Intrinsic Pathway of Coagulation and Arterial Thrombosis

David Gailani, Thomas Renné

Abstract—Formation of a fibrin clot is mediated by a group of tightly regulated plasma proteases and cofactors. While this system is essential for minimizing blood loss from an injured blood vessel (hemostasis), it also contributes to pathologic fibrin formation and platelet activation that may occlude vessels (thrombosis). Many antithrombotic drugs target key elements of the plasma coagulation mechanism such as thrombin and factor Xa, based on the premise that plasma elements contributing to thrombosis are primarily those involved in hemostasis. Recent studies with genetically altered mice raise questions about this paradigm. Deficiencies of the intrinsic pathway proteases factor XII and factor XI are not associated with abnormal hemostasis in mice, but impairment formation of occlusive thrombi in arterial injury models, indicating that pathways not essential for hemostasis participate in arterial thrombosis. If factor XII or factor XI make similar contributions to thrombosis in humans, these proteases could be ideal targets for drugs to treat or prevent thromboembolic disease with minimal risk of therapy-associated bleeding. (Arterioscler Thromb Vasc Biol. 2007;27:2507-2513.)

Key Words: Intrinsic pathways ▪ coagulation ▪ arterial thrombosis

An intricate mechanism has evolved in vertebrates to limit blood loss from damaged blood vessels through formation of clot (hemostasis), while maintaining blood in a fluid state where the circulation is intact.1,2 This system is required for maintaining the integrity of the circulatory system, and perturbations in the balance between procoagulant and anticoagulant forces can lead to bleeding or thrombotic disorders.3 Formation of the key coagulation enzyme thrombin proceeds through a tightly regulated series of reactions involving a group of plasma proteases and cofactors (Figure).4–6 Among the many functions of thrombin are cleavage of fibrinogen to form fibrin and activation of platelets, both major constituents of normal and pathologic blood clots.7 Although the processes leading to thrombotic occlusion of a blood vessel are complex, enhanced thrombin generation attributable to increased procoagulant stimuli or weakening of regulatory mechanisms is thought to be contributory in many situations.

The proposition that thrombosis is “hemostasis in the wrong place”,8,9 implies that the major processes leading to thrombin generation during pathologic coagulation are similar to those involved in hemostasis, perhaps differing only in intensity or location. In line with this reasonable hypothesis, most anticoagulants target thrombin, or plasma proteases such as factor Xa that are required for thrombin generation. Although effective at limiting thrombus growth, these therapies inevitably carry a significant risk of excessive bleeding.10–12 Recent studies with mice lacking proteases of the intrinsic pathway of coagulation (factors IX, XI, and XII) raise questions regarding the premise that hemostasis and thrombosis represent “two sides of the same coin.”13–15 Here, we review clinical data on the contributions of intrinsic pathway factors to normal hemostasis and thromboembolic disease in humans and discuss recent results with models of arterial thrombosis in mice deficient in proteases of the intrinsic pathway.

Intrinsic Pathway Proteases and Normal Fibrin Formation

In 1964, Macfarlane,16 and Davie and Ratnoff17 proposed similar models (the cascade or waterfall hypotheses) for the biochemical reactions involved in fibrin formation (Figure), that are the basis for the prothrombin time (PT) and partial thromboplastin time (PTT) assays used in clinical practice to assess the integrity of plasma coagulation. In these schemes, coagulation proceeds through a series of proteolytic reactions involving trypsin-like enzymes that form a biochemical amplifier, culminating in generation of sufficient thrombin to form a fibrin clot. Initiation of fibrin formation through the “extrinsic pathway” occurs when plasma factor VIIa forms a complex with the integral membrane protein tissue factor (abbreviated TF in Figure).18,19 Tissue factor is not normally found at high concentrations in blood, but is present on cell membranes in subendothelial layers of blood vessels and is exposed to factor VIIa when the endothelium is injured. Alternatively, coagulation may be initiated through the “intrinsic pathway” when factor XII is activated on a charged surface by a process called contact activation.20–22 Activation
of factor XII is followed sequentially by activation of factor XI and factor IX. The intrinsic and extrinsic pathways converge at the level of factor X activation. Factor Xa activates prothrombin to thrombin in the presence of the cofactor factor Va, and thrombin subsequently converts fibrinogen to fibrin.4–7

The intrinsic pathway is typically depicted as a sequence of proteolytic reactions culminating in factor IX activation (Figure, white arrows). However, the hemorrhagic phenotypes of patients deficient in components of this pathway suggest more complex interactions. Deficiency of factor IX or its cofactor, factor VIII, cause hemophilia B and hemophilia A, respectively, the severe forms of which are associated with crippling hemorrhage into joints and muscles, and soft tissue bleeding that can be life threatening.23 Factor XI deficiency, in contrast, is associated with a distinctly different, and usually milder disorder characterized by trauma or soft tissue-related hemorrhage, primarily involving tissues with high fibrinolytic activity.24 Finally, factor XII–deficient patients do not exhibit an abnormal bleeding tendency, even with surgery, despite having markedly prolonged PTT clotting times.25,26 These observations argue strongly against a model in which proteases are exclusively activated in a linear sequential fashion.

In current models of hemostasis, fibrin formation at a wound site is triggered primarily, if not exclusively, by the factor VIIa-tissue factor complex. In these scenarios factor XII is not required for fibrin formation.18,19,27 The significant differences in the bleeding abnormalities associated with factor IX and factor XI deficiency are explained by the observation that factor IX is also activated by the factor VIIa-tissue factor complex (Figure, dotted line 1).28 Although the relative contributions of the 2 mechanisms for factor IX activation are not certain, it may be that activation by factor VIIa-tissue factor is the more important mechanism in many circumstances. Similarly, factor XI may be activated by proteases other than factor XIIa, providing an explanation for the absence of a bleeding diathesis in factor XII deficiency. Thrombin can convert factor XI to the active protease factor XIa,29,30 and it is postulated that thrombin generated early in clot formation activates factor XI, creating a feed-back loop that sustains coagulation (Figure, dotted line 2).31 Thus, redundant mechanisms for factor IX and factor XI activation explain differences in the bleeding phenotypes in patients deficient in components of the intrinsic pathway and raise questions regarding the importance of contact activation initiated coagulation in vivo. Although it is difficult to make a strong case for a role for the classic intrinsic pathway in normal coagulation, it is possible that it is important for fibrin formation in some situations or during certain pathologic processes. The following section reviews data on intrinsic pathway proteins and thromboembolic disease in humans.

### Intrinsic Pathway Proteins and Thromboembolic Disease in Humans

It is postulated that the intrinsic pathway proteases factor IXa (in conjunction with factor VIIIa) and factor XIa, are involved in pathways required for sustained generation of thrombin that influence clot formation and resistance to fibrinolytic degradation,20,27,31,32 Dysregulation of these pathways would be expected, therefore, to contribute to thromboembolic disease. In humans, correlations between plasma levels of factors VIII,33 IX,34 and XI,35 and risk of venous thromboembolism have been demonstrated in large case-controlled population studies. In the Leiden Thrombophilia Study, individuals with plasma factor IX34 or factor XI35 levels in the upper 10% of the normal distribution had an ≈2-fold increased risk of venous thromboembolism, compared with the remainder of the population. Similarly, factor VIII levels above the upper limit of normal (1.5 International Units/mL) gave an odds ratio for venous thromboembolism of ≈5.33 Subsequent prospective studies, in general, support the impression that high factor VIII levels are a moderate risk factor for venous thrombosis.36 These findings are supported by the observation that venous thrombosis is rare in hemophiliacs.37 Because of the rarity of severe factor XI deficiency, it is not clear whether this disorder also protects against venous thrombosis. A recent review of thrombotic events in rare coagulation disorders reported only 5 cases in severe factor XI deficiency,38 2 of which occurred after replacement therapy with factor XI concentrate, a product associated with thromboembolic events.39

Venous thrombi tend to be rich in fibrin and red blood cells, and relatively poor in platelets. It follows, therefore, that levels of plasma proteases involved in fibrin formation influence venous thrombotic risk. A role for intrinsic pathway factors in arterial disease in humans is not as clear as for venous events. Severe congenital coagulopathies such as hemophilia,40 type III von Willebrand disease,41 or Glanzmann thrombasthenia42 (absence or abnormality of the platelet αIIb/βIII integrin) do not appear to affect development of atherosclerosis, although there are suggestions that hemophilia retards arterial plaque formation somewhat in humans43 and mice.44 However, longitudinal studies in the Netherlands
of patients with factor VIII or factor IX deficiency demonstrated a lower incidence of myocardial infarction than in controls, and an 80% reduction in mortality from coronary artery disease, suggesting factor VIII or IX deficiency may inhibit formation of thrombi at sites of plaque rupture. Although 2 recent reviews of case reports concluded that myocardial infarction may be more prevalent than previously suspected in hemophilia A or B, 47,48 a significant number of cases were associated with factor replacement or the use of thrombogenic prothrombin complex concentrates. Since the 1960’s, a role for elevated factor VIII levels in coronary and cerebrovascular disease has been addressed by several large studies (reviewed in reference 36), with conflicting results. Interpretation in some instances is rendered difficult because factor VIII levels fluctuate in response to a variety of stresses associated with acute illness, inflammation, and subclinical conditions; and because of the physical association of factor VIII with von Willebrand factor (vWF), a contributor to arterial thrombosis. Taken as a whole, the data do not allow us to draw firm conclusions regarding an association between factor VIII or IX levels and risk for arterial thrombosis, but indicate that deficiency of these proteins provides some protection from acute arterial thrombotic events.

An association between factor XI and arterial disease has been addressed in several recent studies. Risk factors for myocardial infarction were examined in a subpopulation of the Leiden Thrombophilia Study, the SMILE (Study of Myocardial Infarction—Leiden) project, and high levels of factor XI were associated with an ~2-fold increased risk of myocardial infarction in men. Factor XI activity above the normal range was also identified as a risk factor for stroke and transient ischemic attacks in a retrospective analysis of patients under the age of 55. These data support studies in baboons 51 and rabbits 52 showing that factor XI contributes to the growth of platelet-rich thrombi in the arterial circulation. The consequences of severe factor XI deficiency (activity <0.15 U/mL) on myocardial infarction were studied in 96 Israeli patients over the age of 35 years. Sixteen had histories of myocardial infarction, an incidence not statistically different from what was expected in the general population. In contrast, a recent evaluation of 125 patients with severe factor XI deficiency from a similar study population identified a significantly lower risk for ischemic stroke compared with age and sex-matched controls. These findings raise the interesting possibility that factor XI may be more important for thrombus formation in the carotid artery or heart (the origins of most emboli that occlude cerebral vessels), than for thrombus formation at a site of plaque rupture in a coronary artery.

A contributory role for factor XII in either arterial or venous thromboembolic disease in humans has been difficult to identify, with a plethora of studies giving conflicting results. Factor XII deficiency has long been implicated as a prothrombotic state, dating back to the death of the index case for severe factor XII deficiency from a pulmonary embolism. Multiple case reports have described arterial and venous thrombotic events in factor XII deficient individuals, though some degree of reporting bias seems likely. A recent reevaluation of published reports suggests other congenital or acquired thrombotic risk factors are present in most factor XII deficient patients with thrombosis, and large case-controlled studies in the Swiss 57 and Dutch 58 populations did not find a correlation between factor XII deficiency and adverse outcomes. However, recent work has again brought the issue of factor XII and thrombosis to the forefront.

The SMILE project identified an inverse association between factor XII level and risk of myocardial infarction, with an odds ratio for individuals in the highest quintile of factor XII levels of 0.4 compared with those in the lowest quintile. This suggests a protective effect for higher factor XII levels. This study involved persons with factor XII levels within the broad normal range and did not examine the consequences of severe deficiency. A recent analysis of more than 8500 individuals in Austria partially addressed this issue. Again, overall mortality and death from cardiovascular disease increased as factor XII level decreased, although thrombosis was not distinguished from other types of cardiac disease. However, mortality for patients with 1% to 10% of normal factor XII level (severe deficiency) was similar to mortality for the population median, suggesting a fundamental difference between severe and moderate factor XII deficiency. Elevated levels of activated factor XII (factor XIIa) have been associated with increased risk for coronary heart disease and were a prognostic risk factor for recurrent coronary events, supporting the premise that factor XIIa may contribute to thrombus formation. It is not known whether factor XIIa contributed to thrombotic events in these patients, or was generated as a consequence of the thrombosis or tissue ischemia. In contrast, a recent assessment involving a case–control study from the Second Northwick Park Heart Study indicates that low factor XIIa levels (detected as factor XIIa in complex with C1-esterase inhibitor) were associated with an increased risk of coronary artery disease and stroke in middle-aged men. When evaluating clinical data on factor XII, it is important to note that antibodies to factor XII and reduced factor XII levels have been associated with antiphospholipid antibodies (APA) and the prothrombotic APA syndrome. APAs are relatively common in the general population, and it is possible that they are over-represented in patients with apparent low to low-normal factor XII levels. At this point the available data do not allow us to firmly conclude that factor XII contributes positively or negatively to thrombotic disease in humans.

### Mouse Models of Intrinsic Pathway Protein Deficiencies

Encouraged by the intriguing, and often perplexing, clinical data discussed in the previous sections, we have conducted studies over the past 4 years to assess the importance of intrinsic pathway proteases to arterial thrombus formation in mice. Mice with complete deficiencies of the intrinsic pathway proteins, factors VIII, IX, XI, or XII have been established, facilitating this effort. In contrast to deficiencies of prothrombin and factors V, VII, and X, which cause intrauterine or perinatal death in mice, deficiencies of intrinsic pathway factors are compatible with life and normal reproductive capacity. The hemostatic disorders associated with these deficiencies in mice are similar in some regards to...
the corresponding human conditions; however, important differences must be considered when assessing results of the thromboembolism models discussed in the following section. Like their human counterparts, mice lacking factor VIII, IX, XI, or XII have prolonged in vitro clotting times in PTT assays. Factor VIII– or factor IX–deficient mice have the equivalent of hemophilia, and when challenged by removal of the tip of the tail with a scalpel, the majority exsanguinate.65,66 Although this demonstrates a significant hemostatic defect, spontaneous bleeding seems to be relatively infrequent in factor VIII deficient mice.70 In 1 study ≈20% of animals had spontaneous bleeding, primarily affecting subcutaneous tissue or the thoracic cavity,71 in contrast to the joint and soft tissue bleeds typical of human hemophilia. In our experience, factor IX–null mice do not experience significant bleeding with some types of surgical procedures such as cut-down on the carotid artery. It is not clear whether the observations are attributable to fundamental differences in the hemostatic systems of mice and humans, or simply reflects variation in mechanical stress on tissues attributable to size differences.

Factor XI–deficient mice have normal tail bleeding times15,67 and no obvious abnormality of hemostasis. This is in contrast to humans with severe factor XI deficiency, many of whom experience hemorrhage after trauma or surgery, particularly if the oropharynx or urinary tract are involved.72 It must be pointed out that factor XI–deficient mice have not been systematically challenged by injury to these tissues, so it is not known whether this protease is required for normal hemostasis in mice in some situations. Hemostasis has been tested in factor XII–deficient mice on different genetic backgrounds and, as in factor XII–deficient humans, appears to be normal.68

Intrinsic Pathway Proteases in Arterial Thrombus Formation in Mice

Initially, we compared factor IX and factor XI deficient C57Bl/6 mice using a model of carotid artery occlusion induced by application of ferric chloride to the exterior of the vessel.55 Ferric chloride causes significant damage, with desquamation of the endothelial layer, resulting in exposure of collagen to flowing blood. Deficiency of factor IX or factor XI prevented thrombotic occlusion in this model to a similar degree to a supratherapeutic dose of heparin. The most surprising result from this study was that the antithrombotic effects of factor IX deficiency and factor XI deficiency were not only potent, but comparable, despite the marked differences in hemostasis observed in the tail bleeding time model.15,66,67 This suggested that the contribution of a protease to hemostasis may not be an accurate indicator of its importance to thrombosis. Subsequent studies using intravital microscopy demonstrated that factor XI deficiency causes a pronounced defect in platelet accumulation into thrombi forming in arterioles after laser-induced injury.73,74 This work is consistent with studies demonstrating that inhibition of factor XI blunts tissue factor–induced platelet-rich thrombus formation in arterial shunts in baboons54 and inhibits growth of platelet aggregates after arterial endothelial injury in rabbits.52

Extrapolating from current models of hemostasis, it seemed reasonable to conclude that the processes leading to thrombus formation in the ferric-chloride model would not require factor XII. However, factor XII–deficient mice have a marked defect in occlusive thrombus formation in response to ferric chloride-injury of mesenteric vessels and after ligation injury or mechanical endothelial denudation of the carotid artery.14 A head-to-head comparison of factor XII–deficient and factor XI–deficient mice demonstrated that both lines were comparably protected from thrombus formation.14 Intravital microscopy of mesenteric arteries and veins in factor XII– or factor XI–deficient mice treated with ferric chloride revealed that platelet aggregates form, but that large aggregates are unstable, fragment, and are swept away by the flowing blood, preventing vessel occlusion.14 We subsequently compared factor XII–deficient mice to factor IX– or factor XI–deficient mice in the ferric chloride-carotid artery injury model (unpublished observations, Q. Cheng, D. Gailani, T. Renné, 2007). Factor XII deficiency provided the same degree of protection from occlusion as factor IX or factor XI deficiency. Cumulatively, these findings demonstrate that factor XII and factor XI are essential for thrombus propagation in arteries in mice and suggest that the classic intrinsic pathway of coagulation may be operating during pathologic thrombus growth.

Intrinsic Pathway Proteases in a Murine Model of Cerebral Ischemia/Reperfusion Injury

The importance of factor XII and factor XI to cerebral ischemia/reperfusion injury in mice was investigated using a model of transient occlusion of the middle cerebral artery (MCA),75 in which the MCA is occluded for 1 hour by a fine filament, followed by removal of the filament to reestablish circulation to the ischemic zone. Both factor XII–deficient and factor XI–deficient mice had markedly reduced ischemic injury compared with wild-type animals, with significantly lower mortality and residual neurological deficit. Infusing human factor XII into factor XII–deficient mice normalized the PTT, and resulted in a similar degree of cerebral injury as in wild-type mice. Fibrin deposition in the microvasculature of vessels within the ischemic zone was markedly reduced in factor XII– or factor XI–deficient animals compared with controls. Interestingly, factor XII– or XI–deficient mice did not develop the intracerebral hemorrhage seen in wild-type animals after ischemic/reperfusion, as revealed by T2-weighted nuclear magnetic resonance images. Finally, administration of the factor XIIa inhibitor D-Pro-Phe-Arg-chormethyl ketone to wild-type mice also protected them from cerebral ischemia, without causing excessive bleeding.

The results of this work suggest that the contribution of factor XII to cerebral injury is mediated through the intrinsic pathway, a premise supported by the finding that inhibiting factor IX activity by infusion of active site inhibited factor IXa is protective in this model.76 However, alternative processes are possible. Factor XIIa and related fragments can activate plasma factor VII,77 perhaps priming the extrinsic pathway. Furthermore, factor XIIa may initiate other proteolytic cascades involving complement,78 fibrinolysis,79 and kallikrein/kinin formation80 that may contribute to inflamma-
tion, aggravating ischemia-reperfusion injury related damage. Three studies using bradykinin B2 receptor–null mice addressing the importance of the kallikrein-kinin system in MCA or carotid artery occlusion models came to different conclusions.\textsuperscript{81–83} In our hands, these mice are not protected from ischemia-reperfusion injury in the MCA occlusion model (data not shown). Factor XI circulates in plasma as a complex with high molecular weight kininogen (HK),\textsuperscript{84} a glycoprotein that is cleaved by kallikreins to release bradykinin.\textsuperscript{85} Mice lacking HK have prolonged times to carotid artery occlusion in a Rose Bengal/laser injury model (K. McCrae, personal communication, 2007). These animals will be invaluable in sorting out the importance of kininogens and kinin formation in the thromboembolism models.

### Conclusions

The results with intrinsic pathway protease–deficient mice demonstrate that the reactions required for normal hemostasis are not identical to those involved in forming an occlusive arterial thrombus in the absence of bleeding. The similar antithrombotic phenotypes of mice lacking factor IX, XI, or XII suggest that a process similar to the classic intrinsic pathway may be operating in these models, although a large amount of work remains to be done to definitively establish the biochemical pathways involved. Intravital microscopy indicates that mice lacking factor XII or factor XI are unable to sustain the growth of large platelet rich thrombi in the high shear environment of an artery lumen.\textsuperscript{14,74} As hemostasis is, in large part, an extravascular event, the lower shear forces involved may obviate the need for factor XII and factor XI in normal clot formation, explaining the absence of a bleeding phenotype in factor XII– or factor XI–deficient mice. It is not clear at this point if the importance of factor XII and factor XI to arterial thrombus formation in mice is indicative of a species-specific requirement for these proteins or point to fundamental differences in the processes involved in hemostasis and thrombosis that are broadly applicable and, therefore, have relevance for human disease. It must be kept in mind that the largest studies of intrinsic pathway proteins and thromboembolism in humans primarily examined risk within the broad normal range for each factor level, whereas studies with mice involved severe factor deficiencies. A summary of the phenotypes seen in humans and mice discussed in this paper are presented in the Table.

Although the physiological function, if any, of the classic intrinsic pathway remains to be elucidated, it is possible that inhibiting a protease in this pathway may offer a strategy for preventing or treating arterial thrombosis. At this point we can only speculate as to which protease would provide the best target for drug therapy in humans. Data from multiple species clearly show that factor XII is not required for normal hemostasis, and its inhibition should not result in an increased risk for bleeding. However, of the major proteases in the intrinsic pathway, the association with thrombotic disease in humans is most tenuous for factor XII. Furthermore, factor XII may be a component of other host-defense mechanisms,\textsuperscript{78–80} and the long-term consequences of targeted inhibition of factor XIa in a large patient population is not known. Factor XI is thought to be a dedicated coagulation protease, although there is evidence that it has activities other than activation of factor IX in mice.\textsuperscript{86} Inhibition of factor XIa in nonhuman primates (baboons) is efficacious in preventing formation of platelet rich thrombi in arterial grafts.\textsuperscript{81} However, inhibition of factor XIa in humans may increase bleeding in some patients, and possibly exacerbate mild preexisting bleeding disorders. The hemostatic defect in factor XI–deficient individuals is relatively mild,\textsuperscript{72} and the bleeding risk should be significantly lower for a factor XIa

### Table. The Effects of Intrinsic Pathway Proteases on Hemostasis and Thromboembolism

<table>
<thead>
<tr>
<th>Factor</th>
<th>Intrinsic Pathway Proteases</th>
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<tbody>
<tr>
<td>Factor IX</td>
<td>Factor XI</td>
</tr>
<tr>
<td>Humans</td>
<td>Severe\textsuperscript{23}</td>
</tr>
<tr>
<td>Mice</td>
<td>Severe\textsuperscript{15,66}</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>Severe deficiency probably protective\textsuperscript{45,46}</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>Not known. Increased risk of hemorrhagic stroke</td>
</tr>
<tr>
<td>Mice (experimental)</td>
<td>Inhibition of activity is protective\textsuperscript{76}</td>
</tr>
<tr>
<td>Carotid artery thrombosis</td>
<td></td>
</tr>
<tr>
<td>Mice (experimental)</td>
<td>Severe deficiency protects\textsuperscript{15}</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>High levels increase risk\textsuperscript{14}</td>
</tr>
<tr>
<td>Mice (experimental)</td>
<td>Not done</td>
</tr>
</tbody>
</table>

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Gailani and Renne Intrinsic Pathway of Coagulation and Arterial Thrombosis 2511
inhibitor than for our current anticoagulants. Finally, inhibition of factor IXa may turn out to be a useful in some situations. Although a drug that produces a condition comparable to mild to moderate hemophiliac may not seem an attractive option, studies in rodents have shown this type of therapy to be efficacious and safe on a short-term basis. A better understanding of the physiological and pathologic processes that are dependent on intrinsic pathway proteases will be critical to the development of therapeutic strategies aimed at targeting the prothrombotic activities of these interesting proteins.

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Disclosures

T.R. is named on a patent application covering the use of factor XII as a target for anticoagulant therapy.

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Gailani and Renne  Intrinsic Pathway of Coagulation and Arterial Thrombosis 2513


Intrinsic Pathway of Coagulation and Arterial Thrombosis
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