

What we have learned from Structure of High Molecular Weight Kininogen

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High molecular weight kininogen (HK, Williams-Fitzgerald-Flaujeac factor) is a unique nonenzymatic cofactor of the plasma kallikrein kinin system (KKS), also known as contact activation system or intrinsic pathway, with multiple domains that regulate numerous biological pathways and cell functions including thrombosis, inflammation, and angiogenesis (Figure 1) [1,2]. HK, cleaved HK (HKa), and each of HK domains are important at many points during tissue remodeling and functioning following injury, establishing its role in vascular pathology and disease. Needless to say, the precise mechanisms underlying these effects still remain to be fully delineated.

HK, prekallikrein (PK, Fletcher Factor) and FXII (Hageman factor) are the key components of the KKS pathway of blood coagulation. This pathway is initiated when FXII comes in contact with negatively charged surfaces such as constituents of the sub endothelial matrix (glycosaminoglycans and collagen) and gets auto activated to the active serine protease factor XIIa (α FXIIa) in a reaction involving HK and PK (Figure 1, 6). Of note, although complex and controversial, many other matching null hypotheses attempt to explain how activation of the KKS pathway might occur under physiological conditions (Figure 1, 1 through 5). However, there are increasing concerns regarding the quality and reporting of *in vitro* studies. Some of these concerns include autoactivation of PK, presence of kallikrein (an active form of PK) or encrypted activated FXII in the assay, presence of activated cells and suppression or loss of antithrombotic activity of the endothelial surface under experimental conditions. Although many obstacles such as problems of sensitivity and selectivity have affably been overcome, a search for alternative combination of methods is urgently needed to determine possible roles of KKS in health and disease.

HK has more interaction partners than any of the other blood coagulation factors. The emerging evidence suggests that HK also contribute to host responses to infection via a tight interaction with the microorganism surface proteins. This interaction leads to activation of KKS in human plasma, resulting in cleavage of HK, liberation of the potent proinflammatory peptide bradykinin, and initiation of the intrinsic pathway of coagulation. This initiation of programmed HK self-suicide marks the beginning of tissue healing via induction of inflammation and coagulation, the two host defense system. Notably, peptides derived from HK are used in novel approaches to reduce nanomaterial toxicity [3] and as antimicrobial peptides [4].

HK works like a wheel with many spokes, each with an unique biological function. Take away a spoke and the wheel can continue to spin without concern of loss of its remaining functions, suggesting that while each domain can function independently, all HK domains are designed to work together to provide optimal benefit for cytoprotection of normal tissues (Figure 1). On the other hand, take away the wheel and almost no physiological abnormality is apparent suggesting that alternative mechanism(s) exists that compensates, to certain extent, for the deficiency of HK in humans.

In summary, although our understanding of how HK interacts with other proteins has shed some light on the distinct role(s) that each HK domain might play, many aspects of HK function still remain unclear. Why is HK or each domain of HK uniquely vital to the functioning of tissues and organs while HK deficiency is not lethal? Why does HK have diverse specific interaction partners? How does HK cross the blood brain barrier? Does the central nervous system have its own KKS, which might be similar to its counterpart the renin-angiotensin system? If human species is better off without having HK, PK, or FXII, what can we do to encourage DNA to delete their genes? More importantly, why are critical amino acid residues in HK, PK, and FXII protected from point mutation or deletion? Is it possible that maximal biologic adaptability of these proteins is truly essential at times of health, injury, or illness?

Disclosure of conflict of interests

The authors state that they have no conflict of interest.

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Received July 13, 2011; Accepted July 13, 2011; Published July 15, 2011

Citation: Kolte D, Zia S (2011) What we have learned from Structure of High Molecular Weight Kininogen. *J Clin Toxicol* 1:102e. doi:10.4172/2161-0495.1000102e

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