What Does It Take to Make the Perfect Clot?

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Abstract—The coagulation process has been conceptualized as being primarily dependent on adequate levels of the coagulation proteins. This concept was based on the clear relationship between the bleeding tendency and factor levels in hemophilia. The field is now evolving toward conceptualizing coagulation as being actively regulated by the specialized cellular components of the process. Rather than conceiving coagulation as only a “cascade” of proteolytic reactions, the coagulation reactions occur as overlapping steps on cell surfaces. Components of the old “extrinsic’’ and “intrinsic” pathways of coagulation can be thought of as participating in the initiation and propagation of coagulation reactions, respectively. Thus, these pathways are not redundant as they are portrayed in the cascade model, but play distinct and complementary roles. Our understanding of how specific cellular features control the processes of hemostasis and thrombosis is developing rapidly. This review discusses some aspects of the cellular control of coagulation. (Arterioscler Thromb Vasc Biol. 2006;26:41-48.)

Key Words: hemostasis | partial thromboplastin time | platelets | prothrombin time | tissue factor

Our goal in writing this short review is to discuss aspects of the coagulation process where the field has shown significant progress in understanding in recent years. We have particularly focused on areas that have been influenced by the idea that cells, rather than the coagulation proteins, direct and control the coagulation process. We have focused our comments on concepts that we believe are especially important to understanding coagulation as a cell-surface phenomenon. This means that to some extent this review is also an “editorial” that reflects our opinions of what topics are especially important. Although many, many workers have contributed to these areas, we have necessarily been selective in our discussion and citations of the literature. This ensures that we will have offended nearly every worker in the field to some extent by the time we are done. We apologize in advance for the many topics and contributions we have passed over in this endeavor.

We chose the title, “What does it take to make the perfect clot?” because of our sense of wonder that a process as complex as hemostasis ever works as it should. The perfect hemostatic clot forms at a site of injury—sometimes an injury so small as to be completely invisible. It seals the inured vessel to stop bleeding but is not propagated through the vascular tree. Thus, the “perfect clot” does not disrupt blood flow unnecessarily to other tissues. In addition, the clot forms the framework on which wound healing occurs and is sufficiently labile to be removed during healing. Given all of these requirements, it is a wonder that hemostasis ever occurs properly.

The “Coagulation Cascade” Does Not Explain How Hemostasis Is Controlled

Most of the readers of this review were probably taught about hemostasis using a modification of the coagulation cascade1 or “waterfall”2 models proposed in the 1960s. These models were major conceptual advances, because they proposed the concept that a series of proteolytic reactions could act as a
biological amplifier—a paradigm now well recognized to underlie many physiological processes. In the modern versions of the coagulation cascade, the interactions of the proteins are outlined in a Y-shaped scheme, with distinct “intrinsic” and “extrinsic” pathways initiated by factor XII (FXII) and FVIIa/tissue factor (TF), respectively. The pathways converge on a “common” pathway at the FXa/FVa (prothrombinase) complex. The coagulation complexes are generally noted to require phospholipid and calcium for their activity. This scheme was not actually proposed as a literal model of the hemostatic process in vivo. However, the lack of any other clear and predictive concept of hemostasis meant that most physicians and students of coagulation de facto viewed the cascade as a model of physiology.

The limitations of the coagulation cascade as a model of the hemostatic process are highlighted by certain clinical observations. Patients deficient in the initial components of the intrinsic pathway—FXII, high-molecular weight kinogen, or prekallikrein—have a prolonged activated partial thromboplastin time but no bleeding tendency. In spite of this fact, components of the intrinsic pathway must have an important role in hemostasis, because patients deficient in factor VIII or IX have a serious bleeding tendency, although the extrinsic pathway is intact. Similarly, patients deficient in FVII also have a serious bleeding tendency, although the intrinsic pathway is intact. Thus, the intrinsic and extrinsic pathways cannot operate as independent, redundant pathways in vivo as they do in the cascade model.

**Cells Control the Coagulation Process In Vivo and Regulate the Amount and Tempo of Thrombin Generation**

It is widely acknowledged that the coagulation reactions occur on specific cell surfaces in vivo rather than on phospholipid vesicles as they do in the prothrombin time and activated partial thromboplastin time assays. About 15 years ago, our group hypothesized that the key to understanding the hemostatic process was the correct incorporation of the roles of cells into a conceptual model.

Hemostasis requires the formation of an impermeable platelet and fibrin plug at a site of injury but also requires that the powerful procoagulant substances activated in the process remain localized to the site of injury. This is accomplished by localizing the procoagulant reactions on specific cell surfaces. Different cells play different roles in the coagulation process, because they possess different procoagulant and anticoagulant properties. For example, it is clear that blood platelets play a major role in supporting procoagulant reactions and that vascular endothelial cells play a key role in maintaining the anticoagulant properties of the vasculature.

We began developing a cell-based conceptual model of hemostasis by developing a cell-based experimental model. Based largely on data obtained in that model system, we proposed that hemostasis occurs in distinct, but overlapping, steps: initiation, amplification, and propagation. The process requires the participation of 2 cell types: TF-bearing cells and platelets. A key means of regulating the process is to keep the cell types separated until an injury makes activation of coagulation desirable.

**Initiation Phase**

The initiation step is localized to cells that express TF, which are normally outside the vasculature. The FVIIa/TF complex activates small amounts of factors IX and X. Factor Xa then associates with FVa to form prothrombinase complexes on the TF-bearing cells. The FVa for prothrombinase assembly can come from 1 of several sources. Platelets adhere to collagen and other extracellular matrix components at a site of injury. The adhesion process partially activates the platelets and promotes secretion of partially activated FV from their α granules. Zymogen FV can also be activated by FXa or by noncoagulation proteases. Factor Xa localized to the cell surface is relatively protected from inactivation by plasma protease inhibitors. However, any FXa that dissociates from the TF-bearing cell is rapidly inhibited in the fluid phase by TF pathway inhibitor (TFPI) or antithrombin (AT). Thus, the presence of inhibitors effectively localizes FXa activity to the surface on which it was formed. By contrast, FIXa can move from the TF-bearing cell through the fluid phase to a nearby platelet or other cell surface, because it is not inhibited by TFPI and is inhibited much more slowly by AT than is FXa.

A low level of activity of the TF pathway probably occurs at all times in the extravascular space. The coagulation proteins leave the vasculature, percolate through the tissues, and are found in the lymph roughly in proportion to their molecular size. Thus, FVII is probably bound to extravascular TF even in the absence of an injury, and the extravascular factors X and IX can be activated as they pass through the tissues. This idea is consistent with the finding that low levels of the activation peptides from coagulation factors are present in the blood of normal individuals. This has been called “basal” coagulation or “idling.” This process does not lead to clot formation under normal circumstances, because the really large components of the coagulation process, that is, platelets and FVIII complexed with von Willebrand Factor (vWF), are kept sequestered in the vascular space. Coagulation only proceeds when damage to the vasculature allows platelets and FVIII/vWF to spill out into the extravascular tissues.

**Amplification Phase**

The small amount of thrombin generated on TF-bearing cells has several functions. One major function is activation of platelets. Although platelets have already adhered at the site of injury and become partially activated, the addition of thrombin can induce a higher level of procoagulant activity than adhesive interactions alone. Another function of the thrombin formed during the initiation phase is the activation of the cofactors V and VIII on the platelet surface. Thrombin also activates FXI on the platelet surface. By the end of the amplification phase, the stage is set for large-scale thrombin generation in the propagation phase.

**Propagation Phase**

The propagation phase occurs on activated platelets. Its key features include the following concepts: (1) FIXa activated during initiation binds to FVIIIa on the platelet surface; (2) additional FIXa is supplied by platelet-bound FXIa; (3)
because FXa cannot effectively move from the TF-bearing cell to the platelet, it must be provided directly on the platelet surface by the FIXa/VIIIa complex; and (4) FXa rapidly associates with platelet surface FVa and produces a burst of thrombin generation of sufficient magnitude to clot fibrinogen.

The platelet is probably the only cell on which propagation of coagulation can occur effectively. The platelet surface is specialized to coordinate assembly of the tenase (FIXa/VIIIa) and prothrombinase (FXa/Va) complexes. In addition, large numbers of platelets can be recruited to a site of injury to provide enough surface for large-scale thrombin generation.

**A Cell-Based Model Explains Some Aspects of Hemostasis That a “Cascade” Model Does Not**

The cell-based model of coagulation suggests that there are intrinsic and extrinsic pathways in the coagulation process, but we must modify our definition of these pathways a little. The extrinsic or TF pathway consists of the FVIIa/TF and the FXa/Va complex. It operates on the TF-bearing cell to initiate the coagulation process as illustrated in Figure 1.

The intrinsic pathway does not include FXII or its cofactors prekallikrein and high-molecular weight kininogen, which do not appear to be necessary for hemostasis. Thus, we can consider the intrinsic pathway to consist of FXI(a), the FIXa/VIIIa complex, and the FXa/Va complex. It operates on the platelet surface during the propagation phase to generate a burst of thrombin as illustrated in Figure 2. Thus, both of these pathways are needed for hemostasis, because they operate on different surfaces and play distinct roles.

**Hemophilia Is a Failure of Platelet-Surface Thrombin Generation**

The conceptual model described above makes it clear what goes wrong in hemophilia. Platelet adhesion at a site of injury occurs normally in hemophilia, as does production of FXa and small amounts of thrombin on TF-bearing cells during the initiation stage of coagulation. However, platelet surface FX activation by FIXa/FVIIIa is abolished and, therefore, platelet surface thrombin generation fails. The FVIIa/TF complex cannot effectively substitute for the FIXa/VIIIa complex, because it produces FXa on the “wrong” surface. Although it is possible for some FXa to diffuse from its site of production on TF-bearing cells through the fluid phase to the platelet surface, the presence of AT and TFPI is a significant barrier to this process. In addition, the amount of FXa produced by the FVIIa/TF complex may be limited by TFPI. Finally, platelet adhesion at the site of injury “covers over” the sites of TF expression, providing an essentially insurmountable barrier to the movement of FXa and other activated factors.

Histological examination of clots in hemophilic patients reveals that the periphery of the initial platelet plug is stabilized by a fibrin meshwork, whereas the inner portion of the platelet plug shows little or no fibrin formation. The
authors conclude that “these observations suggest that fibrin formation in the periphery of the plug is less dependent on factor VIII than in central areas.” In other words, the portions of the clot in proximity to tissues that express TF show evidence of thrombin generation. These data suggest that thrombin generated in proximity to FVIIa/TF activity can support production of a small amount of fibrin in hemophilia. However, that fibrin is limited in its amount and distribution and is insufficient to support normal hemostasis.

**Factor XI Acts as a “Booster” of Thrombin Generation**

This scheme also addresses the role of FXI in coagulation. The role of FXIIa is to enhance the amount of platelet surface FIXa. Additional FIXa increases the supply of platelet surface Fxa and thereby enhances thrombin generation. Thus, whereas FXI is not essential for platelet surface thrombin generation, it serves as a booster mechanism.

Our data may at least partially explain why the bleeding tendency in FXI deficiency is so variable. Platelets from different individuals show widely varying abilities to support “tenase” and prothrombinase activity, even in the presence of identical levels of the procoagulant and anticoagulant proteins. Platelets from different individuals also show a great variability in the degree to which thrombin generation is enhanced by FXI. It is interesting that those with the lowest thrombin generation in the absence of FXI do not always show the greatest increase on addition of FXI. We speculate that individuals that produce large amounts of thrombin in the absence of FXI are unlikely to have hemorrhagic manifestations of FXI deficiency, whereas individuals whose platelets produce low levels of thrombin in the absence of FXI would be more likely to exhibit a bleeding tendency because of FXI deficiency.

The “Right” Amount and Pattern of Thrombin Must Be Generated

Thrombin plays 2 very distinct roles in the coagulation process, depending on when and where it is generated.

**Thrombin Generated on the TF-Bearing Cell Amplifies the Procoagulant Signal**

(Amplification Phase)

The small amount of thrombin produced on TF-bearing cells is critical in amplifying the procoagulant response and ensuring that initiation of coagulation is successful (Figure 3). Once formed, thrombin can move from the TF-bearing cell to nearby platelets, where it binds to its high-affinity receptor, GPb. This protein serves as scaffolding that facilitates interaction of thrombin with substrates on the platelet surface, including: (1) cleaving protease-activated protein 1 (PAR-1), which plays a key role in platelet activation; (2) activating FVIII and releasing it from vWF; and (3) activating FXI. These activities set the stage for subsequent large-scale, platelet-surface thrombin generation.

The Burst of Thrombin Generated on the Platelet Surface Produces a Stable Clot Structure

(Propagation Phase)

The large amount of thrombin generated on the platelet is responsible for producing a stable hemostatic clot (Figure 4). Whereas thrombin produced on the platelet surface early in the course of coagulation may initially cleave substrates on the platelet surface and continue to amplify the procoagulant response, it also leaves the platelet and acts to promote stabilization of the platelet plug in a fibrin meshwork. Thus, the platelet-produced thrombin has multiple actions in addition to clotting fibrinogen. It also stabilizes the clot by: (1) activating FXIII; (2) activating thrombin activatable fibrinolysis inhibitor (TAFI); (3) cleaving the platelet PAR-4 receptor; and (4) being incorporated into the structure of the clot.

Some of the literature suggests that it is the amount of thrombin generated during hemostasis that determines whether clotting is effective, on the one hand, or whether thrombosis occurs, on the other hand. Studies in vitro show very clearly that the structure and stability of a fibrin clot are closely related to the amount of thrombin added to a fibrinogen solution to initiate clotting. However, in vivo, the thrombin responsible for clot formation is not “dumped” all at once into the system. Rather, thrombin generation ramps up as activated factors and cofactors accumulate on the platelet surface. Thus, the amount of thrombin in the system is

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**Figure 3. Roles of thrombin produced on the TF-bearing cell.**

Thrombin exosite 1 binds to a recognition site on platelet PAR-1, and the bound thrombin cleaves PAR-1, exposing a new amino terminal that binds to a recognition site within the 7-transmembrane domain. PAR-1 activation signals a number of platelet changes including degranulation of α granules, changes in surface phospholipid composition, and inside-out signaling that activated platelet glycoprotein IIb/IIa. Thrombin also cleaves factor VIII from vWF, releasing it to bind to the platelet surface, and thrombin activates factor XI, which is bound to the platelet surface, probably through GP Ib.

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**Figure 4. Roles of thrombin produced on the platelet surface.**

Thrombin cleaves fibrinopeptides A and B from fibrinogen (shown bound to glycoprotein IIb/IIIa), exposing recognition sites that polymerize the fibrinogen into fibrin strands. Thrombin binds to fibrin and is incorporated into the growing clot. Fibrin acts as a template to accelerate thrombin activation of TAFI. Also, thrombin cleaves factor XIII, releasing the 2 B chains from the 2 activated A chains that have transglutaminase activity. Also, thrombin binds to and cleaves PAR-4, exposing a new amino terminal that binds to a recognition site within the 7 transmembrane domain.
constantly changing during the process of clot formation. The rate of thrombin generation is a major determinant of the ultimate clot structure. In addition, whereas clot formation begins after only a small amount of thrombin has been produced, the structure of the clot evolves and remodels in response to the levels of thrombin achieved after fibrin polymerization has begun. Thus, it is likely that ultimate clot structure is a complex function of the pattern of thrombin generation and not just the total amount produced.

**How Do You Make Sure You Get Enough Thrombin for Hemostasis But Not Too Much?**

As noted above, it seems that the amount of thrombin generated is not the major factor in determining whether hemostasis is effective. Rather, the rate and peak level of thrombin activity seem to be most important. It is not so clear what parameters are most associated with the risk of thrombosis. The failure to properly limit or localize thrombin generation during the hemostatic process appears to be one mechanism that can lead to thrombosis. Thus, it is important to have effective mechanisms to match the site and amount of thrombin produced to the degree of injury.

**Localization of Platelets and Coagulation Reactions to the Site of Injury**

It is a delicate balancing act to keep blood in a fluid state until injury occurs, efficiently produce a hemostatic clot, then prevent the clot from extending to cause undesired vascular compromise. The safest way to produce sufficiently high local levels of the activated procoagulants for clot formation is to ensure that production of activated factors is concentrated at the site where a clot is desirable. This is accomplished by rapid and effective localization (adhesion) of platelets at a site of injury. This process brings the platelet surface into close proximity to the initiating cells, which are normally extravascular, thus removing a barrier to the movement of procoagulant proteases from the initiating cell surface to the platelet surface.

Two major mechanisms tend to localize the coagulation reactions to the vicinity of an injury. First, the plasma protease inhibitors are much less effective in inactivating coagulation proteases on the surface of cells than when the proteases are in solution. Thus, activated factors that diffuse away from the appropriate cellular location are susceptible to rapid inhibition. Second, an array of antithrombotic mechanisms tends to prevent propagation of coagulation on healthy intact endothelium. These mechanisms include the endothelial thrombomodulin (TM)/protein C/protein S system that inactivates factors Va and VIIIa; an ecto-ADPase that suppresses amplification of platelet activation by ADP release; and endothelial surface heparanoids that can bind and enhance the activity of plasma AT. The level of expression of these different antithrombotic mechanisms varies between vascular beds and can be modulated by inflammatory stimuli and vascular pathology.

**Graded Platelet Activation**

As they adhere to extracellular matrix proteins at a site of injury, platelets become activated to a certain extent. The thrombin produced on the initiating cell is also a strong platelet agonist. However, the combination of binding to collagen and stimulation with thrombin results in activation of platelets to a much more potent procoagulant state than activation with either stimulus alone. This highly activated platelets have been termed “collagen and thrombin activated” platelets. Although the many types of collagen differ in their potency, most types of collagen are able to participate in platelet activation. Collagens are present in the vascular basement membrane, vessel wall, and extravascular stroma. Thus, it seems likely that platelets bound to a site of vascular injury become activated to the collagen and thrombin activated state. We hypothesize that this is a mechanism by which the most procoagulant form of activated platelets is initially produced at the site of an injury. As additional platelets accumulate, they are blocked from interaction with collagen by the intervening layer of platelets, and, thus, the procoagulant activity of the surface decreases as the highly active initial layer of platelets is “paved over.”

**Adequate Levels of Coagulation Factors**

Although platelets are critical to formation of the primary hemostatic plug, an effective clot cannot be formed without adequate levels of procoagulant factors. The levels of coagulation factors in the plasma of normal individuals vary widely (generally 50% to 150% of the level in normal pooled plasma). This suggests that a wide range of factor levels is compatible with normal hemostatic function. However, even within the normal range, variations can affect the rate and extent of thrombin generation.

The effect of the levels of coagulation factors on the pattern of thrombin generation is complex. For most of the coagulation factors, changing the level between 50% and 150% has little effect on the rate and pattern of thrombin generation. Decreasing level of factors VIII, IX, or XI <50% results in a modest decline in thrombin generation, with a dramatic decline only after levels fall below 10% to 20% of normal. Thus, the wide range of levels found in the normal population probably has little effect on thrombin generation and, therefore, little effect on hemostatic function.

The pattern with FX is a little different than the above-mentioned factors. Again, changes between 50% and 150% have essentially no effect on thrombin generation. However, thrombin generation is maintained down to FX levels as low as 1% to 5% in vitro experiments before falling off sharply. Thus, variation in FX levels probably contributes little to the pattern of thrombin generation unless combined with a deficiency of other factors.

The relationship between prothrombin levels and thrombin generation is strikingly different from the other coagulation factors. In the case of prothrombin, the rate of thrombin generation, peak activity reached, and total amount of thrombin produced are proportional to the prothrombin level. The rate of thrombin generation and peak activity achieved during clot formation significantly affect the structure and stability of the resulting fibrin clot. This means that any variation in prothrombin level is reflected in the pattern of thrombin generation and could have an effect on the hemostatic effectiveness of the resulting clot. The relationship between
prothrombin level and thrombin generation holds even for supernormal prothrombin concentrations. Thus, elevated plasma prothrombin leads to an increase in the rate and amount of thrombin generation. This may be the reason that elevated levels of prothrombin are correlated with a risk of arterial and venous thrombosis and also why depression of the functional prothrombin level is the parameter most closely associated with effective anticoagulation with coumadin. FVIII and FXI levels above the normal range result in a modest increase in the rate of thrombin generation, and elevated levels of these factors have also been reported to be associated with the risk of thrombosis.

Is It Necessary to “Turn Off” Platelet Surface Thrombin Generation Once Hemostasis Is Complete?

Normally, TM on endothelial cells binds thrombin that escapes from the site of appropriate clot formation or is formed inappropriately in the vicinity of healthy endothelial cells. Defects in the protein C system, such as protein C or S deficiency and FV_Ledln (protein C resistance), have clearly been associated with the risk of thrombosis. In many reviews, the protein C system is referred to as a mechanism for “turning off” coagulation. However, the data suggest that this is not strictly true. Activated protein C (aPC) has much more limited ability to inactivate FVa on the surface of platelets than it does on similarly composed phospholipid vesicles or on endothelial cells. This may be because of a protective property of the platelet surface and/or modifications to platelet FVAs that impede its inactivation by aPC. Because protein C is normally activated by the thrombin/TM complex on endothelial cells, it seems most likely that the physiological role of aPC is to act on the endothelial surface to limit prothrombinase (FXa/FVa) activity. This mechanism would ensure that the coagulation reactions are not propagated on healthy, uninjured vessel walls.

What, then, terminates the coagulation reactions and prevents vascular occlusion at any site of injury? We think that it may, in fact, not be necessary to enzymatically “terminate” the coagulation process. Recent data suggest that a site of initiation of coagulation can be “paved over” by deposition of platelets and fibrin. The activated factors formed at the surface where the initiating cells come in contact with collagen-bound platelets cannot diffuse through the overlying layer of clot. Thus, depletion of zymogen factors and sequestration of activated factors within a hemostatic clot may be all that is required to appropriately terminate thrombin generation.

What About All of the Thrombin Produced After the Clot Begins to Form?

In most models of coagulation, the formation of the fibrin clot occurs (or at least begins) at the start of the propagation phase when the burst of platelet surface thrombin generation is just beginning. Consequently, >95% of the total amount of thrombin production takes place after initial clot formation. This “excess” thrombin has been proposed to activate the TAFI, thereby protecting the clot against proteolysis. However, it also appears to have several other important roles as outlined below.

Thrombin Activated After Clot Formation Participates in Ongoing Remodeling of the Clot Structure

Although a clot forms nearly as soon as the burst of platelet surface thrombin generation begins, the structure of the clot continues to evolve. If the initial rate of thrombin generation is slow, the clot has a loosely packed structure composed of thick fibrin fibers with low-structural rigidity. By contrast, clots formed by a robust burst of thrombin generation develop more tightly packed, rigid structures and are more resistant to mechanical and enzymatic disruption. Although we cannot be sure whether it is the rate or peak level of thrombin activity that determines clot structure, it is clear that these parameters are more important than the total amount of thrombin produced.

Thrombin Activated After Clot Formation Activates TAFI

TAFI is a carboxypeptidase that removes terminal lysine residues from fibrin, thereby removing potential binding sites for fibrinolytic enzymes and enhancing clot resistance to fibrinolysis. Greater levels of thrombin activity are needed to activate TAFI than to form a fibrin clot. Failure of TAFI activation is thought to contribute significantly to the bleeding tendency in hemophilia. Patients with hemophilia often stop bleeding immediately after an injury, only to experience severe delayed rebleeding. This is consistent with a scenario in which an initial platelet plug forms and is stabilized by a small amount of fibrin around the periphery of the wound. The thrombin to form this fibrin is dependent on FVIIa/TF activity. However, this is not enough thrombin to activate significant amounts of TAFI. Rebleeding occurs when the fibrin, which is not protected by TAFI activity, is removed by fibrinolysis.

The presence of FXI, which boosts the rate of thrombin generation and the peak level of thrombin activity, also increases TAFI activation and enhances clot resistance to fibrinolysis. This phenomenon may not only have relevance to bleeding disorders, but also to thrombosis, because high levels of TAFI are associated with the risk of thrombosis. Thus, the peak level of thrombin activity (which is reached well after the clot is formed) seems to be an important determinant of clot resistance to fibrinolysis via its effects on TAFI activation.

Thrombin Activated After Clot Formation Cleaves Platelet PAR-4

Platelets bear 2 proteolytically activated receptors for thrombin: PAR-1 and PAR-4. Both PAR receptors contribute to full activation of human platelets. However, PAR-4 requires higher levels of thrombin for activation. Thus, it seems likely that it is activated during the propagation phase of coagulation rather than earlier in the process, during initiation. This may play a role in ensuring full degranulation and retraction of activated platelets.
Thrombin Activated After Clot Formation

Remains Bound to the Clot

It is clear that active thrombin remains associated with fibrin/platelet clots and is protected from inhibition by AT. Although there are no data on the biological role of this excess thrombin, we speculate that it provides a reservoir of procoagulant activity. If the clot were disrupted by physical trauma, blood would come into contact with the sequestered thrombin, thus reinforcing the clot by additional platelet activation and fibrin accretion.

Thrombin Activated After Clot Formation

Participates in Inflammation and Wound Healing

Thrombin not only participates in hemostatic processes, but also has cytokine and growth factor-like activities that seem to play a role in inflammation and wound healing.56,57 Furthermore, thrombin receptor agonists can accelerate wound healing.58,59 It is possible that the excess thrombin plays a more important role in the processes that follow hemostasis than in the process of clot formation itself. Our data suggest that healing of cutaneous wounds is delayed in hemophilic mice, even when bleeding is not excessive.60

In summary, although the coagulation cascade is a useful model of the interactions of the coagulation proteins, hemostasis is an active metabolic and homeostatic activity carried out by cells within a living organism and is an integral and inseparable part of the overall response to injury. The coagulation proteins are necessary components of this response, but cells control its duration, intensity, and localization.

Acknowledgments

This work was supported by grant RO1 HL48320 from the National Institutes of Health and by the US Department of Veteran’s Affairs (M.H.).

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Arterioscler Thromb Vasc Biol. 2006;26:41-48; originally published online October 27, 2005;
doi: 10.1161/01.ATV.0000193624.28251.83
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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