TF antigen and activity are found in abundance in human atherosclerotic plaques, particularly in the lipid-rich core. TF is also readily induced in the arterial wall by balloon injury and accumulates in the resulting neointima. In chronic atherosclerosis, the macrophage is likely to be the major source of TF within the plaque. TF accumulates as an early event associated with the migration of monocytes to the vessel wall in response to chemoattractants, such as MCP-1, and their differentiation into macrophages.

As smooth muscle cells (SMC) become activated in the developing plaque, they provide a second source of TF. Macrophages and SMC accumulate lipid and become foam cells, ultimately degenerating into a necrotic core rich in TF. Spontaneous plaque rupture or acute interventions expose active TF in the core to circulating blood, triggering thrombosis. In acute arterial injury, SMC appear to be the chief source of TF.

In normal vessels, the induction of TF in the medial SMC is not sufficient to generate fibrin, presumably because the TF is not readily accessible on the luminal surface. In contrast, endothelial denudation of previously injured arteries may expose intimal TF to circulating blood, resulting in rapid fibrin deposition. In advanced human atherosclerosis, it is likely that even in areas that do not contain "unstable" or "stable" plaques, the vessel wall is not normal and more closely resembles that of a previously injured artery possessing an active intima. Interventions, such as balloon angioplasty, coronary atherectomy, or stent placement may expose intimal TF, leading to fibrin deposition.

As the initiator of coagulation, TF is a potential target for inhibiting the thrombotic complications of atherosclerosis. TFPI (reviewed in 52) is currently under clinical investigation as an anticoagulant and its effects on intimal hyperplasia in animal models are being studied. Direct factor Xa inhibitors, such as tick anticoagulant peptide (TAP) and leech anticoagulant peptide (ATS), are also under investigation (53-54). Finally, the recent crystallization of TF (55) and the TF:VIIa (56) should provide important new insights into the design of molecules for directly inhibiting TF.

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