phagosomes, thereby creating an environment toxic and often lethal to ingested microbes. Consequently, one would predict that neutrophils unable to support MPO-dependent biochemistry would leave the host susceptible to frequent and severe infections, akin to the clinical predicament of patients with chronic granulomatous disease, whose phagocytes have defective reduced nicotinamide adenine dinucleotide phosphate oxidase activity and thus cannot generate oxidants. However, individuals with inherited MPO deficiency kill ingested bacteria such as Staphylococci and Streptococci, but do so more slowly than do normal neutrophils. In contrast to the clinical experience of those with inherited MPO deficiency, one third of the patients with acquired MPO deficiency reported by Theocharides et al had severe infections, although not those typical for patients with inadequate neutrophil number or function. The basis for the higher prevalence of infection in these patients vs in patients with inherited MPO deficiency is unknown, but an unexplained observation published nearly half a century ago may provide a subtle clue. Klebanoff reported that the microbicidal activity of normal neutrophils treated with the peroxidase inhibitor sodium azide, which blocks MPO activity, is significantly more impaired than that of neutrophils from MPO-deficient individuals, as if the latter had developed or enlisted antimicrobial activities as partial compensation for the genetic absence of MPO. The lack of such adaptation in acquired MPO deficiency may explain, in part, the greater morbidity from infection in the 2 patients with acquired MPO deficiency reported here. Of course, defective biosynthesis of other host defense glycoproteins likely would also contribute to greater susceptibility to infection. It is noteworthy that the patient with myelofibrosis with incidental inherited MPO deficiency did not have infectious complications.

Calreticulin figures not only in the biology of myeloid precursors but also in the clearance of dead or apoptotic neutrophils (see figure). An effective inflammatory response must culminate in restoration of tissue homeostasis, which relies on efferocytosis, the active engagement of tissue macrophages to bind, ingest, and clear spent neutrophils from the site, thereby eliminating agents that would otherwise sustain inflammation chronically. Initiation of efferocytosis reflects the balance of competing “eat me” and “don’t eat me” signals from neutrophils that prevents ingestion of viable cells but promotes clearance of apoptotic cells by local macrophages. Phosphatidyl serine and other cell surface elements on apoptotic bodies bind to receptors on tissue macrophages through a complex and incompletely understood series of signaling events to drive their ingestion. Calreticulin associates with the “eat me” signal phosphatidyl serine on the cell surface of apoptotic, but not viable, cells to promote internalization. Although the mechanism by which calreticulin redistributes from ER to the plasma membrane is not known, it is plausible that KDEL-deficient calreticulin, as identified by Theocharides et al, would fail to reach the cell surface, thereby depriving the apoptotic neutrophil one of the determinants that drive its removal by macrophages, and leaving the uningested cell to undergo necrosis and promote inflammation. Such a scenario occurs in the setting of cyclin-dependent kinase deficiency, whereby apoptotic smooth muscle cells lack surface calreticulin and resist efferocytosis by local macrophages. Uncleared, the residual smooth muscle cells undergo necrosis and foment prolonged inflammation. If true in the context of myelofibrosis with mutated calreticulin, failed efferocytosis of apoptotic cells would compound the other defects that compromise effective host defenses in affected patients. Taken together, the observations of Theocharides et al set the stage for further exploration of how mutant calreticulin, both as a participant in quality control of nascent glycoprotein synthesis in the ER and as a ligand for efferocytosis of apoptotic cells, figures in the full lifespan of cells, from the birth of glycoproteins to the delivery of dead cells to their final resting place.

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Comment on Le Gall et al, page 3260

Coagulation signaling to epithelia

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In this issue of Blood, Le Gall et al show that matriptase, a member of the type II transmembrane serine protease family, is a key coordinator of tissue factor (TF)-dependent activation of protease-activated receptor-2 (PAR2) on epithelial cell lines by coagulation proteases. An expanding body of literature points to an important role of coagulation protein-mediated cell signaling of vascular repair by the activation of PARs. PARs constitute a family of 4 seven-transmembrane G-protein coupled receptors (PAR1–4) that mediate cellular
The matriptase zymogen on epithelial cells. In a series of detailed and well-controlled biochemical experiments using transfected cell lines and recombinant protease domains, the authors showed that FVIIa and FXa activate signaling responses, including increased PAR2-dependent mitogenic extracellular signal-regulated kinase phosphorylation. The downstream effects of matriptase activation by the coagulation proteases was not only limited to PAR2 signaling, but also induced the activation of additional matriptase substrates, the fibrinolytic serine protease pro-urokinase plasminogen activator (pro-uPA) and the mitogenic growth factor pro-hepatocyte growth factor (pro-HGF) (see figure).

Where and how does this activation take place in vivo? Matriptase is expressed in virtually all epithelia, and is found localized along the basolateral surfaces and adherens junctions of simple polarized epithelia, where it plays a key role in epithelial homeostasis. Null and hypomorphic mutations in the matriptase gene ST14 are linked to defects in epidermal barrier formation in humans displaying inherited skin disease autosomal recessive ichthyosis with hypotrichosis. The recent generation of murine models of inducible matriptase ablation in the whole animal, and tissue-specific ablation in the gastrointestinal tract and salivary epithelium, has revealed that matriptase is essential for the maintenance of epithelial barrier integrity.

Matriptase is expressed in cells as an inactive precursor, prostasin, and is also capable of auto-activation at the cell surfaces, an unusual mechanism among the serine proteases. Here, the authors report a new pathway for matriptase activation associated with tissue injury. Matriptase-mediated signaling might occur in vivo when the plasma proteins FVIIa and FXa contact TF-expressing keratinocytes and other epithelial cells at sites of wounding, inflammation, or altered vascular integrity.

It is becoming clear that matriptase activation and cellular responses are tissue-context specific and dependent on the extracellular milieu. Whether differential activation of matriptase by proteases elicits different protease-specific cell signaling responses is at present unclear. Membrane-anchored protease-dependent PAR2 cleavage may be expected to target PAR-signaling responses to specific cellular microdomains such as within lipid rafts, whereas soluble proteases would cleave PARs independent of location. Moreover, released FXa or trypsin could generate a response with high magnitude but limited duration, whereas activation of matriptase by membrane-targeted proteases could generate prolonged PAR2 signaling responses.

The link between matriptase and coagulation initiation could be expected to contribute to the pathogenic effects of extrinsic pathway activation in cancer and inflammation. Although vascular inflammation induced by TF is unlikely to involve matriptase because matriptase is not expressed by endothelial cells, bleeding or ectopic expression of FVIIa could trigger TF and matriptase-dependent pathologies that are both dependent and independent of PAR2 in epithelia. Tumor-expressed matriptase activation by coagulation proteases could contribute to facilitating the activation of pro-HGF, pro-uPA, and potentially other matriptase substrates alongside PAR2 and fibrin downstream of TF to promote tumor growth and dissemination.

Future investigations of PAR2 activation by the TF-dependent FVII/Xa/matriptase pathway are warranted in order to extend these findings to human pathology.

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Coagulation signaling to epithelia

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