Conflict-of-interest disclosure: The author declares no competing financial interests.

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PAI-1: cardiact friend or foe?

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In this issue of Blood, Xu and colleagues provide evidence that suggests PAI-1 is cardioprotective as demonstrated by the observation that spontaneous cardiac fibrosis occurs in aging PAI-1--/--mice, preceded by early changes in cardiac vascular barrier integrity, enhanced inflammation, dysregulated extracellular matrix remodeling, and, eventually, pervasive fibrosis and compromised cardiac function. Whether PAI-1 is a mediator or inhibitor of cardiac fibrosis is still controversial. Other studies have demonstrated that PAI-1 contributes to cardiac fibrosis potentially through blocking plasmin activation of pro-matrix metalloproteases. However, these studies were performed in cardiac injury challenged young mice, that is, after coronary occlusion/myocardial infarction. Interestingly, in one of these studies, myocardial hemorrhage and inflammation were enhanced in PAI-1--/--mice, in association with greater infarct size compared with wild-type mice, but fibrosis was attenuated. In the current study by Xu et al, investigating spontaneous cardiac changes with aging, increases in spontaneous myocardial hemorrhage and inflammation were observed in PAI-1--/--mice. However, cardiac fibrosis was enhanced in PAI-1--/--mice relative to age-matched wild-type mice. Increased fibrosis in 1-year-old PAI-1--/--mice, in the absence of injury, has also been observed. The Xu study characterizes the temporal development of spontaneous cardiac fibrosis in PAI-1--/--mice. Evidence for spontaneous hemorrhage and up-regulation of proinflammatory cytokines in cardiac tissue occurred in young mice (at 12 weeks), preceding the development of fibrosis observed in aged mice (at 36-48 weeks). Taken together, these results may suggest different effects of PAI-1 on myocardial fibrosis leading to a more profibrotic effect in response to cardiac injury and leading to a more antibibotic effect in response to aging. These contrasting effects may, in turn, be mediated by differences in the relative contribution of protease inhibitor-dependent (eg, hemorrhage and breakdown of the cell–extracellular matrix interface) and independent (cell signaling) regulatory functions of PAI-1. Also of interest is whether the age-dependent increases in plasma PAI-1 concentrations observed in mice and humans may play an important role in the maintenance of normal cardiac architecture and cardiac functional homeostasis with aging.

The development of cardiac fibrosis has been observed in other mice with altered expression of coagulation and fibrinolysis proteins. Mice expressing low levels of tissue factor (TF) or its ligand, factor VII (FVII), and mice overexpressing uPA also develop cardiac fibrosis, whereas the absence of uPA in mice prevents cardiac fibrosis in response to myocardial infarction. In low-TF mice, altered regulation of uPA expression was also observed and uPA levels were increased in PAI-1--/--mice in the Xu study, consistent with increased matrix remodeling. Therefore, uPA may be a driving force regulating the cardiac fibrosis phenotype in these models. PAI-1 may regulate fibrosis by inhibiting proteolytic damage at the cell–extracellular matrix interface caused by uPA proteolytic activation of plasmin and/or by altering uPA/uPA receptor signaling. In addition, the absence of PAI-1 may lead to increased plasmin activation of the profibrotic cytokine, TGF-β, concomitantly with increased TGF-β synthesis (as shown in the Xu et al study). In vivo studies that selectively alter functional properties of PAI-1 and uPA will further contribute to an understanding of how these proteins regulate events leading to cardiac fibrosis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Identification of the HNA-3a antigen

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In this issue of Blood, Curtis et al identify the human neutrophil antigen 3a (HNA-3a), which is contained within the choline transporter-like protein–2.1 Antibodies to HNA–3a have been implicated in significant numbers of fatal TRALI reactions, and the discovery reported by Curtis et al will lead to the identification of HNA-3a–negative donors to make transfusions safer.

Among the 5 HNA systems, HNA-3 was the only one that had yet to be characterized. This effort was critical because antibodies directed to HNA-3 are responsible for causing numerous cases of transfusion-related acute lung injury (TRALI), especially fatal TRALI.2,3 Antibodies to HNA-3a cause neutrophil (PMN) agglutination, priming of the PMN oxidase, and PMN-mediated killing of pulmonary endothelial cells in HNA-3a–PMNs and do not affect those granulocytes that do not express the antigen.2,5 A German group has also just described the identical protein as the HNA-3a antigen.6

The identification of the molecular basis of HNA-3a and its allele HNA-3b should lead to the rapid manufacture of appropriate laboratory materials that will ensure the accurate identification of donors who are HNA-3a–deficient and may have antibodies against HNA-3a. Solid-phase assays to detect anti–HNA-3a should also be quickly developed.

Antibodies to HNA, especially HNA-3a, are likely to be found in multiparous female donors, and screening of female donors should be considered when the reagents are available.2,7 However, several studies of blood donors have found that HNA antibodies are rare even among multiparous females.8 Some blood centers are already testing multiparous apheresis platelet donors for HLA antibodies and not allowing those with high-titer antibodies to donate. It is likely that assays used to test these donors for HLA antibodies will soon include reagents to detect anti–HNA-3a. However, preventing people with leukocyte antibodies from donating platelets will not prevent all cases of TRALI, because bioactive lipids and soluble CD40 ligand, which accumulate in stored platelet components, also can cause TRALI.9,10 Ultimately, the identification of HNA-3a will make transfusions safer after appropriate screening of blood donors for antibodies to HNA-3a.

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