Megakaryocyte/platelet-leukocyte interactions – role in thrombopoiesis and thrombosis

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Although direct interactions between megakaryocytes/platelets and leukocytes have long been described, their (patho)physiological consequences remain unclear. Recent studies have proposed that some leukocytes, like neutrophils, "pluck" megakaryocytes to facilitate platelet production in situations when platelet counts are low (thrombocytopenia). Conversely, this process also increases release of immature platelets during a thrombo-inflammatory state, which elevates the risk of recurrent thrombo-ischemic events. Emperipolesis is a physiological process whereby neutrophils do not only attach to megakaryocytes, but are also engulfed while remaining intact. In gray platelet syndrome and COVID-19, conditions both linked to development of cardiovascular disease, elevated emperipolesis is associated with altered platelet maturity and function. Therefore, it is imperative to understand whether emperipolesis drives pro-thrombogenic function of platelets and a thrombo-inflammatory environment.

Neutrophils and platelets also cooperate with each other to promote clot formation. These interactions are called "platelet-neutrophil aggregates" (PNAs). This interaction triggers an adhesive neutrophil phenotype, promoting the release of proteolytic enzymes, endothelial attachment and coagulation activation. Platelet-neutrophil-endothelial crosstalk drives thrombo-inflammation and contributes to ischaemic events, like myocardial infarction and stroke. Yet, there is neither a predictive assay nor a clear pathophysiological understanding of how these PNAs form or contribute to thrombotic outcomes. PNAs are more abundant in patients with myeloproliferative neoplasms, where pro-coagulant platelets trigger NETosis of *JAK2*^{V617F}-mutated neutrophils. However, the mechanisms driving PNA formation and thrombosis are poorly defined.

The student will assess several pathophysiological mechanisms by which leukocytes directly interact with megakaryocytes and platelets.

For the rotation, the student will be trained in approaches optimised in our lab to produce viable platelets in culture and examine different parameters of platelet function, aggregometry, maturity and response to agonists. The impact of leukocytes on platelet production and function will be examined in presence or absence of *JAK2*^{V617F}. The rotation could pave the ground for a PhD investigating the role of leukocytes in thrombopoiesis and thrombosis. The PhD project will be co-supervised by Professor Simon Mendez-Ferrer at the Department of Haematology, to expand the student's training and leverage *JAK2*^{V617F}-mutated animals models and expertise in bone marrow niche and emperipolesis. For PhD, the findings observed in *JAK2*^{V617F} haematopoiesis will be interrogated in the context of emperipolesis and dysfunctional platelet generation associated with grey platelet syndrome. This project could unravel key aspects of thrombopoiesis and thrombosis that have been previously under-recognised, alongside candidate targets to prevent abnormal platelet generation or function.