxin-11 show a robust loss of secretion from all three granules. Deletion of VAMP-8, in mouse platelets, attenuates release; however deletion of VAMP-2, -3, and -8 is required for robust defects in hemostasis. SNARE regulators control where, when, and how SNAREs interact. Munc18b is a Syntaxin-11 chaperone required for secretion. Syntaxin Binding Protein 5/Tomosyn-1 regulates VAMP access to t-SNARE heterodimers. Munc13-4 is a docking factor that is especially important for dense granule release. SNARE post-translational modifications also affect function. Phosphorylation of SNAP-23 by IκB Kinase (IKK) controls SNARE complex formation and secretion. Acylation of SNAP-23 and Syntaxin-11 is critical for secretion. From our studies of platelet SNAREs, we have gained insights into other platelet membrane trafficking events, such as endocytosis and autophagy. VAMP-3, Syntaxin-2/4, as well as ADP-Ribosylation Factor 6 (Arf6), contribute to fibrinogen uptake by circulating platelet. Interestingly, platelet endocytosis is also important for platelet spreading and for their response to certain Toll-like Receptor (TLR) agonists and viruses. Our studies of platelet secretion have led to a greater understanding of other forms of membrane trafficking in platelets and have suggested how these dynamic processes contribute to platelet function in circulation. Supported by NIH grant HL56652.

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