Transplant arteriopathy (TA) is an important limitation to graft survival following solid organ transplantation. TA is a result of immune-mediated mechanisms and results in intimal hyperplasia (IH) and vascular occlusion. Our understanding of the mechanism for this process is expanding to include an important role for host derived-circulating cells, including cells that adopt a smooth muscle cell phenotype within the intima of vessels. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Chen and colleagues add to this understanding of TA in a new and unexpected way that suggests that the tissue factor (TF)-thrombin–PAR-1 pathway may provide an important link between the bone marrow and blood vessels.

How Does TFPI Overexpression Affect the Phenotype of Circulating CD34+ Cells?

In this study by Chen, the mechanism of action of TFPI overexpression was mediated through effects on bone marrow-derived cells. Multiple studies have demonstrated that the bone marrow responds to acute or chronic vascular injury through mobilization of diverse cell populations. These cells have been characterized for their capacity to express markers shared by hematopoietic and endothelial cells and have been demonstrated to home to injured vessels. As TF plays a critical role in vascular disease, it was hypothesized that overexpression of TFPI in circulating cells may inhibit this process. In this model, aortic transplants were performed across immunologic barriers to generate TA. TFPI overexpression reduced intimal hyperplasia in spite of similar immunologic injuries. To ensure that the results could be interpreted in the context of chronic rejection, the group used mouse aortas from strains that have a full major histocompatibility complex mismatch to elicit a robust immune response. Additionally, they provide evidence suggesting that there are discrete cell populations (CD34+ CD45+ α-SMA+) that are responsible for the development of immune-mediated intimal hyperplasia and yet another subset of cells (CD34+ CD45− α-SMA+) that might mediate repair of damaged vessels (as shown in the Figure). Notably and unexpectedly, following allogeneic transplant, TFPI overexpression resulted in distinct differences in these circulating populations favoring the reparative phenotypes. Finally, Chen demonstrates that the mechanism for this inhibition of TA is through local attenuation of PAR-1 signaling through homing of CD34+ cells to the transplanted aortas. These studies shed new light on the mechanism of immune-mediated vascular injury and suggest new therapeutic strategies to test. Notably, might pharmacological inhibition of thrombin inhibit TA? Finally, as with most science, the study raises new questions.

Tissue Factor-Thrombin–PAR-1 Pathway: A Novel Link Between Bone Marrow and Blood Vessel

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Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org
DOI: 10.1161/ATVBAHA.111.240507

Figure. Mechanism by which circulating subsets of CD34+ cells affect transplant arteriopathy (TA) following allogeneic aortic transplantation. TF indicates tissue factor; IH, intimal hyperplasia.
To affect the phenotype of circulating CD34<sup>+</sup> cells, TFPI overexpression must in some way mediate the generation, mobilization, or homeostasis of circulating CD34<sup>+</sup> subsets. In this transgenic model, TFPI is tethered and not released from cells. Thus paracrine or endocrine effects are not likely to be responsible for such effects. As the differences were seen in the allogeneic and not the syngeneic setting, immune mediators are likely necessary for these effects. Might inflammatory mediators modulate α-SMA expression (and thus TFPI expression) to mediate the local inflammatory milieu in the bone marrow regulating differentiation and release? It has been shown that inflammatory mediators may regulate α-SMA promoter activity. Once expressed, and as was demonstrated in the treated arteries, overexpression of TFPI can regulate local tissue dynamics. In this case, the phenotype of proliferating and mobilized cells might be affected through inhibition of thrombin generation or inhibition of PAR-1 signaling.

Taken together, these studies by Chen and colleagues add to the growing understanding that the TF-thrombin–PAR-1 pathway coordinates a unique interface between thrombosis and inflammation. In addition, they suggest that this pathway is able to coordinate cross-talk between bone marrow and blood vessels.

**References**


**Key Words:** bone marrow • tissue factor pathway inhibitor
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Arterioscler Thromb Vasc Biol. 2012;32:3-4
doi: 10.1161/ATVBAHA.111.240507
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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