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Novel mediators and biomarkers of thrombosis

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Abstract

Spurred by advances in understanding the molecular basis of thrombosis, this issue of the *Journal of Thrombosis and Thrombolysis* is devoted to exploring aspects of novel paradigms and their potential impact on diagnosis and treatment. Complex interplay of between blood and vascular cells, inflammation, and pro- and anti-coagulant pathways determines the formation and stability of arterial and venous thrombosis. A causal role for inflammation in coronary artery disease is currently being tested in large clinical trials. Basic science observations implicate inflammation in venous thromboembolic disorders, and inflammatory processes may have a similar influence on device thrombosis. In this article and throughout this issue of the Journal, we discuss biomarkers and mediators associated with arterial and venous thrombosis, atrial fibrillation, and other clinical scenarios.

Arterial thrombosis

Cardiovascular disease (CVD) risk is strongly associated with inflammatory biomarkers, such a C-reactive protein (CRP) and myeloperoxidase (MPO). Although evidence that any one inflammatory marker or pathway causes ischemic complications is lacking, the hypothesis of a causal relationship between inflammatory and thrombotic pathways that culminates in the development and complications of atherosclerosis is currently being tested in ongoing clinical trials. There is reason to postulate that at least some of the beneficial effects of statin therapy may derive from their rapid - within hours to days - ability to affect thrombotic and inflammatory parameters.

Several studies have suggested a role of leukocytes in the progression of CVD. Elevations in leukocyte count, in particular neutrophil and to a lesser extent, monocyte count, has been shown to predict ischemic events (1). Data from animal models suggest that leukocytosis *per se*, may promote CVD. Interestingly, retrospective analysis of the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial indicates that bleeding complications are also more likely to occur in patients presenting with elevated white blood counts (2). Bleeding and thrombosis share other common predictors, and the application of systems biology approaches to platelets has begun to identify biomarkers predictive of thrombo-hemorrhagic complications (3). Other emerging paradigms in arterial thrombosis

are discussed in the article by Wisler and Becker in this issue of the *Journal of Thrombosis and Thrombolysis* (4).

The central role of platelets in arterial thrombosis, while well-established, has been re-defined. The historic perspective – namely, that the main function of platelets was to interact with one another to create a thrombus – has been expanded to include their contributions to diverse biologic processes, such as inflammatory and angiogenesis. Platelets participate both through direct interactions with leukocytes and the endothelium, and by generating or releasing bioactive molecules during platelet activation. More recently, the transfer of small compounds and RNA between platelets and from platelets to other cells has been observed and is the subject of the review by Clancy and Freedman in this issue (5). Through these and other mechanisms, platelets contribute to processes beyond hemostasis (6), such as transplant vasculopathy as described by Modjeski and Morrell (7).

The contribution of the coagulation system to arterial thrombosis extends beyond thrombin generation, important for platelet activation and essential for fibrin formation. Thrombin may influence events underlying atherosclerosis with potent effects on multiple cells involved in plaque formation and stability. Coagulation activity is associated with plaque, and more extensive coronary atherosclerosis is associated with accelerated thrombin generation (8). The ability to model thrombin generation in vitro may provide a basis to identify individuals at heightened risk and methods to do so are described by Brummel-Ziedens and colleagues (9). In experiment models, genetic and pharmacologic approaches to manipulate coagulation alters the composition and may reduce the extent of plaque formation, as detailed by Kalz et al. (10).

Venous thrombosis

Knowledge of venous thromboembolic disease (VTE) has advanced substantially, as have treatment options. The new oral anticoagulants established the clinical feasibility of targeting thrombin and Factor X and may have broader uses in other conditions. At the same time that these new drugs are emerging as alternatives to vitamin K antagonists, a demonstrable, albeit modest, effect of aspirin was observed in reducing recurrent events in patients with previous VTE (reviewed in (11)). The clinical benefit of aspirin is in keeping with observations from model systems of a role for platelets in venous thrombosis (12). Release of von Willebrand factor from damaged venous endothelium may contribute to platelet adhesion (13) and subsequent leukocyte recruitment. Neutrophil release of extracellular DNA may provide a scaffold upon which venous thrombosis propagates (14). The contribution of inflammation to venous thrombosis may also be inferred from the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER) trial, in which the HMG co-A reductase inhibitor rosuvastatin reduced incidence of deep venous thrombosis without altering bleeding in individuals with heightened inflammation, as marked by elevated CRP levels (15). In an inferior vena cava ligation model of venous thrombosis in mice, rosuvastatin therapy for two days decreases thrombus burden in association with a reduction in inflammatory events (16). Small cellular fragments termed “microparticles,” have been the subject of much investigation, and may

serve as a novel link between venous thrombosis and cancer (17). The underlying genetic basis for venous thrombosis is also slowly being elucidated (18).

Atrial fibrillation – at the crossroads of arterial and venous thrombosis

The reason(s) that atrial fibrillation (AF) predispose to thromboembolic events are not known, although a simplified explanation may implicate stasis. The ability of anti-platelet agents to reduce the risk of cardioembolic events in AF suggests that platelets may contribute to the pathophysiology (11). Platelet activation occurs with AF and rapid atrial pacing, providing a possible mechanistic link (19). Other biomarkers that have proposed to improve the prediction of thromboembolotic (TE) events in this patient population include von Willebrand factor, D-dimer and cerebral imaging (20). Elevations in troponin-I in patients with AF predict stroke, major bleeding and cardiac death (21). Their role in clinical management remains unclear.

Cardiac devices – valves and ventricular assist devices

The growing use of ventricular assist devices (VAD), transcatheter deployment of aortic valves and repair of mitral valves has prompted renewed interest in platelet – device interactions and coagulation along their surfaces (reviewed in (22) (23)). Bleeding and thrombosis/thromboembolic events complicated both VADs and are major complications after TAVR. Improved access and devices will lower complication rates, and will offer a better understanding of risk factors. Preliminary data has suggested that active infection substantially increases the risk of VAD thrombosis. The interactions between host hemostatic systems and infections is also considered in this issue of the Journal.

Future Directions

Our understanding of thrombosis has evolved beyond the traditional textbook definitions to reveal complex interactions of leukocytes, platelets, the endothelium, and likely red blood cells, with influences from systemic inflammation, infection, and metabolic alterations. Although the molecular underpinnings of these interactions remain elusive, they suggest additional biomarkers that could potentially be used to identify individuals at risk for CVD and VTE as well as help identify patients at higher risk following cardiac events such as AF and cardiovascular interventions such as TAVR.

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