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Editorial

Collagen-induced thrombosis in large vessels using native prothrombotic substrates

Developing models that mimic endogenous thrombus growth is central in our efforts to unravel the mechanisms of thrombotic disorders. The complexity of blood cell-vessel wall interactions is perhaps best captured in the context of a functioning vasculature, which has driven the development of numerous murine models of thrombosis [1]. These models can be categorized by their method of injury (chemical, mechanical, thermal) and the vessels that they target. Over the last decade, murine models have been coupled with intravital microscopy to provide both spatial and temporal information on the evolution of clot formed in both the microvasculature and large vessels [2–4]. An outstanding issue in all of these models is the nature of the prothrombotic surface and how closely that surface resembles a real injury.

Take for example the ferric chloride model, which is perhaps the most widely used thrombosis model owing to its long history in the field and straightforward, inexpensive preparation [5]. This model is considered to be partially collagen mediated, where the oxidative stress caused by ferric ions results in disruption of the endothelium and subsequent exposure of the collagen-rich subendothelial matrix [6]. Ferric ions migrate across the endothelium in iron-rich vesicles via an endocytotic-exocytotic pathway [7]. These vesicles come in contact with blood on the intimal surface of the vessel. Platelets can adhere to and activate on these vesicles. Furthermore, even low concentrations of ferric ions can alter the structure and diminish the adhesiveness of collagen, VWF and fibrinogen [6]. These observations suggest that thrombus formation may be partially an artifact of the model itself, rather than in response to a natural prothrombotic surface. If the ferric chloride model is suspect, then this leaves us lacking a good collagen mediated murine thrombosis model.

In this edition of Thrombosis Research, Cooley introduces an elegant new model of thrombosis that addresses some of the shortcomings of the ferric chloride model [8]. In the model, the epigastric artery is removed from one mouse and placed into a carotid artery or femoral vein of another mouse. The epigastric vessel is inserted into a large vessel with one of three surfaces—adventitia, endothelial cells or subendothelial matrix—exposed to the flowing blood. The adventitia gave the most potent response with large thrombi protruding deep into the lumen over 30 minutes. The response to the subendothelial matrix was relatively modest. A peak in initial platelet accumulation was observed within 10 minutes, but thrombi growth was limited to an area near the surface of the inserted vessel. From a physiological perspective these observations are congruent with the rationale that a deep injury into the adventitia would provoke a stronger response than a superficial injury in the intima. There was little observed platelet accumulation on the intact endothelium, as expected, as this surface should be non-thrombogenic.

The advantage of this model over others is the type of prothrombotic substrate, namely an allogenic transplant of a vessel segment in the absence of chemical, mechanical or thermal perturbations. This approach is akin to that taken by Baumgartner and colleagues in the first in vitro flow assays where human blood is perfused over a denuded rabbit subendothelial matrix [9]. However, performing this type of assay in vivo does not require anticoagulation like an in vitro flow assay, and thus a more robust coagulation response is possible. Another feature is the focal nature of the model. Only 0.5 mm of the smaller artery was exposed within the larger vessels making imaging and analysis easier than in a more diffuse injury such as in the Rose Bengal model.

The complexity of the surgery, in particular the eversion of the epigastric artery to expose the endothelial cell and subendothelial matrix surfaces, may limit this model to laboratories with personnel trained in microsurgery. Although this model uses what may be considered a more physiological substrate, there is still a need to perform the histological and functional characterization such as the superb study by Hechler and colleagues on the laser injury model in the mesenteric arterioles [10]. The adventitia consists primarily of types I and III collagen, suggesting that this is likely a collagen mediated injury as suggested by the author. However, based on the significant fibrin deposition in the adventitial model and evidence of TF in the adventitia of murine and human vessels [11,12], the presence of TF cannot be ruled out. Further work is also needed to determine the relative importance of the collagen and VWF receptors, as well as the role of immobilized and circulating tissue factor within this model. Nevertheless, this is a welcome addition to our toolbox of methods for studying thrombosis in large vessels.

Conflict of Interest Statement

No conflicts to declare.

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