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Review

Microparticles in atrial fibrillation: A link between cell activation or apoptosis, tissue remodelling and thrombogenicity

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ABSTRACT

Microparticles (MPs) are small membrane vesicles that are shed from virtually all cells in response to stress. Widely described in atherothrombotic diseases, recent data suggest a role for circulating MPs in the hypercoagulable state associated with supraventricular tachyarrhythmia. During atrial fibrillation, several mechanisms, such as high ventricular heart rate, low or oscillatory shear stress, stretch, hypoxia, inflammation and oxidative stress, are potent inducers of apoptotic cell death, which leads to the shedding of procoagulant MPs within the vasculature. As key regulators of cell–cell cross-talk and important mediators of inflammatory, thrombogenic and proteolytic pathways, MPs directly or indirectly contribute to the amplification loops involved in atrial fibrillation. Because high levels of platelets and endothelial-derived MPs are identified during stroke and are associated with infarct size and clinical outcome, they are proposed to be a potent marker of ischaemic risk. During pulmonary vein isolation, the additional increases of platelet and leukocyte MP levels suggest the extent of tissue damage and reflect a transient activation of the coagulation cascade that could favour ischaemic stroke. Conversely, the observed decreases of several apoptotic markers some months after the restoration of sinus rhythm suggest that the extent of apoptotic processes is reversible and might enable restoration of haemostasis. In this review, we will summarise the current evidence supporting the roles of apoptosis and cell activation in the development of the prothrombotic state observed in atrial fibrillation, with a particular focus on procoagulant MPs.

1. Introduction

Circulating MPs are small membrane vesicles that are shed from virtually all cells in response to activation, apoptosis or thermic injury. In the vasculature, MPs shed by stimulated or apoptotic cells are hallmarks of tissue damage; the degree of shedding correlates to the proportion of stimulated cells. Having long been viewed as cellular dust, MPs are now considered a key component in the haemostatic response [1]. Circulating MPs, mainly from platelets, leukocytes and endothelial cells, provide an additional phospholipid surface to support the assembly of blood coagulation factors, thereby promoting the coagulation cascade and thrombin generation. In the vasculature, they are the main carriers of circulating tissue factor, the principal initiator of vascular thrombosis [1]. MPs are widely described in atherothrombotic diseases, and recent advances suggest they have a role in the hypercoagulable state associated with supraventricular tachyarrhythmia [2–5]. Due to their inflammatory, thrombogenic, proteolytic, and endothelium-damaging properties, MPs directly or indirectly contribute to the noxious amplification loops associated with the marked thrombotic propensity observed in atrial fibrillation (AF) [2,6] (Fig. 1). Moreover, because high levels of platelet- and endothelial-derived MPs are identified during stroke and are associated with infarct size and clinical outcome, they are proposed to be a potent marker of ischaemic risk [7–10].

In this review, we will summarise the current evidence supporting the roles of apoptosis and cell activation in the development of the prothrombotic state observed in AF, with a particular focus on procoagulant microparticles.

Apoptosis in atrial fibrillation

When exposed to stress, cell death occurs secondary to increased membrane permeability and remodelling [11]. Rising cytosolic Ca^{2+} concentrations allow cytoskeleton cleavage through calpain [12] and caspase activation, which leads to the externalisation of normally internalised procoagulant aminophospholipids on the cell membrane. This process of membrane remodelling ultimately results in the

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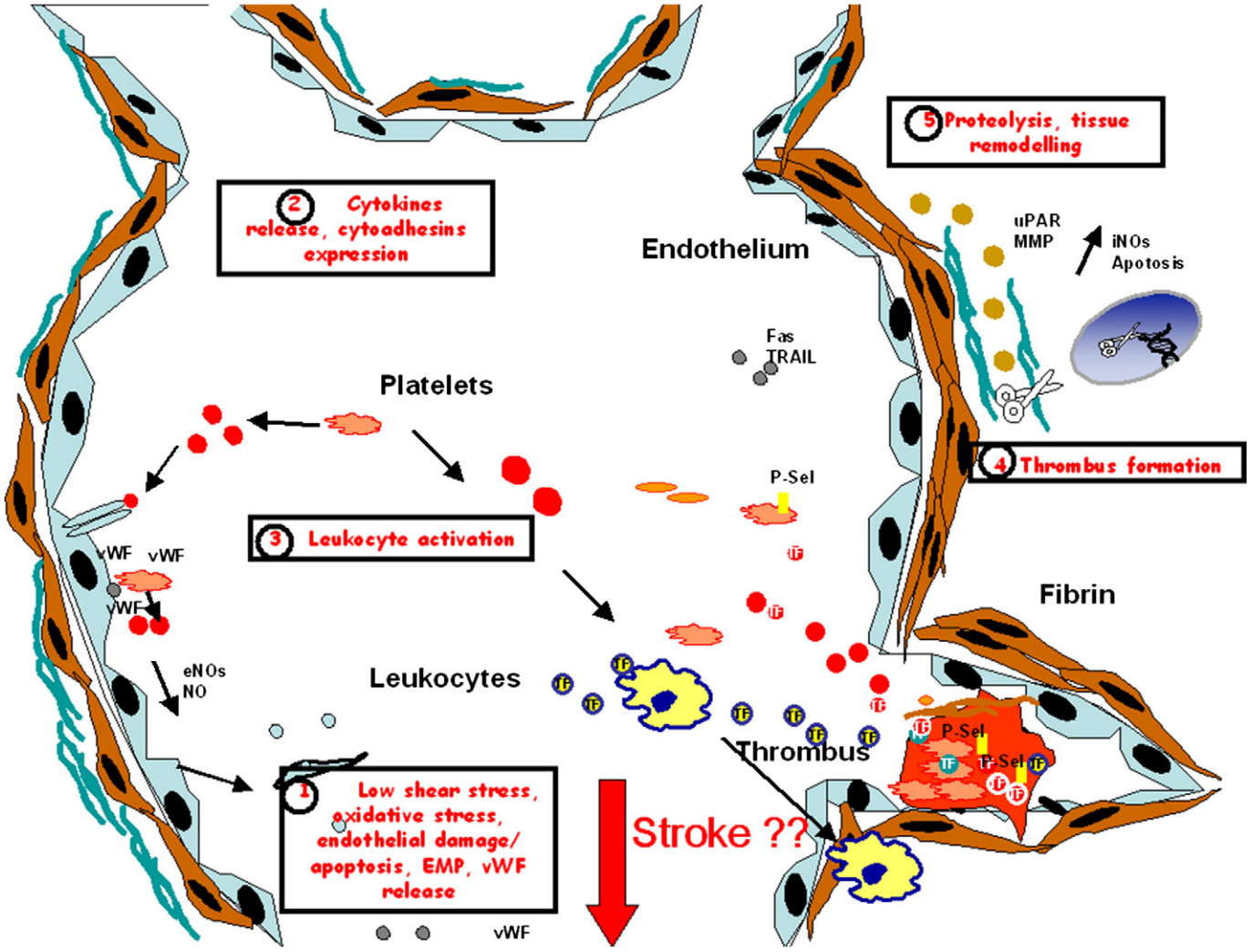

Fig. 1. Deleterious role of circulating and trapped MPs in atrial fibrillation. During atrial fibrillation, low or oscillatory shear stress, hypoxia, stretch, inflammation and oxidative stress are likely to promote apoptotic cell death and the release of circulating microparticles. Endothelial damage is characterised by the release of several marker such as endothelial-derived microparticles (EMPs) or vWF antigen [1]. Behaving as noxious shuttles of biological information, circulating MPs promote cytokines release, cytoadhesins expression, leukocyte activation and endothelial damage [2,3]. At sites of endothelial damage, the swift recruitment of MPs harbouring tenase, prothrombinase and tissue factor activities are mandatory for the growth of the thrombus [4] and could be a determinant of the risk of stroke. Within the atrial tissue, MPs shed by apoptotic cells harbouring functional metalloproteinase or uPAR that lead to plasmin generation could contribute to tissue remodelling through fibrillar matrix proteolysis [5].

shedding of MPs that express phosphatidylserine (PS) at their outer leaflet [11].

Within the atrium, all of the cellular lineages, including endothelial cells, fibroblasts and cardiomyocytes, are potentially subjected to programmed cell death. Increased apoptosis has been detected in tissue samples from animal and human hearts with AF [13]. Compared to tissues from patients in sinus rhythm, fibrillating atria have significantly more myolysis, nuclear alteration, and apoptosis activation [13,14]. The detection of elevated serum levels of apoptosis mediators, including Fas in patients with AF, is another illustration of the importance of programmed cell death during AF [15]. The degree of myolysis and an increased apoptotic pattern could be significant predictors for the development of postoperative AF [16]. Indeed, atrial histology shows degenerative changes that may correlate with advanced age and left atrial enlargement.

It is likely that apoptotic processes begin relatively early in the course of AF and associated tissue remodelling. Evidence from experimental models of pacing-induced AF suggests that apoptosis, leukocyte infiltration, and increased cell death occur early and precede arrhythmogenic structural remodelling [17]. In endothelial cells undergoing cell death, membrane phosphatidylserine (PS) typically precedes DNA fragmentation [18] (Fig. 2). The process of membrane remodelling that occurs during apoptosis is ultimately resolved by the shedding of membrane microparticles that express various effector signalling proteins for the thrombotic processes, including PS and tissue factor (TF)[1]. Depending on the stage of apoptosis, the exposure of procoagulant phospholipids at the outer leaflet of activated or apoptotic cells induces an increase of the activity of the tenase complex by 25% to 60%. Endothelial apoptosis could be associated with enhanced expression of TF antigen, or activity under proinflammatory conditions when cells were pre-treated by lipopolysaccharide. Apoptosis induction is also associated with a swift decrease of various anticoagulant activities [18]. Consequently, the induction of endothelial apoptosis leads to a significant increase in thrombin formation. Moreover, apoptotic endothelial cells become proadhesive to non-activated platelets and promote their slight activation, suggesting an amplification pathway to thrombosis. [19]. Consistent with this paradigm, acute-onset AF is associated with local cardiac platelet activation [20] and endothelial dysfunction [21]. During AF, tissue factor, which is the main inducer of blood coagulation, is overexpressed in damaged