Coagulation proteases and cardiovascular disease

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There is increasing interest in the many possible mechanisms through which coagulation proteases may promote arterial cardiovascular disease (CVD). Atherosclerosis and thrombosis are the principal pathologies underlying coronary heart disease (CHD), ischaemic stroke, and peripheral arterial disease (PAD) (1). Circulating coagulation proteases (as well as their final substrate, fibrinogen) may be biomarkers for risk of arterial thrombosis and thromboembolism; and may also influence the structure of fibrin clots and thrombi (2). Both coagulant and anticoagulant proteases can influence multiple cells in the vessel wall and in vital organs; and hence can influence processes including haemostasis, atherosclerosis, ischaemia and reperfusion injury, inflammation, organ and vessel remodelling, and fibrosis (3) (Figure 1).

Selective anticoagulation with new agents which target specific proteases has increased knowledge of this multitude of physiological and pathological actions; and clinical trials of NOACs (non-vitamin K-dependent oral anticoagulants; also referred to as DOACs, for direct oral anticoagulants) have shown reduction in risk of major bleeding compared to traditional vitamin K antagonists (VKAs), especially in intracranial bleeding; but in some trials increased risk of gastro-intestinal bleeding (4). These results require explanation of the possible mechanisms for organ-specific haemostasis.

For this theme issue of the journal, we invited experts in several of these areas to provide brief reviews.

Lowe and Rumley review evidence from prospective epidemiological studies for associations of circulating levels of coagulation proteases, fibrinogen, and activation markers of coagulation and fibrinolysis with risk of CVD (5). To date, plasma fibrinogen shows the strongest and most consistent associations with CVD; however, genetic studies do not support causality, and there is limited evidence that lowering fibrinogen levels reduces CVD risk. These associations may result from up-regulation of pro-inflammatory cytokines such as interleukin-6. In contrast, the common genetic polymorphisms for factors II, V and the von Willebrand factor:VIII complex (non-O blood group) show associations with CHD risk, consistent with potential causal roles in arterial thrombosis, as with venous thrombosis. The associations of fibrin D-dimer and tissue plasminogen activator (t-PA) antigen levels with CHD risk, consistent with potential activities but not its anticoagulant activities. The cytoprotective selective APC variant, 3K3A-APC is currently undergoing clinical trials in ischaemic stroke.

Antoniak et al. review the role of tissue factor (Tf)-FVII(a) activation of PARs in pathologic heart remodeling associated with myocardial infarction, viral myocarditis and hypertension (9). Cardiomyocyte TF is essential to maintain heart haemostasis. TF-dependent activation of coagulation and activation of PARs contribute to initial size of myocardial infarction, as well as pathologic heart remodelling including hypertrophic growth of cardiomyocytes and fibrosis.

Bridge et al. review the associations of clot properties and CVD. Fibrin clot structure is altered by levels of fibrinogen, thrombin, but also by metabolic disturbances including diabetes mellitus and hyperhomocysteinemia; as well as treatment with aspirin, anticoagulants, statins and fibrates (10). Change in fibrin clot structure in vitro, to a denser clot with smaller pores, which is more resistant to lysis, is strongly

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associated with CVD (both arterial and venous) and may be in part genetic. Pharmacological therapies, which “normalise” fibrin clot structure may be beneficial in prevention and treatment of CVD.

Schurgers and Spronk review differential cellular effects of old and new anticoagulants on the genesis and progression of atherosclerosis. Inhibition of coagulation proteases not only attenuates fibrin formation, but may also influence atherosclerosis and vascular calcification (11). Animal models revealed that VKA therapy induced both intima and media calcification and accelerated plaque vulnerability, whereas specific and direct inhibition of thrombin or FXA attenuated atherosclerosis.

Finally, Vanasse et al. review organ-specific bleeding patterns of anticoagulant therapy in recent clinical trials of NOACs versus traditional VKAs. As a group, NOACs showed similar antithrombotic efficacy as warfarin, but a reduced overall risk of major bleeding (12). The reduction in bleeding risk with NOACs was greatest with intracranial haemorrhage. In contrast, the relative risk of gastrointestinal bleeding was increased with some NOACs. Potential mechanisms for the reduced risk of intracranial bleeding include lower blockade of high local concentrations of FXa or thrombin generated in response to internal TF-mediated coagulation activation; in concert with high concentration of TF (and low expression of TFPI) in the cerebrovascular microcirculation. Possible mechanisms for the increased risk of gastrointestinal bleeding include the variable amounts of active drug that accumulates in the gastrointestinal tract, which has the potential to induce local bleeding.

In conclusion, the explosion of recent basic and clinical studies of coagulation proteases, and of their selective inhibition, has greatly increased our knowledge of their multiple roles in physiology and pathology (Figure 1). The development of new, selective anticoagulant agents; and the increasing experience from clinical trials of such agents will have a major impact on the prevention and treatment not only of CVD, but potentially also of other disease states, including infections such as sepsis.

Conflicts of interest
None declared.

References