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Functional intersection of the kallikrein-related peptidases (KLKs) and thrombostasis axis

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Abstract

A large body of emerging evidence indicates a functional interaction between the kallikrein-related peptidases (KLKs) and proteases of the thrombostasis axis. These interactions appear relevant for both normal health as well as pathologies associated with inflammation, tissue injury, and remodeling. Regulatory interactions between the KLKs and thrombostasis proteases could impact several serious human diseases, including neurodegeneration and cancer. The emerging network of specific interactions between these two protease families appears to be complex, and much work remains to elucidate it. Complete understanding how this functional network resolves over time, given specific initial conditions, and how it might be controllably manipulated, will probably contribute to the emergence of novel diagnostics and therapeutic agents for major diseases.

Keywords

activation cascade; kallikrein; kallikrein-related peptidase (KLK); plasmin; thrombogenesis; thrombolysis; thrombostasis

Introduction

The study of the human kallikrein-related peptidases (KLKs; for a recent review see Sotiropoulou et al., 2009) has witnessed remarkable progress over the past decade. Initial studies of the properties of KLK proteins from tissue extracts were obfuscated by the lack of both an understanding regarding the total number of uniquely different KLK proteins and an associated commonly accepted nomenclature. The deciphering of the genomic organization of the human KLK gene locus (Gan et al., 2000; Harvey et al., 2000; Yousef et al., 2000), as well as the adoption of a commonly accepted nomenclature (Lundwall et al., 2006), resolved these two fundamental issues. The vast body of work has associated several cancer pathologies with differential regulation or expression of individual members of the KLK family, and has served to elevate the importance of the KLKs in serious human disease and their diagnosis (Diamandis et al., 2000; Diamandis and Yousef, 2001; Yousef and

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Diamandis, 2001, 2003; Borgoño et al., 2004). Studies of the functional properties of KLK proteins have progressed from individual members (Lilja, 1985; Watt et al., 1986; Lundstrom and Egelrud, 1991; Kishi et al., 1997; Little et al., 1997; Brattsand and Egelrud, 1999; Nelson et al., 1999) to the interaction among sets of KLKs active in specific tissues (Lovgren et al., 1997; Brattsand et al., 2005; Michael et al., 2006). Similarly, initial studies of KLK substrate specificities has progressed from analysis of individual substrates under a single buffer condition to specificity profiling using peptide or phage libraries (Janssen et al., 2004; Debela et al., 2006; Li et al., 2008), as well as studies of the effects of a broad range of cosolvents upon enzymatic activity (Angelo et al., 2006). Furthermore, the early association of KLKs with important pathologies has progressed to detailed studies of signaling through specific receptor molecules (e.g., the PARs), providing a molecular description of the role of specific KLKs in hormone-like signal transduction pathways (Oikonomopoulou et al., 2006b; Hollenberg et al., 2008; Ramsay et al., 2008a; Vandell et al., 2008), as well as widespread acceptance of disease-specific association of particular KLKs (particularly KLK3 with prostate cancer) and with significant diagnostic utility (Stamey et al., 1987; Catalona et al., 1991; Lilja et al., 2008).

Because the KLKs are initially secreted as inactive pro-forms that must be proteolytically cleaved to achieve functional activity, there has been substantial interest in the potential for activation cascades or networks among sets of coexpressed KLKs. This set of activation interactions among the KLKs, defining a network of regulatory interactions among the KLKs, is termed the KLK ‘activome’. As with other forms of characterization, studies of the KLK activome have progressed from individual pairwise studies (Lovgren et al., 1997; Denmeade et al., 2001) to high-throughput efforts to provide a comprehensive description of the entire KLK activome potential (Yoon et al., 2007, 2009). These and other studies have demonstrated a vast potential for self-activation and reciprocal cross-activation among the KLKs, resulting in complex networks that contrast with more classical linear-type cascades (e.g., the blood-clotting cascade). Interest is expanding to understand how the KLK family might functionally interact with members of other major protease families, such as the matrix metalloproteases and thrombostasis enzymes. The purpose of this review is to summarize available data related to the functional interactions between the KLKs and proteases of the thrombostasis system (i.e., both thrombogenic and thrombolytic proteases). A thorough review of such interactions was provided by Borgoño and Diamandis in 2004 (Borgoño and Diamandis, 2004); however, significant additional new data has been reported. These data provide compelling evidence that a substantial functional intersection exists between these two major protease families.

Proteolytic activation of pro-KLKs by thrombostasis proteases

Plasmin and urokinase-type plasminogen activator (uPA) have both been shown to activate pro-KLK6, and plasmin is currently the most efficient known activator of pro-KLK6 (Blaber et al., 2007; Yoon et al., 2008). Pro-KLK11 can be activated by both thrombolytic and thrombogenic proteases, including plasmin, uPA, factor Xa, and plasma kallikrein; of these proteases, plasma kallikrein is the most efficient activator (Yoon et al., 2008). Pro-KLK12 can similarly be activated by a set of both thrombolytic and thrombogenic proteases, including plasmin, uPA, thrombin, and plasma kallikrein; however, in this case thrombin is the most efficient activator. Indeed, the activation profile of thrombin against the KLK pro-sequences as substrates indicates that thrombin has a significant and unique specificity for pro-KLK12 (Yoon et al., 2008). Pro-KLK14, like pro-KLK6, can be activated by the thrombolytic proteases plasmin and uPA, with plasmin being the more efficient activator of the two (Yoon et al., 2008).

Plasmin, and to a lesser extent uPA, stand out as 'general activators' of the KLK pro-peptide sequences; in this regard, both Arg- and Lys-P1 pro-peptides appear efficiently hydrolyzed. Factor Xa and plasma kallikrein exhibit a similar activation profile against the KLK pro-peptide sequences, with a pronounced Arg selectivity, and with plasma kallikrein generally the more active of the two proteases (Yoon et al., 2008). Figure 1 shows a 'heat map' indicating the percent hydrolysis of KLK pro-peptides by different thrombostasis proteases. In this representation the extent of hydrolysis is indicated by the gradation of hue, where red=100%, and blue=0%, and the standard spectrum of colors (i.e., red, orange, yellow, green, blue) define the intermediate percent hydrolysis values. Available data comparing the hydrolysis rates by thrombostasis proteases of KLK pro-peptide sequences versus the intact native pro-KLK protein (Figure 2) suggest that some interactions can utilize exosites separate from the pro-peptide region to enhance catalysis. In particular, Figure 2 indicates that the uPA/pro-KLK6, plasma KLK/pro-KLK12, uPA/pro-KLK12, and plasmin/pro-KLK6 hydrolytic rates are enhanced with the intact pro-KLK protein, thereby identifying the presence of potential exosite interactions.

Proteolytic activation of thrombostasis proteases by mature KLKs

(MOUSE)Klk1 (mouse mGK-6) can activate single-chain uPA (independent of plasmin) in plasminogen-deficient mice (List et al., 2000). The urine from plasminogen$^{-/-}$ mice contained active two-chain uPA as well as a protease capable of activating exogenously added pro-uPA. Mass spectrometry and peptide mapping identified this protease as mGK-6 the mouse ortholog of (HUMAN)KLK1 (true tissue kallikrein). These results demonstrate that KLK1 is an activator of pro-uPA in the urinary tract; furthermore, as KLK1 occurs in other tissues, in addition to plasma, it is also a likely physiological activator of pro-uPA in other locations and tissue microenvironments.

(MOUSE)Klk1 can convert single-chain tissue plasminogen activator (tPA) to two-chain tPA (Rajapakse et al., 2007). Single-chain tPA and two-chain tPA are different in plasminogen activating ability and affinity to fibrins. It has been shown that two-chain tPA has ten times the plasminogen activating ability as compared with single-chain tPA (Japanese Patent Laid-Open No. 118717/1984). Single-chain tPA has very low plasmin-generating activity in the absence of cofactor fibrin, whereas two-chain tPA shows full activity without fibrin (Stubbs et al., 1998). Thus, (MOUSE)Klk1 could trigger activation of the tPA/plasmin system in the absence of fibrin (Rajapakse et al., 2007).

As regards the ability of other members of the KLK family to proteolytically activate thrombostasis proteases, KLK2 has been shown to activate single-chain uPA, leading to the generation of plasmin (Frenette et al., 1997), KLK4 can activate single-chain uPA, leading to the generation of plasmin (Takayama et al., 2001), and KLK8 has also been shown to have a single-chain tPA converting activity (Rajapakse et al., 2005).

Proteolytic inactivation/degradation of thrombostasis proteases/proteins

KLK3 from human seminal plasma can degrade fibrinogen (Watt et al., 1986), producing fibrin/fibrinogen degradation products that can profoundly impair the hemostatic process. KLK4 can digest the α-chain of fibrinogen; as KLK4 expression is upregulated in prostate cancer its potential involvement in cancer pathology could be via the degradation of collagen and fibrinogen in the extracellular matrix, thereby facilitating cancer cell invasion (Obiezu et al., 2006). KLK5, and to a lesser extent KLK8, have been shown to degrade both the α- and β-chains of fibrinogen (Brattsand et al., 2009). Cryptic tPA and plasminogen binding sites are located within the fibrinogen molecule, and a portion of the α-chain contains both plasminogen and tPA binding sites (Tsurupa and Medved, 2001). Thus, KLK4, 5, and 8 cleavage of fibrinogen α-chain can regulate functional interactions between

components of the thrombolytic system. Internal cleavage of uPA by KLK5, potentially resulting in functional inactivation of uPA, is predicted based upon positional scanning synthetic combinatorial peptide libraries (Borgoño et al., 2007a).

The interactions described above, as well as the prior description of pro-KLK activations by thrombostasis proteases, and the proteolytic activation of thrombostasis proteases by mature KLKs, are summarized in Figure 3. In this Figure the arrowheads indicate specific proteolytic activities, typically resulting in activation of inactive protease pro-forms. In some cases, the specific proteolytic activity results in inactivation of the target protease (indicated by a blunted line).

Generation of angiostatin-like fragments from plasminogen by KLKs

Angiostatin is a fragment of plasminogen (containing kringle domains 1–4) that is a biologically active inhibitor of angiogenesis (O'Reilly et al., 1994). Angiostatin is produced by the proteolytic cleavage of plasminogen by metalloelastase (matrix metalloprotease 12) (Dong et al., 1997). KLK3 (prostate-specific antigen) has been shown to be able to convert Lys-plasminogen to biologically active angiostatin-like fragments by cleavage between Glu439 and Ala440 located between kringle domains 4 and 5 (Heidtmann et al., 1999). A study of the enzymatic properties of KLK5 suggested that it can potentially release angiostatin from plasminogen, as well as 'cystatin-like domain 3' from low-molecular weight kininogen, and fibrinopeptide B and peptide β15–42 from the Bβ chain of fibrinogen (Michael et al., 2005). Related processing of plasminogen to release angiostatin-like fragments has also been reported for KLK6 (Bayes et al., 2004), KLK13 (Sotiropoulou et al., 2003), and KLK14 (Borgoño et al., 2007c).

Protease-activated receptor (PAR) signaling

Protease-activated receptors (PARs) are G-protein-coupled receptors that can be activated by proteolytic cleavage and unmasking of a tethered receptor-triggering ligand (for review see Traynelis and Trejo, 2007). Cleavage downstream of such positions can 'disarm' PARS – rendering them incapable of subsequent proteolytic activation (Hansen et al., 2008). Activated PARs trigger responses ranging from vaso-dilation to intestinal inflammation, increased cytokine production, and increased nociception (Hansen et al., 2008; Hollenberg et al., 2008; Ramsay et al., 2008b). PARs play a key role in the body's innate immune defense system as a primary trigger of the inflammatory response and pain sensation owing to tissue injury or remodeling caused by pathogenic processes (Hollenberg et al., 2008). The coagulation cascade and PARs together provide a mechanism that links tissue injury to cellular responses, and PARs account for the majority of the cellular effects of thrombin (Coughlin, 2005).

In vivo, the enzymes of the coagulation cascade are physiological regulators of PAR activity. Thrombin can activate PARs 1, 3, and 4 *in vivo* (Coughlin, 2005; Ludeman et al., 2005). Factor-VIIa/Xa complex can activate both PAR1 and PAR2 (Ruf et al., 2003; Ruf and Mueller, 2006; Versteeg and Ruf, 2006). Plasmin can both activate and disarm PAR1 (Kimura et al., 1996; Kuliopulos et al., 1999) and can activate PAR4 (Quinton et al., 2004). In certain circumstances factor Xa can activate PAR1 (Blanc-Brude et al., 2005; Bhattacharjee et al., 2008), and PAR2 can be activated by factor Xa (Camerer et al., 2000). Fibroblasts appear to be the only cell type in which the effects of factor Xa are mediated mainly via PAR1 and not PAR2 (Blanc-Brude et al., 2005). PAR4 can be activated by several different proteases, including thrombin (Kahn et al., 1998; Xu et al., 1998). Activation of PAR4 can play a key role in generating two hallmarks of the inflammatory response: edema and granulocyte infiltration.

(MOUSE)Klk1 activates PAR4 in a rodent paw edema model (Houle et al., 2005); thus, the kallikreinkinin system is an important contributor to the inflammatory response. KLK4 activates both PAR1 and PAR2 but not PAR4 (Ramsay et al., 2008a). KLK14 can both activate and disarm PAR1, thereby preventing its activation by thrombin (Oikonomopoulou et al., 2006a). Immunohistochemical analysis demonstrates the coexpression of KLK4 and PAR2 in primary prostate cancer and bone metastases, indicating that KLK4 signaling via PAR2 could be important in prostate cancer. PAR2 is activated by KLK5, 6, and 14 (Oikonomopoulou et al., 2006a,b). KLK14 is as potent as thrombin for the activation of PAR4 (Oikonomopoulou et al., 2006a). KLK6 can activate PAR1 on NSC34 neurons and both PAR1 and PAR2 on Neu7 astrocytes (Vandell et al., 2008).

The above data highlight the potential for functional overlap between the kallikrein-related peptidases and thrombostasis system in PAR signaling and regulation (Figure 4A). Like thrombin, the KLKs are now considered as important ‘hormonal’ regulators of tissue function (Oikonomopoulou et al., 2006b).

uPAR cleavage

uPAR is a surface receptor for uPA that can result in the localization of plasmin-generating activity to the surface of cells, and is therefore a key element in processes affecting cell migration and tissue remodeling (Blasi and Carmeliet, 2002). Furthermore, by interacting with other molecules (e.g., vitronectin, integrin adhesion proteins, caveolin, and a G-protein-coupled receptor) uPAR can facilitate the initiation of several intracellular signal transduction pathways that involve cytosolic and transmembrane kinases, cytoskeletal components, and others (see the review by Blasi and Carmeliet, 2002).

The function of uPAR is regulated in part through proteolytic cleavage that can lead to the shedding of uPA-binding domain. KLK4 regulates the function of uPAR; KLK4 cleaves soluble recombinant uPAR both in its D1–D2 linker sequence and at the carboxy terminus of D3 (Beaufort et al., 2006). As the D1 amino-terminal domain of uPAR is required for high-affinity interactions between uPA and uPAR (Ploug, 2003), this action of KLK4 upon uPAR would effectively reduce the localization of plasmin-generating activity at the cell surface. The uPAR interactions involving members of the KLK family and the thrombostasis proteases are illustrated in Figure 4B.

Inhibitor function

Lymphoepithelial Kazal-type-related inhibitor (LEKTI, product of the *SPINK5* gene; Chavanas et al., 2000) contains 15 different serine protease inhibitory domains (Mägert et al., 1999). The inhibitory functions of the LEKTI domains are diverse and can inhibit plasmin (Mitsudo et al., 2003; Egelrud et al., 2005) as well as specific KLKs (including KLK5 and KLK7) (Egelrud et al., 2005; Schechter et al., 2005). The balance between KLKs and LEKTI is essential for normal skin desquamation and barrier function (Chavanas et al., 2000; Ekholm et al., 2000; Komatsu et al., 2002, 2008; Bitoun et al., 2003; Caubet et al., 2004; Egelrud et al., 2005; Schechter et al., 2005). The presence of KLKs and LEKTI can both be detected in serum (Mägert et al., 1999; Yousef and Diamandis, 2001), and thus potentially interact functionally with plasmin and other thrombostasis proteases.

Growth hormone (hGH) is proteolytically processed by plasmin and thrombin in both the pituitary and periphery (Baumann, 1991; Garcia-Barros et al., 2000). KLK5–8 and KLK10–14, as well as LEKTI are also expressed in the pituitary, localized to hGH-producing cells; thus, thrombostasis proteases, KLKs, and LETKI have been postulated to be involved in the regulation of hGH processing (Komatsu et al., 2007). Therefore, stratum corneum, blood,

and pituitary provide emerging evidence of important *in vivo* regulatory interactions between specific KLKs, thrombostasis proteases, and their inhibitors.

KLK5 is inhibited by α-2-antiplasmin (Michael et al., 2005) and is also predicted based on positional scanning synthetic combinatorial peptide libraries (Borgoño et al., 2007b). Newly identified SPINK9 inhibitor (product of the *SPINK9* gene) from human skin has been shown to inhibit KLK5 (Brattsand et al., 2009; Meyer-Hoffert et al., 2009). Although SPINK9 does not appear to inhibit other proteases (including thrombin and plasmin), its effective inhibition of KLK5 eliminates the degradation of fibrinogen by KLK5.

Other hydrolysis reactions involving KLKs

A putative proteolytic *inactivator* of KLK11 is plasmin (however, this cleavage can only partially inactivate KLK11; Luo et al., 2006) and both proteases are colocalized in semen. Mature KLK2 was shown to inactivate plasminogen activator inhibitor-1 (PAI-1) the primary inhibitor of uPA (Mikolajczyk et al., 1999), thus potentially effectively increasing the relative levels of active uPA. KLK3 has also been shown to bind to and inactivate protein C inhibitor (PAI-3/PCI) (Catalona et al., 1991) which is also an inhibitor of uPA.

Thrombin can activate MMP-2 (Lafleur et al., 2001). MMP20 can activate (PORCINE)pro-Klk4 (Ryu et al., 2002) an activity that is essential for the maturation (deproteination) of enamel (Lu et al., 2008). Thus, there is additional uncharacterized potential for intersection of these three different protease families.

Summary

One area of current interest in KLK research is an integrated understanding of the functional role of the KLKs in health and disease. In this regard, study of the intersection between the KLK and thrombostasis axes suggests an important and extensive interaction. KLKs are expressed in a wide range of tissues at both the mRNA and protein levels, with highest expression levels within select major tissues and lower levels of expression in many others (Clements et al., 2001; Yousef and Diamandis, 2001; Komatsu et al., 2003). Of particular note is that contact between thrombostasis proteins in plasma, and secreted KLKs in the extracellular matrix, is facilitated under conditions of vascular permeability such as occurs during inflammation, edema, and tissue injury; thus, functional interaction between these two protease axes defines pathogenic conditions. Reports of coexpression of thrombostasis proteases and members of the KLK family are emerging in disease states, particularly cancer (Pettus et al., 2009). Research into the functional interaction between the KLKs and thrombostasis proteases is therefore likely to result in significant new advances in the diagnosis and treatment of important diseases associated with inflammation, tissue injury, and remodeling.

Presumably, only a subset of functional interactions between the KLK and thrombostasis axes has been identified to date. The mesh-like network of the activation connectivities within the KLK activome is much more complex in contrast to more simple schemes of linear activation cascades (e.g., the coagulation cascade), and when combined with the additional interactions involving the thrombostasis axis, the complexity is increased. It is difficult to simply look at such networks and comprehend how they would resolve over time for a particular initial condition or stimulus. However, such networks can be considered as a series of simultaneous rate equations, the majority of which can be approximated by Michaelis-Menten kinetics. Simulations of such networks can be constructed, assuming that the relevant kinetic constants and initial concentrations of components are known. Rate data are currently reported mostly for particular KLK/peptide substrate combinations, and there is limited data for intact protein substrates. Efforts to develop methods to quantify *in vivo*

concentrations of particular KLKs have also been reported (Oikonomopoulou et al., 2008). In principle, kinetic rate data for different enzyme/substrate combinations, produced through the effort of independent investigators, can be combined to facilitate construction of the overall network. As such kinetic data are keenly sensitive to buffer conditions of pH and cosolvents, only data collected under identical conditions can effectively be combined. In this regard, phosphate buffered saline (0.15 M NaCl, pH 7.4) might serve as a useful, commonly accepted condition. However, another challenge in understanding KLK regulation is knowing the exact physiological condition of KLK action. Studies have shown that the presence of metal ions, salts, and glycans can substantially alter the kinetic properties of KLKs (Lovgren et al., 1999; Angelo et al., 2006). Additionally, determining solute concentrations within local physiological environments is a challenge. Thus, functional networks determined under ‘standard’ conditions are probably highly plastic under actual physiological conditions.

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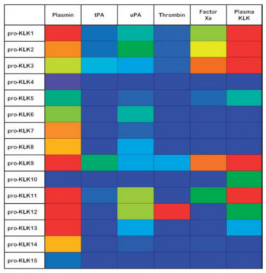

Figure 1. A 'heat map' indicating the percent hydrolysis of KLK pro-peptides by different thrombostasis proteases

In this representation the extent of hydrolysis is indicated by the gradation of hue, where red=100%, and dark blue=0%, and the standard spectrum of colors (i.e., red, orange, yellow, green, blue) define the intermediate percent hydrolysis values. The indicated hydrolysis is for pH 7.4 conditions over 24 h (Yoon et al., 2008).

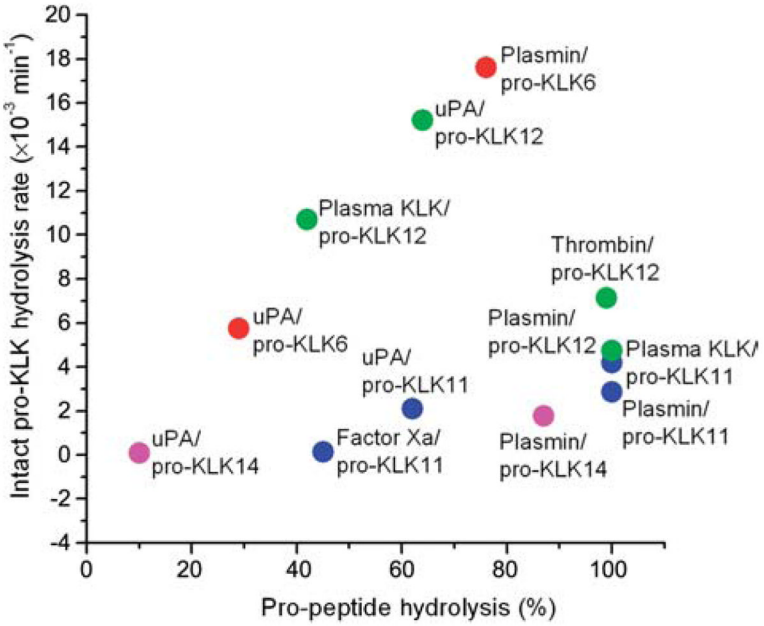

Figure 2. A comparison of the percent hydrolysis of KLK pro-peptides (abscissa) with the hydrolysis rate for intact pro-KLK proteins (ordinate) (Yoon et al., 2008)

Data points are colored according to the individual pro-KLK protein being hydrolyzed. The plot identifies hydrolyses that exhibit enhanced rates for the intact pro-KLK relative to the pro-KLK peptide (e.g., uPA/pro-KLK6, plasma KLK/pro-KLK12, uPA/pro-KLK12, and plasmin/pro-KLK6), thereby identifying potential exosite interactions present within the intact pro-KLK protein.

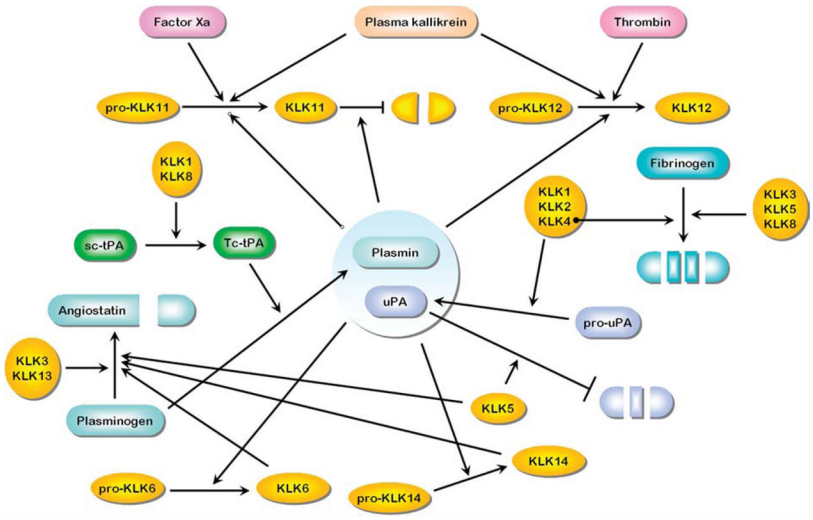

Figure 3. Interactions between the thrombostasis and KLK axes involving activation and proteolytic processing (see text for individual references)

Arrowheads indicate specific proteolytic activities, typically resulting in activation of inactive pro-forms. In some cases, the specific proteolytic activity results in inactivation of the target protease (indicated by a blunted line).

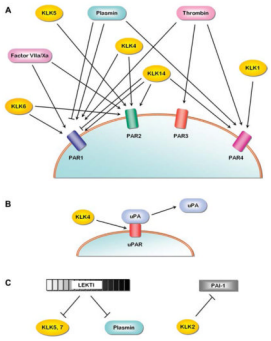

Figure 4. Additional regulatory interactions involving the KLKs

(A) Intersection between the thrombostasis and KLK axes and PAR signaling; (B) control of uPAR binding of uPA by KLK4; (C) intersection of thrombostasis and KLK axes related to specific inhibitors (see text for individual references). The meaning of the arrowheads and blunted lines follows the convention defined in the legend to Figure 3.