Stabilin-1-Mediated Efferocytosis Protects against Vascular Leakage in Sepsis: A Novel Therapeutic Approach?

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Sepsis is a complex clinical syndrome with high lethality characterized by systemic inflammation and organ failure.[1] Although intensive research over the past decades has identified several mechanisms contributing to sepsis pathology, sepsis represents a major therapeutic burden. Current therapeutic strategies are limited to rapid initiation of antibiotic therapy and further supportive treatment, including fluids, the use of vasopressors and functional organ replacement.[2] Therefore, sepsis was recently identified by the World Health Organization as a global health priority.[3]

In the context of sepsis pathogenesis and progression, an important mechanism is vascular leakage due to disruption of the vascular barrier by inflammatory stimuli.[4,5] Maintenance of vascular integrity is supported by the efficient removal of apoptotic endothelial cells. The phagocytic clearance of damaged cells by macrophages, a process termed efferocytosis, induces resolution of inflammation and suppression of pro-inflammatory cytokines.[6,7]

In the previous issue of *Thrombosis and Haemostasis*, Lee et al[8] proposed a new mechanism, by which macrophage Stabilin-1 (STAB-1), a phagocytic receptor mediating efferocytosis by recognizing phosphatidylserine on apoptotic cells,[9] promotes the clearance of apoptotic vascular endothelial cells damaged by severe inflammation. This function of STAB-1 protects against disruption of vascular integrity in the course of sepsis.[8] Low pH values, which are present in patients with septic shock, promote the macrophage expression of STAB-1.[9] Genetic deletion of STAB-1 decreased the survival of septic mice in the model of cecal ligation and puncture. Decreased sepsis survival in STAB-1 deficiency was associated with diminished efferocytosis, increased vascular permeability and enhanced organ dysfunction. Interestingly, the pro-inflammatory mediator high-mobility group box 1 (HMGB1)[10–12] inhibited STAB-1-dependent efferocytosis of apoptotic cells. Consistently, blockade of HMGB1 with a neutralizing antibody improved the phagocytic capacity of macrophages and reduced sepsis mortality.

Previous work by Palani et al[13] demonstrated that STAB-1 on monocytes suppresses the activation of Th1 lymphocytes; thus, STAB-1 may also exert an immunosuppressive action. In addition, STAB-1 may regulate lymphocyte migration and inflammatory cell recruitment.[14] How the sepsis-protective action of STAB-1, as shown by Lee et al in this issue of *Thrombosis and* Haemostasis,[8] may reconcile with its previously described immunomodulatory functions, requires future investigation. Thus, a therapeutic approach aiming at increasing STAB-1 function needs to be carefully evaluated.

Taken together, the study by Lee et al demonstrated the important role of macrophage STAB-1 in protecting against vascular barrier dysfunction in sepsis via mediating enhanced efferocytosis of apoptotic endothelium.[8] Testing the proposed sepsis-protective mechanism of STAB-1 merits further experimental and pre-clinical assessment.

Conflict of Interest
None.

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