Nature Reviews Nephrology | Published online 15 Jan 2018; doi:10.1038/nrneph.2018.2

SEPSIS

The podoplanin–CLEC2 axis in sepsis

During vascular inflammation, the podoplanin receptor CLEC2 and the fibrin and collagen receptor GPVI on platelets help prevent inflammation-mediated bleeding, but the roles these receptors play in inflammation itself are unclear. Rayes and co-workers investigated the contribution of CLEC2 and GPVI to inflammation in mouse models of inflammation and sepsis, a systemic inflammatory response that can result in multiple organ failure, including acute kidney injury (AKI).

First, the researchers demonstrated that platelets protect against lipopolysaccharide (LPS)-induced inflammation in mice, as experimentally induced thrombocytopaenia (that is, depletion of platelets in the blood) accelerates LPS-induced multiple organ damage. This protective effect is mediated by CLEC2, as platelet-specific deletion of CLEC2 increases the clinical severity of LPS-induced inflammation, including decreased liver and kidney function. Of note, although podoplanin is the only known endogenous ligand for CLEC2 and is highly expressed by podocytes, podocyte-specific deletion of podoplanin did not alter LPS-induced AKI. Second, in mice subjected to caecal ligation and puncture (CLP), a sepsis model that includes bacterial infection, the researchers showed that the interaction of macrophage podoplanin with platelet CLEC2 is required for the recruitment of macrophages to the site of infection to promote bacterial clearance, whereas pharmacological disruption of the podoplanin–CLEC2 axis (using an anti-podoplanin antibody) increased cytokine release from macrophages — exacerbating the cytokine storm — and inhibited immune cell recruitment to the site of infection.

"The demonstration that platelets regulate the inflammatory response in this way is novel and unexpected," says Julie Rayes. "The therapeutic potential of the podoplanin–CLEC2 axis might allow the development of drugs to treat various thrombo-inflammatory and inflammatory diseases as well as cancers."

Grant Otto

> "disruption of the podoplanin–CLEC2 axis … increased cytokine release from macrophages"

ORIGINAL ARTICLE Rayes, J. et al. The podoplanin–CLEC-2 axis inhibits inflammation in sepsis. *Nat. Commun.* **8**, 2239 (2017)

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