VAMP-3-mediated Endocytosis Mediates Platelet Response to Viruses in the Vasculature

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Platelet endocytosis is very important, especially for fibrinogen uptake. Platelets contain several integral membrane proteins called soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptors (SNAREs). Of these SNAREs, the v-SNAREs reside on the granule membrane while the t-SNAREs are present on the plasma membrane. Cellubrevin/VAMP-3, a v-SNARE, is important for endocytosis in other cell types, but its exact role in platelets is not known. VAMP-3 KO platelets were characterized as defective in fluid-phase pinocytosis and receptor-mediated endocytosis. In nucleated dendritic cells, innate immune responses to HIV-1 are mediated by pathogen phagocytosis/endocytosis, degradation to release Toll-Like Receptor (TLR) ligands, and subsequent TLR activation. It was asked whether this process is recapitulated in platelets. Responses to both TLR 7/9 ligands and HIV-1 virions was significantly reduced in the VAMP-3 KO platelets suggesting a requirement for endocytosis of said ligands. Inhibition of responses to HIV-1 virions in the presence of Dynamin-dependent clathrin-mediated endocytosis (e.g. Dynasore) and pH-tropic drugs (e.g. chloroquine and NH4Cl), suggested the need for viral trafficking to and degradation in acidic compartments to release single strand RNA. This activates the TLR7/9 signaling cascade to activate the platelets, leading to the exteriorization of P-Selectin, an adhesion molecule, from the alpha-granules. Through this way, the platelet leukocyte complexes are formed, and they are detected by other immune cells, helping mount a response to the pathogen causing the inflammation. Collectively, these studies present VAMP-3 as a major regulator of platelet endocytosis in mediating both physiological and pathophysiological functions.

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