

Review Article

Serpinc1/Antithrombin III in kidney-related diseases

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The gene *Serpinc1* encodes a serine protease inhibitor named antithrombin III (ATIII). This protease demonstrates both anticoagulant and anti-inflammatory action. ATIII is the most important coagulation factor inhibitor, and even minor changes in ATIII can significantly alter the risk of thromboembolism. ATIII can also suppress inflammation via a coagulation-dependent or -independent effect. Moreover, apart from ATIII deficiency, ATIII and its gene *Serpinc1* may also be related to many diseases (e.g. hypertension, kidney diseases). The present review summarizes how ATIII affects the progress of kidney disease and its mechanism. Further studies are required to investigate how ATIII affects renal function and the treatment.

Introduction

Serpinc1 is the short name for serpin peptidase inhibitor, clade C (antithrombin), member 1. This gene encodes 464 amino acids and is located on chromosome 1q23–25.1. It is composed of seven exons that span 13.4 kb of genomic DNA [1]. *Serpinc1* provides instructions for the production of antithrombin III (ATIII), which is a type of serine protease inhibitor (serpin). Serpins have a well-conserved secondary structure with an exposed reactive center loop, which interacts with the protease active site to inhibit protease activity [2].

ATIII, encoded by the gene *Serpinc1*, is a serine protease inhibitor in the coagulation cascade (Figure 1). It can profoundly accelerate protease inhibition by interacting with a heparin-like substance on the endothelial cell surface. Moreover, ATIII exhibits powerful anti-inflammatory effects, partially by increasing the production of prostacyclin (PGI₂). Even minor changes in *Serpinc1* can increase the risk of thromboembolism [3]. So far, publications about the relationship of *Serpinc1* and the kidney focus primarily on renal injury caused by ATIII deficiency, as well as the diagnosis and treatment of kidney diseases induced by ATIII deficiency. The present review provides a comprehensive review of the following areas: (i) the mechanism of ATIII action, (ii) *Serpinc1* and diseases, (iii) the relationship between ATIII and kidney disease, and (iv) ATIII's potential as a treatment for kidney-related diseases.

The mechanism of ATIII action Coagulation and hemostasis

ATIII is the most important coagulation factor inhibitor (Figure 1). It is a non-vitamin K-dependent protease which inhibits coagulation by lysing thrombin and factor Xa [4]. ATIII resembles α_1 -antitrypsin in structure, but it inhibits thrombin much more powerfully than elastase does. It also blocks other serine proteases in the coagulation cascade, including factors XIIa, XIa, IXa, and Xa. The inhibitory effect of ATIII can be enhanced by heparin, a negatively charged polysaccharide found in mast cells near the walls of blood vessels and on the surface of endothelial cells. ATIII activity is markedly potentiated by heparin, which acts as an anticoagulant by accelerating the formation of irreversible complexes between ATIII and the serine protease-clotting factors [5].

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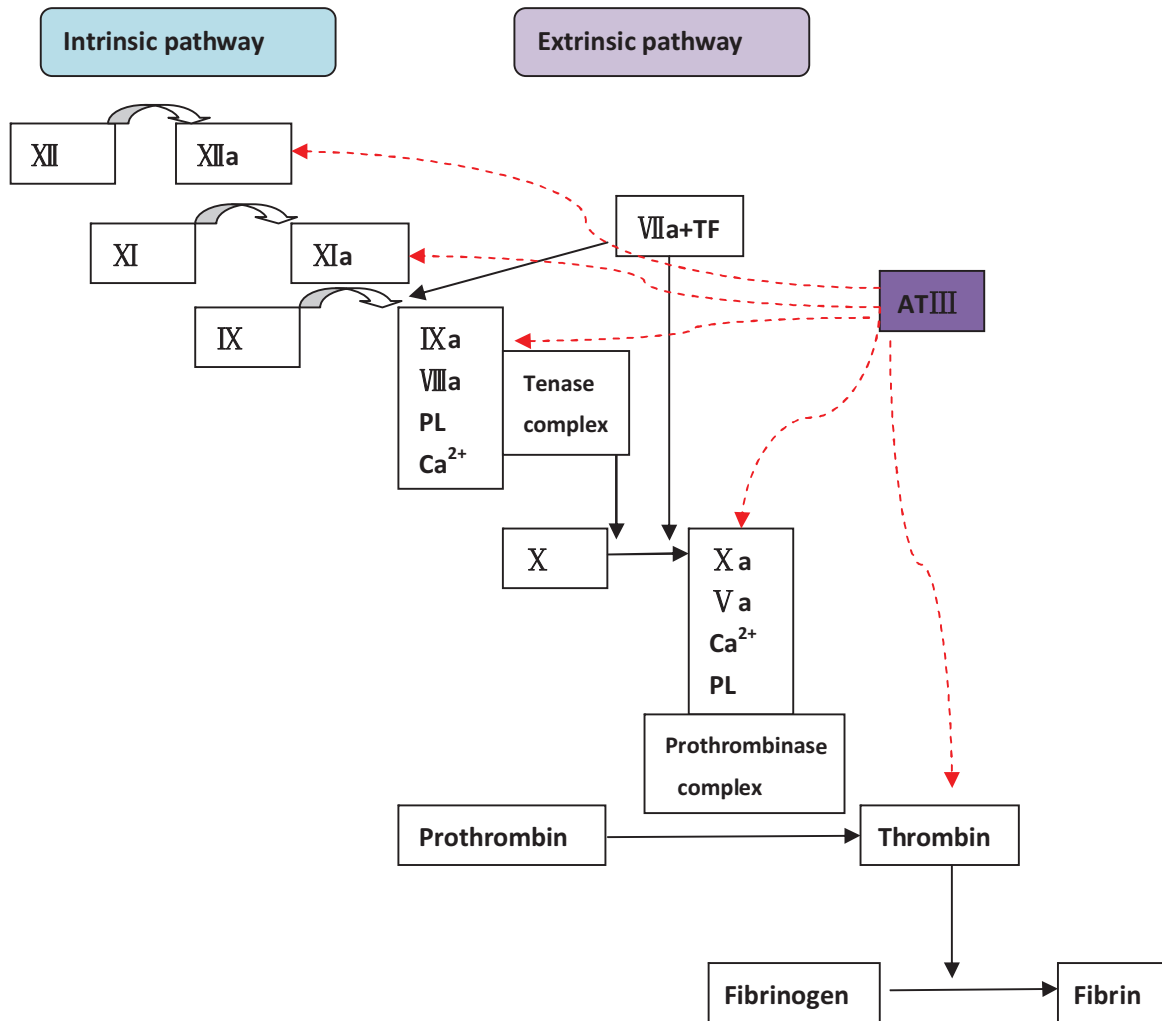


Figure 1. Bioeffects of ATIII in the coagulation cascade
PL, phospholipid.

Anti-inflammation

In addition to regulating coagulation, antithrombin inhibits inflammation within the vascular endothelium. Some anti-inflammatory actions of antithrombin are mediated by its anticoagulation action, whereas others are not [5,6].

Coagulation-dependent effect

First, antithrombin can block thrombin-induced inflammatory pathways. It inhibits the activation of platelets and endothelial cells by thrombin, with both these cells contributing to local inflammation.

Activated platelets stimulate leukocyte activity by secreting cytokines. In response to thrombin, endothelial cells and platelets express P-selectin, which further promotes the interaction with neutrophils. Then the activated neutrophils release enzymes that lead to the exacerbation of coagulation-dependent inflammation [7,8].

Second, ATIII not only blocks the thrombin-induced inflammatory pathway, but also inhibits other proinflammatory coagulation enzymes, e.g. antithrombin inhibits factor Xa-induced production of interleukin (IL)-6 and IL-8, as well as other molecules involved in monocyte recruitment and adhesion to endothelial cells [6].

Coagulation-independent effect

There is evidence that antithrombin also demonstrates anti-inflammatory action independent of its anticoagulation activity. The leading mechanism is that antithrombin induces endothelial cells to release PGI₂ [5,9–11]. Many studies have proved that PGI₂ demonstrates anti-inflammatory action [12]. PGI₂ suppresses not only the aggregation

and activation of platelets, but also the adhesion of neutrophils to the vessel wall. Moreover, it reduces the production of various cytokines and chemokines produced by endothelial cells [13–16]. Other mechanisms include activation of leukocytes, which inhibit the rolling and adhesion of blood vessel neutrophils and lead to less tissue damage, e.g. ATIII prevents pulmonary vascular injury by inhibiting leukocyte activation in rats that have been given endotoxin [17].

SerpinC1 and diseases

ATIII deficiency

It has been reported that there are two types of ATIII deficiency: inherited and acquired. The incidence of ATIII-inherited deficiency is relatively rare (1:10 000) in the general population [18]. However, in patients with thromboembolism, the prevalence of ATIII deficiency ranges from 0.5% to 5% [19]. ATIII deficiency is found in 4–6% of young patients with venous thrombosis, which is a risk factor for thromboembolic disease. Lab tests show that both quantitative and qualitative ATIII deficiencies exist in these patients [20].

Inherited ATIII deficiency is an autosomal dominant disease with a morbidity of around 1/5000. Thromboembolic complications appear around the age of 20. In the fourth to fifth decades of life, two-thirds of the patients are symptomatic [18,21]. The major complications of ATIII deficiency include idiopathic thrombosis and recurrent venous thromboembolism. It has been reported that pregnancy and surgery are risk factors for thromboembolism. At least 220 mutations in the *SerpinC1* gene have been found to cause hereditary antithrombin deficiency. Most of these mutations change single protein-building blocks in antithrombin, which disrupts its ability to control coagulation. Martinez-Martinez et al. [22] reported that genetic mutations could affect the mobile domains of antithrombin-induced conformational instability, resulting in protein polymerization that is associated with a severe clinical phenotype. In addition, a temporal and severe deficiency of antithrombin may contribute to a thrombotic event.

Hereditary antithrombin deficiency

Hereditary antithrombin deficiency can be divided into types I and II, based on the location of the mutation on the *SerpinC1* gene. Hereditary antithrombin deficiency type I is caused by a *SerpinC1* gene mutation that prevents the hepatic cells from producing antithrombin [23]. Patients with this type of antithrombin deficiency have only one working copy of the *SerpinC1* gene in each cell, which results in the production of approximately half the normal amount of antithrombin. Affected patients do not have enough antithrombin to inactivate coagulation factors, and this leads to the increased risk of thromboembolism. Mutations that cause hereditary antithrombin deficiency type II result in the production of an altered antithrombin with a reduced anticoagulating effect [24]. Individuals with this type of antithrombin deficiency typically have normal levels of antithrombin in the plasma, but it does not function properly. Maruyama et al. [25] conclude that the Arg⁵⁶Cys mutant is responsible for type II heparin-binding site deficiency. They also hold a view that the Ala⁴⁵⁹Asp and Pro¹¹²Arg mutants are associated with type I antithrombin deficiency.

Acquired antithrombin deficiency

Acquired deficiency of ATIII can be found in patients who have had liver cirrhosis, liver cancer, nephropathy, disseminated intravascular coagulation (DIC), sepsis, preeclampsia, or trauma, and in patients receiving L-asparaginase, oral contraceptives, severe toxicants, or heparin therapy [18]. Overall, patients with the acquired type of antithrombin deficiency are exposed to a high risk of thromboembolism, due to depletion of a protein critical to anticoagulation in plasma. Low antithrombin levels could be detected not only during but also before the thrombotic event. Acquired antithrombin deficiency occurs in different medical conditions with a similar risk of thrombosis [26].

Hypertension

Hypertension is a major public health issue and a leading cause of morbidity and mortality [27]. It is a multifactorial polygenic disease induced by an interplay of genes and environment [28–30]. Previous studies have reported that inflammation is a risk factor in the development of hypertension [31–34].

Genome-wide association studies have identified hundreds of blood pressure-related phenotypes and genomic regions [35,36]. A transcriptome analysis in Dahl salt-sensitive (SS) rats showed that *SerpinC1* is a candidate gene for salt-sensitive hypertension in SS rats [37]. Liang et al. [37] found that 15 expressed sequence tags in the renal cortex and 39 in the renal medulla were differentially expressed between SS-13^{BN} and all the other three strains (SS, SS-18^{BN}, and SS-20^{BN}). The differentially expressed genes included *SerpinC1*. This suggested that the gene *SerpinC1* is

associated with blood pressure. The correlation between *SerpinC1* and blood pressure still needs further investigation. Case reports have indicated that *SerpinC1* is also related to hypertension. Tomczykowska et al. [38] reported a significantly lower plasma level of ATIII in hypertensive patients compared with healthy individuals. Furthermore, ATIII protects against salt-induced hypertension and proteinuria in pregnancy, which is irrelevant to its anticoagulating effect. ATIII may thus be beneficial for the treatment of preeclampsia [39]. Thrombophilia is a pathologically hypercoagulable state. It causes many complications during pregnancy, including preeclampsia, stillbirth, and recurrent abortions. ATIII deficiency is the major cause of inherited thrombophilia. According to a large-scale, case-control study, thrombophilia is significantly associated with severe preeclampsia [40]. However, the plasma ATIII level was not found to be significantly different in patients with preeclampsia or in the control group [41].

The relationship between ATIII and kidney disease

The previous studies about the relationship between *SerpinC1* and the kidney focus mainly on the thrombotic disorder, which is caused by low ATIII levels resulting from different kidney diseases [42]. Patients who have kidney diseases often demonstrate a high risk of thrombosis due to the loss of a large amount of ATIII [43]. In patients whose serum albumin is <2.0 g/dl, the condition is even worse when losing ATIII [42]. Apart from the anticoagulating function, noteworthy ATIII processes include anti-inflammatory properties, which can affect the progression of kidney disease. Similar to hypertension, the published evidence supports inflammation possibly being one of the causes of kidney diseases [8,44–48]. Important clues have been shown to link inflammation to the pathogenesis of diabetic nephropathy. Clues to the involvement of inflammation in diabetes date back 100 years [49,50], when sodium salicylate was first demonstrated to diminish glycosuria in patients with diabetes. Different inflammatory molecules are considered to be critical factors in the development of microvascular diabetic complications, including nephropathy [49,50]. Generally, the impact of ATIII on kidney function is mostly based on decreasing hypercoagulative state. At the same time, the complex relationship with the inflammatory component could also be a cause.

Nephrotic syndrome

Thrombosis and hypercoagulability occur more frequently and present more severely in patients with nephrotic syndrome (NS). It can be interpreted as the deficiency of ATIII, which is associated with severe proteinuria [51,52]. Moreover, Blavy and Kouame reported that an obvious decrease in ATIII is found in patients with NS [53]. Citak et al. [54] reported that a hypercoagulable state and thromboembolism in both the arterial and the venous circulations are relatively more common in patients with NS. It has been reported that the concentration of ATIII depends on the type of NS. Its level is obviously lower in focal segmental glomerular sclerosis and minimal change nephropathy compared with other types. As for glomerulonephritis, ATIII can inhibit mesangial cell proliferation by inhibiting the effect of thrombin. It stimulates DNA synthesis and human mesangial cell growth [55].

Acute and/or chronic kidney injury

For patients with acute kidney injury (AKI), a low ATIII level caused by the consumption leads to diminished protection against intravascular coagulation and progression of the AKI [42]. In addition, ATIII activity decreases slightly during the acute stage of acute glomerulonephritis and moderately in the relapse stage of nephrotic syndromes. A small increase in urinary ATIII antigen levels was noted in the acute stage of glomerulonephritis, with a considerably bigger increase observed during the relapse stage of the nephrotic syndrome [56]. In rare cases, abnormal antithrombin function can lead to bilateral renal infarction, causing severe AKI and subsequently chronic kidney injury. The abnormal antithrombin function usually results from ATIII deficiency and a prothrombin gene mutation [57]. It is noteworthy that all kinds of nephropathy can decrease plasma ATIII levels as a result of severe proteinuria. Consequently, the low ATIII level can aggravate the renal damage.

Kidney cancer

Antithrombin is a type of hemostasis activation marker in patients with kidney cancer. Zietek et al. [58] reported that ATIII activity in the blood of patients with kidney cancer increases, partially as a result of a compensatory mechanism saving these patients before thromboembolic complication. The measurement of ATIII in renal carcinoma can be a prognostic indicator of hemorrhagic and thromboembolic complications. Similarly, ATIII activity increases in patients with bladder carcinoma. This increase of ATIII activity is associated with an increased risk of hemorrhagic complications and a reduced risk of thromboembolic complications [59]. The role of ATIII in malignancy of the urinary system still needs further investigation.

ATIII as a potential treatment for kidney-related diseases

ATIII is known to play a significant therapeutic role in a variety of kidney diseases such as NS and renal ischemia–reperfusion (I/R) injury. It inhibits thrombin and other serine proteases generated by the coagulation cascade. High-dose ATIII has been shown to have a strong anti-inflammatory effect in mouse models of endothelial damage, such as DIC and I/R injury [60].

Hemodialysis

Numerous studies have shown that ATIII has some positive effects on hemodialysis patients. Schrader et al. [42] reported on ATIII being given to patients with dialysis-dependent renal failure. Supplementation of ATIII can be beneficial in these patients by reducing the incidence of thrombosis of the extracorporeal system. Schrader et al. [42] recommended using a low dose of ATIII to reduce the incidence of thrombosis in the extracorporeal system, whereas a high dose of ATIII should be avoided. Furthermore, Kolb et al. [61] pointed out that hemodialysis itself has some effect on blood coagulation. The thrombin–ATIII (TAT) complex, as a parameter for forecasting thrombotic events, was measured during hemodialysis. Predialysis values of the TAT complex were found to be generally elevated in hemodialysis patients, but only patients with acute renal failure had a constant increase of TAT during hemodialysis.

The reason why ATIII can be used for thrombosis prevention in dialysis patients is that it can reduce the hypercoagulable state caused by long-term hemodialysis. A previous study investigated the association between continuous venovenous hemofiltration using polyacrylonitrile filters and an intrinsic coagulation pathway [62]. It identified that patients who developed thrombosis within the first 24 h post-hemodialysis had a low baseline level of ATIII and heparin cofactor II. Moreover, the level of TAT complex rises significantly in these patients [62]. In a study of ATIII replacement therapy, Schrader et al. [63] found that the dosage of ATIII should be individualized. More recently, another study reported that a single dose of ATIII could be used as a potential alternative anticoagulant for AKI patients on continuous renal replacement therapy [64].

Kidney transplantation

For patients undergoing kidney transplantation, recombinant antithrombin is considered to have a therapeutic effect. Cowan et al. [65] reported that recombinant ATIII could be a useful therapeutic agent to ameliorate both early graft damage and the development of systemic coagulation disorders in pig-to-human xenotransplantation. In a study of patients undergoing kidney transplantation, Pawlicki et al. [66] found that there was a lower ATIII activity on postoperative day (POD) 7, and a higher fibrinogen concentration and platelet count on POD 14, in recipients with a postoperative hematoma than in those who did not develop this complication. Considering that antithrombotic prophylaxis increases the risk of hemorrhagic complications, it should be used with caution in patients after a kidney transplantation.

Renal ischemia–reperfusion injury

Emerging evidence suggests that ATIII regulates renal I/R injury. ATIII can not only inactivate thrombin and other serine proteases in the coagulation cascade, but also suppress the inflammatory response of the immune system [67,68]. Maeda et al. [60] showed that high-dose ATIII alters the consequences of vascular injury by reducing mural thrombus formation and limiting the inflammatory reaction of the vessel wall, without exerting a prolonged inhibitory effect on positive vascular remodeling. The treatment with ATIII reduces inflammatory cell infiltration, as determined by the CD11b⁺ cell density in the adventitial area. Appropriate use of ATIII in patients with acute vascular injury or undergoing procedures that have a risk of vascular endothelial injury will result in rapid and effective repair of the damaged vessels [60]. According to other studies about renal I/R injury, the coagulation system is activated 2 h after injury and the activity of coagulation reaches a peak at 12 h [69]. In this process, plasma ATIII levels start to decline at 2 h and reach their lowest point at around 12 h, and then start to recover [69]. Another study showed that ATIII can significantly increase PGI₂ levels in cultured human umbilical vein endothelial cells [5]. Moreover, ATIII is also reported to reduce renal I/R injury in rats [70]. A study by Ozden et al. [70] found that antithrombin strongly suppressed the accumulation of lipid peroxidation products and neutrophils. Mizutani et al. [10] reported that antithrombin could suppress I/R injury by inhibiting leukocyte activation and, therefore, improve the blood flow of kidneys and reduce vascular permeability. The study proved that antithrombin inhibits the activation of leukocytes via an increased production of PGI₂. Recently, Wang et al. [71] found that patients with low ATIII activity had a higher risk of developing AKI after cardiac surgery. This indicates that *SerpinC1* significantly reduced the risk of renal damage caused by I/R injury.

Table 1: Summary of potential treatments for kidney-related diseases

Clinical condition	Effect of concentrated treatment with antithrombin
Hemodialysis	<ul style="list-style-type: none"> • Reduces the hypercoagulable state of blood
Kidney transplantation	<ul style="list-style-type: none"> • Defensive function: ameliorates both early and late graft damage • Development of systemic coagulation disorders
Renal I/R injury	<ul style="list-style-type: none"> • Inactivates thrombin and other serine proteases of the coagulation cascade • Anti-inflammatory effects
Nephritic syndrome	<ul style="list-style-type: none"> • Prevents thrombosis
Sepsis/SIRS/MODS	<ul style="list-style-type: none"> • Prevents fibrin deposition and controls inflammation

Nephrotic syndrome

Clinical evidence supports a therapeutic role for ATIII in NS patients [72,73]. Hypercoagulability is a recognized complication of NS, which commonly affects the venous system. Arterial thrombosis has rarely been reported and, in the literature, only six cases of arterial thrombosis have been reported in adults [72]. The outcome in these cases was unsatisfactory because of the high rate of limb loss and recurrence of thrombosis. The successful treatment is reported of a 39-year-old patient with arterial thrombosis who had anticoagulant therapy of 1000 units of ATIII [72]. Another study points out that, for children with a high risk of arterial thrombosis, it might be advisable to adopt the prophylactic ATIII therapy before the use of albumin and diuretics [73].

Sepsis, SIRS, and MODS

ATIII can be used to treat many other diseases. First, ATIII can prevent lung and kidney failure in sepsis. It can inhibit fibrin deposition and decrease inflammation in sepsis, thereby limiting damage to the lungs and kidneys. Second, ATIII can reduce inflammatory responses such as the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) [74]. As one of the most vulnerable organs in SIRS and MODS, the kidney benefits from ATIII treatment [74]. Third, it has been reported that ATIII therapy can help improve kidney diseases such as renal shock [75]. Finally, Sokratov [76] reported that the administration of ATIII-enriched plasma to rabbits with acute Masugi nephritis inhibited prothrombinase formation, and increased the release of component C3 from the kidneys.

Conclusion

ATIII demonstrates both anticoagulant and anti-inflammatory actions within the vascular endothelial environment. Therefore, its deficiency can lead to activation of the coagulation cascade and/or inflammatory pathway, by increasing intravascular consumption and endothelial leakage. Furthermore, ATIII plays a significant role in kidney disease. It affects renal function in various ways and, therefore, ATIII deficiency can result in acute or chronic renal damage. ATIII also shows great value in treating kidney disease (Table 1). As recent studies have focused on the value of ATIII in kidney diseases, the role of ATIII in patients with kidney disease is much clearer than before. Despite the reported role for ATIII in anti-inflammatory processes, further investigations are needed to explore how ATIII affects the renal function and treatment of kidney disease. The role of ATIII in kidney injury appears to be complex because few studies have been carried out to explore this area. In the present review, we summarized the latest studies of the relationship between ATIII and kidney disease, which may help to improve future diagnosis and treatment.

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Author Contribution

Feng Wang and Mingyu Liang conceived and designed the work. Zeyuan Lu collected the references. Feng Wang and Zeyuan Lu wrote the draft. Feng Wang and Mingyu Liang revised and reviewed.

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Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

Abbreviations

AKI, acute kidney injury; ATIII, antithrombin III; DIC, disseminated intravascular coagulation; I/R, ischemia–reperfusion; IL, interleukin; MODS, multiple organ dysfunction syndrome; NS, nephrotic syndrome; PGI₂, prostacyclin; POD, postoperative day; SIRS, systemic inflammatory response syndrome; SS, salt-sensitive; TAT, thrombin–ATIII.

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