Role of Inflammation in Modulating Thrombotic–Fibrinolytic Balance in Venous Thrombosis

Marc S. Penn, Chinedu Igwe

Although no doubt an oversimplification, in many respects, a significant portion of cardiovascular trials in the late 1990s and early 2000s demonstrated that whether we do not clot we do not die as long as we do not bleed to death. These trials were focused on novel anticoagulants targeting platelets and thrombin-mediated thrombosis. These studies focused on potent anticoagulants that ultimately demonstrated limited efficacy because they were not targeted at the disease or the disease process. Rather, they were systemic anticoagulants that led to a decrease in coagulation throughout the body, not focused on the area of vascular injury that led to greater adverse events than therapeutic benefit.

Luther et al demonstrated that venous thrombosis results in the increased expression of a broad array of chemokines that lead to the recruitment of TEM cells into the vessel wall (Figure). These TEM cells become activated in a nonantigen-dependent manner leading to the local release of interferon-γ. The increased interferon-γ expression results in recruitment of monocytes and neutrophils to the clot. The monocyte and neutrophil recruitment significantly decreases MMP-9 (matrix metalloprotease-9) expression, neovascularization, and recanalization of the clot ultimately leading to delay in clot resolution. They define this novel physiology of TEM cell through detailed expression analysis and TEM-cell depletion studies in a murine model of inferior vena cava partial ligation sufficient to induce thrombosis.

The detailed molecular studies on chemokine and TEM-cell recruitment are of interest and could lead to a significant shift in the development of novel therapeutics for the resolution of acute and possibly chronic venous thrombosis. Targeted development of inflammatory-mediated mechanisms involved in the resolution of venous clot could lead to the development of therapeutics that would lead to resolution of clot at the site of vascular injury without the need or risk of adverse events associated with systemic anticoagulation.

Importantly, the investigators went beyond the murine studies to further define the relevance of their findings in human disease. The incidence of vascular thrombosis increases with age as evidenced by the increased prevalence of deep vein thrombosis in patients aged >66 years after vascular procedures. Interestingly, so does the incidence of left atrial appendage clot, another tissue exposed to a low flow state in an inflammatory milieu as present in atrial fibrillation. Luther et al demonstrate that the levels of splenic and circulating TEM cells are significantly enhanced with age in response to inferior vena cava thrombosis. Thus, these data further support the TEM cell as a specific circulating cell population that could be investigated in the future for its utility as a potential diagnostic and treatment for the presence and resolution of venous thrombosis.

To further offer relevance of their studies to human disease, the investigators demonstrated that there was a significant increase in the presence of CD4+ and CD8+ TEM cells within the vessel wall of varicose veins compared with the number of circulating CD4+ and CD8+ TEM cells. Although these data suggest a mechanistic link between inflammation and adverse venous remodeling, future studies will need to determine whether these TEM cells are modulating local thrombosis that contributes to the development and progression of varicose veins.

In summary, the study by Luther et al significantly refines our understanding of the mechanism by which inflammation...
regulates clot maturation and resolution. Future preclinical and clinical studies have the opportunity to expand on their early clinical data to determine the relevance of these findings to other instances of vascular thrombosis beyond venous thrombosis, including arterial plaque rupture and left atrial appendage clot. Further refinement of the mechanisms of T_{EM} cell activation and their down-stream effects may offer novel targets for enhancement of venous clot resolution that offer the real potential to not increase the risk of bleeding.

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**Disclosures**

None.

**References**


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