Editorial

Cells regularly invade and migrate through tissues during embryogenesis, angiogenesis, cancer, and a number of other normal and pathological processes (1). Since much of this movement frequently occurs through quite formidable barriers, it is dependent upon the action of highly regulated and specific proteinases that can locally digest tissue proteins without the widespread damage associated with, for example, chronic inflammatory disease. This "targeted" proteolysis is accomplished in large part by the plasminogen activating system, a versatile, temporally controlled enzymatic cascade that when activated, generates locally expressed extracellular proteolytic activity. Activation of this system is initiated by the release of plasminogen activators (PAs) from cells in response to signals (e.g., growth factors, cytokines, hormones) liberated during tissue remodeling, inflammation, and thrombosis, and leads to the formation of plasmin. Remarkably, this same system in blood (i.e., the fibrinolytic system) functions to maintain vessel patency by specifically removing fibrin deposits from the vasculature. This diversity of function suggests that the plasminogen activating system is broadly used in human physiology. At the clinical level, excessive plasmin formation is frequently associated with bleeding and/or various destructive conditions (e.g., cancer, pemphigus, inflammatory joint disease), emphasizing that PA activity must be precisely regulated. This regulation is achieved initially at the level of PA biosynthesis, and ultimately at the level of specific PA inhibitors (PAIs) that prevent the escape of this potentially destructive protease system. Although four molecules with PAI activity have been described, PAI-1 appears to be the primary inhibitor of plasminogen activation in vivo (2).

Because regulation of the PA system appears to be of such fundamental importance, it has long been suspected that abnormal expression of PAI-1 itself also would be associated with human disease. In fact, individuals with elevated PAI-1 in their blood may be at increased risk to develop thrombotic disease, including myocardial infarction, and transgenic animals expressing excessive PAI-1 develop thrombi in their extremities (reviewed in reference 2). Against this background, workers in the field have speculated that plasminogen activation control would be completely compromised in PAI-1-deficient individuals, and that the resulting severe hyperfibrinolytic state would be inconsistent with normal development and hemostasis. A number of recent observations suggest that this idea is only partially correct. For example, individuals with low PAI-1 in their blood have been identified (reviewed in reference 3), and Fay et al. (4) elegantly demonstrated and characterized a complete PAI-1 deficiency in a 9-yr-old girl. None of these individuals have obvious physical or developmental abnormalities, but all of them present with mild to moderate, life-long bleeding problems. Whether the young girl will ultimately develop fertility problems as well (the PA system has been directly implicated in ovulation, implantation, and pregnancy [1, 5]) remains to be seen.

In this issue, Carmeliet et al. (6, 7) comprehensively and rigorously confirm the human studies and extend them in a number of important ways. These investigators created PAI-1-deficient mice by completely deleting the PAI-1 gene using homologous recombination. The animals not only survived, but their litter size and growth rate seemed to be normal, suggesting normal fertility and development (6). Again, except for a slight hyperfibrinolytic state (e.g., more efficient lysis of clots injected into their jugular veins and relative resistance to endotoxin-induced venous thrombosis [7]), no apparent gross or histological abnormalities were associated with the lack of this inhibitor.

What can this mean in terms of the role of PAI-1 in vivo in tissues? Either PAI-1 is not important in this setting, which seems unlikely in view of its exquisite regulation during tissue morphogenesis and remodeling (1, 5), or alternative back-up mechanisms come into play. This possibility seems more likely since, as already mentioned, other molecules with PAI activity have been described, and plasma contains high levels of less specific protease inhibitors (e.g., α_2-macroglobulin, C_1-esterase inhibitor, etc.) that may dampen this system in the absence of PAI-1. Moreover, the system has a built-in redundancy in that it is controlled both by PAIs and by plasmin inhibitors (i.e., α_2-antiplasmin). Regulation at the level of plasmin activity itself may be sufficient to control this system in the mouse, and may account for the observed lack of spontaneous or delayed rebleeding after injury in this model (7). In this regard, it will be interesting to develop mice lacking both inhibitors.

Whatever the mechanism, it seems clear that mice and humans can survive and probably reproduce without PAI-1. Since both develop a hyperfibrinolytic state with a mild bleeding diathesis, it is also clear that PAI-1 plays a major role in controlling plasminogen activation in the blood. Elevated PA activity appears to promote tumor cell invasion, while decreased PA activity may be atherogenic. Thus, one must wonder whether individuals with little or no PAI-1 are at increased risk to develop metastatic disease, or are at decreased risk for cardiovascular disease. Although little human data are available, the PAI-1-deficient mice may provide a useful model for these and related studies.

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