**Introduction**

Vascular wall remodeling after arterial injury involves the migration and proliferation of smooth muscle cells (SMCs) into the intima and the development of a neointima that reduces luminal diameter. Many factors may play a role in SMC proliferation, including platelet-derived mitogens and thrombin. The cellular events associated with neointimal proliferation in response to vascular injury may be induced in part by the platelet-rich thrombus that forms at the site of vascular injury. Platelet-rich thrombosis is dependent on a dynamic interaction between platelet adhesion and aggregation, exposure of membrane-bound tissue factor (TF), elaboration of factor Xa by the TF/VII complex, and localization of the Xa/Va complex on a phospholipid surface most likely provided by adherent platelets (Fig. 1). Platelet adhesion is mediated by specific binding of platelet membrane receptors to the subendothelial adhesive glycoproteins such as collagen, and subsequent platelet deposition is determined by several mechanisms, including extent of arterial injury, shear-dependent platelet adhesion and aggregation and elaboration of platelet agonists.

**Experimental observations**

We have recently shown that the factor Xa/Va complex and thrombin localize to the site of arterial injury, are resistant to physiologic anticoagulants (e.g., antithrombin III), and may promote thrombin elaboration for up to 5 days after injury of normal vessels in New Zealand White rabbits. The activity of the Xa/Va complex that localizes to the injured arterial wall is regulated by platelet deposition after injury, providing a membrane for assembly of the complex, and TF-mediated activation of factor X. As TF is critical for the initiation of coagulation cascade, we created a model where a sequential injury to the arterial wall...
dominal aorta of New Zealand White rabbits was used, to define whether the subendothelium and the media of an aorta with neointima, 30 days after a first catheter over-inflation, expose TF; and to define also the time course after arterial injury of the increase in procoagulant activity and its determinants on the luminal surface. We evaluated also whether this activity was associated with a more robust and more prolonged procoagulant activity compared to that in a normal aorta. Procoagulant activity dependent on TF and platelets was evaluated at 4 hours after a repeated injury, while procoagulant activities dependent on factor Xa/Va and thrombin were also evaluated at longer intervals after a repeated injury. Prothrombotic activity was characterized ex vivo in injured segments that were incubated with barium-adsorbed plasma and with chromogenic substrates to define the presence of procoagulant activity bound to the vessel wall. Animals with neointima showed increased platelet adhesion 4 hours after injury, when compared to animals with normal vessels, suggesting availability of upstream activators of the prothrombinase complex. At the same interval, functional activity of complexes inducing activation of factor X, evaluated ex vivo with chromogenic substrates, was detectable in animals with neointima, and was consistently reduced (81%) after incubation of the injured segments with 2.5 mg/ml of a specific antibody to rabbit TF. Animals with neointima showed increased platelet adhesion 4 hours after injury, suggesting availability of upstream activators of the prothrombinase activity. Thus, in our experimental conditions, platelet coverage and procoagulant activity were detected after repeated injury of the abdominal aorta of rabbits. Since injured segments of aorta with the neointima expressed capacity to support prothrombinase activation, as indicated by activation of factor X from upstream active coagulation complexes, and because a TF antibody was effective in reducing activation of factor X in the injured vessels, our data suggest that exposure of TF to the vascular wall after arterial injury. Arterioscler Thromb Vasc Biol 1998; 18: 250-7.

Conclusions

Since in experimental models it is possible to modulate the procoagulant and platelet responses to arterial wall injury with the use of specific inhibitors of thrombin, factor Xa, TF/VIIa, and platelet adhesion and aggregation, characterization of the expression of VCAM and ICAM will provide insight to address the following issues: 1) relevance of biological extracoragulative role of prothrombotic moieties, 2) establishing whether endothelial and SMC activation early after injury are procoagulant and/or platelet-dependent.

References