Does Tissue Factor Expression by Vascular Smooth Muscle Cells Provide a Link Between C-Reactive Protein and Cardiovascular Disease?

Nigel Mackman, Mark B. Taubman

C-reactive protein (CRP) is an acute-phase protein that participates in host defense against bacterial pathogens (reviewed in1,2). It has been used as a biomarker of inflammation, and several studies have shown that it has predictive value for cardiovascular events (reviewed in3). Based on these studies, blood CRP levels are being used increasingly by clinicians to help assess cardiovascular risk and to guide decisions on preventive therapies. CRP levels are also being used as secondary end points in numerous atherosclerosis trials, such as those involving statins. Statins were shown to reduce levels of both low-density lipoprotein (LDL) and CRP in individuals at risk for cardiovascular disease (CVD). This led to a clinical trial that examined the effect of statin therapy on primary prevention in healthy individuals with low LDL cholesterol but elevated CRP levels.4 The results suggested that the ability of statin therapy to reduce inflammation may be as important as its effects on LDL cholesterol in preventing CVD. Despite its value as a predictor of cardiovascular events, it is unclear whether CRP directly contributes to the development and progression of atherosclerotic disease or is simply a marker of the vascular inflammatory process that accompanies atherogenesis.

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Tissue factor (TF) is the primary cellular initiator of the blood coagulation cascade, which generates various proteases, including thrombin, and ultimately leads to fibrin deposition.5,6 TF also localizes factor VIIa to the cell membrane where it can cleave protease activated receptor 2 (PAR-2) and activate cells.7 Inhibition of TF with various agents, including tissue factor pathway inhibitor (TFPI) and inactivated factor VIIa, reduces thrombosis in several animal models,8,9 indicating that TF plays a major role in the formation of an occlusive thrombus after vessel injury. In addition, mice with low levels of TF in the vessel wall have prolonged occlusion times in a mouse model of carotid artery injury demonstrating that vessel wall TF drives thrombosis.10 Vascular smooth muscle cells (VSMCs) appear to be the primary source of TF in the arterial wall. Indeed, TF is constitutively expressed by VSMCs, and its expression is increased after arterial injury.11,12 We recently found that thrombosis in a mouse carotid artery injury model was markedly reduced in TFlodex/floxed/SM22Cre mice, which have a selective deletion of TF in VSMCs (unpublished data). VSMCs and macrophages within atherosclerotic plaques express high levels of TF, and this is thought to mediate thrombosis after plaque rupture.13–18

TF also plays a role in intimal hyperplasia resulting from arterial injury. Both pharmacological and genetic approaches have shown that reduced TF expression or activity are associated with less intimal hyperplasia after arterial injury.8,19–22 Again, TF expression by VSMCs appears to be critical for this process because TFlodex/floxed/SM22Cre mice have reduced intimal hyperplasia after injury of the femoral artery (unpublished data Wang L, Miller C, Swarthout RF, Rao M, Mackman N, Taubman MT. 2008). TF appears to contribute to intimal hyperplasia by enhancing migration or proliferation of VSMCs. VSMCs with low levels of TF have reduced migration, and TF:factor VIIa–dependent activation of PAR-2 induces VSMC migration.21,23 The TF-factor VIIa complex also activated the ERK1/2 signaling pathway and induced cell proliferation.24 Intimal hyperplasia is seen not only in conditions associated with arterial injury, such as that produced by percutaneous coronary interventions and stenting, but also accompanies the development of atherosclerotic plaques. At present, the role of TF in the progression of atherosclerosis is unclear. Genetically reducing TFPI levels promoted atherosclerosis in a mouse model of atherosclerosis,25 whereas we found that decreasing TF in hematopoietic cells did not affect atherosclerosis.26 However, the specific role of VSMC-derived TF has not been examined.

In this issue of ATVB, Wu and colleagues provide compelling evidence that CRP induces TF expression and decreases TFPI in both human and mouse VSMCs (Figure). In an elegant series of studies they show that CRP engages the Fcγ receptor IIIa on the surface of VSMC and increases intracellular levels of reactive oxygen species and activation of the ERK1/2 mitogen activated protein kinase. CRP-treated cells expressed higher levels of TF and lower levels of TFPI, resulting in a net increase in procoagulant activity. This work extends an earlier study showing that CRP activated ERK1/2 and induced TF expression in VSMCs.28 These cell culture studies prompted Wu and

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colleagues to analyze TF and TFPI expression in arteries of transgenic mice (CRP-Tg) expressing human CRP in their serum. They found increased levels of TF and decreased levels of TFPI in medial VSMCs of their carotid arteries compared with those observed in wild-type mice. A previous study showed that these CRP-Tg mice have increased arterial thrombosis and increased intimal hyperplasia after femoral artery injury compared with wild-type mice.29 The increase in arterial thrombosis is likely attributable to the change in balance between TF and TFPI. The increase in intimal hyperplasia may be mediated through increased TF expression. CRP also induces TF expression in cultured human endothelial cells, which may contribute to the pro-thrombotic phenotype of these mice.28 However, Wu and colleagues did not detect TF expression in the endothelium of the carotid arteries of CRP-Tg mice. Moreover, the generation of reactive oxygen species and activated ERK1/2 are important pathways involved in VSMC activation. Therefore, the effect of CRP on intimal hyperplasia may also be attributable to direct effects of CRP on VSMC growth and migration rather than as a consequence of enhanced TF expression.

Further studies are needed to determine whether levels of CRP in humans correlate with levels of TF in VSMCs and possibly in the circulation, so called blood-borne TF. It is likely that CRP will also affect the expression of other proteins that promote thrombosis, intimal hyperplasia, and the progression of atherosclerosis.
Disclosures

None.

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