Fifty years of research on the plasma kallikrein-kinin system: From protein structure and function to cell biology and in-vivo pathophysiology

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For forty years my laboratory has been studying the kallikrein-kininogen-kinin system (KKS). I was challenged by my mentor Dr. Sol Sherry in whose laboratory I was completing my postdoctoral fellowship in 1966–1967 to find out what major plasma esterase was being activated by exposure of plasma to glass beads. Although both factors XII and XI were candidates, neither accounted for the high enzyme levels. I then purified plasma kallikrein for the first time. Based on these results, we derived a synthetic substrate assay which we used to assay prekallikrein in human and rodent plasma.

We next investigated the natural substrate of plasma kallikrein. Kininogens were described as the proteins (1) from which proteases released the peptides bradykinin (BK) and lysyl-bradykinin (Lys-BK) (Fig. 1). By 1967, two forms of purified human plasma kininogens had been described: Low-molecular-weight kininogen (LK) and high-molecular-weight kininogen (HK) (2). Both are substrates for the proteolytic release of Lys-BK and BK by tissue and plasma kallikreins, respectively. HK is a β globulin, 120 kDa polypeptide with a plasma concentration about 80 μg/ml (670 nM). LK is a β globulin with a plasma concentration of 60 μg/ml and a molecular weight of 68 kDa. HK, along with prekallikrein and factor (F)XII, is a component of the plasma KKS, also known as the intrinsic activation system of coagulation or the contact system. The KKS has generally been known to be activated by contact with negatively charged macromolecules, leading to binding and activation of FXII (FXIIa); activation of prekallikrein (PK) to kallikrein (Kal) by FXIIa; cleavage of HK by kallikrein with release of bradykinin (BK); and formation of cleaved kininogen (HKa) (Figs. 1 and 2). By 1982, the entire sequence of HK and LK as well as the nucleotide sequence of the kininogen gene was known (3).

From 1975 onward this view expanded thanks to the detection of healthy individuals with total or partial deficiency of HK (1, 4) in my laboratory and that of Wuepper, as well as studies of kininogen-deficient rats (5) and the development of different detection assays and more sophisticated techniques. The primary sequence of HK was determined (Fig. 3). HK is a multifunctional, multidomain protein (Fig. 1); and each HK domain may have distinct functions (6). We learned that PK exists as a biomolecular complex with HK in normal plasma (7). This association explains the reason why Ms. Williams (who lacked HK and LK) had low plasma activity of PK (40% of normal) which was discovered by adding purified HK to her plasma. We discovered that FXI also complexes with HK. HK accelerates the reciprocal activation of FXII by kallikrein and the activation of FXI. The association of HK with kallikrein and FXIa (Fig. 4) protects both enzymes from plasma inhibitors such as C1 (C1-INH) inhibitor and α_2-macroglobulin (8, 9). The KKS activation properties are regulated by HK's light chain, which contains both a surface-binding domain 5 (HKD5) and a zymogen binding domain 6 (HKD6) (10).

The KKS and artificial surfaces

The "anti-adhesive properties" of HKa are attributable to the conformation changes generated by HK cleavage. Only after HK cleavage to HKa is the molecule able to displace surface-bound fibrinogen from glass (11). Platelet reactivity with surfaces was found to be directly proportional to adsorbed fibrinogen (12), and at plasma concentrations HK completely inhibited thrombin-induced platelet aggregation (13). We demonstrated that normal neutrophils contain HK antigen and have binding sites for HK (14). After activation, plasma kallikrein (Kal) stimulates neutrophil aggregation (15) and degranulation (16). Both responses were absent in Ms. Williams' neutrophils and were re-

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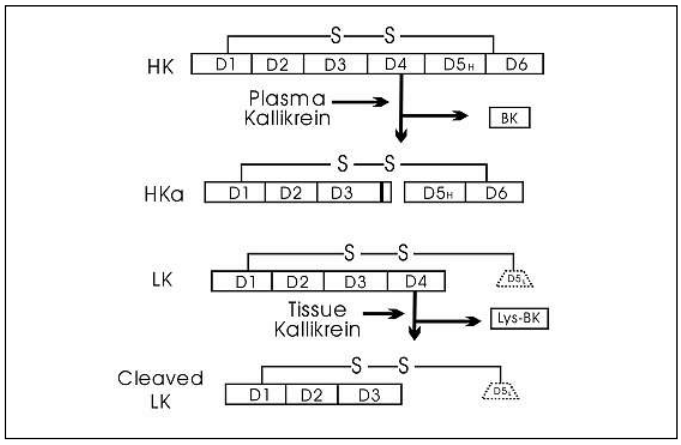

Figure 1: Representation of the domain structure of kininogens in 1987. HK: consists of a single chain of six units designated domains (HK D1-D6). HK is divided into a heavy chain (HKD1-HKD3) and a light chain ($HKD5_H$-HKD6). The heavy and light chains are linked by HKD4, which contains the sequence of bradykinin (BK). After releasing BK by proteolytic cleavage, the cleaved HK (HKa) contains a heavy chain and a light chain that remain connected by a disulfide bond. LK: is formed by a heavy chain (LKD1-LKD3), which is identical to HK's heavy chain, a small unique light chain ($HKD5_L$) and HKD4 that contains the sequence of lysyl-bradykinin (Lys-BK). LK heavy and light chains are linked together by a disulfide bond. LK is cleaved by tissue kallikrein releasing Lys-BK.

stored upon the addition of HK from normal plasma (14). We noticed that the heavy and light chains of HK had different functions; the heavy chain is responsible for HK's cysteine proteinase inhibitory activity, while the cofactor functions were a consequence of determinants on the light chain (17).

Kinins and cells

Involvement of HK and KKS was reported in sepsis (18), hereditary angioedema attacks (19), plasma prorenin activation, and angiotensin levels (20). BK is sufficient but not necessary to cause pain (21). Prolylcarboxypeptidase (PCP), an exopeptidase that cleaves small, biologically active peptides, was identified on endothelial cell surface as an activator of prekallikrein (besides FXIIa) (22). Two BK receptors (BK-2R and BK-1R) were identified and characterized and their ligands searched for. BK-2R is stimulated by BK and is present constitutively in different cells. BK-1R is stimulated by lysyl-bradykinin and its expression is induced by bacterial endotoxin and inflammatory mediators (23).

KKS and cell adhesion

Cell adhesion molecules are integral membrane proteins that have cytoplasmic, transmembrane and extracellular domains. The cytoplasmic tail often interacts with cytoskeletal proteins which serve as the actual anchor within the cell as well as interacting with signaling molecules which allow cellular responses. The extracellular domains of adhesion molecules are on the cell surface and communicate with other cells or matrix associating with other adhesion molecules of the same type; associating with other adhesion molecules of a different type, binding to a receptor, or binding to an intermediary 'linker' which itself associates with other adhesion molecules. Several different adhesion molecules have been identified and are divided into four major families, cadherins, immunoglobulin-like, selectins and integrins. The integrin family is involved in the inflammatory response, activating other cells, inducing the production and/or secretion of inflammatory mediators or attracting inflammatory cells to the site of injury. Hence their deficit or over-expression

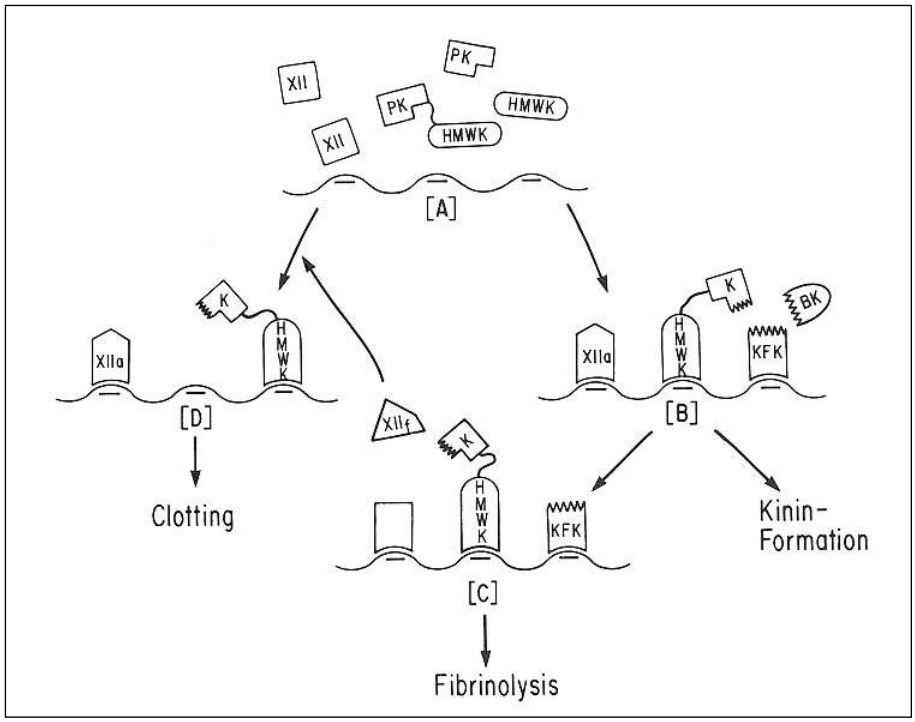

Figure 2: Representation of the relationships between contact factors as envisioned in 1982. Factor XII (XII), prekallikrein (PK) and high-molecular-weight kininogen (HMWK) are found in plasma. PK and HMWK occur as a complex (A) where they may bind to the endothelial cell (B) and induce kinin formation and fibrinolysis (C) or the clotting cascade (D). (Reproduced with permission from Haemostasis and Thrombosis, Basic Principles and Clinical Practice, Colman et al., First edition. Chapter 3, Lippincott. 1982).

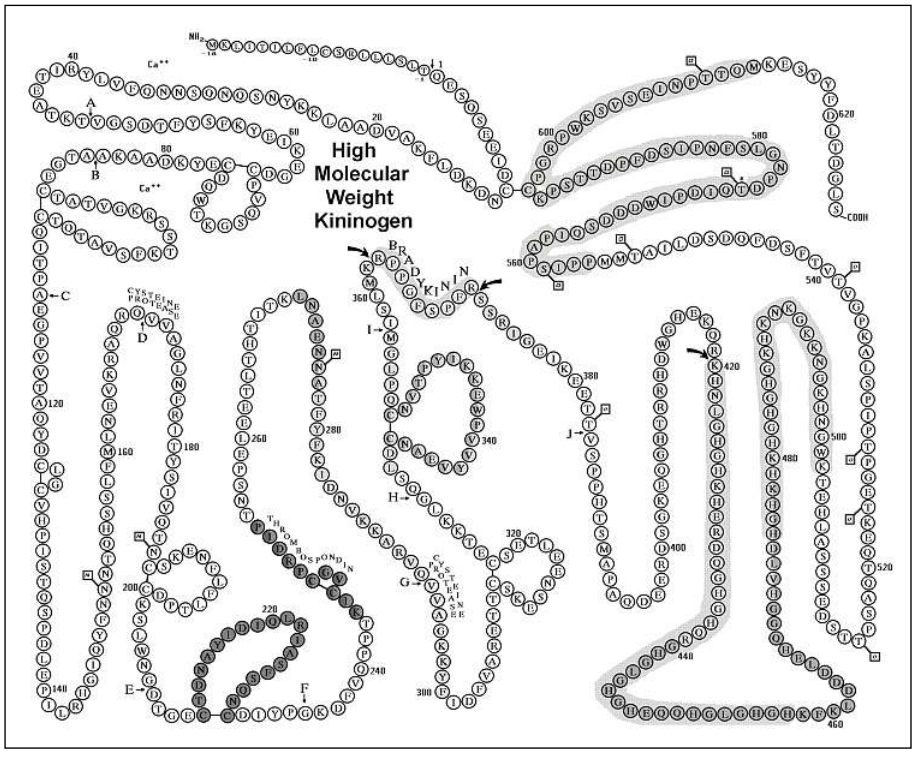

Figure 3: Representation of the primary structure of high molecular weight kininogen in 1994. Primary sequence and genetic structure of human plasma high-molecular-weight kininogen. Numbers 1–626 are amino acid (aa) locations with leader sequence - 18 through - 1. Letters A through J are the locations of the intron/exon junctions. Domain 1 (aa 1–113) is encoded by exons 1, 2 and 3. Domain 2 (aa 114–234) is encoded by exons 4, 5 and 6. Domain 3 (aa 235–357) is encoded by exons 7, 8 and 9. Domain 4 (aa 358–383) is encoded by exon 10_{BK}. Domain 5 (aa 384–502) is encoded by 5' portion of exon 10_{HK}. Domain 6 (aa 503–626) is encoded by the 3' portion of exon 10_{HK}. The curved arrows indicate plasma kallikrein cleavage sites. Boxed O are the locations of O-linked carbohydrate chains. Boxed N is the location of an N-linked carbohydrate chain. Cysteine protease sites (QVVAG) and the thrombospondin binding site (aa 244–254) are indicated as well. (Reproduced with permission from Haemostasis and Thrombosis, Basic Principles and Clinical Practice, Chapter 11. Colman et al., Lippincott, 3rd edition.)

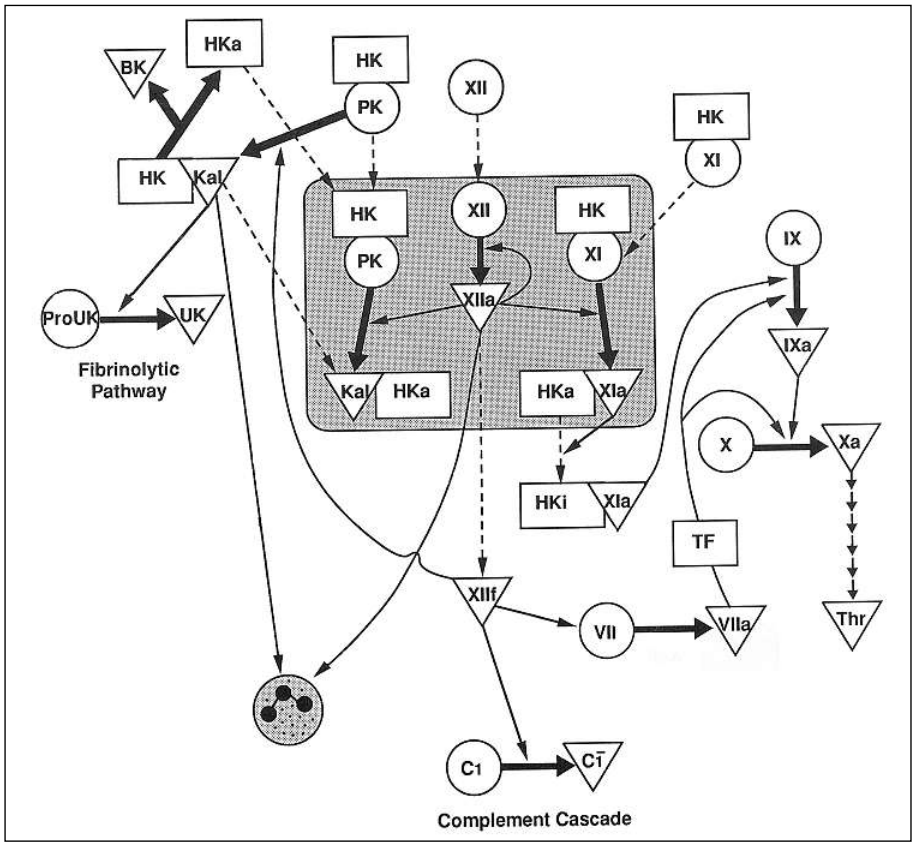

Figure 4: Relations between HK and the intrinsic coagulation, fibrinolysis and complement pathways as visualized in 1994. The following components are depicted: Bradykinin (BK), factor (F)IX, FXI, FXII, high-molecular-weight kininogen (HK), cleaved kininogen (HKa), kallikrein (Kal), prekallikrein (PK), prourokinase (ProUK), thrombin (Thr), urokinase (UK), first component of complement (C1), activated first component of complement (C1̄), activated species (a), FVII, FXII fragments (XIIf), tissue factor (TF), FX, inactivated HK (HKi), (Reproduced with permission from Haemostasis and Thrombosis, Basic Principles and Clinical Practice, Chapter11. Colman et al., Third edition. Lippincott, 1987)

may limit or prolong the inflammatory response. Despite these advances, by 1992 (Ms. William's death) there were still many questions to be answered and concepts to be developed. Questions such as: "How does HK protect plasma kallikrein and FXIa from enzymatic inhibition?", "Are the anti-adhesive properties of HK responsible for platelet reappearance in cardiopulmonary bypass?", "What is the mechanism of HK anti-adhesive properties?", "Does HK mediate neutrophil aggregation? And, if so,

which mechanisms are involved?", "Why does HK decrease in sepsis and during hereditary angioedema attacks?"

Cell biology and KKS

During the last 40 years the scientific community has been witness and active participant in the development of more precise and sophisticated laboratory techniques that allow us to literally look into the cell and begin to uncover the molecular mechanisms behind the clinical signs and symptoms observed in clinical practice. Thus, the era of receptor-ligand interaction, receptor-integrin complex formation and interaction, extra- and intracellular molecular signaling, gene and antibody therapy arrived. These laboratory techniques enabled us to look more thoroughly into the participation of HK in the inflammatory process including the KKS association with vascular injury (24) and activation of complement in humoral immune response (25).

HK and inflammation

In the last seven years we have focused on HK's role in inflammatory bowel disease (IBD) and arthritis, since these ailments may manifest as two different entities or as components of the same disease (26). IBD includes Crohn's disease and ulcerative colitis (UC). Both are associated with a number of chronic inflammatory disorders that affect other organ systems. Analyzing human tissue from patients afflicted with IBD, we found increased interstitial kallikrein and BK1R expression as well as high levels of C1-INH (27, 28). C1-INH is a serine protease inhibitor (serpin) that inactivates several different proteases: C1r, C1s, and MASPs (mannan-binding lectin-associated serine proteases) in the complement system, FXI and thrombin in the coagulation system, tissue plasminogen activator (tPA) and plasmin in the fibrinolytic system, and FXII and kallikrein in the contact system. Thus, the KKS is potentially involved in human IBD. We studied the effect of KKS in a model of colitis which requires a rat strain genetically susceptible to inflammation, the Lewis rat, and uses a stimulator of the innate immune system obtained from the wall of Streptococci group A (peptidoglycan-polysaccharide; PG-APS) to induce systemic inflammation. We found that HK levels are dramatically decreased in the inflamed rats (29). We also found that the cause of the susceptibility of Lewis rats to stimulation of the KKS is the presence of a point mutation at nucleotide 1586 which results in Ser511 in Brown-Norway rats to Asn511 in Lewis rats (30). This results in a change in the glycosylation resulting in a more rapid cleavage of the mutant HK to plasmin kallikrein.

We back crossed the susceptible Lewis rats to resistant Brown-Norway rats which are HK-deficient (5). After five and six generations we obtained a rat with 97–98% of Lewis genome and deficient in HK (5–10% of normal) as well as the normal HK levels on the same genomic background. When we challenged these HK-deficient rats with PG-APS to induce IBD, the animals had significantly decreased disease expression (less bowel lesions and decreased systemic inflammation) (31). In this model of IBD, the rats also develop arthritis; the evolution of the arthritis gave variable results in the HK-deficient rats. Hence, we examined the involvement of HK in inflammatory arthritis through two different animal models. In one animal model, Lewis rats were injected intraperitoneally with the same compound (PG-APS) as in previous studies and followed through the evolution of the acute and the chronic phases of arthritis. First we found that both BK-1R and BK-2R are involved in both acute (32) and chronic inflammatory arthritis (33) and that in the acute phase, BK-2R blockade moderately improves the inflammatory process. Our findings in the chronic phase pointed to what other researchers had suggested, that BK-1R and BK-2R signaling showed physiologic antagonism (34); and that both BK-R modulate the expression of selected cell adhesion molecules during the inflammatory response (35). The second model involved HLA-B27 transgenic rats. In this model the rats "spontaneously" develop both colitis and arthritis, mirroring patients with the HLA-B27 gene. Exposure to bacteria is required since rats kept in germ-free environments do not develop the syndrome. The KKS involvement was established by the improvement of both animal models when treated with a monoclonal antibody (mAb) targeting HK domain 5. The treatment was as effective when given at the same time as the antigenic compound (PG-APS injected rats) (36) as when given after the disease had well established in the HLA-B27 model (37). There were no clinical or pathologic side effects secondary to the treatment in either model. As final confirmation, when we challenged Lewis (98.5% genome; 6th generation) HK-deficient rats with PG-APS to induce inflammatory arthritis, the HK-deficient rats failed to develop arthritis (38) while their HK-normal littermates did develop a chronic, erosive arthritis.

Kininogen receptors and signaling pathways

Simultaneous to in-vivo studies, various research groups performed in-vitro studies and began to uncover some of the intracellular, molecular and signaling events that underlie HK functions. These researchers have shown that HK has more than one receptor on the endothelial cell: urokinase-type plasminogen activator receptor (uPAR) (39), complement protein C1q receptor (40), and cytokeratin-1 (41). These receptors seem to form a protein complex-receptor when bound to HK (42, 43); therefore, antibodies to any of these receptors would inhibit HK binding to cell surface. HKa or its D5 domain promote cell detachment by binding to the amino-terminal portion of vitronectin, preventing vitronectin interaction with uPAR on the surface of endothelial cells. This inhibition of adhesion or cell detachment induction is Zn^{2+} dependent (44). The expression of uPAR and Mac-1 (CD11b/CD18 integrin complex) on a neutrophil surface enhances neutrophil adhesion to vitronectin. This adhesion is further stimulated by the binding of uPA to uPAR, forming an uPA/uPAR complex on the neutrophil cell membrane. This adhesion enhancement is accompanied with increased phosphorylation of the focal adhesion kinases (FAK) and mitogen-activated protein kinase cascade (MAPK) (45). Both of these kinase families have been demonstrated to play crucial roles in cell migration (in the inflammatory process, cells such as monocytes, fibroblasts, etc.) (44). HK and HKa not only detach inflammatory cells (neutrophils and monocytes) from vitronectin by binding to Mac-1, but also inhibit these inflammatory cells from adhering to fibrinogen or to intercellular-adhesion molecule-1(ICAM-1) on endothelial cells (46). We narrowed HK and HKa

anti-adhesive properties to HKD5, and within HKD5, mainly to the amino-acid sequence H475-G497. HKD5 sequence G440-H455 has a lesser anti-adhesive effect (47).

In addition to its extracellular inhibition of adhesion, in-vitro studies of human monocytes revealed that HKa also can induce, by intracellular signaling, the release of cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6) and chemokines (IL-8 and MCP-1) as a function of time. We focused our studies on IL-1β since it has a major role in the inflammatory response. HKa induces the release of IL-1β as a function of concentration. We localized IL-1β release to HKD3 and HKD5. Within HKD3, the product of exon 7 (E7CP; HKD3 amino acid sequence G255-Q292) was responsible. Within HKD5, the amino acid sequences: K420-D474 and H475-S626 caused the release and synthesis of IL-1β. Exploring the intracellular effect of HK binding to Mac-1 on monocytes, we found out that the binding stimulates the nuclear factor-kappa B (NF-κB), c-Jun N-terminal kinases (JNK) and p38 MAP kinase signaling pathways (48). Consequently, our in-vitro findings show that HKa not only disrupts uPAR-integrin signaling pathways, but can also initiate several interrelated signaling cascades, helping us to understand why the HK- deficient rats developed only a minimal inflammatory response to PG-APS injections. In both experimental models (IBD and arthritis) PG-APS induces both, a cytokine and chemokine response. This response seems to be mediated, in part by HKa and HK deficiency appears to limit the capability of leukocytes to respond to the inflammatory stimulus and hence, develop only minimal disease.

Mechanism of inflammation related to KKS

In summary (Fig. 5), at the onset of an inflammatory insult, HK-PK complexes adhere to endothelial cell membranes, PK is cleaved to Kal and Kal cleaves HK, releasing BK and HKa. BK stimulates BK-2R and inflammatory cell adhesion molecules. Simultaneously, leukocytes marginate within the blood vessel

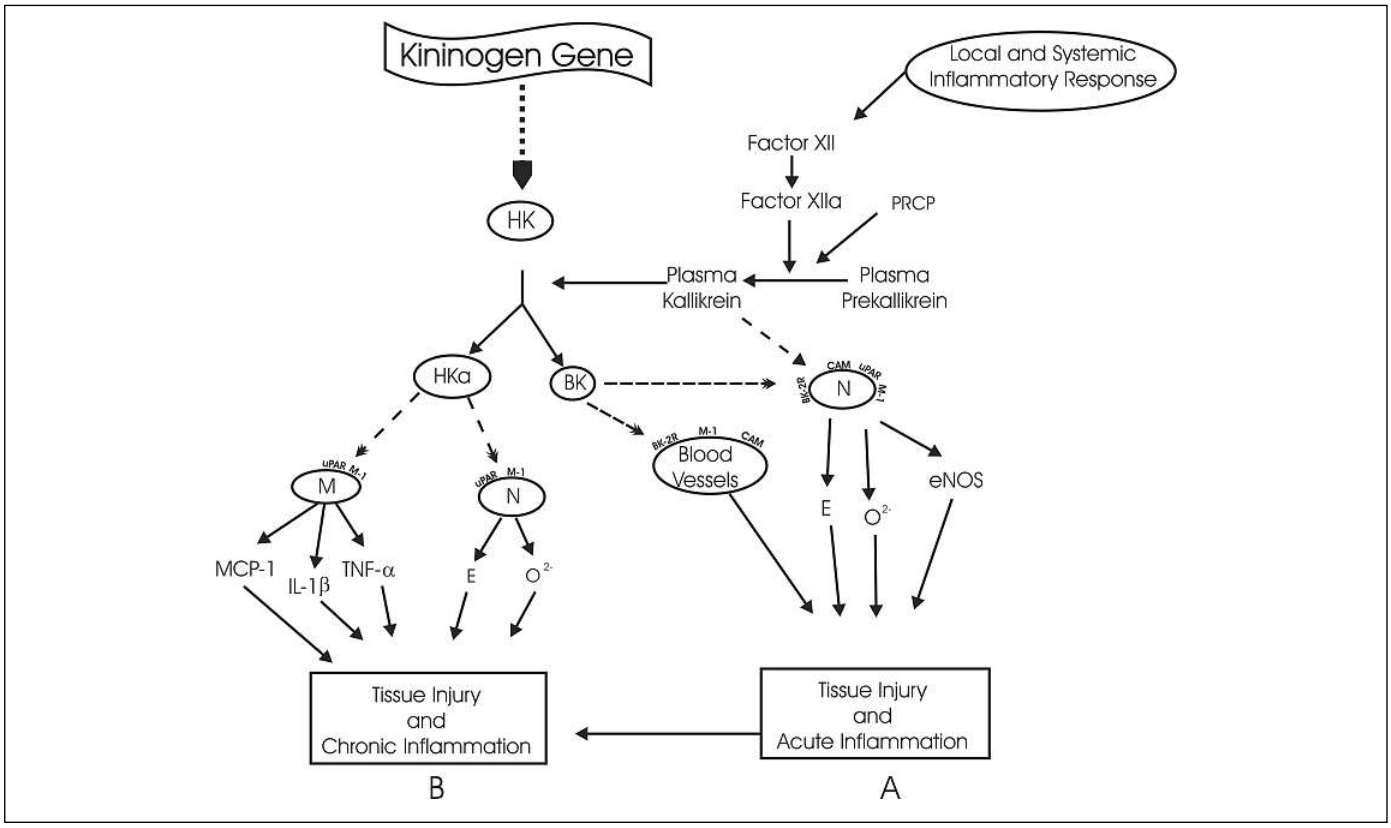

Figure 5: Role of the kallikrein-kinin system (KKS) in inflammation as envisioned in 2007. A) Acute processes: The kininogen gene codes for high molecular weight kininogen (HK). Following bacterial pathogen exposure, the KKS is initiated by activation of plasma factor XII to factor XIIa or by prolylcarboxypeptidase (PRCP) on the endothelial cell and leukocyte surface. Factor XIIa/PRCP cleaves plasma prekallikrein generating the enzyme plasma kallikrein, which in turn cleaves high-molecular-weight kininogen (HK) to yield bradykinin (BK) and cleaved high-molecular-weight kininogen (HKa). Kallikrein is chemotactic, induces neutrophil (N) aggregation and stimulates the release of elastase (E) and superoxide (O^{2-}) as potent inducers of tissue injury. BK through its receptor BK-2R and cell adhesion molecules (CAM) stimulate intracellular signaling and the release and synthesis of other mediators generating pain (prostaglandin release), vascular dilation (prostaglandin I_2) or permeability (endothelial nitric oxide system: eNOS). This pathway initiates an acute inflammatory response. B) Chronic processes: HKa has several activities, via the generation of factor XIIa and activation of factor XI the coagulation cascade is promoted. HKa receptors including urokinase-type plasminogen activator receptor (uPAR) and Mac-1 (M-1) are located on the surface of monocytes (M) and neutrophils (N). Through these receptors, HKa stimulates the release of cytokines tumor necrosis factor (TNF)-α interleukin (IL)-1β, chemokines monocyte chemoattractant protein-(MCP)1 and IL-8 from monocytes and superoxide (O^{2-}) and elastase from neutrophils. All these elements induce tissue injury and eventually chronic inflammation.

and migrate towards the extracellular matrix or the place of inflammatory insult. BK-1R expression is induced, and its stimulation induces the activation of more cell adhesion molecules regulating the neutrophils adhesion cascade. HKa binds to neutrophils and monocytes and inhibits their adhesion to fibrinogen and/or vitronectin, inhibiting their migration, thus, keeping them where they are (site of injury). In a parallel manner, HKa binding to monocytes induces the production and release of inflammatory cytokines and chemokines. HKa is eventually inactivated by proteases and has a biological half-life of nine hours. The persistence of HKa seems to maintain the inflammatory response which explains why kallikrein inhibition, HK deficiency or treatment with anti-HK antibodies decreases PG-APS induced inflammation (Fig. 5).

We have learned much about HK and the KKS. Nevertheless, this new century launches with a new set of intriguing questions. Receptors and their interaction with HK and the KKS are being described, such as the protease activated receptors (49). New functions have been suggested such as the presence of HK fragments in milk and its role in the growth and development of the newborn (50). Other signaling pathways are still waiting to be detected, explored and described. As our search for knowledge continues, our voyage will be filled with astounding revelations and captivating questions.

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