Invasive bacterial infections are major clinical problems. The emergence and spread of antibiotic resistance in bacteria is becoming a growing health threat. The key to finding novel treatments for human bacterial infections lies in understanding the interactions between the host and pathogen. During bacterial infection, the host responds to invading microbes with a number of different defense mechanisms. Some bacteria can, however, circumvent the host defense. In severe infections, such as sepsis and septic shock, the coagulation and fibrinolytic systems are compromised. The coagulant/anti-coagulant balance is disrupted, causing severe thrombosis or bleeding (2, 42, 54, 56, 57). Hemostatic factors hold the potential as novel therapeutic targets for treatment of bacterial infection-related diseases. However, we are just beginning to understand the function of hemostatic system in host/pathogen interaction.

The infectious process starts with the first contact between the bacteria and the human host. Different bacterial species gain access to the human body through different sites, such as the skin, nasopharynx, lungs, gastrointestinal, or urogenital tract. Bacterial invasion is generally mediated by bacterial surface and secreted products that can negate host innate and acquired defense systems. Both the ability to produce invasive molecules and to elude host defense are critical for causing systemic diseases (10, 16).

The hemostatic system plays an important role in systemic infection. An interesting example of the interaction between host coagulation system with pathogens is the horseshoe crab, which uses endotoxin to trigger a clotting response that presumably walls off the bacteria, providing an initial defense against invasion (39, 41, 70). The clotting system of horseshoe crab consists of three serine proteases and one clotting factor such as plasminogen and fibrinogen for infection. Furthermore, genetic variations in host hemostatic factors also influence host response to bacterial infection.

The Coagulation System

The primary function of the coagulation system is to stop bleeding on an injury until repair occurs. Through the activation of a cascade of plasma proteins, blood clots are formed at the site of injury or blood flow disturbance through fibrin deposition and platelet congregation (FIGURE 1) (24). In the event of injury to blood vessel wall, tissue factor (TF) normally sequestered in the subendothelial layer is exposed. TF binds and activates circulating factor VII (FVII). The complex of TF and activated FVII (FVIIa) will then activate factor X (FX) and factor IX (FIX). Activated FXa will form prothrombinase complex with activated factor V (FV). The prothrombinase complex (FVaFXa) then cleaves prothrombin to thrombin, which then cleaves fibrinogen to form fibrin. FIX activation also amplifies the clotting reaction through interaction with activated factor VIII, which accelerates FX activation.

Overactive coagulation will cause wide-spread thrombosis. Therefore, it has to be kept in check by anticoagulation systems. This is achieved through anticoagulation and fibrinolytic systems. Together, coagulation, anticoagulation, and fibrinolysis maintain a delicate physiological balance (FIGURE 1).

The main function of the anticoagulation system is to prevent or slow the propagation of clots. The major anticoagulants include antithrombin (AT), tissue pathway inhibitor (TFPI), and activated protein C (APC). AT is produced by the liver and inhibits several coagulation factors such as thrombin, FVIIa, FIXa, and Fxa (80, 84). TFPI is a serine protease that inhibits FXa. In the presence of FXa, TFPI also inhibits the TF-FVIIa complex (12, 13, 79). Protein C is an inactive plasma serine protease. When thrombin is produced, it can bind to thrombomodulin present on the vascular endothelial surfaces. The thrombin/thrombomodulin complex can then cleave protein C into APC. APC generation is enhanced by the endothelial cell protein C receptor (EPCR) on the endothelial surface. APC, with cofactor protein S, can cleave and inactivate FVa and FVIIIa to negatively regulate coagulation (1, 23, 29).

The fibrinolytic system functions to break down existing fibrin clots. The major protease of fibrinolytic
The initial observation of interactions between microbes and the fibrinolytic system was made in the 1930s. Tillett and Garner (93) observed that streptococci from human infection samples possessed fibrinolytic ability. On the other hand, isolates from veterinary infections did not produce lytic activity for human fibrin (93). Several other studies also suggested that the fibrinolytic activity of β-hemolytic streptococci was species specific and dependent on the source of the pathogenic isolate. Streptokinase (SK) was identified as the streptococcal plasminogen activator (63, 64, 72, 86). SK has been proved to be useful clinically in dissolving blood clots that cause heart attacks (60, 68). The crystal structure of the catalytic domain of human plasmin complexed with SK has been solved (97). SK can convert plasminogen into an active serine protease without proteolysis. Formation of the SK/plasminogen complex can induce conformational change in the activation domain of plasminogen. This complex can hydrolytically activate other circulating plasminogen molecules. Furthermore, this complex is resistant to host plasmin inhibitors such as α2-antiplasmin. Streptococci are proposed to gain fibrinolytic activity through two independent pathways (10). One pathway involves the direct binding of plasmin to the bacteria surface by high-affinity molecules, such as PLG-binding group A streptococcal M-like protein (PAM) (102). In another pathway, streptococci form a SK/plasminogen complex with fibrinogen as a cofactor (62, 95, 96).

The interaction of SK with host plasminogen is highly species specific. SK generated by streptococcal isolated from different host species can only activate plasminogen from that host (63, 64, 86). It was demonstrated that human plasminogen can only be activated by SK generated by human pathogenic streptococcal stains. Mice are generally very resistant to infection by human pathogenic group A streptococcus (GAS). This remarkable species specificity of streptococcal infection has been proposed to result from the species-specific interaction between SK secreted by GAS and the preferred host’s plasminogen. Transgenic mice expressing the human plasminogen protein have been generated to study the role of the fibrinolytic system in GAS infection. A marked increase of susceptibility to GAS was observed in these transgenic mice in a subcutaneous infectious model. Furthermore, the increased susceptibility of the transgenic mice to GAS infection is largely abrogated by deletion of the SK gene. These results demonstrate that SK is a key determinant for host specificity of streptococcal infection (91).

Similar to Streptococcus, Staphylococcus aureus makes staphylokinase (SAK), which is also a plasminogen activator. Unlike SK, SAK has to activate plasminogen through proteolysis. The SAK/plasmin complex is sensitive to inhibition by α2-antiplasmin inhibitor, whereas the SK/plasmin complex is not (30). However, in vivo data on the importance of SAK in

**Interaction of Plasminogen with Pathogens**

It was well established that the fibrinolytic system is important for the invasion of some bacteria into the blood stream. Recent studies have suggested the important roles of plasminogen (11, 15, 22, 26, 59, 61, 62, 91) and fibrinogen (59, 95, 96) in host/pathogen interactions.

**REVIEWS**

![Figure 1. Scheme of the coagulation-anticoagulation system](http://physiologyonline.physiology.org)

Activation of the coagulation system culminates in generation of thrombin, which cleaves fibrinogen to form fibrin clots with platelets on the site of vascular injury. The coagulation system is negatively regulated by tissue factor pathway inhibitor (TFPI), antithrombin (AT), and activated protein C (APC). Fibrinolytic system also regulates coagulation by generation of plasmin, which dissolves fibrin clots. Fibrinolytic system is negatively regulated by plasminogen activator inhibitor 1 (PAI-1). A delicate balance between coagulation and anticoagulation is necessary to prevent pathophysiological conditions such as excessive bleeding or thrombosis.
Staphylococcus pathogenicity is lacking. Based on the studies on SK, it is likely that SAK also plays a critical role in the virulence of Staphylococcus. Plasminogen activator has also been implicated in the pathogenesis of plague by Yersinia pestis (90). It was shown that Y. pestis required a 9.5-Kb plasmid for virulence when injected subcutaneously in mice. The virulence plasmid encoded a protease, the product of pla gene, which demonstrated plasminogen activator activity and weak coagulase activity. If the plasmid was inactivated, the lethality of the bacteria was decreased by a million fold (65, 66, 88, 89, 90).

A number of plasminogen receptors (PlgR) have been identified in group A and C streptococci isolated from humans (Table 1). These PlgRs include glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (8, 101) and α-enolase (SEN) (74), as well as the streptococcal M-like protein (PAM). PAM binds plasminogen with high affinity and without the assistance of fibrinogen (3, 5, 81, 83). The surface-bound plasminogen can be activated by SK or host plasminogen activator. In this way, PAM concentrates plasmin on the surface of the bacteria. The role PAM plays in the streptococcal interaction with host plasminogen was investigated with mice with or without circulating human plasminogen (91). Human plasminogen markedly increased mouse susceptibility to PAM+ strain infection, suggesting that concentrating host plasminogen/plasmin on the surface of bacteria enhanced bacterial invasion. Furthermore, mice with human plasminogen exhibited higher susceptibility to PAM+ strain than to PAM- strain, demonstrating that interaction of PAM with host plasminogen facilitated bacteria invasion. Epidemiological studies also demonstrated the importance of streptokinase and plasminogen in host/GAS interaction. It was shown that, among PAM+ GAS strains, strains isolated from invasive infectious cases bound more plasminogen than strains isolated from noninvasive infectious cases in the presence of fibrinogen and streptokinase (67), supporting the studies in the murine model. Furthermore, streptokinase gene expression was significantly higher in the

Table 1. Bacterial products interacting with host plasminogen and fibrinogen

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Product</th>
<th>Host factor</th>
<th>Interaction</th>
<th>Function</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pyogenes</td>
<td>SK</td>
<td>PLG</td>
<td>Activation</td>
<td>Increase virulence</td>
<td>59, 91</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>SAK</td>
<td>PLG</td>
<td>Activation</td>
<td>Increase virulence</td>
<td>30</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>Pla</td>
<td>PLG</td>
<td>Activation</td>
<td>Increase virulence</td>
<td>90</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>GAPDH</td>
<td>PLG</td>
<td>Binding</td>
<td>Adhesion to uPAR/antiphagocysis</td>
<td>8, 101</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>SEN</td>
<td>PLG</td>
<td>Binding</td>
<td>Increase virulence</td>
<td>74</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>PAM</td>
<td>PLG</td>
<td>Binding</td>
<td>Increase virulence</td>
<td>3, 5, 81, 83, 91</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Flagella</td>
<td>PLG</td>
<td>Binding</td>
<td>Enhancement of formation of plasmin by host plasminogen activator</td>
<td>53</td>
</tr>
<tr>
<td>Escherichia coli, Salmonella typhimurium</td>
<td>Fimbriae</td>
<td>PLG</td>
<td>Binding</td>
<td>Facilitate penetration through basement membrane</td>
<td>49, 75</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>Outer cell surface lipoprotein A</td>
<td>PLG</td>
<td>Binding</td>
<td>Acceleration of formation of plasmin by host plasminogen activator</td>
<td>35</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Aspartase</td>
<td>PLG</td>
<td>Binding</td>
<td>Stimulating formation of plasmin by tPA</td>
<td>87</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>M proteins</td>
<td>Fibrinogen</td>
<td>Binding</td>
<td>Antiphagocytosis</td>
<td>82</td>
</tr>
</tbody>
</table>
Collectively, these observations demonstrate that host plasminogen plays a critical role in pathogenesis of a broad range of invasive pathogens.

**Interaction of Fibrinogen with Pathogens**

Fibrinogen plays multiple roles in the bacterial/host interaction. At the site of a local microbial infection, a number of secreted bacterial products, such as endotoxin, in conjunction with the cascade of cytokines released by host inflammatory cells induces a vigorous response in the surrounding host vasculature, including high-level expression of tissue factor, PAI-1, and a variety of other prothrombotic factors, that triggers the coagulation cascade to form thromboses. The resulting local vascular thrombosis serves to wall off the site of infection and limit pathogen invasion and spread. As discussed above, bacterial plasminogen activators (PA) such as SK appear to overcome this thrombotic host defense, including endogenous PAI-1 and α2-antiplasmin, by activating plasmin to dissolve fibrin clots and clear the surrounding vasculature to facilitate bacterial spread (FIGURE 2). Therefore, fibrin clots should play an important role in stopping bacteria spread.

To test the role of fibrin in GAS pathogenesis, mice were treated with ancrod, a snake venom that can degrade plasma fibrinogen. Ancrod-treated mice exhibited marked increased susceptibility to streptococcal infection localized to the right flank subcutaneous tissue, suggesting decreasing fibrinogen level facilitated bacterial spread (91). Further test was per...

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**FIGURE 2. Model of bacteria invasion using host fibrinolytic system**

Bacterial plasminogen activators such as streptokinase (SK) facilitates bacterial invasion. A: at the site of bacterial infection (GAS), a vigorous inflammatory reaction is induced to release a cascade of cytokines, which will activate local coagulation system by inducing the expression of coagulation factors such as tissue factor (TF) and PAI-1, resulting in formation of local thrombosis. Host fibrinolytic system (PLG) is insufficient to dissolve the thrombosis due to the inhibition of PAI-1. As a result, bacteria are contained locally. B: invasive bacteria such as GAS produce plasminogen activators such as SK to activate host plasminogen (PLG) and form a complex of SK/plasminogen (SK/PLG). Since the SK/plasminogen complex is resistant to host fibrinolytic inhibitors, bacteria are able to dissolve local thrombosis to spread systemically.
formed by introducing bacteria directly into circulation. In this infection model, SK activation of human plasminogen would not play a prominent role in facilitating bacteria spread in mice. The difference in susceptibilities to GAS infection between mice with and without human plasminogen was negated in this systemic infection model, supporting the role of fibrin clots in host defense against systemic invasion (91). Fibrin was also shown to be able to protect mice from infection-stimulated hemorrhage caused by *Toxoplasma gondii* (44).

In addition to its hemostatic function, fibrinogen also plays important roles in the inflammatory response. Fibrinogen has been shown to alter leukocyte functions, including cell adhesion, migration, and cytokine expression. Leukocyte integrin receptor α₂β₃/Mac-1 binds immobilized fibrinogen and regulates leukocyte activities. Mice with genetically engineered fibrinogen lacking the α₂β₃/Mac-1 binding motif showed severely compromised inflammatory response to bacterial infection. The leukocyte clearance of infected *Staphylococcus aureus* was significantly decreased in the peritoneal cavity (31). Fibrinogen may also play a role in modulating bacterial-phagocyte interaction. All pathogenic GAS isolates express cell-wall anchor M proteins. These M proteins are members of the M-protein family and can bind fibrinogen. It has been shown that GAS binds fibrinogen to resist phagocytosis. The mechanism whereby fibrinogen binding can contribute to phagocytosis resistance remains to be elucidated. Fibrinogen could either mask the conserved targets for antibodies in the streptococcal wall or compete with streptococcal-associated C3bi for the binding to α₂β₃/Mac-1 to stop the signals required for initiating the phagocytic process. GAS strains with M proteins deficient in fibrinogen binding were more sensitive to phagocytosis in human blood (82). The importance of fibrinogen in pathophysiology of streptococcal infection was further demonstrated by a study showing that M protein formed complexes with host fibrinogen to activate the neutrophils that release heparin-binding protein. Heparin-binding protein induced vascular leakage that could cause extensive pulmonary damage (37).

These observations demonstrate the complicated relationships of fibrinogen with invading bacteria. As one of the most abundant plasma proteins, fibrinogen serves as the interface of coagulation and inflammation, at the same time, becoming one of the major players in bacteria/host interaction.

**Genetic Variations in Coagulation and Host Response to Infections**

Vascular inflammation and thrombosis are interrelated (27, 56, 57, 58). In the event of bacterial infection, the inflammatory response can induce TF expression in monocytes via nuclear factor κB (NF-κB) activation, thus initiating coagulation (9). On the other hand, coagulation can result in vascular cell activation to recruit leukocytes. Thrombin generation can also induce expression of cytokines from endothelial cells and mononuclear cells (43). A number of animal studies demonstrated that decreasing thrombosis improved survival when challenged with bacterial infections and endotoxin (21, 55, 77, 99). Among various animal models and clinical trials in sepsis patients, improved survival was noted in the APC-treated groups (6). The mechanism of APC’s function in sepsis treatment is still unclear. It is shown that APC can block the production of TNF, both in circulation and in tissue (69, 103). APC can also block NF-κB in monocytes and endothelial cells to inhibit the induction of inflammatory cytokines and adhesion molecules (46, 100). APC may also downregulate genes that are upregulated in inflammation and upregulate anti-apoptotic genes (36, 45). It appears that coagulation and inflammation are intertwined in a complicated network, and APC pathway is at the crossroads.

A number of host hemostatic proteins have been implicated in deciding the susceptibility of host to bacteria infection. Individuals vary considerably in their susceptibilities to infections and in their abilities to recover from infections. Like many complex trait genetic diseases, the molecular mechanisms underlying susceptibility to bacterial infections involve multiple genes in the immune, inflammatory, and coagulation systems. The differences in host susceptibility can be partially explained by polymorphisms of these genes. Recent studies have demonstrated that a common genetics polymorphism in coagulation factors, FV Leiden, improved the survival rates in both sepsis patients and mice challenged with endotoxin LPS (47). Of note, LPS is a pervasive toxin produced by the gram-positive bacteria. LPS can promote cytokine production in the mice, which in part mimic the septic shock syndrome observed in human sepsis cases (7). This observation provided further evidence of the importance of hemostatic system on host susceptibility to bacteria infection. FV is a central regulatory protein in the blood coagulation cascade. It is located at the crossroads of the procoagulant and anticoagulant pathways. It serves as a critical cofactor for FXa to form the prothrombinase complex, which cleaves prothrombin to active thrombin, whereas FVa is also the proteolytic target for APC. APC cleaves at position 504 and 305 of FV protein. Three independent polymorphisms in FV gene have been described: FV Cambridge
(R306T), FV Hong Kong (R306G), and FV Leiden (R506Q, which corresponds with R504Q in mice). FV Leiden allele is highly prevalent in the Caucasian population with an incidence between 4 and 6% (25, 76). FV Cambridge is very rare, whereas FV Hong Kong is present in 3–5% of southeastern Asians (14, 33). FV Leiden renders the FV protein 10-fold more resistant to APC cleavage. FV Leiden is currently the most common known genetic risk factor for thrombosis (32, 78). Furthermore, the surprisingly high prevalence of this deleterious mutation was speculated to be maintained as a balanced gene polymorphism, such as malaria-sickle cell selection, by positive selection during evolution. Kerlin et al. showed that FV Leiden heterozygotes had a significant survival advantage in human severe sepsis and in an animal model of endotoxemia (47). The survival benefit of the FV Leiden mutation might be attributed to the increased thrombin release, which has a positive feedback on APC pathway. This hypothesis is supported by another study in which infusing animals challenged by endotoxin with a small amount of thrombin significantly improved the survival rate (92). However, homozygous FV Leiden mice failed to show improved survival. The reason is unclear. Furthermore, the protective effect of FV Leiden in the endotoxemia model was only observed in a certain dose of LPS, at which half of wild-type mice died from LPS challenge (LD_{50}) (98). No protective effect was observed when mice were challenged with LD_{90} or LD_{95}, suggesting that the protection is subtle and can be overwhelmed by LPS challenge at a higher dose. To demonstrate the complexity of the influence of FV Leiden on infectious disease susceptibility, FV Leiden was associated with an increased risk for skin infection and short-term death from sepsis as well as a decreased risk for urinary-tract infection in a Danish population study (4). The conflicting results could be due to the difference in the inclusion and exclusion criteria adopted by the two studies. More work both on the mechanism of host/pathogen interaction and the epidemiology of infectious diseases is required to clarify the mechanisms underlying these phenomena.

Conclusion and Perspective

It is clear that the coagulation system plays important roles in host/pathogen interactions and host responses to infections. Local thrombosis can serve as a part of the first line of host defense against bacterial invasion in mammals. More primitive animals have evolved similar systems to combat bacterial invasion. On the other hand, bacteria evolved an effective mechanism to circumvent this ancient host defense by producing a variety of plasminogen activators or binding proteins to dissolve local thrombosis. Intervention of this widely distributed invading mechanism among invasive bacteria could lead to a novel therapeutic approach for infectious diseases.

An intriguing question to study host/pathogen interactions remains: Are there polymorphisms in host hemostatic factors under positive selection due to bacterial infections? Bacterial infection is believed to be one of the most important selective forces in evolution. A classic example of balance-positive selection is the resistance against malaria conferred by sickle cell anemia mutation. FV Leiden mutation may also confer selective advantage against infections, as suggested by the severe sepsis study. The completion of the genomic sequences of many hosts and pathogens, as well as the recently published human haplotype map database, provide a tremendous opportunity to study whether some hemostatic factors are under positive selection. Studies on roles of variations of hemostatic factors in bacterial infections will not only identify novel therapeutic targets for treatment of infectious diseases but also provide individualized guidance for prevention and treatment of infectious diseases.

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