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REVIEW ARTICLE

The initiation and effects of plasma contact activation: an overview

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Abstract The plasma contact system sits atop the intrinsic coagulation cascade and plasma kallikrein–kinin pathway, and in vivo its activation contributes, respectively, to coagulation and inflammation mainly via two downstream pathways. This system has been widely investigated, its activation mechanisms by negatively charged surfaces and the interactions within its components, factor XII, prekallikrein and high molecular weight kininogen are well understood at the biochemical level. However, as most of the activators that have been discovered by in vitro experiments are exogenous, the physiological activators and roles of the contact system have remained unclear and controversial. In the last two decades, several physiological activators have been identified, and a better understanding of its roles and its connection with other signaling pathways has been obtained from in vivo studies. In this article, we present an overview of the contact pathway with a focus on the activation mechanisms, natural stimuli, possible physiological roles, potential risks of its excessive activation, remaining questions and future prospects.

Keywords Contact activation · Kallikrein–kinin · Coagulation · Inflammation · Factor XII

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Abbreviations

FXII	Factor XII
FXI	Factor XI
PK	Prekallikrein
HK	High molecular weight kininogen
BK	Bradykinin
KK	Kallikrein
B1R	Kinin B1 receptors
B2R	Kinin B1 receptors
polyP	Polyphosphate
uPAR	Urokinase-type plasminogen activator receptor
gC1qR	Globular heads of complement C1q
PRCP	Prolylcarboxypeptidase
Hsp90	Heat shock protein 90
FVII	Factor VII
TF	Tissue factor
APTT	Activated partial prothrombin time
ACT	Activated coagulation time
HAE	Hereditary angioedema
C1IHN	C1 inhibitor
OSCS	Oversulfated chondroitin sulfate

Introduction

The plasma contact system was firstly named for its activation by contact with glass surface (contact activation), which promotes blood clotting in vitro [1]. It consists of three serine proteases, coagulation factor XII (FXII or Hageman factor), coagulation factor XI (FXI), plasma prekallikrein (PK), and the non-enzymatic cofactor high molecular weight kininogen (HK); these proteins are also referred as contact factors. And after the discovery, it was pointed out by Ratnoff that this phenomenon is initiated by FXII, which is converted to its activated form (FXIIa) when

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binding to a negatively charged surface [2]. FXIIa can initiate intrinsic coagulation pathway through its substrate FXI and also trigger plasma bradykinin (BK) producing pathway by another substrate PK. The activated formed of PK, kallikrein (KK), is able to cleave HK to release BK a vasoactive factor and inflammatory mediator. Therefore, contact system is also known as kallikrein–kinin system [3].

The mechanisms of contact system activation in vitro and biochemistry of its components have been well illustrated, but the in vivo roles of this system are just beginning to emerge. Despite great progress has been achieved, it still remains unclear partly due to the elusive physiologic role of FXII [4]. Contact system is in the upstream of both intrinsic coagulation cascade and plasma BK formation pathway, and has been found to extensively involve in signaling pathways including thrombus formation and its opposite fibrinolysis, complement activation, blood pressure regulation, vascular permeability, etc. [3, 5]. For convenience's sake, the effects are divided into two categories—those associated with coagulation system are mediated by FXIa, while those related to inflammation are mainly triggered by KK-mediated BK formation. BK can initiate various intracellular signaling pathways via the G-protein coupled receptors, kinin B1 receptors (B1R) or/and kinin B2 receptors (B2R) in different cell membranes, and excessive BK can cause various diseases [6]. In addition to platelets and tissue factor, the crosstalk among various pathways, particularly that between coagulation and inflammation, could also be formed by contact system with the linkage of FXII or a platform provided by "contact surface", such as polyphosphate (polyP) [7–9].

Intriguingly, it is suggested that contact system is not necessary for some species to response against vessel injuries, because some contact factors do not exist in birds and all fish, and their deficiency do not affect normal hemostasis in human and mice [10, 11]. Thus, the long-standing debate about its contribution to the effective coagulation in mammals has been putting to the test again. We suggest that it may function for subtle regulation in thrombus formation and immune response, but produce undesired effects when activated improperly or excessively. Schmaier et al. have done significant work and provided insightful reviews for understanding this system both physiologically and pathologically [9, 12]. But the complex nature requires further exploration to offer clues for appropriate intervention or new drugs development. In this article, we first present an overall view about various mechanisms and stimulators of contact activation, which has not been described in detail in most related reviews; next, we will summarize the main downstream effects of contact system and penitential risks when activated excessively; we will also discuss its pathophysiological roles and the potential application of current knowledge for therapeutic benefits and the remained puzzles.

The mechanisms of contact activation

The classical activation pathway

A classical pathway for contact activation, also known as FXII autoactivation, has been established: the normally slow rate of FXII autoactiavtion is greatly accelerated in the presence of negatively charged surface [13]. The surface induces the conformational change of bound FXII and facilitates its activation by FXIIa (auto-activation) or KK (trans-activation) [14]. FXII is activated by the cleavage at Arg353–Val354 to generate 80 kD α-FXIIa, which is responsible for FXII autoactivation, and consists of a 30 kD catalytic light chain and a 50 kD heavy chain [15]. The formed FXIIa then converts PK to KK in the presence of HK [16]. KK can also activate FXII, thus forming an amplification loop, allowing the active enzymes produced to overcome the suppression of physiological inhibitors [17]. Additionally, α-FXIIa can be further cleaved by KK to generate β-FXIIa, which remains the activity to activate PK but not FXI or FXII, and is able to dissociate from the surface (contact phase) [18]. In 1980s, with the availability of purified contact proteins (FXII, PK) and their chromogenic substrates, the mechanism and kinetics of the classical activation pathway have been illustrated by in vitro biochemical experiments, mostly using 500 kD high molecular weight dextran sulfate (DS500) as the activating surface (Fig. 1a).

Beginning from glass surface, many other negatively artificial surfaces or poly-anionic molecules have been found to be able to accelerate contact activation, such as silica, kaolin, ellagic acid and sulfated polysaccharides, of which DS500 is one of the potent and best characterized contact activators [14, 19]. When the surface of long-chain dextran sulfate provides a platform for the aggregation of contact factors, FXII binds to the surface and undergoes conformation change, leading to FXII autoactivation [20]. The reaction rate is positively related with degree of sulfation and molecular size/chain length of the polysaccharides, while it shows bell shape as the concentration of each dextran sulfate increases [21, 22].

Moreover, a different paradigm of contact activation has been proposed, which suggests that it's a broad recognition pattern required only negatively charged surfaces rather than chemical structure specificity; for this reaction can be activated with nearly equal efficiency by either anionic-hydrophilic or hydrophobic surfaces [21, 23]. It is also reported that some natural glycosaminoglycans, such as dermatan sulfate, chondroitin sulfate-E and heparin,

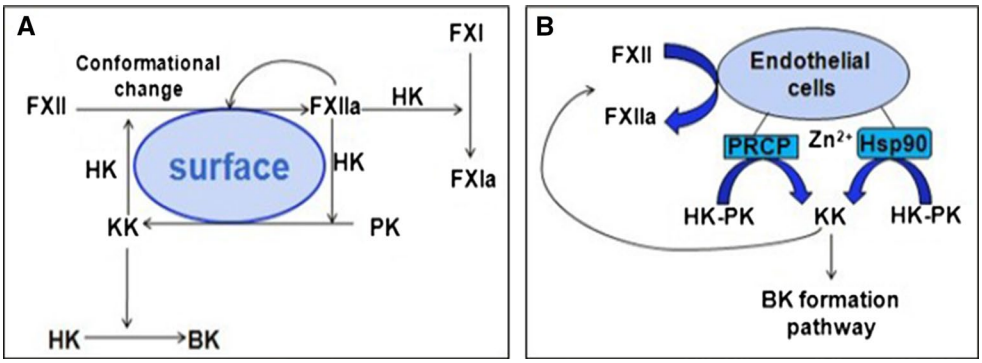

Fig. 1 The activation mechanisms of contact system: **a** the classical pathway, in which the initiating event is FXII binding and autoactivation driven by a negatively charged surface; **b** the alternative pathway, in which HK-PK binding and PK activation is the initiating event driven by the surface of cell membranes; (*FXII* factor XII, *FXIIa* activated factor XII, *FXI*, factor XI, *PK* prekallikrein, *KK* kallikrein, *HK* high molecular weight kininogen, *BK* bradykinin, *PRCP* prolylcarboxypeptidase, *Hsp90* heat shock protein 90)

only induced contact activation in vitro initially, and subsequently inhibition occurred possibly due to the activation of serine protease inhibitors in plasma, like C1 inhibitor (C1IHN) and antithrombin [21].

On the other hand, apart from the nonphysiologic agents, in the last 10 years, many endogenous substances have been discovered and referred as "natural activators", such as the following molecules.

Polyphosphate

PolyP released from activated platelets is recognized to be a new player in hemostasis and thrombosis [24]. PolyP can initiate contact activation in a FXII-dependent way, leading to both procoagulant and BK-mediated proinflammatory effects [25]. Synthetic polyP of mean chain length longer than 45 phosphate units can act as a contact surface and induce both the cleavage of XII and XI [25]. These findings have led to the proposal that polyP is the long-sought platelet FXII activator and help to illustrate part of the procoagulant mechanism of platelets [26]. Moreover, polyP can also act on other proteins in the coagulation cascade, such as promoting the activation of FV by thrombin, indirectly activating FXI, etc., collectively resulting in the formation of stable thrombus [8]. Compared with bacterial polyP, which contains >300 phosphate units, the length of platelet-derived polyP is short; thus, it is more effective for accelerating rather than initiating coagulation via contact activation, of which the optimal activity requires very long-chain polyP [27, 28].

However, new evidences showed that the mechanism of FXII activation by polyP70 (polyphosphate with the length of 70 phosphate units) in vivo is different from the normal adopted concept. When binds to polyP70, uncleaved single chain FXII has the activity to hydrolyze its synthesized or physiological substrate (S2303 (H-D-Pro-Phe-Arg-pNA-2HCl), FXI and PK), without changing into α-FXIIa, a two-chain enzyme [29]. In this case, polyP70 functions as the cofactor of FXII to enhance the otherwise negligible activity of FXII [29].

Amyloid protein

Misfolded protein aggregates have been found to be able to activate FXII, which selectively triggers kallikrein–kinin pathway—their partiality to activate only one of FXIIa's substrates PK without generating detectable FXIa results in the separation of the two downstream pathways of contact system [4, 30]. Consistently, elevated levels of FXIIa and KK have been observed in the patient diagnosed with systemic amyloidosis or Alzheimer's disease. Based on the finding, the author proposed that the BK-mediated inflammatory response may have protective effects against the "abnormal proteins", and that during contact activation by classic activators (e.g., kaolin), the absorbed plasma proteins from solution may undergo conformational change, then these formed "misfolded proteins" activate FXII and PK, while they are not required for FXI activation [30]. It is also possible that different types of activating surface tend to produce different activated forms of FXII by modulating the conversion of α-FXIIa to β-FXIIa, thus initiating different downstream cascades.

Nucleic acid

Nucleic acids, particularly RNA (both forms from eukaryon and prokaryon), have also been identified as promoters of blood clotting. Research showed that extracellular RNA derived from damaged cells can augment (auto-)activation of contact proteases and promote coagulation both in vitro and in vivo [31]. However, differing from misfolded proteins, RNA mainly results in FXII and FXI activation, and contributes to coagulation and pathological thrombus formation. Experiments also showed that hepatitis C virus

RNA has stronger affinity with FXII or FXI than with PK or HK [31]. Taken together, the understanding of procoagulant mechanism and undesired effects of RNA have led to the supposition that it can be a safe target for antithrombotic treatment, based on which some nucleic acid scavengers, such as RNase, had been designed [32].

The alternative activation pathway

The FXII-independent activation of the plasma kallikrein/kinin system has been proposed in recent years and referred as an alternative pathway. It has been demonstrated that the initiating event is independent of FXII binding and autoactivation, but Zn^{2+} and HK-dependent PK activation on endothelial cells [33, 34]. When HK-PK complexes assemble on the surface of endothelial cells, with HK serving as the binding site and cofactor of PK activation, kallikrein activity is observed in FXII-deficient plasma, but not in PK-deficient plasma [35]. KK generated on the cell surface then cleaves HK (its captor and native substrate), liberating KK from the complexes and producing BK; KK also activates FXII and single chain urokinase. Differing from FXII-dependent pathway, the alternative one is believed to occur constitutively in vivo, which is responsible for basal BK formation and maintenance of vascular hemostasis [34].

The binding of HK–PK complex to cell surfaces can be mediated by more than one receptor, including uPAR (urokinase-type plasminogen activator receptor), cytokeratin1, gC1qR (globular heads of complement C1q) and glycosaminoglycans of proteoglycan [36, 37]. Zn^{2+} concentration plays an important role in regulating PK activation in the alternative pathway by facilitating the binding of HK to endothelial cells, as well as contributing to the preferential binding of PK to endothelial cells over FXI or FXIa [36]. The local elevated Zn^{2+} concentrations, which are required for FXI but not PK binding, may be due to the activated platelets or other blood cells in the injury sites [33]. Additionally, when tested in vitro the contact activating capacity of phosphatidylinositol phosphate is Zn^{2+} dependent, while the capacity of DS500 is also affected by Zn^{2+} concentration [38].

Both heat shock protein 90 (Hsp90) and the serine enzyme prolylcarboxypeptidase (PRCP) on the surface of endothelial cells have been identified as physiological activators of kallikrein/kinin system [39–41]. Hsp90 and PRCP can activate PK–HK complex in the absence of FXII but with the presence of Zn^{2+} (Fig. 1b). The exact initiative mechanism of alternative pathway has not been totally illustrated, but some researchers suggested that Hsp90 acts through accelerating PK autoactivation in the presence of HK [42]. Moreover, it had been reported previously that PK can be auto-catalytically cleaved by its own activated form KK, in the presence of certain negatively charged surface [43].

As for membrane-mediated activation, except endothelial cells, surfaces of some exogenous microorganisms can also assemble and activate the kallikrein/kinin system. While the mechanisms may be different, for instance, the surface of Gram-negative curliated bacteria can serve as such a platform and initiate contact pathway via FXII activation [44].

Downstream effects of the contact system

The roles in coagulation and thrombosis

Coagulation is essential to avoid blood loss in the injured sites of vascular vessel (hemostasis), but inappropriate formation of thrombus often triggers various cardiovascular diseases by obstructing blood flow (thrombosis) [45]. Traditional opinion treats thrombosis as the result of excessive generation of fibrin when coagulation and anti-coagulation are out-of-balance, assuming that hemostasis and thrombosis occur by the same pathway. However, the modern concept has distinguished the mechanism underlying the physiological process from that under pathological conditions and recognized the different roles of extrinsic and intrinsic coagulation pathway. The extrinsic pathway is critical for hemostasis and its activation is related to the interruption of vascular integrity. While the intrinsic one also contributes to hemostasis, it is associated with thrombosis and inflammation under pathological conditions [46]. Plasma contact system is the initial stage of the intrinsic coagulation pathway. Therefore, this pathway can be triggered by FXIIa and FXIa produced by contact activation when plasma encounters certain negatively charged macromolecules either exogenous or endogenous such as extracellular RNA, platelet-derived polyP and misfolded protein aggregates [26, 30, 31].

FXII in hemostasis

The role of FXII in hemostasis has been confusing almost since its discovery in 1958, for unlike other coagulation factors such as FVIII and FIX (deficiency causes bleeding disorder hemophilia A and B, respectively), its deficiency in Hageman do not induce abnormal or spontaneous bleeding [2]. As this phenomenon is found both in other patients with FXII deficiency and in $FXII^{-/-}$ animal models consistently, it was believed that FXII is dispensable for normal hemostasis in vivo. And further researches contributed to establish the "revised version", in which physiological coagulation is initiated by the extrinsic pathway while FXII contributes very little to this process [46, 47]. When

circulating blood is exposed to the injured vessel wall, factor VII (FVII) binds to tissue factor (TF) and results in FVII autoactivation, inducing the generation of thrombin. In the coagulation cascade, thrombin produced through extrinsic pathway can feed back to activate FXI on the surface of platelets; thus, the intrinsic pathway gets involved and accelerates blood clotting [47]. The finding that FXI can be FXII-independently activated by thrombin may explain the mechanism behind the fact that FXII is dispensable for normal hemostasis, whereas people with hereditary deficiencies in FXI suffer from mild bleeding disorder [48].

Nevertheless, when plasma are tested in vitro, contact factors, like other components of coagulation cascade, are important for fibrin formation and their deficiency is associated with prolonged clotting time. Based on the molecular mechanism of contact activation, diagnostic clotting tests have been developed for detecting defects of coagulation factors in intrinsic pathway and monitoring the effects of anticoagulant administration. Among which, the activated partial thromboplastin time (aPTT) test, mostly with kaolin as the contact activator, is a useful tool in clinical clotting analyses and widely applied in laboratory, while activated coagulation time (ACT) has been obsoleted due to its insensitivity [49].

FXII in thrombus formation

Since the role of FXII in hemostasis was believed to be of little importance, the enthusiasm to explore physiological activators of contact system waned in the past. But in the last decade, researchers discovered that FXII is required for pathological thrombosis, as demonstrated by the gene-modified animal models. Renné et al. discovered that while FXII-deficient mice, like human, have no bleeding abnormalities, these mice were defective in thrombus formation, which could be restored by administrating human FXII [50]. Further evidence showed that mice lacking FXII or those treated with FXII inhibitor were protected against stroke (ischemia-induced brain infarction) [51]. These findings suggested that hemostasis and thrombosis have different regulatory mechanisms, instead of occurring by the same pathway assumed previously. Thus, FXII was believed to be a promising target for developing safety anti-thrombotic drugs with low tendency of bleeding [52, 53]. However, if FXII is required for a firm fibrin clot, the clots made in individual with very low level of FXII may be weak and prone to detach, which is potentially dangerous for it may cause embolic disease like pulmonary embolism. Therefore, deeper research and longer observation are needed to fully understand its role in thrombosis [54].

Among others, intravascular RNA and platelet-derived polyP are believed to be thrombogenic in vivo by activating contact system and initiating the intrinsic coagulation pathway. Experiments showed that polyP could promote plasma clotting in vitro and induce thrombus formation in mice, which are protected in the model of lethal pulmonary thromboembolism when FXII is deficient or FXIIa is inhibited [6].

The roles in inflammation and complement activation

When Margolis described the connection between glass surface and blood coagulation in 1956, he speculated that the "contact phenomenon" may physiologically function against injury as the initial stage of responses, of which are not confined to coagulation [1]. He seemed to be proven right, as increasing investigations show that the contact system functions as a part of the host immune defenses against invading bacteria and other microbes [55] Study also showed that it can be activated on bacterial surface to generate antibacterial peptides [56]. Additionally, clotting per se is important for limiting the dissemination of affection in the early immune response [57]. However, when activated excessively under pathological conditions, the beneficial effects of contact activation can be overwhelmed by the potential risks such as hypotension, increase of vascular permeability and generation of anaphylatoxins, which are often closely correlated and can be triggered simultaneously such as in inflammatory state or mast cell-mediated allergic reactions [58].

Increase of vascular permeability

Several substances have been reported to cause the increase of vascular permeability via activating FXII and initiating BK formation pathway. PolyP released from activated platelets caused capillary leakage/local edema (a hallmark of inflammatory reactions) in wild-type mice, while mice lacking FXII or B2R were protected [25]. Heparin and polyP released from activated mast cells could also induce BK generation through activation of kallikrein–kinin pathway [59, 60]. Thus, apart from histamine, the proinflammatory activities of mast cells are at least partly mediated by BK induced by its other released substances, such as heparin and polyP.

The increase of vascular permeability induced by the contact pathway results in edema which is involved in various diseases. Among others, the pathogeny of hereditary angioedema (HAE) has been widely investigated. HAE is induced by excessive activation of the BK producing pathway, either due to deficiency of functional C1IHN (HAE type I and type II), or mutation of FXII (HAE type III) [61]. C1IHN is the main physiological inhibitor for complement C1, KK and FXIIa in plasma, and its defect in limiting BK formation causes edema in patients [62, 63].

Blood pressure regulation

Kallikrein–kinin system plays an important role in blood pressure regulation mediated by the vasoactive peptide BK [64]. Normally, BK is rapidly degraded by various enzymes, either in plasma or on cell surfaces, such as angiotensin-converting enzyme. But under some pathological conditions, the increased level of BK causes serious hypotension by increasing the vascular permeability, or stimulating the generation of other vasodilators, such as NO, PGE_2 and PGI_2 [65]. The effects of BK are mostly mediated by the constitutively expressed B2R on endothelial cells, while B1R is involved in inflammatory state.

The excessive activation of contact system can cause hypotension as observed in the baboon model and in patients who received injection of heparin contaminated with oversulfated chondroitin sulfate (OSCS) [66, 67]. It has been demonstrated that the side effect of impure heparin is due to OSCS, which caused hypotension by contact activation and elevating BK levels [68]. These events are reminiscent of the transient systemic hypotension in pigs induced by highly negatively charged dextran sulfate, which can be blocked by Heo-140, a B2R antagonist [69]. Collectively, these researches supported a role of BK in hypotension induced by negatively charged polysaccharides and revealed the partiality of some molecules to activate kallikrein–kinin pathway, without triggering intravascular coagulation. Additionally, a potential anticoagulant fucosylated chondroitin sulfates also induced hypotension in rat [70]. Therefore, the capacity of contact activation should be carefully assessed when the anticoagulants under development are negatively charged, especially macromolecules like sulfated glycosaminoglycans.

Complement activation

The crosstalk between coagulation and complement is at least partly mediated by contact system, for instance, FXIIa is able to activate classical pathway of complement [71]. Researchers also have found that some plasma factors are shared (but usually have different roles) by both human coagulation and complement system as summarized in a recent published review [72]. Among others, C1IHN is an important physiological inhibitor targeting components both in complement cascade and contact system.

In 2008, the anaphylactoid reactions happened in patients who received injection of OSCS-contaminated heparin caused great attention. It was reported later that except inducing BK generation, OSCS also indirectly affects the complement system via contact activation. OSCS could promote the activation of FXII and PK, then KK converts the complement components C3 and C5 to anaphylatoxins C3a and C5a, respectively [67]. The process was found to be independent of Ca^{2+} and Mg^{2+} which are required by the normal pathway mediated by C3 and C5 convertase [67]. Since the qualified heparin can mildly activate FXII but do not cause the side effect like OSCS, the different mechanisms underlying their effects on the contact system were further investigated. Research found that OSCS could bind tightly both to FXII and FXIIa, while heparin only had high affinity with FXII, as shown by surface plasmon resonance [73]. Thus, the author hypothesized that heparin induces little downstream reactions because FXIIa may dissociate from the surface once it is formed, while on the surface of OSCS FXIIa continues to form FXIIa–KK–HK complex, which is favorable for producing more BK and anaphylatoxins [73].

The physiological functions of contact system have been found to be far more than its original proposed role in coagulation, which itself has been putting to the test, while its involvement in inflammation-associated diseases has caused more and more attentions [74, 75]. Except HAE, its critical role in mast cell-mediated anaphylaxis and Alzheimer's disease has also been investigated [58, 76]. Some researchers also suggest that FXII is involved in cell growth, angiogenesis and vasoactive regulation [12]. Moreover, the contact system proteins do not always play a part through the contact pathway; they may function by intervening other physiological systems, for example renin–angiotensin system [77].

Concluding comment

Overall, when the contact pathway is initiated by different types of stimulators in vivo, one of its downstream effects may occur partially and intensively, thus producing the specific result accordingly. Here, we suggest the initiation of contact activation may influence the kallikrein–kinin pathway more than coagulation cascade in most conditions (we describe this process in a revised version of contact system in Fig. 2), such as the effects driven by mast cell-derived heparin and misfolded protein, for the following reasons: first, the mutual amplification loop existing between FXII and PK greatly promotes the generation of active enzymes FXIIa and KK, though FXII autoactivation can occur in the presence of a proper surface without PK, the activating rate is much slower compared with that in the presence of PK; second, the content of the two substrates of FXII is different, the plasma concentration of PK (450 nM) is tenfold higher than that of FXI (30 nM) [34]; third, both activated forms of FXII (α-FXIIa and β-FXIIa) have the activity to activate PK, while only α-FXIIa can convert FXI to FXIa, additionally, β-FXIIa can be released from the surface and has higher possibility to interact with plasma proteins in fluid phase; fourth, the inhibition capacity of the main physiological

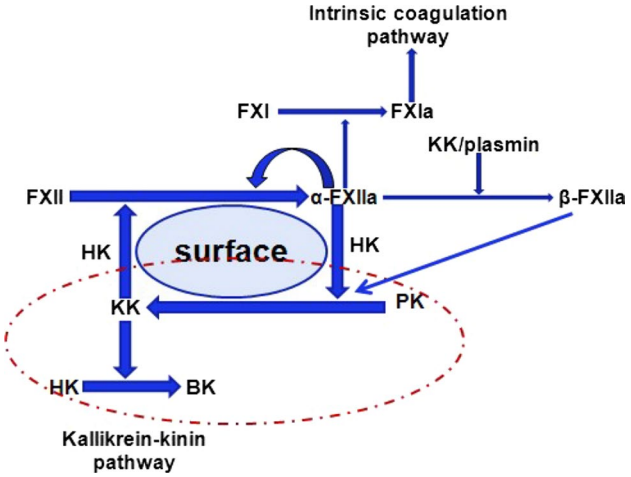

Fig. 2 A revised version of contact system and its downstream cascades: intrinsic coagulation pathway and kallikrein–kinin pathway; (the size of arrows indicate the intensity of reactions)

inhibitor C1IHN can be enhanced by glycosaminoglycan towards C1s, C1r, and FXIa but not FXIIa or kallikrein [78]. But further researches are needed to understand how the functions of contact system are being regulated in vivo, and to assess the outcome of contact activation.

Excessive contact activation mostly occurs under pathological conditions in vivo and produces undesired effects, like pathological thrombus formation and excessive inflammation response, when plasma encounters certain anionic surfaces that are normally do not exist (or do not exist abundantly) in plasma. In such cases, proper intervention is necessary to limit the detrimental result. Moreover, in addition to the serious side effects caused by OSCS the heparin contaminant, it was also reported that the activity of FXII activation could offset the antithrombotic effect of an algal sulfated galactan [79]. Therefore, the potent capacity of contact activation should be avoided when negatively charged macromolecules are being developed as anticoagulant or for other application.

As more and more information about the underlying mechanisms is available, we now can better understand its involvement in various diseases and develop drugs targeting contact factors or activating substances for anti-thrombotic and anti-inflammatory benefits. However, the complexity of activation and regulation of contact pathway hinders our ability to predict the exact consequence. Even the in vivo role of one of its components FXII has not been completely illustrated. Large patient studies showed that FXII levels and overall survival have a bell-shaped correlation [80]. Accordingly, when treating FXII as a promising target the inhibition ratio may be pivotal and should be taken into account. Further investigation is needed to understand the threshold between the protective and deleterious effects of contact system activation. Moreover, if under certain condition, the two downstream cascades driven by contact activation occur separately, then it may be possible to target FXI for interfering the intrinsic coagulation pathway and PK for reducing the generation of BK.

Despite the great achievements, there are still many puzzles remained, such as how this system interacts with other physiological systems or signal pathways, how the proteases in contact system are co-regulated by different inhibitors like C1INH, antithrombin, etc. Notably, while heparin, the important anticoagulant, is effective to prevent catheter thrombosis produced mainly by contact activation, heparin released from activated mast cells is a contact activator in vivo and potentially produce redundant inflammatory response [58, 59]. Better understanding of the activation and regulation mechanism of contact pathway can allow us to develop safe and effective new drugs and produce well-quality of heparin by controlling the purification procedures and sources.

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Compliance with ethical standards

Conflict of interest The authors state that they have no conflict of interest.

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