answer some of these questions by comparing medical and psychological toxicities of related HSC donors with unrelated donors.

To conclude, the current widespread international practice of overlapping recipient and donor care teams raises serious concerns about possible conflicts of interest. O’Donnell et al., and others, highlight the lack of clear guidelines for related donors and strongly encourage existing regulatory frameworks to develop explicit standards to ensure uniformity of care. It behooves us as a transplantation community to protect and serve the needs of HCT recipients and their donors.

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

REFERENCES


Students of coagulation enjoy learning the story of Mr John Hageman, who was identified by Dr Oscar Ratnoff and colleagues as having a deficiency in a coagulation factor resulting in delayed blood clotting in vitro. In life, Mr Hageman did not have a bleeding diathesis, and he died of pulmonary embolism, stimulating more than 50 years of work focusing on the role of the intrinsic coagulation pathway protein, factor XII/Hageman factor, in coagulation and fibrinolysis. Because activated factor XII (factor XIIa) is a direct albeit weak activator of plasminogen, it may be fair to view factor XIIa as a serine protease that functions on both sides of the hemostasis balance.

Recent studies have shown that the major mammalian plasminogen activators, urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA), trigger robust cell-signaling responses in some cell types. LDL receptor–related protein–1 (LRP1) functions as a receptor for tPA, which is capable of triggering cell signaling that results in activation of factors such as ERK1/2 and Akt. Because matrix metalloprotease–9 (MMP–9) also initiates cell signaling upon binding to LRP1, this receptor and perhaps other receptors in the LDL receptor gene family may be considered protease-activated receptors or PARs, like the thrombin receptor/PAR1. However, unlike proteases that activate PAR1, tPA and MMP–9 do not require enzymatic activity to trigger LRP1-dependent cell signaling.

The cell-signaling pathways activated by uPA downstream of uPAR have been recently reviewed. The ability of factor XII to bind to uPAR and activate cell signaling represents a newly discovered factor XII activity typically associated with a protease in the fibrinolysis system. Binding of both factor XII and uPA to uPAR also builds on a model in which uPAR is recognized as a third category of PARs (see figure). With continuing research, it is quite possible that the continuum of proteases that bind to uPAR and activate cell signaling may grow.

Although the relationship between the binding sites for uPA and factor XII in uPAR remains to be completely elucidated, many of the properties of the interaction of factor XII with uPAR mirror the interaction of uPA with uPAR. These include (1) the cell-signaling factors activated (eg, ERK1/2 and Akt); (2) cell signaling occurring independently of
protease enzymatic activity; (3) the requirement for partnership with integrins; and (4) recruitment of receptor tyrosine kinases (in this study, the EGF receptor) into the cell-signaling pathway. Using a battery of in vitro and in vivo assays, LaRusch et al demonstrate that the factor XII–uPAR interaction promotes angiogenesis. A natural extension of this work is to question whether the factor XII–uPAR interaction supports other physiologic and/or pathophysiologic processes in which uPAR-dependent cell signaling has been implicated. An example would be the ability of uPAR-initiated cell signaling to promote epithelial-mesenchymal transition (EMT) in cancer.

Another question that arises from this work regards how the factor XII–uPAR interaction is regulated. This question is particularly interesting because the zymogen form of factor XII is active in cell signaling at concentrations well below its normal plasma level. The activity of the zymogen eliminates formation of factor XIIa as a control mechanism. Interaction with zinc may be important. The ability of zinc to bind to factor XII and induce factor XII conformational change was described by Joseph Shore and colleagues. Finally, factor XII–initiated cell signaling in endothelial cells may be regulated by changes in the availability of uPAR on the luminal surface of endothelial cells, where it contacts plasma proteins, such as circulating factor XII.

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Factor XII bridges coagulation and fibrinolysis again

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