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 \(^1\) and thrombin-mediated thrombosis. \(^2\) 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.

The need to clot at the time of traumatic injury to preserve life is critical. Thus, homeostasis is maintained through an ongoing intricate balance of thrombosis and fibrinolysis that favors fibrinolysis in normalcy. The end-organ consequence of vascular disease or injury is because of locally mediated alterations in the fibrinolytic–thrombotic balance leading to local thrombosis and down-stream ischemia. Over the past decade, there has been a growing understanding of the role of inflammation and oxidation on the local fibrinolytic–thrombotic balance. In atherosclerosis, this imbalance is perturbed through development and rupture of vulnerable plaque; in venous thrombosis, it is mediated through vascular injury or remodeling. In both cases, inflammation plays a central role in the initiation of local vascular thrombosis, clot formation, and cessation of flow.

In this issue of the journal, Luther et al\(^3\) significantly expand our understanding of the link between inflammation and thrombosis through the demonstration of a critical role for effector memory T-cell (T\(_{EM}\)-cell) activation in venous thrombosis. \(^3\) In distinct contrast to the majority of work to date that demonstrated a role for inflammation in the initiation of vascular thrombosis, this study shows that T\(_{EM}\)-cells do not initiate or determine the extent of venous thrombotic burden; rather, their data demonstrate a role for inflammation in the delayed resolution of the clot. Specifically, T\(_{EM}\)-cell recruitment leads to delayed neovascularization and resolution of venous clot.

Luther et al\(^3\) demonstrated that venous thrombosis results in the increased expression of a broad array of chemokines that lead to the recruitment of T\(_{EM}\)-cells into the vessel wall (Figure). These T\(_{EM}\)-cells become activated in a nonantigen-dependent manner leading to the local release of interferon-\(\gamma\). The increased interferon-\(\gamma\) 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 T\(_{EM}\)-cell through detailed expression analysis and T\(_{EM}\)-cell depletion studies in a murine model of inferior vena cava partial ligation sufficient to induce thrombosis.

The detailed molecular studies on chemokine and T\(_{EM}\)-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. \(^3\) Interestingly, so does the incidence of left atrial appendage clot, \(^3\) another tissue exposed to a low flow state in an inflammatory milieu as present in atrial fibrillation. Luther et al\(^3\) demonstrate that the levels of splenic and circulating T\(_{EM}\)-cells are significantly enhanced with age in response to inferior vena cava thrombosis. Thus, these data further support the T\(_{EM}\)-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\(^+\) T\(_{EM}\)-cells within the vessel wall of varicose veins compared with the number of circulating CD4\(^+\) and CD8\(^+\) T\(_{EM}\)-cells. Although these data suggest a mechanistic link between inflammation and adverse venous remodeling, future studies will need to determine whether these T\(_{EM}\)-cells are modulating local thrombosis that contributes to the development and progression of varicose veins.

In summary, the study by Luther et al\(^3\) 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 Tem* 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.

Acknowledgements
The Skirball Foundation, New York, NY; Corbin Foundation, Akron, OH.

Disclosures
None.

References

Key Words: Editorials ■ chemokines ■ fibrinolytic therapy ■ inflammation ■ T-lymphocytes ■ venous thrombosis
Role of Inflammation in Modulating Thrombotic–Fibrinolytic Balance in Venous Thrombosis
Marc S. Penn and Chinedu Igwe

Circ Res. 2016;119:1256-1257
doi: 10.1161/CIRCRESAHA.116.310105
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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