Within atherosclerotic lesions Tissue Factor (TF)-Factor VIIa (FVIIa) not only contributes to thrombotic events but also alters vascular remodeling through enhancement of migration. Moreover, the TF-FVIIa-FXa complex activates protease-activated receptors (PAR). TF/FVIIa/PAR-2 signaling has also been shown to promote proliferation and metastasis of tumor cells. Since coagulation factors promote inflammation which plays a major role during atherosclerosis as well as tumor metastasis this study sought to investigate the effects of FVIIa on the inflammatory response in vascular cells. FVIIa induces interleukin-8 (IL-8) and IL-6 in primary smooth muscle cells (SMC), which was correlated to the expression of TF and PAR-2 as shown by immunoassay and qRT-PCR. The effect was dose-dependent and required TF, the proteolytic activity of FVIIa and PAR-2. Secondary effects of downstream coagulation factors were excluded. No proinflammatory FVIIa effect was observed in endothelial cells (EC) and mononuclear cells (MNC), expressing either TF or PAR-2. In atherosclerotic lesions mRNA expression of PAR-1, PAR-2 and IL-8 was elevated compared to healthy vessels indicating a role for PAR-1 and PAR-2 signaling in atherosclerosis. In addition to the procoagulant and promigratory role of the TF-FVIIa complex we identify a proinflammatory role of FVIIa in human SMC dependent on
expression of TF and PAR-2 that provides yet another link between coagulation and inflammation.