Tissue-Specific Hemostasis in Mice

Nigel Mackman

Abstract—Blood coagulation is essential to maintain hemostasis in organisms with a vascular network. Formation of a fibrin-rich clot at a site of vessel injury is a highly complex process that is orchestrated by the coagulation protease cascade. This cascade is regulated by 3 major anticoagulant pathways. Removal of a clot is mediated by the fibrinolytic system. Defects in the regulation of clot formation lead to either hemorrhage or thrombosis. Tissue factor, the primary cellular initiator of blood coagulation, is a transmembrane receptor that is expressed in a tissue-specific manner. The 3 major anticoagulants are tissue factor pathway inhibitor, antithrombin, and protein C, the latter requiring a transmembrane receptor called thrombomodulin for its activation. Tissue factor pathway inhibitor and thrombomodulin are expressed by endothelial cells in a tissue-specific manner, whereas antithrombin and protein C circulate in the plasma. Fibrinolysis requires the activation of plasminogen to plasmin, which is mediated by tissue-type plasminogen activator and urokinase-type plasminogen activator. Interestingly, tissue-type plasminogen activator is expressed by a subset of endothelial cells of discrete size and location. These observations, together with the phenotypes of mice that have defects in the procoagulant, anticoagulant, and fibrinolytic pathways, indicate that hemostasis is regulated in a tissue-specific manner. (Arterioscler Thromb Vasc Biol. 2005;25:2273-2281.)

Key Words: coagulation ■ anticoagulants ■ fibrinolysis

This review focuses on how the procoagulant, anticoagulant, and fibrinolytic pathways regulate the generation and removal of fibrin in a tissue-specific manner in mice. Decreased levels of fibrin lead to hemorrhage because of impaired hemostasis, whereas increased levels of fibrin result in intravascular thrombosis. The major advantage of mice is that we can use knockout technology to disrupt individual genes in the procoagulant, anticoagulant, and fibrinolytic pathways and analyze the effect on hemostasis and thrombosis in vivo. In addition, we can combine various mutations in an attempt to rebalance fibrin generation and restore hemostasis. Additional advantages are that mice can be humanized for a chosen gene, and mutations can be studied on a defined genetic background. Studies of mutant mice have significantly increased our understanding of hemostasis and thrombosis and provided an important resource for testing the efficacy of new procoagulant, anticoagulant, and clot-dissolving drugs. Where possible, I will compare the phenotypes of mice and humans with defects in the procoagulant, anticoagulant, and fibrinolytic pathways.

In 1999, Rosenberg and Aird1 proposed a model of vascular bed-specific hemostasis. This model was based on clinical observations of deep vein thrombosis in the lower limbs of patients with congenital deficiencies in antithrombin, protein C, and protein S, the tissue-specific expression patterns of thrombomodulin, tissue-type plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), and plasminogen activator inhibitor (PAI-1), and the pattern of fibrin deposition in mice with mutations in thrombomodulin or lacking tPA and uPA. These results suggested that coagulation is regulated in a tissue-specific manner. My laboratory and that of others have extended this model of tissue-specific hemostasis to include the procoagulant molecule tissue factor and the anticoagulants tissue factor pathway inhibitor (TFPI) and antithrombin.

Regulation of Clot Formation

The Procoagulant Pathway

Blood clotting is triggered by the binding of plasma factor VII/VIIa (FVII/VIIa) to tissue factor, which is expressed by perivascular cells.2,3 The tissue factor:FVIIa complex activates both FX and FIX by proteolytic cleavage and leads to the formation of small amounts of thrombin. This serine protease plays a central role in blood coagulation by cleaving fibrinogen and activating FXI and FXIII, as well as the cofactors FV and FVIII. Finally, FXIIIa cross-links soluble fibrin monomers, which stabilize the thrombus.

Historically, the formation of a fibrin clot has been viewed as a general mechanism that occurs in the same way at all sites of vascular damage. Early studies found that plasma “intrinsically” clotted when exposed to a negatively charged surface because of the activation of FXII. This observation was used to identify proteins (FXII, FXI, FIX, and FVIII) of the intrinsic coagulation pathway. In contrast, the extrinsic coagulation pathway (tissue factor and FVII) required the
addition of the exogenous agent, such as tissue thromboplastin or tissue factor, to initiate clotting. In 1991, the revised model of coagulation proposed that the extrinsic and intrinsic pathways did not function as 2 parallel pathways that converged on the common pathway but rather operated in series.\(^6\) It was suggested that thrombin generated by the extrinsic pathway was the physiological activator of FXI, which then activated the intrinsic pathway (Figure 1). Because of the rapid inhibition of the tissue factor:FVIIa complex by TFPI, the intrinsic pathway was thought to be required for the amplification of the clotting cascade.

Mice lacking the different clotting factors have been generated (Table 1). However, mice deficient in proteins of the extrinsic and common pathways die during embryonic development or shortly after birth, which precludes the analysis of adult mice. Therefore, a second generation of mouse lines was made that expresses low levels of these clotting factors (Table 2). In addition, a knock-in approach was used to introduce the prothrombotic FV Leiden mutation into mice.\(^3\) These mouse lines permit the analysis of the role of the different clotting factors in hemostasis and thrombosis in adult mice.

**Anticoagulant Pathways**

There are 3 major anticoagulant pathways that regulate the coagulation cascade: TFPI, antithrombin, and the protein C pathway (Figure 1). TFPI is a Kunitz-type proteinase inhibitor that inhibits the tissue factor:FVIIa complex in a FXa-dependent manner.\(^6\) TFPI is expressed by the endothelium and is attached to the cell surface of endothelial cells via a glycosylphosphatidylinositol anchor.\(^7\) In addition, TFPI is present in plasma. The protein C pathway is comprised of 2 circulating proteins, protein C and protein S, and 2 endothelial transmembrane proteins, endothelial protein C receptor (EPCR) and thrombomodulin (Figure 1).\(^8\) Binding of thrombin to thrombomodulin changes its substrate specificity from fibrinogen to protein C, whereas binding of protein C to EPCR facilitates its cleavage by the thrombomodulin-thrombin complex. Activated protein C, in association with its cofactor protein S, reduces coagulation by cleavage of the cofactors FVIIa and FV. Antithrombin inhibits all of the coagulation proteases generated during blood coagulation, particularly thrombin and FXa. Other anticoagulants include heparin cofactor II and protein Z, which inhibit thrombin and FXa, respectively.

All of the genes expressing the various anticoagulant proteins, except protein S, have been inactivated in mice (Table 1). However, mice lacking 1 of the 3 major anticoagulants do not survive. Alternative strategies have been used to analyze the role of the different anticoagulant pathways in hemostasis in adult mice. These include mice expressing low levels of EPCR and mice that express a mutant thrombomodulin with reduced activity (Table 2). In addition, a 50% reduction in the levels of protein C is compatible with a normal life span but is associated with a prothrombotic phenotype.\(^9,10\) These results indicate that the combined activities of the 3 major anticoagulant pathways (TFPI, protein C, and antithrombin) are required to regulate the clotting cascade.

**The Fibrinolytic Pathway**

The fibrinolytic system removes fibrin clots from the circulation to maintain blood flow (Figure 1). Plasminogen is activated by both tPA and uPA.\(^11,12\) A recent study showed that annexin II enhanced the activation of plasminogen by tPA.\(^13\) The major inhibitor of fibrinolysis is PAI-1. In addition, α2-antiplasmin and thrombin activatable fibrinolysis inhibitor limit fibrinolysis.

Mice lacking the components of the fibrinolytic system survive to adulthood with few life-threatening events (Table 1).\(^11,12\) For instance, mice lacking PAI-1 have a mild hyperfibrinolytic state but do not have impaired hemostasis.\(^14\) However, not surprisingly, mice lacking plasminogen are predisposed to severe thrombosis.\(^15\) These studies suggest that tPA and uPA have overlapping functions, but there is no compensation for loss of plasminogen.

**Tissue-Specific Hemostasis**

The major hemostatic challenges in normal life are birth, pregnancy, surgery, and traumatic injury. Birth induces physical damage to blood vessels as the neonate is squeezed.
through the birth canal. In humans, infants with deficiencies in various clotting factors often present with hemorrhage shortly after birth. In mice, pups lacking in FVII, FV, FX, prothrombin, or fibrinogen are often white rather than the normal pink after birth because of intraabdominal hemorrhage and frequently die within 24 hours. During pregnancy in mice and humans, hemostasis in the mother is required for implantation of the fetus, placental development, and to limit postpartum hemorrhage after separation of the placenta from the uterine wall. Surgery and traumatic injury induce physical damage to vessels.

Regulation of Tissue-Specific Hemostasis by the Extrinsic and Intrinsic Pathways of Coagulation

In general, hemostatic defects in humans and mice are not observed until clotting factor levels are reduced to <1% of normal levels. In humans, a deficiency in tissue factor is not detected, and a deficiency in FVII is rare (1 in 500,000). Conversely, in mice, pups lacking in FVII, FV, FX, and muscles, which are sites of low-tissue factor expression. In humans, infants with deficiencies in FVII experience a wide range of symptoms, including mucosal bleeding, easy bruising, epistaxis, increased menstrual blood loss, and traumatic and postsurgery bleeding. In addition, severe FVII deficiency is associated with excessive postpartum bleeding, which can be managed using a FVII concentrate. However, spontaneous muscle hematomas are rare.

Consistent with these findings, mice lacking proteins of the extrinsic coagulation pathway (tissue factor or FVII) die during embryonic development or shortly after birth (Table 3). FVII<sup>−/−</sup> mice survive embryonic development but experience uniform fatal perinatal bleeding. Seventy percent of FVII<sup>−/−</sup> neonates exhibit fatal intraabdominal bleeding within the first 24 hours, and the remainder die of intracranial hemorrhage before weaning.

TABLE 1. Survival of Mice Lacking Procoagulant, Anticoagulant, and Fibrinolytic Proteins

<table>
<thead>
<tr>
<th>Gene</th>
<th>Survival at Mean (%)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Procoagulant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF</td>
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<tr>
<td>FVII</td>
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<tr>
<td>FXII</td>
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<td>74</td>
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<tr>
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<td>75</td>
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<tr>
<td>FIX</td>
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<td>34,35</td>
</tr>
<tr>
<td>FXIII</td>
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<td>37</td>
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<tr>
<td>FV</td>
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<td>76</td>
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<tr>
<td>FX</td>
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<td>77</td>
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<tr>
<td>PT</td>
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<tr>
<td>FVIII</td>
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<tr>
<td>Fbg α-chain</td>
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<td>81</td>
</tr>
<tr>
<td>Fbg γ-chain</td>
<td>25–100</td>
<td>82</td>
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<tr>
<td>Anticoagulant</td>
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<td></td>
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<tr>
<td>TFPI</td>
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<tr>
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<tr>
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<tr>
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<td>60</td>
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<td>HCII</td>
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<tr>
<td>Fibrinolysis</td>
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<td>TAFI</td>
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<td>89</td>
</tr>
<tr>
<td>tPA</td>
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<td>53</td>
</tr>
<tr>
<td>uPA</td>
<td>100</td>
<td>53</td>
</tr>
<tr>
<td>Annexin II</td>
<td>100</td>
<td>13</td>
</tr>
<tr>
<td>PAI-1</td>
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<td>90</td>
</tr>
<tr>
<td>α2-AP</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>Plg</td>
<td>100</td>
<td>15,92</td>
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</tbody>
</table>

TAFI indicates thrombin-activatable fibrinolysis inhibitor.

In addition, we observe occasional intracranial hemorrhages in these mice. Interestingly, low-tissue factor mice have only a slightly prolonged tail bleeding time. These results led us to propose a model in which tissue-specific expression of tissue factor provides additional hemostatic protection to a defined set of organs. For instance, TF is required to maintain hemostasis in vital organs, such as the brain, highly vascularized organs, such as the placenta, organs subjected to a severe hemostatic challenge, such as the uterus, and organs that are prone to mechanical damage to the vasculature, such as the heart and lung (Figure 2).

Mice that express very low levels of murine FVII (<0.5% of wild-type levels) have been generated by targeted replacement of the wild-type FVII gene with a tetracycline-regulated FVII allele. Importantly, these mice exhibit tissue-specific bleeding that is essentially identical to that of low-tissue factor mice (Table 3). This supports our model that the tissue factor:FVIIa complex regulates hemostasis in a tissue-specific manner.

Humans deficient in proteins of the intrinsic coagulation pathway (FXII, FXI, FIX, and FVIII) exhibit either no hemostatic defect or a relatively mild phenotype. Indeed, hemophilia A (FVIII deficiency) and B (FIX deficiency) are relatively common X-linked disorders and occur at a frequency of 1 in 5,000 and 1 in 25,000, respectively. The classic sites of bleeding in hemophilia patients are the joints and muscles, which are sites of low-tissue factor expression. In addition, these patients exhibit easy bruising and prolonged...
hemorrhage after trauma or surgery. Women with hemophilia B also exhibit excessive postpartum hemorrhage. Mice lacking proteins of the intrinsic pathway are viable (Table 1). Mouse models of hemophilia A and B have been generated and exhibit a high rate of survival at weaning (Table 1). An early study observed no spontaneous bleeding in FVIII/H11002/H11002 mice. In a subsequent study, spontaneous bleeding was observed in FVIII/H11002/H11002 mice under normal handling conditions in 21.7% of homozygous males and 10.3% of homozygous females. The most common site of bleeding was the thorax. Only 1 joint bleed was observed in FVIII/H11002/H11002 mice. However, the time frame of analysis was not reported. Bleeding sites in FIX/H11002/H11002 mice have not been reported. Importantly, female mice lacking FVIII or FIX have normal pregnancies, but FVIII/H11002/H11002 and FIX/H11002/H11002 mice often experience fatal hemorrhages after tail transection (Table 3). Although FXII/H11002/H11002 and FXI/H11002/H11002 mice do not exhibit spontaneous or excessive injury-related bleeding, they have reduced thrombosis when challenged with collagen or epinephrine, suggesting that FXII and FXI contribute to thrombosis in mice.

It is of note that the mouse models of hemophilia A and B do not exhibit the same frequency of bleeding into joints and in skeletal muscle as in humans. Nevertheless, hemophilic mice have clearly impaired hemostasis. Mouse models have been used extensively to develop new strategies for the treatment of human hemophilia. These studies use the restoration of tail hemostasis to determine the efficacy of different treatments. However, the measurement of tail bleeding times can be quite variable, and a positive result does not necessarily mean that hemostasis is restored in all vascular beds. Additional hemostatic challenges to different tissues would increase the value of these studies and increase the applicability of these results to the treatment of hemophilia patients.

Table 3 shows that the bleeding sites of mice lacking the intrinsic pathways factors, FVIII or FIX, and mice lacking or deficient in the extrinsic factors, TF or FVII, are remarkably different (Table 3). Data from mice lacking either FVIII or FIX, together with the clinical observations with hemophilia patients, indicate that hemostasis in certain tissues, such as skeletal muscles and joints, is more dependent on the intrinsic pathway because of the low levels of tissue factor expression in these tissues (Figure 2).
Role of the Different Anticoagulant Pathways in Tissue-Specific Hemostasis

Patients with deficiencies in the anticoagulants protein C, protein S, and antithrombin are predisposed to venous thrombosis, particularly in the lower limbs. Women with antithrombin deficiency are prone to pregnancy-associated venous thromboembolism. Severe deficiencies in protein C and protein S result in purpura fulminans, venous thrombosis, and/or pulmonary embolism in the newborn. To date, there are no reports of humans deficient in TFPI. Patients with deficiencies in the anticoagulants protein C, protein C, or antithrombin all die either embryonically or in the perinatal period because of thrombosis (Table 1). These data demonstrate that each of the 3 major anticoagulant pathways plays a critical role in regulating the coagulation cascade.

The surface of the endothelium is antithrombotic because of the expression of TFPI and thrombomodulin. However, TFPI and thrombomodulin are expressed in a tissue-specific manner, suggesting that the TFPI and protein C pathways do not contribute equally to regulating coagulation in different tissues. For instance, TFPI mRNA is expressed at high levels in the placenta; at low levels in the lung, heart, and uterus; at very low levels in the liver and testis; and is undetectable in the brain. Thrombomodulin is expressed at high levels in the lung and heart; lower levels in the kidney, liver, and placenta; and very low levels in the brain. EPCR is predominantly expressed on large-vessel endothelial cells and may help to prevent deep vein thrombosis in large veins. One study used a knock-in strategy to introduce a point mutation into the thrombomodulin gene that severely reduced the capacity of the mutant thrombomodulin (TMPRO) to generate activated protein C. Mice with low thrombomodulin activity are viable but exhibit selective fibrin deposition in the lung, heart, and spleen but not other vascular beds, suggesting that local thrombomodulin-thrombin activation of protein C is important in limiting coagulation in these tissues.

Recently, my laboratory and others tested the model of tissue-specific anticoagulation by examining the effect of a deficiency of each of the 3 major anticoagulant pathways on the tissue-specific defects of low-tissue factor mice (Table 4). We focused on the placenta and heart, because low-tissue factor mice have hemostatic defects in both of these tissues, and they exhibit large differences in the expression of TFPI and thrombomodulin. Strikingly, we found that the hemostatic defect in the placenta of low-tissue factor mice was rescued by an absence of TFPI but not by an absence of thrombomodulin or EPCR (unpublished data). In contrast, TFPI deficiency failed to rescue the hemostatic defect in the heart of low-tissue factor mice. Preliminary studies indicate that the hemostatic defect in the heart of low-tissue factor mice is rescued by an absence of EPCR but not by an absence of thrombomodulin or EPCR (unpublished data). Furthermore, a 50% reduction of antithrombin also reduces cardiac fibrosis in low-tissue factor mice (unpublished data).

Figure 3 shows a model of tissue-specific regulation of coagulation by the 3 major anticoagulant pathways. All 3 of the anticoagulant pathways are present and function in all of the tissues, but the relative contribution of each pathway is different in the various tissues. For instance, we propose that TFPI limits tissue factor-dependent coagulation in the placenta, the thrombomodulin–protein C pathway limits tissue factor-dependent coagulation in the heart, and antithrombin inhibits coagulation in the liver. This model may explain why mice cannot survive without 1 of the 3 major anticoagulant pathways.
Differentially affect fibrin deposition in different tissues. tPA

combined tPA and uPA deficiency have extensive spontaneous

viable with no overt phenotype. However, mice with com-

bining low-tissue factor mice with tPA

procoagulant, anticoagulant, and fibrinolytic pathways by

regulation of fibrin deposition in the heart with a smaller

found that tPA played the most important role in local

contribution from thrombomodulin. Mice lacking tPA and

reduced thrombomodulin function exhibited myocardial in-

size. In addition, in the mouse lung, tPA is expressed by

endothelial cells of bronchial arteries but not in cells of the

pulmonary circulation. tPA−/− mice and uPA−/− mice are

viable with no overt phenotype. However, mice with com-

bined tPA and uPA deficiency have extensive spontaneous

fibrin deposition (Table 4), which suggests that the 2

plasminogen activators can compensate for each other. Inter-

estingly, mice lacking tPA and uPA only have sinusoid

fibrin deposits within the liver.51 The milder phenotype of
tPA−/−/uPAR−/− mice indicates that uPA can activate plas-

minogen in the absence of its receptor. PAI-1 is also ex-

pressed in a tissue-specific manner, suggesting that it may
differentially affect fibrin deposition in different tissues.

More recently, Christie et al53 examined the effect of

combining tPA and uPA deficiency with the TMPRO

mutation on fibrin deposition in the heart. Fibrin deposition

was evaluated in single, double, and triple mutant mice. It was

found that tPA played the most important role in local

regulation of fibrin deposition in the heart with a smaller

contribution from thrombomodulin. Mice lacking tPA and

reduced thrombomodulin function exhibited myocardial in-
farctions. Currently, we are attempting to rebalance the

procoagulant, anticoagulant, and fibrinolytic pathways by

crossing low-tissue factor mice with tPA−/−, TMPROPRO, and
tPA−/−/TM PROPRO mice. We will examine the effect of these
crosses on fibrin deposition and cardiac fibrosis. These
studies demonstrate the utility of the mouse in analyzing
multiple hemostasis-regulating gene interactions.

Combining Mutations in the Procoagulant,
Anticoagulant, and Fibrinolytic Pathways
In humans, it is clear that the risk of venous thrombosis is
increased in individuals with >1 risk factor. For instance,
individuals carrying both the prothrombotic FV Leiden and

prothrombin 20210A mutations have an increased risk of
thromboembolism compared with individuals with a single
mutation.56 Similarly, combinations of mutations that
promise hemostasis increase the risk of fatal bleeding. Con-
versely, fibrin generation may be rebalanced by combining
prothrombotic and prohemorrhagic mutations. For instance,
FV Leiden appears to modify the hemophilia A phenotype by
increasing fibrin generation.57 However, the heterogeneity
of the human population makes it very difficult to evaluate the
relative contribution of different factors to a thrombotic or
hemorrhagic phenotype.

Mice offer the opportunity to combine specific mutations
and analyze the phenotype on a defined genetic background.
Table 4 shows a summary of the different combinations of
mutations that have been generated by different laboratories.
Mice with reduced fibrin generation can be crossed with mice
with increased fibrin generation to rebalance the procoagulant
and anticoagulant pathways. Alternatively, mice with differ-
ent prothrombotic and anticoagulant pathways. For instance,
combining FV Leiden and TFPI−/− leads to embryonic thrombosis that is not observed with the individual
mutations.59 In contrast, combining fibrinogen−/− with mice
lacking protease-activated receptor 4 or mice lacking platelets
leads to fatal hemorrhage (Table 4). Combining mutations can
also reveal phenotypes not observed in deficient mice.
For instance, protein Z−/− mice are not thrombotic, but the
absence of protein Z enhances the thrombotic phenotype of
FV Leiden mice (Table 4).60

One early rebalance experiment combined fibrinogen−/−
with plasminogen−/− mice.60 The absence of fibrinogen res-
cued the pathologies associated with plasminogen deficiency,
indicating that the majority of these defects are because of
excess fibrin deposition. Surprisingly, protein C−/− embryos
were not rescued by a deficiency in FVII,62 whereas FXI
deficiency prolongs the survival of protein C−/− neonates.63

At present, it is unclear why the absence of FVII failed to
rescue the protein C−/− embryos. We and others have shown
that either low levels of TF or a complete deficiency of FVII
rescues TFPI−/− embryos from lethality,64,65 consistent with the
notion that these mice die from excessive coagulation. How-

ever, FVII−/−/TFPI−/− neonates die of fatal bleeding after
birth because of the absence of FVII. Low-tissue factor mice
also rescue thrombomodulin−/− embryos, again suggesting
that death of thrombomodulin−/− embryos is attributable to
unregulated coagulation.50 Similarly, low levels of tissue
factor rescue EPCR−/− embryos.65 Interestingly, low levels of
tissue factor prolonged the survival but did not rescue
antithrombin−/− embryos (unpublished data). These data sug-

gest that either low levels of tissue factor cannot restore
normal levels of fibrin deposition in the absence of antithrom-
bin or that antithrombin has coagulation-independent roles in
embryonic development.

Conclusions
Why has a system of tissue-specific hemostasis evolved? One
possibility is that hemostasis is customized for a given tissue
because each tissue is subjected to unique hemostatic chal-

lenges. For instance, blood vessels in a tissue, such as the
heart, are subjected to high pressure and mechanical stresses that are likely to result in more frequent injury and would require a different hemostatic regulation than a tissue with low pressure without mechanical stresses, such as the liver. Future studies should better define how the different procoagulant pathways initiate clotting in different tissues, and the roles of the anticoagulant and fibrinolytic pathways in a tissue-specific hemostasis. Understanding the process of tissue-specific hemostasis is important for the clinical treatment of thrombosis. Administration of anticoagulants targeting the extrinsic pathway of coagulation may be more effective in reducing thrombosis in the heart, whereas targeting the intrinsic pathway may reduce thrombosis in skeletal muscle.

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