**Barry Firkin Oration: Platelet receptors: expression, function and shedding**

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Extensive research over several decades has studied the structure and function of adhesion receptors expressed on anucleate platelets, and the mechanisms of how these receptors regulate bleeding and thrombus formation in flowing blood using a wide range of experimental approaches, model systems and analysis of human healthy donor and patient samples associated with a wide range of haematological diseases. As key examples, the platelet adhesive receptor glycoprotein (GP)Ib-IX-V complex, comprised of transmembrane GPIbα disulfide-linked to GPIbβ forming a complex with GPIX and GPV, is an important receptor for binding of von Willebrand factor (VWF) associated with subendothelial matrix or in plasma when exposed to high shear stress, and also the receptor, GPVI which also forms a complex with GPIb-IX-V and binds collagen and other ligands. GPIb-IX-V and GPVI are vital for normal platelet function, and defects of these receptors can cause bleeding/thrombotic complications. Detailed analysis of the biochemistry and amino acid sequences and the structure-function of these receptors using a variety of analytic methods, antibody generation, and assays for expression and platelet activation and adhesive function has identified specific domains involved in ligand binding, complex formation with other receptors, cytoplasmic domains recognizing intracellular cytoskeletal or signalling proteins, and other key interactions regulating expression or function of these receptors. In addition, additional studies have identified and purified specific proteins from rattlesnake, cobra or viper venoms that can either induce VWF binding to GPIbα, or cleave GPIbα and inhibit VWF binding, or bind to GPVI and activate platelets, or lead to shedding of GPVI from platelets. Importantly, further studies have also identified cytoplasmic amino acid sequences in GPIb, GPV and GPVI that bind to intracellular calmodulin, which was subsequently found to regulate ectodomain receptor shedding by membrane-associated A-Disintegrin-And-Metalloproteinase (ADAM) sheddases, including ADAM17 that cleaves GPIbα and ADAM10 that cleaves GPVI. Subsequent studies then investigated the ADAM10-mediated ectodomain shedding of GPVI generating soluble GPVI (sGPVI) in terms of pathways regulating this process, and developing specific reagents and assays for analysing sGPVI levels in human blood plasma and ADAM10 activity on platelets, and how these vary under conditions of elevated shear stress in experimental models and also in patient samples with platelet dysfunction and altered bleeding or thrombotic risk. Ongoing studies are continuing to investigate the regulation of GPIb-IX-V and GPVI expression, function and shedding, and future relevance as biomarkers or therapeutic targets. The recent developments regarding GPIb-IX-V and GPVI effectively illustrate how basic research based on new observations and discoveries can develop over time, leading to new insights and understanding of complex biological systems