AUSTRALIAN SOCIETY FOR BIOPHYSICS

Abstract: 85O

Mechanotransduction in Neutrophils

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Hemodynamic forces play major roles in vascular function and homeostasis. Blood content and vessel walls constantly sense and respond to hemodynamic forces, namely shear stress and tensile stress. Understanding the mechanism that controls these events is essential for the prevention and treatment of a wide range of cardiovascular disorders.

My lab is specialised in developing physiologically relevant bioengineered models of the circulatory system to systematically investigate the effect of hemodynamic forces on immune and endothelial cells.

For this presentation, I will share our recent findings on the direct effect of shear stress on neutrophil extracellular trap formation (NETs). Neutrophils are the most abundant type of circulating leukocytes that in addition to contributing to host defence, are recognised as an important driver of chronic inflammatory disorders. One of the main characteristics of neutrophils is their ability to shed their DNA in the form of extracellular traps or NETs. These NETs provide a scaffold for trapping bacteria and different types of blood cells. Consequently, excessive and uncontrolled NETosis leads to the activation of coagulation pathways and is thrombogenic.

In circulation, neutrophils are constantly exposed to hemodynamic forces. However, it is not known how transient changes in hemodynamic forces, for example, an increased shear stress caused by stenosis, could affect their basic biology.

Here, using a combination of microfluidics, live cell imaging, phosphoantibody screening, molecular pharmacology and siRNA gene knockdown techniques, we have studied the effect of shear stress on NETosis and the response of neutrophils to other NET-inducing agents such as LPS, ATP and PMA. Furthermore, we have identified the mechanosensitive ion channels and signalling pathways that control shear-induced NETosis in human neutrophils. Our findings provide further evidence on the mechanisms driven by shear stress and activated mechanosensitive ion channels on NETosis and platelet aggregation in the NET area.