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Editorial Open Access

Recent Research Perspectives on *in vivo* Auto-activation Surfaces of Factor XII

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Editorial

The identification of a convincing *in vivo* surface that supports constitutive auto-activation of Factor (F)XII has proven to be a formidable task [1]. Nonetheless, extracellular RNA [2], platelet-released polyphosphates [3] and misfolded and aggregated proteins [4] have recently been described as FXII binding surfaces, which induce auto-activation of the zymogen. Following these developments, a recent report by Oschartz et al. [5] proposed that heparin serves as an *in vivo* auto-activation site for FXII during IgE-antigen-mediated mast cell activation. In the study, the authors showed that heparin treatment of normal human plasma resulted in activation of the FXII zymogen and sequential activation of downstream plasma kallikrein-kinin system (KKS) components, namely plasma prekallikrein (PPK) and high molecular weight kininogen (HK), resulting in bradykinin formation. This heparin-mediated activation cascade was absent when the authors used FXII-deficient plasma suggesting FXII is responsible for initiating plasma KKS activation. Moreover, heparin-induced bradykinin-mediated microvascular leakage and edema formation was abolished in $F12^{-/-}$ mice, which are deficient of FXII and defective in contact system-driven bradykinin generation, further corroborating a role for heparin as a FXII activator and trigger of FXII-dependent bradykinin formation.

Most remarkably, the results of the Oschartz et al. [5] study reveal that heparin-mediated FXII activation exclusively initiates downstream PPK activation, driving bradykinin formation. In this regard, the authors showed that heparin treatment of plasma did not activate FXI, an additional substrate of activated FXII responsible for the initiation of the intrinsic coagulation pathway. This observation has been demonstrated previously with misfolded proteins [4], but not extracellular RNA [2] or platelet polyphosphates [3]. Thus, it appears that some, but not all, FXII activation surfaces can differentially direct plasma KKS activation independent of a coagulation response. How a given FXII activator regulates this response is unclear, but the authors propose it may involve the generation of different molecular forms of the enzyme. A similar hypothesis was presented by Maas et al. [4], who suggested the preferential formation β-FXIIa, which activates PPK while remaining inactive against FXI, could be responsible for the biased effect of FXII activation in response to misfolded proteins.

Ultimately, however, the mechanisms of FXII auto-activation described by Oschartz et al. [5] and others are non-physiologic and only reported to occur in disease processes, for example, following cellular injury [2] and platelet activation [3] during thrombus formation, in protein misfolding diseases, such as systemic amyloidosis [4], and in mast cell-mediated anaphylaxis [5]. Nevertheless, these studies validate auto-activation of FXII as a genuine *in vivo* phenomenon, which, most notably, occurs constitutively in disease states [6]. A cell based pathway of FXII activation has been hypothesised, which is perhaps responsible for constitutive FXII activation in physiologic settings. This pathway results in kinetically favourable FXII activation by plasma kallikrein following activation of a complex of HK and PPK on the cell surface [7-9]. As this pathway occurs independent of FXII [10], activation of the zymogen is likely a secondary outcome of kallikrein formation, increasing the rate and extent of PPK activation, rather than initiating downstream activation cascades.

Overall, the Oschartz et al. [5] study presents a novel paradigm of constitutive FXII auto-activation and FXII-dependent bradykinin formation in mast cell-mediated reactions. In addition, the data validate previous findings regarding selective FXII activation of inflammatory processes in the absence of hemostasis. Although our understanding of such processes has significantly evolved over recent decades, the mechanisms governing these unique pathways require further elaboration. As such, the Journal of Autacoids is committed to providing some answers, with its open access policy and special features well suited to surely attracting a large audience and facilitating advancement in the field.

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