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Review

Pathophysiological dynamics in the contact, coagulation, and complement systems during sepsis: Potential targets for nafamostat mesilate

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ABSTRACT

Sepsis is a life-threatening syndrome resulting from a dysregulated host response to infection. It is the primary cause of death in the intensive care unit, posing a substantial challenge to human health and medical resource allocation. The pathogenesis and pathophysiology of sepsis are complex. During its onset, pro-inflammatory and anti-inflammatory mechanisms engage in intricate interactions, possibly leading to hyperinflammation, immunosuppression, and long-term immune disease. Of all critical outcomes, hyperinflammation is the main cause of early death among patients with sepsis. Therefore, early suppression of hyperinflammation may improve the prognosis of these patients. Nafamostat mesilate is a serine protease inhibitor, which can inhibit the activation of the complement system, coagulation system, and contact system. In this review, we discuss the pathophysiological changes occurring in these systems during sepsis, and describe the possible targets of the serine protease inhibitor nafamostat mesilate in the treatment of this condition.

Introduction

Sepsis is a life-threatening condition resulting from a dysregulated host response to infection, leading to severe organ dysfunction.[1] It is a significant cause of morbidity and mortality worldwide, accounting for approximately 19.7 % of all deaths.[2] Patients who survive sepsis remain at long-term risk of readmission and death,[3,4] and they may suffer from long-term cognitive impairment and functional disability.[5] This poses a great burden on patients and their families, as well as strains on public healthcare resources.[6] Such challenges further intensify the demands on critical care medicine.[7,8] Experts in critical care medicine have successively updated guidelines for the diagnosis and management of sepsis and septic shock.[9–12] Nevertheless, the pathogenesis of sepsis remains under investigation. Unfortunately, at present, there is no effective treatment for sepsis. Sepsis is characterized by concurrent excessive inflammatory response and immune suppression,[13] which manifest as fever or hypothermia, leukocytosis, or leukopenia. Hyperinflammation and immunosuppression are the dominant causes of death in the early and late stages of sepsis, respectively.[14]

In early stage sepsis, pattern-recognition receptors on host immune cells identify components of the pathogen, such as teichoic acid in Gram-positive bacteria and lipopolysaccharide in Gram-negative bacteria. This recognition process induces the release of inflammatory cytokines and activates signaling transduction pathways, thereby triggering systemic inflammatory response syndrome (SIRS).[15,16] Patients with early stage sepsis may simultaneously suffer from compensatory anti-inflammatory response syndrome[17–21] due to immune cell apoptosis and functional defects,[22–24] as well as alterations in cytokine expression,[25] leading to immune suppression. If the patient's immune response cannot be maintained at an appropriate level, patients may suffer from a persistent inflammation-immune suppression catabolism syndrome.[26] Therefore, the discovery of means to restore homeostasis is of great significance for improving the survival of patients with sepsis.

Nafamostat mesilate (NM), also termed FUT-175, is a synthetic broad-spectrum serine protease inhibitor. It exerts strong inhibitory effects on various serine proteases, such as trypsin[27] and serine protease components of the complement system,[28] coagulation system,[29] contact system,[30] etc.

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Thus, it is primarily utilized in the treatment of acute and chronic pancreatitis[31] and disseminated intravascular coagulation (DIC).[32] In addition, NM has been used in the treatment of Middle-East respiratory syndrome. Its mechanism of action is primarily associated with the inhibition of transmembrane serine protease 2 (*TMPRSS2*).[33] The virus Middle-East respiratory syndrome-coronavirus and severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) share structural similarities. Hence, this drug has also been used in the treatment of the novel coronavirus disease-2019 (COVID-19). *TMPRSS2* activation is related to the entry of SARS-CoV-2 into cells. The spike protein of SARS-CoV-2 is cleaved by *TMPRSS2* on the surface of airway epithelial cells. This leads to binding with angiotensin-converting enzyme 2 (ACE2), which facilitates membrane fusion and entry into the cell.[34,35] Therefore, inhibition of serine protease may help to reduce the entry of SARS-CoV-2 into cells, achieving a therapeutic effect against COVID-19. Several clinical[36–39] and preclinical[40–42] studies of NM have been conducted, with some indicating positive effects on COVID-19. Thus, NM may improve the outcome of patients with sepsis.

Evidence suggests that NM can attenuate inflammation and consequent organ damage *in vitro* and *in vivo*,[43–46] and benefit patients with sepsis on blood purification.[47] The mechanism by which NM improves sepsis may be related to changes in the pathophysiological function of the following three systems.

Contact System

Contact system, also termed plasma kallikrein-kinin system, consists of high-molecular-weight kininogen (HK), coagulation factor XII (FXII), coagulation factor XI (FXI), and prekallikrein (PKK).[48] This system has essential physiological functions, including maintaining normal coagulation, regulating vascular permeability, promoting fibrinolysis, and promoting pro-inflammatory responses.[49] These functions are mainly generated through FXII activation and cleavage of HK by PKK.[50] A schematic diagram of the contact system is shown in Figure 1. In this section, we discuss the functions of HK and relevant research progress. Its downstream products FXII and FXI are discussed in the coagulation system section of this article.

HK

HK is an important component of the contact system associated with numerous diseases, such as hereditary angioedema,[51] coronary heart disease,[52] and rheumatoid arthritis.[53] Moreover, HK is a useful biomarker for various parenchymal malignancies, including lung squamous cell carcinoma,[54] hepatocellular carcinoma,[55] colorectal cancer,[56,57] and glioma.[58]

Studies on the role of HK and its downstream products in the development of various types of inflammation have attracted our attention. Research progress on the role of kininogen in the pathogenesis of infectious disease is shown in Table 1.

In vitro studies

Scholars found that lipopolysaccharides (LPS) of *Escherichia coli* (*E. coli*), as well as peptidoglycan and teichoic acid of *Staphylococcus aureus* (*S. aureus*), activated the contact system and triggered the activation of PKK in purified human plasma.[59]

In vitro studies confirmed that plasma levels of HK were significantly lower in various bacterial infections compared to the normal levels observed in healthy individuals.[60,61] The contact system could be activated by bacterial surface components, including fibrous bacterial surface proteins, curli, and fimbriae in *E. coli* and *Salmonella*, caused the consumption of HK and the production of bradykinin (BK), and activated the pro-inflammatory pathway. Apart from bacteria, fungi (e.g., *Candida albicans*) also activate the contact system and the absorption of HK by their cell surface mannoproteins.[62,80]

Nevertheless, activation of the contact system was not recorded in *Streptococcus pneumoniae* infections, indicating that

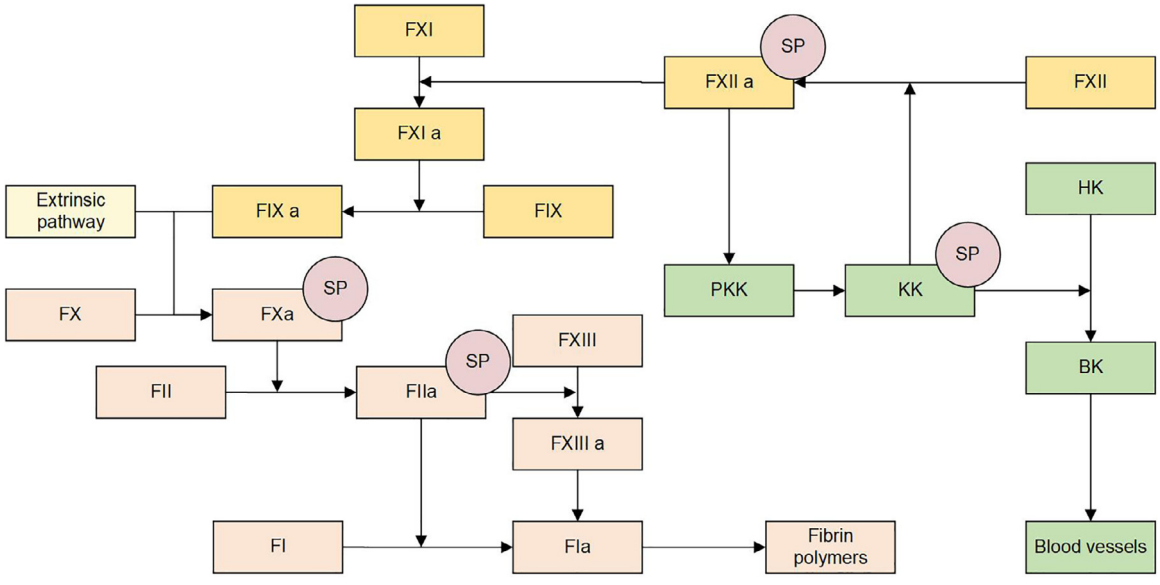

Figure 1. Potential effects of NM on the contact and intrinsic coagulation systems. Dark/light yellow indicates the intrinsic/extrinsic pathway of the coagulation system. Green indicates the contact system. Orange indicates the common pathway of coagulation.
BK: Bradykinin; FI: Coagulation factor I; FII: Coagulation factor II; FIX: Coagulation factor IX; FX: Coagulation factor X; FXI: Coagulation factor XI; FXII: Coagulation factor XII; FXIII: Coagulation factor XIII; HK: High-molecular-weight kininogen; KK: Kallikrein; NM: Nafamostat mesilate; PKK: Prekallikrein; SP: Serine protease.

Table 1
Research progress on the role of kininogen in the pathogenesis of inflammatory disease.

Author	Year	Research object	Pathogen/disease	Conclusions
Kalter et al.[59]	1983	*In vitro*	*E. coli* and *Staphylococcus aureus*	A mixture of purified human FXII, PKK, and HK was activated by those components.
Herwald et al.[60]	1998	*In vitro*	*E. coli* and *Salmonella*	Plasma HK, FXII was activated by those bacteria.
Mattsson et al.[61]	2001	*In vitro*	*Staphylococcus aureus*	Plasma levels of BK were significantly higher in *Staphylococcus aureus* septic patients instead of *Streptococcus pneumoniae*.
Rapala-Kozik et al.[62]	2008	*In vitro*	*Candida albicans*	Plasma HK was absorbed by *Candida albicans'* cell surface mannoproteins.
Yang et al.[63]	2017	Mice	Endotoxemia	HK knockout can reduce the mortality of endotoxemia mice.
Ding et al.[64]	2018	Mice	*Klebsiella pneumoniae*-induced sepsis	Depletion of HK did not improve the survival rate in septic mice.
Hu et al.[65]	2020	Mice	Polymicrobial sepsis	Expression of kininogen 1 in the lung tissues of septic mice was significantly increased, downregulating kininogen 1 expression attenuate sepsis-induced acute lung injury.
Köhler et al.[66]	2020	Mice	*Streptococcus pyogenes* sepsis	Depletion of kininogen 1 inhibited the spread of *Streptococcus*, reduced levels of pro-inflammatory cytokines.
Pixley et al.[67]	1992	Baboons	Lethal hypotensive bacteremia	Contact system was activated, HK was significantly lower.
Pixley et al.[68]	1993	Baboons	Lethal bacteremia	Contact system was activated, HK was significantly lower. Using a mAb to factor XII, hypotension was reversed and life was extended.
Jansen et al.[69]	1996	Baboons	Lethal bacteremia	Release of IL-6 was decreased in anti-factor XII-treated animals.
Silasi et al.[70]	2019	Baboons	Heat-inactivated *Staphylococcus aureus*	Anti-FXI antibody 3G3 inhibited the activation of contact, coagulation, and complement system, prolong the survival time of baboons.
Mason et al.[71]	1970	Human	Gram-negative bacteremia	Plasma level of HK was significantly lower.
Smith-Erichsen et al.[72]	1982	Human	Septic shock	Plasma levels of PKK and HK were significantly lower.
Aasen et al.[73]	1983	Human	Surgical patients with complicating septicemia	Plasma levels of PKK were significantly lower.
Martinez-Brotons et al.[74]	1987	Human	Septic shock	Plasma levels of FXII, PKK, and HK were significantly lower.
Wuillemin et al.[75]	1995	Human	Meningococcal septic shock	Plasma levels of FXII, PKK, and FXI were significantly lower.
Asmis et al.[76]	2008	Human	Sepsis	Contact system was activated, 47 kDa HK was significantly higher.
Leskelä et al.[77]	2021	Human	Endotoxemia	Endotoxemia is highly correlated with the contact system and serine protease.
Ruiz-Sanmartín et al.[78]	2022	Human	Sepsis	Plasma kininogen 1 exerts a negative correlation with mortality in septic patients.
Fang et al.[79]	2023	Human	Sepsis/COVID-19	Network pharmacology indicated that *KNG1* is the potential target against sepsis/COVID-19.

BK: Bradykinin; COVID-19: Novel coronavirus disease-2019; FXI: Coagulation factor XI; FXII: Coagulation factor XII; HK: High molecular weight kininogen; IL-6: Interleukin-6; KNG: Kininogen; *KNG1*: Kininogen 1; PKK: Prekallikrein.

this system is not activated by all bacterial species. Subsequent murine experiments, which involved *Klebsiella pneumoniae* infection, corroborated this finding.[64]

Murine models

A study demonstrated that HK knockout reduced mortality among mice with endotoxemia.[63] Nevertheless, further research asserted that exhaustive depletion of HK did not improve survival in mice with *K. pneumoniae*-induced sepsis.[64] This finding may be explained by the fact that the Gram-negative bacterium *K. pneumoniae* does not activate HK and its downstream pathway.

Another study demonstrated that the expression of kininogen 1 (*KNG1*) in the lung tissues of septic mice significantly increased, and downregulation of *KNG1* expression could attenuate sepsis-induced acute lung injury.[65] Depletion of mouse *KNG1* using antisense oligonucleotides inhibited the spread of *Streptococcus* and reduced the levels of pro-inflammatory cytokines.[66]

Primate models

Baboon models were used to investigate the activation of the contact system and the plasma levels of its components. Pixley et al.[67] showed that injections of a lethal dose of *E. coli* into baboons resulted in a significant reduction in HK, with clinical symptoms of irreversible fatal hypotension. However, following the injection of FXII monoclonal antibody C6B7 to inactivate FXII, the plasma levels of HK significantly increased, and the clinical symptoms and survival time were significantly improved as well.[68] Further investigation in baboons showed that C6B7 could significantly reduce the levels of pro-inflammatory cytokines, and significantly weaken the activation of the complement system. These observations suggested the existence of crosstalk between the contact system, the endogenous coagulation system, and the complement system.[69]

Human data

It was observed that patients with Gram-negative bacteremia had significantly lower levels of HK in their plasma compared to patients without Gram-negative bacteremia.[71] Subsequent clinical studies[72–76] confirmed these conclusions. Köhler et al.[66] also reported that the plasma levels of KNG1 were negatively correlated with Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores in patients with sepsis. A study utilizing high-performance liquid chromatography/tandem mass spectrometry showed that human endotoxemia is highly correlated with the contact system and endogenous coagulation system.[77] A single-center study from Spain revealed a negative correlation between plasma KNG and mortality in patients with sepsis [78]. Recently, a network

pharmacology study identified KNG1 as a possible therapeutic target for both sepsis and COVID-19.[79] In addition to its important role in the contact system, HK may be involved in pro-inflammatory responses. Early studies found that HK influences leukocyte recruitment[81] and interactions in the vascular system.[82] It has been demonstrated that HK or KNG1 plays an important role in several signaling pathways related to inflammation, such as nuclear factor-κB (NF-κB)[65] and phosphatidylinositol 3 kinase-protein kinase B (PI3K-AKT).[58]

BK and its receptors

BK, the downstream product of HK, has also been associated with signaling transduction of the inflammatory process through bradykinin receptor B1 (B1R) and bradykinin receptor B2 (B2R).[83–85] B1R is expressed in low levels in healthy tissues and is only upregulated under pathological states (e.g., injury and inflammation).[86,87] B2R is the main receptor for BK.[88] By binding to these receptors, BK promotes the release of pro-inflammatory cytokines, including interleukin-6 (IL-6) and IL-8.[89] In COVID-19, the increased secretion of BK may aggravate clinical symptoms.[90,91]

Similar results have been reported in sepsis. Knockout of BK receptors or the antagonist of B1R (R-954) reduced mortality and improved organ dysfunction by maintaining normal vascular permeability and hemodynamic stability in polymicrobial septic mice.[92,93] As mentioned above,[64] this phenomenon does not occur in *K. pneumoniae* infections.[93]

Association between contact and coagulation systems

The contact system is also highly relevant to coagulation. The endogenous coagulation system initiator FXII is crucial for the coagulation system.[50] Notably, HK in the contact system also exerts an effect on coagulation. A study revealed that HK could inhibit platelet adhesion and aggregation,[94] and acted as an antithrombotic agent by inhibiting plasminogen activator inhibitor-1.[95] Subsequent studies confirmed that deletion of the murine kininogen gene in mice delayed thrombosis,[96] highlighting the strong correlation between the contact and coagulation systems.

Coagulation System

The coagulation system comprises both endogenous and exogenous pathways. The endogenous coagulation system is activated by FXII, while the other is activated by tissue factor. Subsequently, a series of downstream serine protease-mediated coagulation cascade reactions are initiated, converting soluble fibrinogen into insoluble fibrin to achieve coagulation.[97] Maintaining the normal physiological function of the endogenous coagulation system is essential for homeostasis. Coagulation system dysfunction is associated with inflammation, implying that inflammation activates coagulation, which in turn significantly affects inflammatory activity.[98] Coagulation dysfunction is a major pathophysiological feature of COVID-19,[99] marked by a significant increase in D-dimer levels[100] that enhances fibrinogen and platelet activation.[101] Pathologically, the dysfunction is characterized by thickened vessel walls, narrowed vessel lumens, and microvascular thrombosis.[102] Clinical manifestations of COVID-19 include deep venous thromboembolism, pulmonary embolism,[99] and organ dysfunction due to microvascular thrombosis.[103] Abnormal coagulation parameters (e.g., increased levels of D-dimer, fibrinogen, and fibrinogen degradation products), as well as prolonged prothrombin time and activated partial thromboplastin time, are strongly associated with poor prognosis of patients with COVID-19.[104]

Similarly, sepsis-induced coagulopathy (SIC) is associated with a worsened prognosis of patients with sepsis.[105] Coagulation system dysfunction occurs throughout the course of sepsis.[106] Clinical studies demonstrated a significant association between DIC and mortality in patients with severe sepsis.[107–109] This association is primarily attributed to the hypercoagulable state of blood in the early stage of sepsis, which leads to numerous microvascular thromboses. This process impairs the function of vital organs, resulting in multiple organ dysfunction syndrome.[110] Furthermore, the consumption of coagulation factors and fibrinogen causes severe bleeding in the late stage of SIC. A schematic diagram of the intrinsic coagulation system is shown in Figure 1. Research progress on the role of FXII, FXI, and FX in the pathogenesis of infectious disease is shown in Table 2.

FXII and FXI

Research studies have been conducted to knockout or antagonism of various coagulation factors in both endogenous and exogenous coagulation systems, such as FVII,[117] FXI,[119,132] and FXII.[112] FXII and FXI are essential components of the contact and coagulation systems. Research progress regarding these two coagulation factors is discussed below.

In vitro studies

An increase in IL-1 secreted by monocytes was observed following the addition of FXIIa and LPS to the culture medium.[111] Except for the pro-inflammatory effects on monocytes, FXII can also induce neutrophil degranulation. Neutrophils in FXIIa-deficient plasma release only 30 % of the elastase released by those in normal plasma. In addition, FXIIa inhibitor D-Pro-Phe-Arg-CH_2Cl (PPACK) and Cl-inhibitor significantly inhibited the release of elastase by >90 % in normal plasma.[114] Subsequent studies indicated that *Acinetobacter baumannii* can inactivate FXII by releasing the metalloprotease CpaA. This weakens an important antimicrobial defense mechanism, thus facilitating bacterial spread.[113]

FXI also plays an important role in immune cell function. PKK and FXI bind to neutrophil cell membranes through kininogen, thereby initiating downstream biological effects.[115]

Murine models

A study showed that the usage of FXII and PKK inhibitor H-D-Pro-Phe-Arg-chloromethylketone significantly reduced the release of BK after *Salmonella* invasion and improved lung injury in rats.[116] FXII-knockout mice exhibited the same inflammatory response as wild-type mice in *S. pneumoniae* pneumonia. However, following infection with *K. pneumoniae*, those mice showed higher survival rates and lower bacterial burden without impairment of their coagulation function.[132]

Table 2
Research progress on the role of FXII, FXI, and FX in the pathogenesis of inflammatory diseases.

Target	Author	Years	Research object	Pathogen/disease	Conclusions
FXII and FXI	Wachtfogel et al.[111]	1986	*In vitro*	Cytochalasin B	FXIIa plays a role in inflammatory responses by activating neutrophils.
	Toossi et al.[112]	1992	*In vitro*	LPS	Activation of FXII-induced monocyte expression of IL-1 protein in the presence of LPS.
	Henderson et al.[113]	1994	*In vitro*	Cytochalasin B	PKK and FXI bound to neutrophil cell membranes through kininogen, initiating downstream biological effects.
	Waack et al.[114]	2018	*In vitro*	*Acinetobacter baumannii*	*Acinetobacter baumannii* inactivated FXII by releasing the metalloprotease CpaA.
	Persson et al.[115]	2000	Mice	*Salmonella*	FXII and PKK inhibitors reduced the release of BK after *Salmonella* invasion.
	Tucker et al.[116]	2008	Mice	Peritoneal sepsis	FXI KO mice reduced their coagulopathy and mortality rates.
	Tucker et al.[117]	2012	Mice	Sepsis	An anticoagulant antibody improved the survival rates of septic mice by selectively inhibiting FXI activation.
	Bane et al.[118]	2016	Mice	Polymicrobial sepsis	FXI KO mice improved survival and reduced cytokine response.
	Stroo et al.[119]	2017	Mice	*Klebsiella pneumoniae, Streptococcus pneumoniae*-induced sepsis	FXII KO mice improved survival and reduced bacterial growth in *Klebsiella pneumoniae* infection.
	Silasi et al.[70]	2019	Baboons	*Staphylococcus aureus*	FXII-neutralizing antibody 5C12 reduced the production of proinflammatory cytokines. Inhibition of FXI decreased inflammation and prolonged the survival time of baboons.
	Hess et al.[120]	2017	Human	ARDS	Non-survivors had significantly higher FXII levels in their BALF compared to survivors.
	Papi et al.[121]	2023	Human	COVID-19	The inhibition of FXIIa did not confer a clinical benefit over placebo.
FX	Jones and Geczy[122]	1990	*In vitro*	LPS	In the presence of LPS stimulation, FXa, together with thrombin, enhances IL-1 generation.
	Laurent et al.[123]	2014	*In vitro*	LPS	Rivaroxaban and fondaparinux suppressed some chemokine secretion produced by activated macrophages.
	Akahane et al.[124]	2001	Rats	LPS	Inhibition of FXa reduces TF and MCP-1 expression in the liver of rat endotoxemia.
	Daci et al.[125]	2020	Rats	LPS	Rivaroxaban pre-treatment attenuates LPS-induced acute vascular inflammation and contractile dysfunction.
	Taylor et al.[126]	1991	Baboons	*E. coli* sepsis	DEGR-Xa can inhibit DIC induced by infusion of *E. coli*, this inhibitor fails to block the lethal effects of the bacterial infusion.
	Welty-Wolf et al.[127]	2006	Baboons	*E. coli* sepsis	Blockade of tissue factor-factor X binding attenuates sepsis-induced respiratory and renal failure of *E. coli* sepsis baboon.
	Schöchl et al.[128]	2017	Baboons	*E. coli* sepsis	Dual inhibition of thrombin and FXa protected organ function and ameliorated inflammation in severe Gram-negative sepsis in baboons.
	Hollenstein et al.[129]	2002	Human	Endotoxin	Danaparoid did not alter endotoxin-induced cytokine levels, activation of leukocytes, but selectively attenuates endotoxin-induced coagulopathy.
	Katoh et al.[130]	2017	Human	Inflammation of NVAF	FXa inhibitors have not only an anti-coagulant effect but also anti-inflammatory effects in patients with NVAF.
	Nakase et al.[131]	2018	Human	Inflammation of acute ischemic stroke	Both apixaban and dabigatran equally showed the anticoagulation activity and the reduction of inflammatory response.

BALF: Bronchoalveolar lavage fluid; BK: Bradykinin; DEGR-Xa: Dansyl-glutamyl-glycyl-arginine chloromethyl ketone; DIC: Disseminated intravascular coagulation; FX: Coagulation factor X; FXI: Coagulation factor XI; FXIIa: Activated coagulation factor XII; IL: Interleukin; KO: Knock out; LPS: Lipopolysaccharides; MCP-1: Monocyte chemoattractant protein-1; NVAF: Non-valvular atrial fibrillation; PKK: Prekallikrein; TF: Tissue factor.

An anticoagulant antibody termed 14E11, which selectively inhibits prothrombotic FXI activation, was used in septic mice. The results indicated that 14E11 can inhibit pro-inflammatory cytokine production, including IL-6 and tumor necrosis factor-α (TNF-α). It can also reduce platelet consumption and its vascular deposition, thus significantly improving the survival rate of mice with sepsis caused by intestinal perforation, without increasing the risk of bleeding.[119] Compared with wild-type mice, FXI knockout in mice reduced coagulopathy and mortality rate, and induced smaller increases in plasma levels of TNF-α, IL-10, IL-1β, and IL-6 during cecum ligation and puncture-induced sepsis.[118,120] Nevertheless, in *S. pneumoniae*- and *K. pneumoniae*-induced pneumonia-derived sepsis, FXI deficiency worsens the survival rate, increases bacterial burden, and enhances inflammatory responses; the capacity of neutrophil phagocytosis was also impaired in FXI-knockout mice.[132]

Primate models

Inhibition of FXII using an FXII antibody significantly improved the prognosis of septic baboons.[67–69] Further investigation confirmed that using FXII-neutralizing antibody 5C12 in baboons with sepsis caused by *S. aureus* reduces the production of pro-inflammatory cytokines (e.g., TNF, IL-1β, IL-6, IL-8, and IL-10), and prevents fever, terminal hypotension, respiratory distress, and multiorgan failure.[112]

The inhibition of FXI exerts similar effects. Pretreatment with the anti-FXI antibody 3G3 in baboons infused with heat-inactivated *S. aureus* inhibited the activation of the contact, coagulation, and complement systems, reduced the production of pro-inflammatory cytokines, and protected the structure and function of multiple vital organs, thus prolonging the survival time.[70]

Human data

FXII levels are significantly higher in bronchoalveolar lavage fluid of non-survivors vs. survivors of acute respiratory distress syndrome. Moreover, FXII can induce various pro-inflammatory cytokines in human lung tissue, including IL-8, IL-1β, IL-6, C-X-C motif chemokine ligand 5 (CXCL5), and TNF-α.[133]

Therefore, inhibition or depletion of FXII or FXI may significantly improve coagulation dysfunction and the prognosis of patients with sepsis. Consequently, numerous small molecules,

peptides, proteins, oligonucleotides, siRNAs, and monoclonal antibodies targeting FXII and FXI have been developed.[134,135] Some of those agents (e.g., garadacimab) are currently under investigation in clinical trials. The first-in-human and randomized dose-escalation trial of FXIIa inhibitor garadacimab was recently completed.[121,136] Of note, treatment with garadacimab did not confer a clinical benefit vs. placebo in patients with COVID-19.[137]

FX

FX is an important component of both the intrinsic and extrinsic coagulation pathways. The role of FX in the occurrence and progression of various inflammation-related diseases, as well as advancements in research on drugs targeting FX, is described below.

In vitro studies

Research indicated a synergistic interaction between FXa and pro-inflammatory cytokines like TNF, IL-1β, and CD40 ligand (CD40L), leading to endothelial dysfunction. This partly explains the vascular complications occurring in sepsis.[138] FXa concentration-dependently stimulates the production of IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) in human umbilical vein endothelial cells. Additionally, it enhances the expression levels of E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), thereby increasing the adhesion of polymorphonuclear leukocytes to endothelial cells.[122] In the presence of suboptimal levels of endotoxin, FXa enhances the production of IL-1 in macrophages.[139] Currently, clinically employed FXa inhibitors include rivaroxaban,[140] apixaban,[141] edoxaban,[142] betrixaban,[123] and among others. Treatment with rivaroxaban significantly suppressed the secretion of chemokines by activated macrophages.[124] This evidence showed that FXa exerts a pro-inflammatory effect during the course of inflammatory disease.

Murine models

Research focused on inhibiting FXa activity to examine its anti-inflammatory role. Subcutaneous injection of DX-9065a, a specific FXa inhibitor, significantly inhibited liver tissue factor expression and plasma MCP-1 concentration in rats with endotoxemia.[125] Similarly, rivaroxaban significantly improved LPS-induced acute vascular inflammation.[128]

Primate models

However, studies in baboons showed a different pattern. Treatment with a dual short-acting thrombin and FXa inhibitor SATI attenuated DIC and protected organ function in septic baboons.[127] Blocking tissue factor-FX binding alleviated sepsis-induced respiratory and renal failure.[126] Single use of dansyl-glutamyl-glycyl-arginine chloromethyl ketone (DEGR-Xa) to block the activity of FXa inhibited the DIC induced by *E. coli* infusion, but could not prevent mortality.[129]

Human models

Similarly, in randomized controlled trials involving healthy volunteers, the FXa inhibitor danaparoid selectively mitigated endotoxin-induced coagulopathy. However, it did not alter endotoxin-induced cytokine levels, leukocyte activation, or monocyte tissue factor expression.[130] The anti-inflammatory effects of rivaroxaban and apixaban have been observed in Japanese patients with atrial fibrillation.[131] Furthermore, the anti-inflammatory effects of apixaban were also recently demonstrated in patients with ischemic stroke in the acute phase.[143]

Association between coagulation and complement systems

The coagulation and complement systems exhibit overlapping functionalities. For example, C3 convertase inhibitor compstatin prevents sepsis-induced complement activation and coagulopathic responses by inhibiting C3 convertase, thereby maintaining the endothelial anticoagulant properties.[144] Inhibition of C5 also significantly improved *SIC* in septic mice.[145] Evidence suggests that FXIIa initiates a classical pathway of the complement system.[146] While within the complement system, C1q can interact with the C1q receptor on platelets, mediating platelet aggregation and activation.[147] Furthermore, mannose-binding lectin-associated serine protease-1 (*MASP1*) in the mannose-binding lectin pathway activated platelets in a murine model of occlusive thrombosis.[148] In addition, complement system activation can induce the release of neutrophil extracellular traps from neutrophils. These neutrophil extracellular traps provide a scaffold for blood cells and platelets to form clots.[149,150] Moreover, the bleeding time of C3-deficient mice was significantly prolonged, and the incidence of thrombus and the size of thrombus were reduced.

Complement System

As an important part of the innate immune system, the complement system is an irreplaceable barrier protecting the body from foreign pathogen invasion.[151] According to its activation pathway, the complement system is divided into three pathways, namely the classical, alternative, and mannose-binding lectin. Based on its biological functions, it can be divided into complement components, complement regulatory proteins, and complement receptors.[152] Complement components include C1–C9, mannan-binding lectin (MBL), MASP, factor B (CFB), factor D (CFD), and factor P; complement regulatory proteins include C1-esterase inhibitor (C1 INH); also termed SERPING1, factor I, factor H, etc.; complement receptors are receptors of the complement components, including CR1–CR5, C4aR, and C5aR.[153] Through combined action, the complement system eventually produces a membrane attack complex (MAC) that lyses cells and stimulates inflammatory responses to remove pathogens.[154] Activation of the complement system also leads to the production of anaphylatoxins (e.g., C3a and C5a), which trigger mast cell degranulation, enhance phagocytosis activity of neutrophils and monocytes, and trigger local inflammatory responses. Moderate complement activation plays an indispensable role in maintaining normal immune function. Nonetheless, excessive complement activation may lead to various diseases, including atypical hemolytic-uremic syndrome,[155] Alzheimer's disease, Parkinson's disease,[156] and amyotrophic lateral sclerosis.[157] A schematic diagram of the complement system is shown in Figure 2. Research progress on the role of C3 and C5 in the pathogenesis of infectious disease is shown in Table 3.

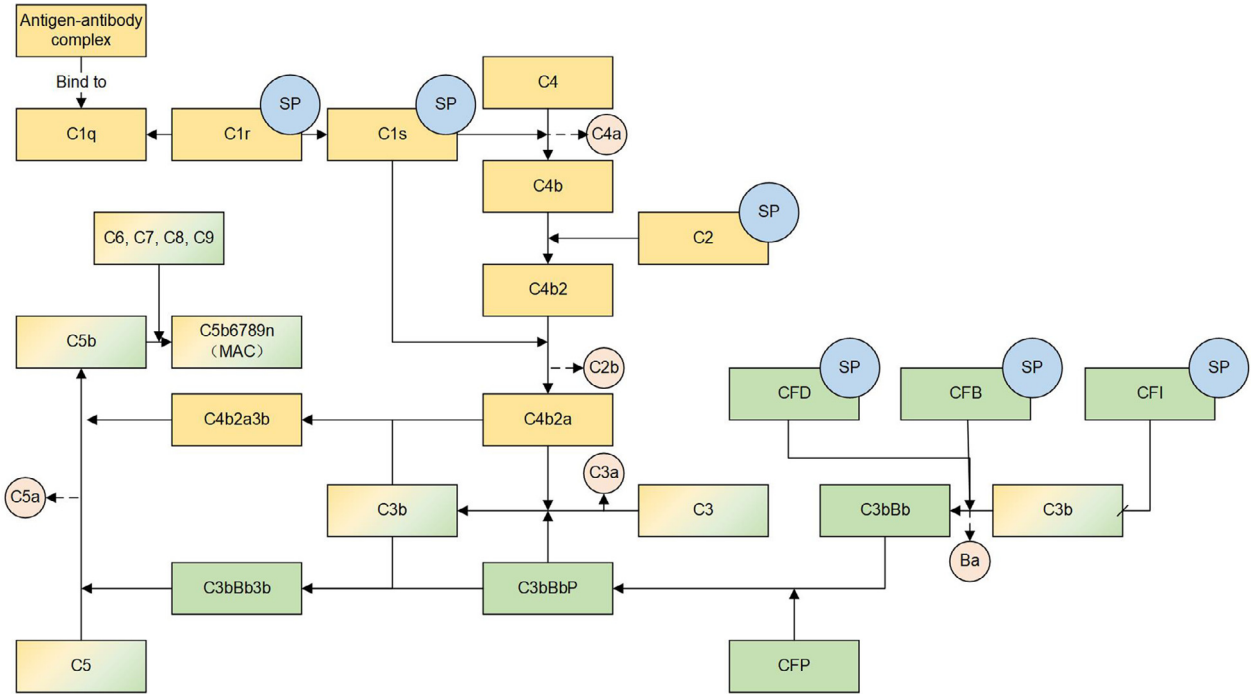

Figure 2. Potential effects of NM on the complement system. Yellow indicates the classical pathway of the complement system. Green indicates the alternative pathway of the complement system. Yellow-green represents the common path of both pathways.
CF: Complement factor; CFB: Complement factor B; CFD: Complement factor B; CFI: Complement factor I; MAC: Membrane attack complex; NM: Nafamostat mesilate; SP: Serine protease.

C3 and C5

In vitro studies

As a strong chemoattractant, C5a can stimulate human polymorphonuclear leukocytes to acquire a polarized morphology.[158] C3a and C5a also induce the release of oxygen radicals in granulocytes; therefore, inhibiting C3a and C5a may attenuate endothelial damage.[159,160]

Studies showed that expression of C5R in rat alveolar epithelial cells and mouse dermal microvascular endothelial cells increased the production of TNF-α, IL-1β, macrophage inflammatory protein-2 (MIP-2), and cytokine-induced neutrophil chemoattractant-1 (CINC-1) under the stimulation of LPS.[161,162] Subsequent experiments conducted in human umbilical vein endothelial cells confirmed these findings.[163]

Importantly, the epithelial integrity was significantly improved by antagonizing C3aR and C5aR expressed on human airway epithelia during SARS-CoV-2 infection.[165]

Murine models

Studies in rats with endotoxin-induced shock suggested that the use of a rabbit anti-rat C5a antibody elevated the plasma levels of C3a and C5a, and significantly improved the mean arterial pressure and vascular permeability.[166] Additional studies confirmed that C5a blockade had protective effects in septic rats.[164,167] Another study showed that C5aR mRNA expression was significantly elevated in lung, liver, kidney, and heart of septic mice. Inhibition of C5aR may markedly increase the survival rates, while reducing the pro-inflammatory cytokine levels and organ bacterial burden.[168] Recently, another murine study using C5aR antagonist PMX 205 suggested that inhibition of C5aR decreased the mortality rate associated with *Neisseria meningitidis*-induced sepsis and the levels of pro-inflammatory cytokines.[172]

Primate and mammalian models

Earlier animal studies had shown a strong activation of the complement system in *E. coli*-infected baboons, manifested by an increase in C3b/c, C4b/c, and C5b-9 levels.[169] Further studies suggested that inhibition of the complement system using cobra venom factor or monoclonal antibodies significantly improved the prognosis of septic pigs.[170,173] This finding has been confirmed in recent studies. C3 convertase inhibitor compstatin significantly improved coagulation function, organ dysfunction, and leukocyte infiltration in baboons.[174] C5 inhibitors reduced mortality and protected against coagulation dysfunction and organ failure in septic baboons.[171,175]

Human data

Scholars reported that the serum levels of C3a, C4a, and C5a were significantly higher in non-survivors than survivors of sepsis. Moreover, their concentrations were highly correlated with mortality. These data confirmed that the complement system was overactivated during sepsis.[185] Overactivation of the complement system was observed in patients with COVID-19.[186] Specifically, in the cytokine storm caused by COVID-19, extensive complement activation and depletion occurred.[187] These effects manifested by a significant increase in the plasma levels of MAC, C4d, and C5a,[180,188] and a significant decrease in the levels of C3 and C4, which were both highly correlated with patient prognosis.[176]

Several inhibitors have been developed to inhibit complement overactivation. Eculizumab (an antibody targeting complement component C5) is among the earliest inhibitors devel-

Table 3
Research progress on the role of C3 and C5 in the pathogenesis of inflammatory diseases.

Author	Year	Research object	Pathogen/disease	Conclusions
Sacks et al.[158]	1978	*In vitro*	Cytochalasin B	C3a and C5a triggered oxygen radical release in granulocytes, leading to endothelial damage.
Marder et al.[157]	1985	*In vitro*	NA	C5a strongly attracted human polymorphonuclear leukocytes and induced their polarization.
Riedemann et al.[159]	2002	*In vitro*	Baculovirus	C5R activation in RAEC enhanced inflammatory responses under LPS stimulation.
Mollnes et al.[160]	2002	*In vitro*	*E. coli*	C5a-C5aR interaction was important in *E. coli*-induced inflammation and could be a target for treating tissue damage.
Laudes et al.[161]	2002	*In vitro*	*E. coli*	C5R activation in MEMDC enhanced inflammatory responses under LPS stimulation.
Monsinjon et al.[162]	2003	*In vitro*	*E. coli*	C3a or C5a caused a strong up-regulation of IL-8, IL-1beta, and RANTES mRNA.
Posch et al.[163]	2021	*In vitro*	SARS-CoV-2	Antagonizing C3aR and C5aR on human airway epithelia improved epithelial integrity.
Huber-Lang et al.[164]	2001	Mice	Sepsis	The blockade of C5aR highly improved the survival rates of septic mice.
Smedegård et al.[165]	1989	Rats	Endotoxin	Neutralization of C5a with reduce the hypotensive response to endotoxin and prevent lethal septic shock both in animals and in man.
Czermak et al.[166]	1999	Rats	Sepsis	C5a blockade reduces bacterial burden in the spleen and liver of septic rats.
Riedemann et al.[167]	2002	Mice	Sepsis	C5a blockade reduces serum levels of IL-6 and TNF-alpha and bacterial counts in various organs were significantly reduced during CLP.
Herrmann et al.[168]	2018	Mice	*Neisseria meningitidis* sepsis	The mortality rates and the level of pro-inflammatory cytokines were both down-regulated by inhibiting C5aR.
Höpken et al.[169]	1996	Pigs	*E. coli* sepsis	Anti-C5a monoclonal antibodies significantly reduced IL-6 synthesis.
Mohr et al.[170]	1998	Pigs	*E. coli* sepsis	Complement depletion and C5a inhibition enhanced oxygen utilization and mitigated severe sepsis symptoms.
Stevens et al.[171]	1986	Baboons	*E. coli* sepsis	Anti-C5a antibodies attenuated some of the systemic manifestations of sepsis.
de Boer et al.[172]	1993	Baboons	*E. coli*	C3b/c, C4b/c, and C5b-9 had increased.
Silasi-Mansat et al.[173]	2010	Baboons	*E. coli* sepsis	C3 convertase inhibitor significantly improved coagulation function, organ dysfunction, and leukocyte infiltration.
Keshari et al.[174]	2017	Baboons	*E. coli* sepsis	The inhibition of C5 cleavage could prevent organ failure and death.
Nakae et al.[175]	1994	Human	Sepsis	Higher serum levels of C3a, C4a, and C5a correlated with increased sepsis severity.
Rother et al.[176]	2007	Human	Paroxysmal nocturnal hemoglobinuria	Eculizumab targeted C5 to effectively treat paroxysmal nocturnal hemoglobinuria, demonstrating the value of complement inhibition.
Diurno et al.[177]	2020	Human	COVID-19	Eculizumab showed potential in treating severe COVID-19 cases in a study and reduced inflammation.
Mastaglio et al.[178]	2020	Human	COVID-19	A patient was safely and successfully treated using AMY-101.
Kulasekararaj et al.[179]	2020	Human	COVID-19	Ravulizumab and eculizumab dampened the hyperinflammatory lung damage.
Carvelli et al.[180]	2020	Human	COVID-19	Blocking the C5a-C5aR1 axis reduced excessive lung inflammation.
Urwyler et al.[181]	2020	Human	COVID-19	Conestat alfa leaded to clinical improvements and reduced inflammation.
Araten et al.[182]	2020	Human	COVID-19	Patients on anti-complement therapy showed no increased susceptibility to SARS-CoV-2 and experienced a mild course of COVID-19.
Mastellos et al.[183]	2020	Human	COVID-19	Targeting C3 and C5, effectively reduced COVID-19 hyper-inflammation.
Zelek et al.[184]	2020	Human	COVID-19	The transient blockade of C5 was sufficient to interrupt the hyperinflammatory cycle in severe COVID-19.

AMY-101: Compstatin-based complement C3 inhibitor; CLP: Cecum ligation and puncture; COVID-19: Novel coronavirus disease-2019; IL: Interleukin; LPS: Lipopolysaccharides; MEMDC: Mouse dermal microvascular endothelial cells; NA: Not available; RAEC: Rat alveolar epithelial cells; RANTES: Regulated upon activation on normal T expressed and secreted; SARS-CoV-2: Severe acute respiratory syndrome- coronavirus 2; TNF: Tumor necrosis factor.

oped and has been used for >16 years.[179] Numerous complement system inhibitors are currently under investigation in clinical trials.

C5 inhibitors ravulizumab, tesidolumab, and eculizumab interrupt the hyper-inflammatory cycle in patients with severe COVID-19, reduce the inflammatory response, and improve clinical symptoms.[177,178,182,184] C3 inhibitor AMY-101 showed a good safety profile in the treatment of COVID-19, reduced markers of inflammatory response, and resulted in significant clinical improvement.[183,181] Recombinant human C1 INH conestat alfa lowers C-reactive protein levels and resolves fever.[189]

Similar to the contact and coagulation systems, excessive activation and consumption of the complement system during the course of sepsis can contribute to an imbalance in immune response, coagulation dysfunction, perfusion deficits, alterations in the tissue and cellular microenvironment, and organ dysfunction.[190–192] Therefore, inhibition of the overactivated complement system can also benefit patients with sepsis.

C1 INH

C1 INH is a natural serine protease inhibitor found in human plasma and a member of the Serpin family. It inhibits various serine proteases, such as C1r, C1s, and MASP2 in the complement system, thrombin and FXI in the coagulation system, and PKK and FXII in the contact system.[193] Thus, animal and clinical studies were conducted to investigate the therapeutic effect of C1 INH. Animal studies showed that C1 INH can reduce hepatic leukocyte–endothelial interaction in septic rats[194]; reduce the expression of TNF-α and improve the bactericidal activity of neutrophils and peritoneal exudate leukocytes and the survival rate of mice[195,196]; and reduce the mortality rate and pro-inflammatory cytokines in baboons.[197] Clinical studies yielded the following results: in a case series, C1 INH weakened the activation of the contact and complement systems[198]; utilization of C1 INH improved sepsis-related capillary leak syndrome[199]; and subsequent research suggested that C1 INH exerted a beneficial effect on renal dysfunction in patients with sepsis.[200]

CFB and CFD

CFB and CFD are serine proteases and crucial constituents of the complement system, participating in the activation of the alternative pathway. This pathway enables direct recognition and targeting of pathogens without the involvement of the antigen-antibody complex. CFB binds to C3b, forming C3bB; subsequently, CFD activates C3bB to generate C3bBb, thereby constituting the alternative pathway C3 convertase.

This cascade triggers a series of complement reactions, ultimately culminating in the formation of the MAC and the destruction of target cells.[201,202] However, overactivation of CFB and CFD also causes damage, leading to various diseases, such as atypical hemolytic uremic syndrome,[203,204] cardiovascular diseases,[205] and several malignant tumors.[206–208] There are available inhibitors targeting CFB and CFD, including modified DNA aptamers,[209] antisense oligonucleotides,[210] and small-molecule inhibitors[211,212]; notably, these inhibitors have been utilized in the treatment of COVID-19.[213] Hence, utilization of these inhibitors in the treatment of sepsis holds promise for favorable outcomes.

Association between complement and contact systems

FXIIa is the common factor of the contact and coagulation systems that can cleave C1r (component of the complement system).[214–216] Members of the serpin family (e.g., C1 INH, and antithrombin) can simultaneously suppress the overactivation of both systems, thus maintaining homeostasis. Moreover, the complement and contact systems have another thing in common, they are the common downstream of diseases (e.g., hereditary angioedema, COVID-19, sepsis, etc.).

How Does NM Treat Sepsis by Acting on the Contact, Coagulation, and Complement Systems

The contact, coagulation, and complement systems contain various serine proteases and are overactivated during sepsis. Therefore, it is possible to concurrently inhibit the functionality of all three systems by inhibiting these serine proteases, thereby intercepting the pathophysiological changes and progression of sepsis. As a broad-spectrum, synthetic serine protease inhibitor, NM exhibits similarities to C1 INH. Hence, it has been clinically utilized in the anticoagulation field. Beyond its inhibitory effects on the coagulation system, it may also inhibit the contact and complement systems. Its usage in the treatment of various inflammatory conditions has been reported.[43–47]

Effects of NM on the contact system in sepsis

The studies above suggested that the contact system and its components play important roles in the development of sepsis. Specifically, HK and its downstream product BK contribute to the development of sepsis caused by polymicrobial infection or Gram-negative bacteria. By knocking out, depleting, or antagonizing HK and its downstream product BK or its receptor, it is possible to significantly improve the survival rate and prognosis of patients with sepsis. This provides new directions for the treatment of sepsis. Focusing on HK, the following interventions can be carried out toward the treatment of sepsis.

First, a reduction in HK production through knockout, depletion, or antagonism. Anti-HK antibody 3E8 significantly reduced the activation of the contact system and HK production in animals.[217] Currently, there is a lack of clinical studies on the reduction of HK production due to limitations in gene editing and mRNA vaccination technology, makes it difficult to reduce HK production, therefore, more effective method to inhibit the contact system should be considered.

Second, reduction of downstream product effects, such as knockdown or antagonism of the BK receptor. BK antagonists have been clinically utilized, though their indications are mostly limited to the regulation of vascular permeability (e.g., in hereditary angioedema).[218] Hence, the therapeutic effects of BK antagonists on sepsis remain unclear.

Third, reduction of HK catabolism by kallikrein (i.e., reduction of the production of downstream products of BK). Drugs targeted at kallikrein effectively reduce the conversion of HK to downstream products, thereby intervening in the development of sepsis. Hence, the development of drugs that can inhibit kallikrein may be clinically important. NM is a drug that inhibits PKK, thus reducing HK catabolism and its downstream biological effect.

Effects of NM on the coagulation system in sepsis

The coagulation system, particularly the endogenous coagulation system, consists of numerous serine proteases (e.g., FIIa, FXa, and FXIIa). Serine protease inhibitors, such as NM, can inhibit these coagulation factors. Therefore, NM is often used in clinical practice as an effective anticoagulant in extracorporeal life support,[219] extracorporeal membrane oxygenation,[220] and continuous renal replacement therapy.[221]

Inhibition of coagulation factors by NM exerts an anticoagulation effect and plays an important role in sepsis. Early administration of NM in sepsis can effectively reduce the consumption of various coagulation factors and fibrinogen. Moreover, it can avoid the vital organ dysfunction caused by microvascular thrombosis in the early stage and the serious bleeding tendency due to the large consumption of coagulation factors in the late stage.

Effects of NM on the complement system in sepsis

The serine protease components within the complement system include C1r, C1s, C2, CFD, CFB, and factor I (Figure 2). The use of serine protease inhibitors may suppress the activity of these components. NM effectively inhibits the activation of the complement system,[222,223] thereby exerting positive effects on patients with sepsis.

NM: potential applications in the treatment of sepsis

Sepsis is highly correlated with the overactivation of the contact, complement, and coagulation systems. NM may inhibit serine protease components (e.g., PKK) in the contact system, and attenuate the vascular leakage caused by BK, thereby preventing the ensuing multiple organ dysfunction syndrome. In addition, NM can inhibit FXIIa, FXa, and FIIa in the intrinsic coagulation system, thus reducing the formation of fibrin clot and the incidence of consequent DIC. Furthermore, it inhibits C1r and C1s in the classical pathway of the complement system, CFB and CFD in the alternative pathway of the complement system, reduces MAC formation, and decreases anaphylatoxins (e.g., C3a C4a, and C5a) (Figure 3).

Conclusions

In this review, we discuss the pathophysiology of sepsis, explore the functional changes in the contact, coagulation, and complement systems, as well as their core components (e.g., HK, BK, FXII, FXI, C3, C5, etc.). NM may exert its therapeutic effect on sepsis by inhibiting the activation on the contact,

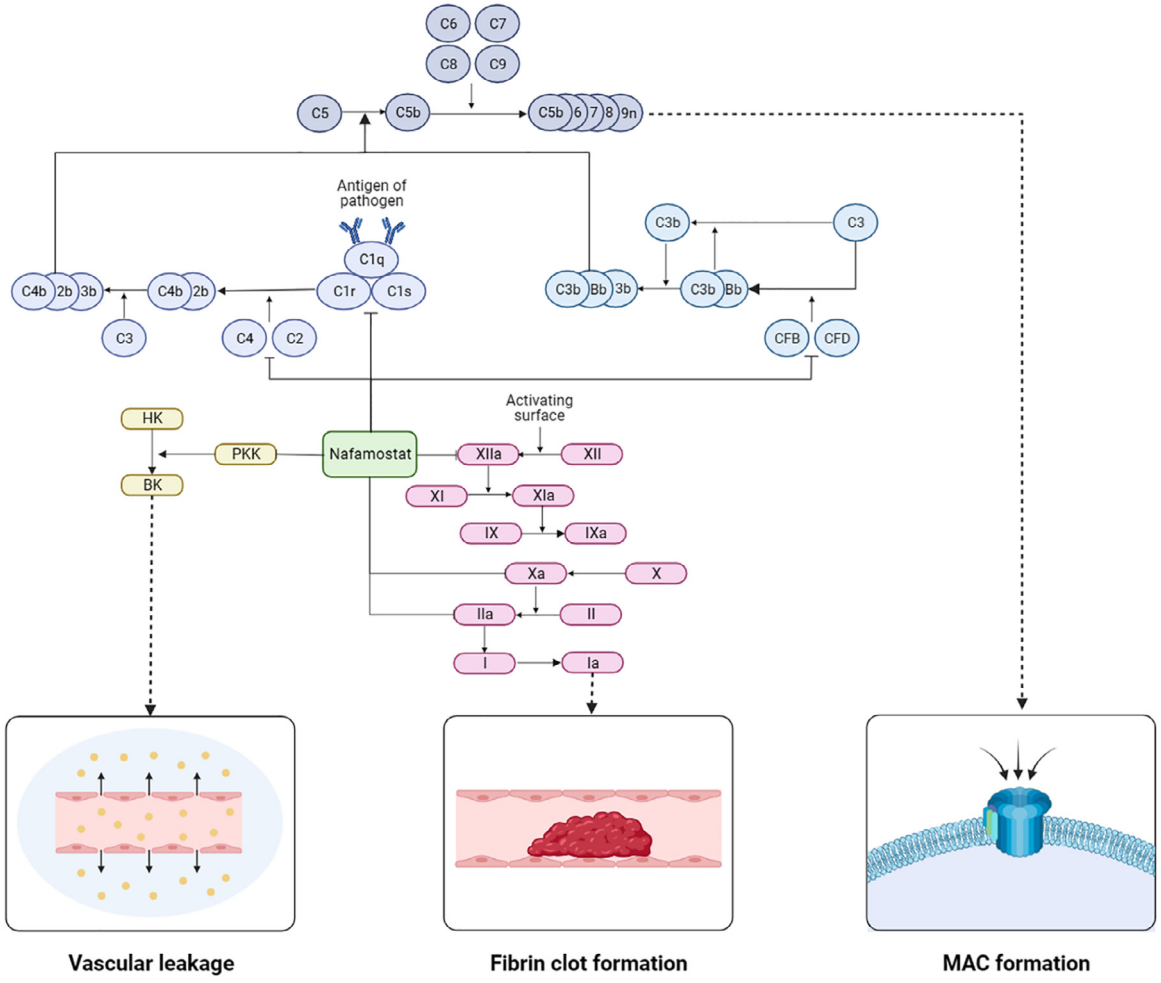

Figure 3. Potential therapeutic effect of NM on the pathophysiological changes in sepsis.
BK: Bradykinin; CFB: Complement factor B; CFD: Complement factor B; HK: High-molecular-weight kininogen; MAC: Membrane attack complex; NM: Nafamostat mesilate; PKK: Prekallikrein.

coagulation, and complement systems, thus improving damage to vital organs and prognosis. Further research is warranted to confirm this hypothesis. Currently, several clinical trials investigating the utilization of NM in the treatment of sepsis, may yield useful results.[224,225]

Author Contributions

Qiaolan He: Writing – review & editing, Writing – original draft, Data curation. **Yilin Wei:** Writing – review & editing. **Yiqi Qian:** Resources, Conceptualization. **Ming Zhong:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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