Tissue Factor, the Emerging Link Between Inflammation, Thrombosis, and Vascular Remodeling

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Tissue factor (TF) is a cell surface protein that is expressed by endothelial cells, monocytes, and smooth muscle cells in response to a variety of stimuli including lipopolysaccharide, growth factors, and lipoproteins (Figure). The main function of TF is to bind coagulation factor VII, leading to activation of both the intrinsic and extrinsic blood coagulation cascades. In normal arteries, TF expression is limited to the adventitia except for sporadic expression in the media. Although TF is important in maintaining vascular integrity in response to injury, abnormal TF expression has broad-ranging importance in a variety of human diseases including disseminated intravascular coagulation in patients with sepsis and arterial thrombosis in patients with unstable angina.

In this issue of Circulation Research, Singh et al further our understanding of the importance of TF in vascular disease by demonstrating the importance of TF expression on the development of neointimal growth in response to hemostasis. Previous studies using this model of carotid artery ligation leading to thrombosis, as well as activity, is significantly increased. These data support the hypothesis that the increased fibrin generation observed in this model is in response to an imbalance in TF and its inhibitor, TFPI. To further test this hypothesis, the authors overexpressed TFPI in the vessel using adenovirus containing a vector encoding for murine TFPI. The authors postulated that this would lead to decreased TF activity, less fibrin deposition, and decreased neointimal formation. In fact, this was what was observed.

What is unclear from the present study is the mode of delivery of the TFPI to the vessel wall. Studies using an adenoviral construct encoding for β-galactosidase as a reporter for cell transfection in the model used by Singh et al showed that transfection only occurred in the adventitia. Ostensibly, this finding is not surprising because the artery did not undergo mechanical injury, and many studies have demonstrated that the media of uninjured vessels is virtually devoid adenoviral gene delivery after intravenous or intra-arterial delivery due to the barrier function of the elastic lamina. Nonetheless, these findings significantly enhance our understanding of the importance of TF in vascular remodeling.

Wilcox et al were one of the first to postulate the importance of TF in vascular disease by demonstrating its presence in carotid endarterectomy specimens. Subsequently, multiple groups have demonstrated TF expression in diseased coronary arteries. The potential functional importance of TF in acute coronary syndromes and vascular remodeling has been highlighted in a number of studies. Multiple studies have demonstrated increased TF expression either directly in the coronary arteries or indirectly in the plasma of patients with unstable angina or myocardial infarction compared with stable angina. The increased TF expression found in patients with acute coronary syndrome leads to increased thrombin generation, which may be at least one mechanism leading to the abnormal arterial thrombosis, endothelial activation/dysfunction, and arterial remodeling.

Within atherosclerotic lesions, TF expression is localized to the shoulder region and surrounding the lipid-rich necrotic core. The proximity of TF to the lipid-rich areas of the atherosclerotic lesions has led our group and others to investigate the potential role of lipid and lipoprotein regulation of TF expression. Multiple studies have demonstrated that LDL and oxidized lipids can induce TF protein expression and activity in endothelial cells, monocytes, and smooth muscle cells. The links between lipoproteins and TF expression, and now TF and vascular remodeling, as demonstrated by Singh et al, could offer a potential mechanism for the surprisingly early benefits patients with acute coronary syndrome obtain with the initiation of high-dose statin therapy. Alternatively, because C-reactive protein (CRP) has been shown to induce TF expression in monocytes, statin therapy could be beneficial by decreasing CRP levels in these patients.

Beyond the role TF has in acute coronary syndrome, TF expression has a potential role in vascular remodeling after angioplasty. Cell culture studies have demonstrated that the TF:VIIa complex is critical for smooth muscle cell migration. Furthermore, TF:VIIa-mediated smooth muscle cell migration can be inhibited by the overexpression of TFPI. Importantly, as demonstrated in tissue obtained from carotid endarterectomy patients, TF is at least partially inhibited by TFPI within atherosclerotic lesions of humans. However, as shown by Singh et al, TFPI, unlike TF, may not increase in...
response to vascular injury. Thus, although the present study and others have demonstrated the potential utility of TFPI in reestablishing the balance between TF and TFPI in the setting of acute arterial injury, it is left to future studies to determine if this is a viable therapeutic approach in humans.

The burgeoning data from experimental and clinical reports convincingly link atherosclerotic and restenotic pathophysiology with upregulation of inflammation and thrombosis as outlined in the Figure. TF expression is tightly regulated by multiple inflammatory proteins, and its expression results in activation of both the extrinsic and intrinsic blood coagulation cascades. Thus, as demonstrated in the present study, TF plays a pivotal role in the late-term consequences of cardiovascular disease.

References

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