TLR9, expressed on macrophages, appears to be important for normal thrombus resolution….  

Regulation of sterile inflammation in the natural resolution of venous thrombosis

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Venous thrombi resolve naturally through a process of tissue organisation similar to that seen during wound healing, and it is increasingly becoming clear that the innate ‘sterile’ inflammatory system is intimately linked to this intravascular ‘healing’ process (1). The initial recruitment of neutrophils followed by their demise and accumulation of macrophages, is a consistent inflammatory signature of venous thrombus formation and subsequent resolution. These cells express a number of pattern recognition receptors (PRRs) that are activated by damage associated molecular patterns (DAMPs) from non-infectious cellular ‘debris’, causing the release of mediators that promote inflammation (2).

DAMPs, present within thrombus, include DNA released from neutrophils (that also act as extracellular traps during thrombus formation) and factors such as uric acid and high mobility group box 1 (HMGB1), described in the manuscript by Dewyer et al in this issue (3). DNA and histones can alter the fibrin architecture in plasma clots by inhibiting plasminogen activation or protecting thrombin from inactivation, respectively, whereby neutrophil extracellular traps lead to decreased susceptibility of plasma clots to lytic resolution (4). In addition to these intracellular DAMPs, extracellular matrix degradation may also release fragments (e.g. biglycans and hyaluronans) that act as danger signals. It is likely, however, that release of haem from red cells, that form the largest cellular component of a venous thrombus, also significantly contributes to this pro-inflammatory signaling environment (5).

Toll-like receptors are only one class of PRRs that sense these danger signals involved in sterile inflammation, and as the manuscript by Dewyer et al (3) concludes, a member of this family of receptors (TLR9), expressed on macrophages, appears to be important for normal thrombus resolution.

Understanding the interaction between PPRs and their ligands, and how these affect inflammatory cell activities in the context of thrombus resolution, may lead to the discovery of therapeutic targets that reduce the incidence of the post-thrombotic syndrome. The precise mechanisms by which inflammatory cells remove the thrombus remain, however, to be defined.

Conflicts of interest
None declared.

References