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Factor XI and Pulmonary Infections

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The glycoprotein factor XI (FXI), and its active protease form factor XIa (FXIa), are undergoing evaluation as therapeutic targets based on mounting evidence that they contribute to thrombotic disease [1]. FXI serves a modest role in hemostasis, and the hope is that drugs that inhibit FXIa, or that lower the plasma concentration of FXI, will prevent thrombosis while having a smaller impact on hemostasis than currently used anticoagulants. In this issue of *Haemophilia*, Salomon and colleagues report that FXI deficiency in humans does not influence the incidence or severity of community acquired pneumonia [2]. To appreciate the importance of this study, we must consider what is known about FXI in the pathogenesis of infection in general, and to injury in the lungs in particular.

FXIa is a protease that promotes thrombin generation by activating factor IX [3]. But it is also a homolog of α -kallikrein, a protease that promotes inflammation and vascular leak by cleaving kininogens to release bradykinin, and by activating factor XII (FXII) [3]. Traditionally, FXI and PK, with the protease precursor FXII and the co-factor high molecular weight kininogen (HK), form a system that triggers coagulation when blood is exposed to artificial surfaces by a process called *contact activation* [4]. It is contact activation that initiates coagulation in the partial thromboplastin time (PTT) assay used in clinical practice. While key to clotting in the PTT, however, contact activation is not required for hemostasis. Unlike FXI deficiency, deficiencies of FXII, PK or HK do not cause abnormal bleeding, implying that their primary functions are unrelated to thrombin generation.

PK, HK and FXII, contribute to several host-defense processes including kinin generation and complement activation. The term kallikrein-kinin system (KKS) is often used instead of contact activation to cover the non-coagulant activities of these proteins [5]. FXI, by virtue of its contributions to hemostasis, is usually not considered a part of the KKS. However, like α -kallikrein, FXIa can activate FXII [3] and cleaves HK to release bradykinin [6], suggesting that it can contribute to inflammatory process through interactions with KKS components [7]. Furthermore, sustained thrombin generation through FXIa may promote

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DISCLOSURE

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inflammation through thrombin-mediated processes such as cleavage of protease activated receptors (PARs) and fibrin formation.

Data from animal models support the conclusion that FXI is a pro-inflammatory protease. In a mouse model of polymicrobial sepsis induced by ligation and puncture of the cecum (CLP), FXI-deficient (*F11*^{-/-}) mice have better survival than wild type (WT) mice [7,8]. FXI-deficiency blunts the early cytokine response after CLP, an effect that may be independent of coagulation [7]. Similarly, survival is improved and inflammation reduced in *F11*^{-/-} mice challenged with *Listeria monocytogenes* [9]. An anti-FXI antibody protects baboons from death induced by a lethal dose of heat-inactivated *Staphylococcus aureus* [10]. Again, as in the mouse CLP model, there is a pronounced reduction in the early cytokine response in animals treated with the antibody.

In contrast to these studies, which involve systemic infection, challenges that primarily target the lungs appear to evoke a more exuberant response in *F11*^{-/-} mice than in WT or FXII-deficient (*F12*^{-/-}) mice. Stroo *et al.* reported that *F11*^{-/-} mice have an exaggerated pulmonary hypersensitivity response to inhaled dust mites, with a greater influx of eosinophils and local levels of the eosinophil chemoattractant eotaxin in lung tissue compared to similarly challenged WT or *F12*^{-/-} mice [11]. More recently, this group reported that *F11*^{-/-} mice do poorly compared to WT or *F12*^{-/-} animals after intrapulmonary administration of two common causes of community acquired pneumonia, *Streptococcus pneumoniae* and *Klebsiella pneumoniae* [12]. *F11*^{-/-} mice challenged with *S. pneumoniae* had reduced survival, an enhanced pulmonary inflammatory response, and increased bacterial outgrowth from lung, blood and splenic tissue compared to WT or *F12*^{-/-} mice. Similar results were observed with *K. pneumoniae* challenge. Neutrophil infiltration of the lungs was particularly prominent in *F11*^{-/-} animals but, interestingly, neutrophils from these animals appeared to have a modest phagocytic defect. A similar but somewhat milder defect was induced in human neutrophils in the presence of an inhibitory antibody to FXI [12].

There is little information available on the effects of FXI/FXIa on neutrophil function. FXI-deficiency is relatively common in Holstein cattle [13]. In addition to a mild bleeding disorder, these animals appear more susceptible to pneumonia, mastitis and metritis. Coomber *et al.* noted reduced myeloperoxidase release in response to complement component C3b from neutrophils from FXI-deficient cattle, but greater alkaline phosphatase release and superoxide production in response to C5a [14]. Itakura *et al.* reported that FXIa inhibits human leukocyte chemotaxis triggered by IL-8 or the peptide f-Met-Leu-Phe [15]. While these data are limited, they suggest that FXI may contribute to regulation of neutrophil migration and/or function.

The prominent leukocyte infiltration in the lungs of *F11*^{-/-} mice challenged with *S. pneumoniae* or *K. pneumoniae* may be relevant to observations we made with mice lacking the fibrinolytic protein plasminogen (*Plg*^{-/-} mice) [16]. *Plg*^{-/-} mice have poor wound healing and develop a wasting syndrome due to widespread fibrin deposition [17]. Superimposing factor IX deficiency (hemophilia B) on the *Plg*^{-/-} genotype reduces wasting, consistent with reduced fibrin deposition. Superimposed FXII deficiency, on the other hand, does not alter

the *Plg*^{-/-} phenotype, supporting the notion that FXII is not involved in hemostasis. While it seemed reasonable to hypothesize that FXI-deficiency would have an intermediate effect on the *Plg*^{-/-} phenotype between those of factor IX and FXII deficiency, instead it caused a severe syndrome characterized by heavy leukocyte infiltration in the lungs, pulmonary fibrosis, stunted growth, and shortened life-span [16]. These effects are difficult to attribute to known FXI functions, and are consistent with a regulatory role for FXI in inflammation or leukocyte function in mice.

The implications of the mouse studies for human pathology are far from clear, but they raise a concern that therapies targeting FXI/FXIa may increase the risk and/or severity of lung infections in humans. The study from Salomon et al. addresses this concern [3]. They identified individuals from a large medical practice in Israel who underwent evaluation for FXI deficiency. Of the more than 10,000 patients who had such an evaluation, 7.9% were partially FXI-deficient (plasma FXI 20–50% of normal) and 4.2% had severe deficiency (FXI <20% of normal). The advantage of conducting this study in the Israeli population is the high prevalence (4 to 5%) of the carrier state for FXI-deficiency, due primarily to two common FXI mutations in people of Jewish ancestry [17]. There were 722 cases of pneumonia during more than 70,000 person/years of follow-up. Patients with partial or severe FXI deficiency, despite being somewhat older and having more co-morbidities than patients with normal FXI levels, had hazard ratios for developing pneumonia that were comparable to patients with normal FXI levels, after adjustment for age (partial deficiency 0.87 [95% CI, 0.67–1.14], severe deficiency 0.95 [0.69–1.30]). The corresponding hazard ratios for severe pneumonia requiring hospitalization were comparable (1.0 [0.70–1.48] and 0.86 [0.53–1.40], respectively). There were no differences between groups in 30- or 90-day mortality.

These data are consistent with the general impression that humans lacking FXI or other components of contact activation are not more prone to infection than the general population. It must be acknowledged that *F11*^{-/-} mice completely lack FXI, while the majority (but not all) of the FXI-deficient patients in the study by Salomon et al. had some FXI in their plasmas. Therapeutic inhibition of FXI is likely to produce a condition more like partial deficiency rather than total deficiency. It is also important to recognize that FXI and its deficiency state in humans were not described until the 1950's, well after the onset of the antibiotic era. It is possible that we reduce the risk of infection associated with FXI deficiency by early initiation of antibiotic therapy in symptomatic individuals. Nevertheless, there is a strong likelihood that the discrepancy between the human and mouse data reflects species differences, factors related to specific mouse strains, or the method of injury/infection used in the mouse models. Unlike humans, and some domestic animals (cattle and dogs), FXI-deficiency is not clearly linked to abnormal hemostasis in mice. This raises the possibility that FXI performs different functions in different species. Furthermore, to our knowledge, published studies involving *F11*^{-/-} mice all used animals derived from a single line on the C57Bl/6 background first described in 1997 [19]. Features unique to this line that are distinct from FXI deficiency may render them more prone to leukocyte infiltration after pulmonary injury. Some of these issues could be addressed by using pharmacologic approaches to reduce FXI in WT mice of various strains prior to pulmonary infection.

The results of the report from Salomon *et al.* should reassure developers of antithrombotic compounds that drugs targeting FXI/FXIa will not significantly compromise host defense in humans (barring unanticipated off-target effects). However, if such compounds become part of standard medical practice, we should not lose sight of the possibility that they may alter host response or susceptibility to infection in a manner that could be clinically consequential in some individuals.

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