PROGRESS REPORT

Procoagulant activity in gastroenterology

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It is now apparent that immune mediated induction of monocyte/macrophage and vascular endothelial cell procoagulant activity is central to initiation of the fibrin formation that is a hallmark of many inflammatory lesions. As such, a role for procoagulant activity has been cited in a variety of diseases including endotoxaemia, murine and human glomerular nephritis, allograft rejection, fulminant murine and human viral hepatitis, vasculitis of immune origin and the adult respiratory distress syndrome. It has been suggested more recently that activation of the immune coagulation system with resultant induction of monocyte/endothelial cell procoagulant activity may be responsible for the vasculitic and thrombotic lesions seen in Crohn's disease, neoplasia, and the thrombogenicity of hypertonic total parenteral nutrition solutions submitted data.

It was recognised by Addison, over a century ago, that white blood cells were able to initiate coagulation, although the mechanism for the induction and modulation of the cellular procoagulant pathways have awaited more recent elucidation.

Although the kinetics and absolute cellular requirements for induction of monocyte/macrophage procoagulant activity subtly vary with the nature of the inducing stimulus, the cellular procoagulant pathway is, in outline, a T helper cell stimulated lymphokine mediated event. Monocyte/macrophages are induced to synthesise and express on their cell surface, procoagulant activity. This may take a variety of molecular forms, including tissue factor, the initiating cofactor of the extrinsic clotting cascade, a direct factor X activator and a direct prothrombinase. In addition, the activated monocyte may be induced to elaborate and secrete inflammatory cytokines, including interleukin 1 (IL-1) and tumour necrosis factor which, in turn, stimulate vascular endothelium to generate procoagulant activity. The end product of this cooperative cellular interaction, that unites immunity, coagulation and inflammation, is the intravascular and perivascular precipitation of fibrin. The haemostatic balance is further displaced in favour of coagulation by the thrombin mediated recruitment of platelets. The consequent disruption of microvascular haemodynamics produces an ischaemic insult to dependent tissues resulting in organ damage.

We, as well as others, have now shown that a rise in procoagulant activity can be seen in a number of specific gastroenterological diseases. We have now shown that the strain dependent susceptibility to murine hepatitis virus – strain 3 – correlates directly with the T lymphocyte controlled expression of a procoagulant monokine that exhibits prothrombin cleaving activity after stimulation by MHV-3 both in vitro and in vivo. The rise in procoagulant activity precedes viral replication by at least 24 hours. After induction of procoagulant activity severe vasculitis is observed in the livers of infected animals, which progresses to severe hepatic necrosis and fulminant hepatitis. We have shown a similar correlation in hepatitis B infection in man, although the pathways for induction remain to be defined.

We have also shown that in patients with Whipple's disease, a systemic disorder in which macrophage infiltration of the small intestine, mesenteric lymph nodes and other tissues of the body is a prominent feature, there was a marked rise in monocyte procoagulant activity during disease activity. After treatment of patients, procoagulant activity returned to normal basal levels. The stimulus for this prothrombinase by cells of untreated Whipple's disease patients is not known. It is possible that the stimulus is some product of the inflammatory tissue injury associated with the disease, or it may be a direct response to some product of the Whipple's agent. The prompt reduction of procoagulant activity during antimicrobial therapy is consistent with the concept of an infectious aetiology for this disease and suggests that the induction of the prothrombinase is somehow linked to the infectious process.

In patients with Crohn’s disease, a marked rise in monocyte procoagulant activity has recently been shown, correlating with increased concentrations of fibrinopeptide A, indicating the ongoing formation of fibrin. Previously, it has been shown that in patients with both Crohn's disease and ulcerative colitis there is activation in blood coagulation. Furthermore, fibrin deposition is a prominent feature of the lesions of Crohn's disease. The raised procoagulant activity directly correlates with disease activity as measured by the Crohn's disease activity index (CDAI) and after treatment falls to near normal levels.

We have also shown a potent induction of both a monocyte and vascular endothelial cell procoagulant activity in cells exposed to total parenteral nutrition solutions, submitted data. We have shown in vitro studies of home total parenteral nutrition patients, that infusions of hypertonic dextrose solutions may result in a marked increase in expression of monocyte procoagulant activity and thrombosis. This
procoagulant activity induced by hypertonic total parenteral nutrition solutions and bacterial lipopolysaccharide in vitro. \(^{32,33}\) It appears that the inhibition of procoagulant activity is mediated by free fatty acids hydrolysed by the emulsified triglyceride. These early results suggest a simple method of minimising total parenteral nutrition-induced thrombosis, – that is, by the concurrent administration of these two solutions.

Study of the cellular procoagulant pathway, as a mediator of disease, has caused us to alter our perspective of many apparently diverse pathologies, and in particular those related to our own field of gastroenterology. Rather than regarding them in isolation, we now see them as diseases of specific aetiology, mediated to a large extent through a final common pathway – that is, an occlusive ischaemia in association with disruption of the endothelium as a physiological interface. This perception suggests to us that by the capacity of therapeutic agents to influence cellular procoagulant activity, their potential in the treatment of a wide spectrum of diseases is very real.

Furthermore, rather than equating the efficacy of these drugs simply with the histological and physiological improvement that they confer, we may measure their activity against a principle effector mechanism of the disease. Ongoing studies in our laboratories are now in progress to define the molecular basis of their activity which will help further our understanding of the pathophysiology of disease and to devise more effective therapeutic strategies.

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