Inflammation and Coagulation in the Cardiovascular System
The Contribution of Influenza

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We need to know more about the functional interplay between the coagulation or fibrinolytic pathways and acute inflammation in the vasculature, especially from the viewpoint of acute infections and sepsis. This is a concept that is relevant in both the macro- and microvasculature. An especially important clinical infection is influenza. The extent to which endemic or epidemic influenza elicits systemic inflammation and coagulation is an evolving story. In this issue of the journal, Keller et al provide a focused dissection of changes in coagulation and fibrinolysis parameters in a murine model of respiratory influenza. Their findings give us reason to remind ourselves about the important pathways involved.

Traditional and nontraditional Framingham risk factors for accelerated atherosclerosis, such as genetic susceptibility alleles or lifestyle issues, provide a background for the acute and chronic infectious diseases that are superimposed on the daily lives of patients. How these exogenous pathogens contribute to disease progression has stimulated much discussion but limited insight. This may be because of, in part, the difficulties in studying these in vivo concepts in patients. Scholarly clinical epidemiology studies have provided support for the view that acute infections are chronologically associated with an acute but transient risk for stroke and myocardial infarction. Arguments continue for a contribution of intrallesional pathogens. However, it is more increasingly appreciated that acute infections are associated with systemic inflammation that increases the risk for superimposed acute arterial vascular events. Parallel concepts have emerged for the venous side of the circulation.5

The authors argue that respiratory influenza increased thrombin generation, fibrin deposition, and fibrinolysis in their animal model. Through the use of varied anti- and prothrombotic murine models, both genetic and pharmacological, the relevant pathways involved in the influenza-induced prothrombotic state is dissected. A reduced capacity to generate activated protein C increased thrombin generation. In contrast, treatment with heparin decreased thrombin generation. Thrombin generation was not changed in mice deficient in plasminogen activator inhibitor type-1 (PAI-1°), which are known to exhibit augmented fibrinolysis at baseline. Taken together, the findings indicate that influenza leads to a prothrombotic state, at least in the murine setting.

A merit of the study is the use of genetically modified animal models to provide insight into the pathways that are operative. A murine model of respiratory influenza is used. Insufflation of known titers of a genetically defined viral influenza strain allows researchers to know when, where and how much of a defined virus enters the host. A limitation of the study is that we are left wondering what happens in patients with influenza. These independent variables are, for obvious reasons, more difficult to control for in the clinical setting. A paucity of knowledge exists about the natural history of influenza infection in the mouse versus human. This is a newer model for study. Such information could be gained by measuring titers of live virus in the varied organs of infected mice as a function of time. The authors nicely exploit nonlethal mutants to dissect out key pathways. It is important to point out that they avoid common pitfalls when studying viral pathogenesis in genetically modified animals. Often the host mutations change the cell or organ tropism of the virus, and therefore affect viral growth properties in living animals, rather than affect the innate and adaptive immune responses of the host to a common load of virus. The authors provide preliminary evidence that the pathways they study
are not affecting the growth of the virus or the host immune response toward the virus.

Thrombin production is augmented in mice infected with influenza, especially at the time of maximal tissue infiltration by leukocytes. This process is augmented in mice with a functional deficiency of thrombomodulin (TM). TM is a transmembrane glycoprotein that forms a high-affinity complex with thrombin, the product of the coagulation cascade. The thrombin-TM complex performs a key anticoagulant function through the conversion of protein C to its catalytically activated form (APC), a process that is augmented by the endothelial protein C receptor (EPCR). The thrombin-TM complex function is especially key at the interface between the endothelium and blood constituents. This pathway is evident throughout the vascular tree. An unexpectedly key role for APC in the microvasculature was well illustrated by studies arguing for the therapeutic importance of pharmacological administration of APC in critically ill patients with sepsis. It is interesting that EPCR is especially abundant in medium and large-sized arterial vessel endothelial cells though the functional relevance of this is not yet clear. The antithrombotic properties of APC, together with its cofactor protein S, are manifested through the inactivation of factor Va and VIIIa. It also has antinflammatory and profibrinolytic properties. The findings in these mice highlight that influenza exerts a prothrombotic effect and that the APC pathway is an important component in this response. Influenza increased D-dimer levels, a surrogate for enhanced fibrinolysis, while also increasing PAI-1 activity in lung tissues of infected mice. D-dimer levels increased even further in the hyperfibrinolytic deficient PAI-1−/− mice or thrombomodulin mutant mice, therefore arguing for the functional importance of these cellular pathways.

One of the challenges trying to define the functional interplay between the coagulation or fibrinolytic pathways and acute inflammation in the vasculature of infected patients is that blood measurements do not sample the robust chemistry that is occurring right at the blood and endothelial interface. With this caveat in mind, the observations provided by Keller et al in model tissues are revealing. However, even with direct histological examination of tissue samples and visualization of changes in overall fibrin deposition the results are not straightforward. The in vivo conversion of fibrinogen to fibrin is not simple to measure and quantify. This may explain the lack of congruence between biochemical evidence of thrombin generation, which was evident in the influenza infected mice, and tissues stained, for fibrin in the study from Keller et al, which did not always track with thrombin generation. The authors rightly point out that electron microscopic visualization of ultrastructure, which also addresses the presence or absence of fibrin deposition, combined with dynamic assessments of tissue deposition of fibrin following administration of radioisotopelabeled fibrinogen precursors, may have shed further insight here.

How does influenza induce the procoagulant state? In this respect, the measured increases in proinflammatory cytokines, such as tumor necrosis factor-α, and the immune interferon, interferon γ, likely will figure prominently. Work from others has demonstrated that influenza induces a tissue factor-dependent, and hence a factor VII-dependent, procoagulant response. It is worthy to note that some viruses seem to be able to coopt tissue factor-independent coagulation pathways. A particularly well-studied example is the murine hepatitis coronavirus (MHV-3). Here interferon γ, a host response, and viral nucleocapsid protein, a pathogen-encoded product, induce a direct prothrombinase known as fibrolein/FGL2.

The extent to which the pathways described in this mouse model of influenza are relevant to the human setting will need careful scrutiny. However, it is fair that we commend Keller et al for their timely study given that it begins to address intermediate phenotypes of the coagulation or fibrinolytic pathways in the acute viremia of influenza.

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References


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