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Tissue Factor, Protease Activated Receptors and Pathologic Heart Remodeling

Silvio Antoniak, Erica Sparkenbaugh, and Rafal Pawlinski

Division of Hematology and Oncology, Department of Medicine, McAllister Heart Institute, University of North Carolina at Chapel Hill, USA

Abstract

Tissue factor is the primary initiator of coagulation cascade and plays an essential role in hemostasis and thrombosis. In addition, tissue factor and coagulation proteases contribute to the many cellular responses via activation of protease activated receptors. Heart is the organ demonstrating high levels of constitutive tissue factor expression. This review focuses on the role of tissue factor, coagulation proteases and protease activated receptors in heart hemostasis and the pathological heart remodeling associated with myocardial infarction, viral myocarditis and hypertension.

Introduction

Tissue factor

Tissue factor (TF) is a 47-kDa transmembrane cell-surface glycoprotein that belongs to the cytokine receptor superfamily and binds coagulation factor VII/VIIa (FVII/VIIa). The TF:FVIIa binary complex exerts both procoagulant and signaling activities and plays an important role in many biological processes, including hemostasis, thrombosis and inflammation (1). TF is constitutively expressed by perivascular and parenchymal cells. Upon vascular injury, these cellular sources of TF are exposed to the blood and play an essential role in the initiation of hemostasis process. However, during many pathologic conditions increased TF expression on vascular cells (leukocytes and endothelial cells), circulating microparticles or ruptured atherosclerotic plaques triggers thrombosis and disseminated intravascular coagulation (1, 2). In addition, perivascular cell TF exposed to the circulating FVII/FVIIa, as a result of increased vascular permeability, can also participate in these processes (1, 2). The contribution of TF to the cellular responses is mediated via generation of downstream coagulation proteases and subsequent activation of protease activated receptors (PARs).

Protease activated receptors

Protease activated receptors (PARs) are a family of seven transmembrane domain, G protein-coupled receptors activated by proteolytic cleavage (3). After their activation, a new

amino terminus peptide is exposed that functions as a tethered ligand (3). The PAR family consists of four members: PAR-1, PAR-2, PAR-3 and PAR-4. Thrombin is the main physiological activator of PAR-1, PAR-3 and PAR-4 (3). In addition, several studies have shown that PAR-1 can be activated by TF:FVIIa:FXa ternary complex, FXa, activated protein C and matrix metalloproteinase-1 (MMP-1) and MMP-13 (4–9). *In vitro* studies have shown that PAR-2 is activated by several proteases, including trypsin, mast cells tryptase and the coagulation proteases FVIIa and FXa, as well as the TF:FVIIa:FXa ternary complex (3, 10, 11). PARs can also be activated by synthetic agonist peptides corresponding to the tethered ligand sequence (3).

Pathologic heart remodeling

In response to both acute and chronic insults, including coronary artery disease, myocardial infarction, hypertension, viral infections, valve abnormalities and inherited mutations, the heart undergoes an extensive remodeling (12–14). At the early stage, remodeling is an adaptive reaction of the heart to maintain cardiac function but over time leads to maladaptive changes resulting in decreased heart function and increased risk for heart failure. Cardiomyocyte hypertrophy, proliferation of cardiac fibroblasts and cardiac inflammation are the three major processes contributing to pathologic heart remodeling (12, 14). PARs are widely expressed by cells within the cardiovascular system including endothelial cells, smooth muscle cells, cardiac fibroblasts and cardiomyocytes (15). In addition, TF expression can be found on extravascular cells such as fibroblasts, smooth muscle cells (SMCs) and cardiomyocytes (16). Coagulation protease-mediated activation of PARs on these cells contributes to the pathophysiology of heart remodeling.

In this review we will discuss the role of TF and PARs in heart hemostasis as well as their contribution to pathological heart remodeling. Specifically, we will focus on the remodeling of the heart in response to the myocardial infarction, viral infections, activation of adrenergic receptors and pulmonary hypertension. We would like to apologize for not always using the original references due to space and word limitations.

Heart Hemostasis

TF is constitutively expressed by cardiomyocytes and fibroblasts in the heart. We and others have shown that heart hemostasis is severely compromised in mice expressing very low levels of TF (17, 18). These low TF mice uniformly demonstrate hemosiderin deposition and fibrosis in their hearts by 3 months of age. A hemostatic defect was first observed in sub-epicardial and perivascular regions of the heart and over time spread throughout the whole heart (17). Mice expressing low levels of murine FVII exhibited a similar pattern of hemosiderin deposition and fibrosis in their hearts (17, 19). Furthermore, mice with a selective deletion of TF in cardiomyocytes exhibited only mild hemostatic defect under normal conditions but a dramatic impairment of hemostasis after treatment with isoproterenol (20). Importantly, heart hemostasis was restored in low TF mice by overexpression of TF in cardiomyocytes (20). These data strongly suggest that cardiomyocyte TF is essential to maintain heart hemostasis.

It has been proposed that in addition to the important role in heart hemostasis, TF may also have non-hemostatic functions in the heart. For example, the fetal heart expresses much higher TF levels compared to the adult heart (21). This led to the hypothesis that myocardial TF may serve as a morphogenic factor in the developing heart (22). Within cardiomyocytes, TF is found in the intercalated discs and z bands, and co-localized with structural proteins such as desmin and vinculin (23–25). Additionally, the cytoplasmic domain of TF has been demonstrated to interact with the cytoskeleton via filamin A (26, 27) and binding of FVII/FVIIa to TF mediates direct changes of the cytoskeleton (28). In addition, it was shown that TF mediates $\beta 1$ integrin signaling via both its extracellular and intracellular domains independently of its procoagulant activity (29). These data lead to the hypothesis that TF may contribute to the structural integrity of myocardium. We tested this hypothesis, in part, by examining hearts of mice lacking only the cytoplasmic domain of murine TF. We found no evidence of hemostatic or structural defects in the heart of these mice at 6 months of age under normal conditions (17). However, we cannot exclude that under pathologic conditions the cytoplasmic domain of TF may play a role in maintaining structural integrity.

Myocardial infarction

Myocardial infarction caused by the thrombotic occlusion of coronary vessels is a leading cause of death in the western world (30). Restoration of circulation not only provides oxygen and nutrients to ischemic tissue but also further injures the myocardial tissue by initiating an inflammatory response. The molecular and cellular mechanisms of ischemia/reperfusion (I/R) injury is very complex and has been described elsewhere (31). Myocardial infarction leads to the loss of viable myocardium; as a compensatory response the initial infarct is replaced with collagen rich fibrotic tissue and neighboring cardiomyocytes undergo hypertrophic growth. However, over time the extensive remodeling weakens heart function and leads to heart failure (30).

I/R injury increases TF expression in the heart (32, 33). The inhibition of TF with either active site-inhibited FVIIa, anti-TF antibody or annexin V-Kunitz inhibitor fusion protein (ANV-6L15) reduces infarct size in animal models of heart I/R injury (33–36). We and other showed that inhibition of FXa (37) or thrombin (33, 38) as well as fibrinogen deficiency (39) attenuates myocardial infarction in animal models. In addition, fibrin degradation fragment E1 exacerbates myocardial infarction by facilitating leukocyte infiltration into myocardium (39, 40). Therefore fibrin generation is one mechanism by which the TF-thrombin pathway contributes to myocardial infarction.

The contribution of thrombin-mediated activation of PAR-1 to myocardial infarction is less clear. We found that PAR-1 deficiency has no effect on the infarct size after cardiac I/R injury (38). In contrast, Strande and colleagues reported that the PAR-1 antagonist SCH 79797 reduces infarct size during myocardial I/R injury in rats (41). The possible off-target effect of SCH 79797 or PAR-4 mediated compensation for PAR-1 deficiency may explain these different findings (42, 43). Interestingly, we found that PAR-1 deficient mice had reduced dilatation of the left ventricle and better preservation of heart function two weeks after I/R injury. *In vitro* studies demonstrated that activation of PAR-1 with either thrombin or agonist peptide leads to a series of molecular and morphological changes that lead to

hypertrophic growth of cardiomyocytes (44, 45). Consistent with these observations, we showed that cardiomyocyte-specific overexpression of PAR-1 induced eccentric heart hypertrophy and decreased heart function (38). Importantly, cardiomyocyte-specific deletion of TF reduced eccentric hypertrophy in PAR-1 transgenic mice, indicating that activation of PAR-1 on cardiomyocytes was mediated by local TF-dependent thrombin generation (38). Interestingly, Loubele and colleagues demonstrated that protective effects of exogenous administration of activated protein C on cardiac I/R injury required PAR-1 (46) suggesting PAR-1 mediated responses may be ligand specific.

The protective effect of TF:FVIIa complex inhibition on I/R-induced myocardial infarction could be also mediated via attenuation of PAR-2 signaling. We showed that PAR-2 deficiency reduces infarct size, oxidative stress, and expression of inflammatory cytokines caused by I/R injury (47). Furthermore, 4 weeks after I/R injury hypertrophy and dilatation of left ventricle were significantly attenuated whereas heart function was better preserved in PAR-2 deficient mice (47). However, this protection could simply be the result of smaller initial infarct size observed in PAR-2 deficient mice. Therefore in the follow up studies we investigated the “infarct independent” contribution of PAR-2 to heart remodeling. Consistent with previous observations, we demonstrated that activation of PAR-2 induced hypertrophic growth and of cultured rat neonatal cardiomyocytes (48). In addition, PAR-2 activation on mouse cardiomyocytes increased expression of the pro-fibrotic chemokine MCP-1. Furthermore, cardiomyocyte-specific overexpression of PAR-2 in mice induced heart hypertrophy, cardiac fibrosis, inflammation and heart failure (48). Finally, in a mouse model of myocardial infarction induced by permanent ligation of the left anterior descending coronary artery, PAR-2 deficiency reduced heart remodeling and improved heart function independently of its contribution to the size of the initial infarct (48). Further studies are required to determine if these effects are mediated solely by TF:FVIIa-dependent activation of PAR-2 or other PAR-2 ligands, for example mast cell tryptase (49, 50).

In contrast to our studies, several recent papers reported that activation of PAR-2 with a PAR-2 agonist peptide has a beneficial effect in *ex vivo* as well *in vivo* models of heart I/R injury (51–53). The protective mechanism involved endothelial cell-dependent vasodilation of coronary vessels (53). The similar differences between genetic deficiency and pharmacologic inhibition of the receptor have been also reported for PAR-4 (54–56). The possible explanations for these contradictory results may include so called “biased agonist” signaling (57, 58), cell type specific responses or accessibility of the inhibitors to the target cells. Importantly, a recent study indicated that commonly used PAR-2 agonist peptide SLIGRL-NH₂ facilitates PAR-2 independent effects (59). We have discussed that in detail in our recent papers (48, 56).

Viral Myocarditis

Myocarditis is defined as inflammation within the myocardium in response to different insults, such as viral infections, autoimmune reactions, toxins and adverse drug reactions. Coxsackievirus B3 (CVB3) was one of the first viruses described and investigated to cause viral myocarditis (60). Viral myocarditis can be divided in three phases. The early phase with virus replication in the heart and innate immune responses, the acute phase with

declining virus load but extensive myocardial inflammation and the late stage with virus clearance, declining myocardial inflammation and ongoing cardiac remodeling leading to dilated cardiomyopathy and heart failure. Viral infections induce TF expression and activate coagulation (61, 62). Interestingly, heart failure induced by viral myocarditis is associated with increased risk of thrombosis, demonstrated by increased incidence of ventricular fibrin deposition and presence of thrombi (63). Data by us and others suggest that the early/acute inflammatory response after infection, but not late/chronic inflammation, leads to increased TF expression and subsequent thrombosis in the heart (23, 63–65).

Thrombin mediated PAR-1 activation was linked to increased susceptibility of endothelial cells to herpes viruses infection *in vitro* (66). However, we have recently shown that PAR-1 deficiency reduces levels of interferon (IFN)- β and CXCL10 during the early phase of infection in mice, resulting in higher viral loads and increased inflammation at day 8 after CVB3 infection (67). As a consequence, pathological heart remodeling was increased in the heart of PAR-1 deficient mice infected with CVB3, as demonstrated by increased fibrosis, hypertrophy and significant reduction in heart function compared to wild type mice. Inhibition of either TF or thrombin in wild type mice also significantly increased CVB3 levels in the heart and cardiac injury, linking TF-dependent thrombin generation to PAR-1 activation (67). Our study revealed an unexpected protective role for the TF/thrombin/PAR-1 pathway during CVB3 infection-induced myocarditis in mice.

With regard to PAR-2 in myocarditis, Weithauser and collaborators observed that PAR-2 reduced toll-like receptor 3 (TLR3) mediated immune responses *in vitro* and *in vivo* during CVB3 infection (68). PAR-2 deficient mice exhibited significantly reduced CVB3 myocarditis associated with increased activation of the IFN- β pathway. The authors further showed that activation of PAR-2 in isolated cardiac fibroblasts reduced TLR3 mediated signaling, resulting in reduced IFN- β expression and STAT1 activation (68). The authors explained this observation due to direct interaction of PAR-2 with TLR3.

Collectively, these observations suggest that targeting TF/thrombin/PAR-1 pathway may impair the innate immune response to CVB3 infection whereas inhibition of PAR-2 may be a new strategy to reduce viral myocarditis induced heart remodeling. However, the PAR-2 activating protease in CVB3 myocarditis has yet to be determined. A possible candidate would be mast cell tryptase (61).

Renin-angiotensin system, hypertension and cardiac remodeling

The renin-angiotensin system (RAS) plays a key role in the development and pathophysiology of hypertension. The major consequences of hypertension are end-organ damage and cardiovascular complications including atrial fibrillation, left ventricular hypertrophy and congestive heart failure (69–71). Angiotensin II (Ang II) is the main effector of the RAS, and most of its effects are mediated by angiotensin type 1 (AT₁) receptors (69, 70). Long-term exposure to Ang II leads to development of cardiovascular remodeling, fibrosis and heart hypertrophy. The mechanism of Ang II-induced heart remodeling may involve the direct action of Ang II on target tissues or may be mediated by an Ang II-induced increase in blood pressure (69, 70). One consequence of AT₁ receptor

activation by Ang II is upregulation of TF expression. Several *in vitro* studies demonstrated that Ang II induces TF expression in smooth muscle cells, endothelial cells and monocytes (72–74). TF expression was also upregulated in hypertensive rats throughout the endothelium and media of blood vessels and blocking the AT₁ receptor with valsartan inhibited the upregulation of TF expression (75). Importantly, elevated levels of plasma TF are observed in patient with hypertension and AT₁ receptor blockage significantly reduced TF activity (76). These data indicate that upregulation of TF expression during hypertension is mediated via the AT₁ receptor and leads to systemic activation of coagulation cascade. Consistent with these observations our preliminary data demonstrate increased levels of thrombin-antithrombin (TAT) complexes in the circulation of Ang II treated mice (Antoniak and Pawlinski, unpublished data). In addition, in mice subjected to chronic Ang II infusion, PAR-1 deficiency reduced the expression of pro-fibrotic genes and attenuated collagen deposition in the hearts and aortas. These effects were independent from changes in blood pressure. The reduced pro-fibrotic phenotype in PAR-1 deficient mice resulted in a better preservation of heart function compared to wild type controls (Antoniak and Pawlinski, unpublished data). In addition, PAR-1 expression in the murine lungs is associated with angiotensin-converting enzyme activity (77).

McGuire and coworkers found that PAR-2 deficiency had no effect on diastolic pressures and only moderately reduced systolic pressures in hypertension induced by a high salt diet (78). In a more recent study the group showed that chronic PAR-2 stimulation in mice causes endothelial and vascular smooth muscle cell dysfunction (79). Interestingly, this effect was partly due to PAR-2 desensitization. PAR-2 activation affects small arteries independently of NO whereas the PAR-2 dependent vasodilation in larger arteries and the aorta is entirely NO-dependent (79). PAR-2 mediated vasodilation of arteries was protective against the negative effects of Ang II-induced dysfunction. The authors hypothesized that Ang II-induced cyclooxygenases increased the sensitivity of the arteries to the PAR-2 agonist (80). However, the effects of PAR-2 activation were very subtle, suggesting that PAR-2 is not a major regulator of blood pressure and vascular tone *in vivo*.

Activation of β -adrenergic receptors with isoproterenol also causes hypertension, activation of coagulation and induces pathologic heart remodeling (81). Sato et al. observed that PAR-2 activation has no effect on isoproterenol stimulation of human airway epithelial cells (82). Further, mast cell tryptase contributed to the cardiac fibrosis but did not influence blood pressure or ventricular dilatation in hypertensive rats (83). Isoproterenol treatment of rat cardiomyocytes and cardiac fibroblasts increased PAR-1 activation that was dependent on MMP-13 activity. MMP-13 inhibition significantly attenuated isoproterenol-induced PAR-1 activation and reduced PAR-1 dependent heart dysfunction (9). In addition, cardiac cells express MMP-1 and its activity is increased after chronic isoproterenol infusion in the rat heart *in vivo* (84). This suggests that not only MMP-13 but also MMP-1 may lead to PAR-1 dependent cardiac pathology in chronic β -adrenergic receptor stimulation.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a complex cardiovascular disease with multiple etiologies. Elevated levels of circulating TF-positive microparticles (85) and increased TF

expression have been observed in the lungs of patients with PAH (86, 87) as well as in rat and mouse models of the disease (88–90). Despite the prevalence of in situ thrombi in the lungs, biomarkers of coagulation are only modestly elevated in the plasma of PAH patients (91).

Pathologic right ventricle (RV) remodeling occurs downstream of increased pulmonary vascular resistance caused by thrombosis, vasoconstriction, and remodeling of the pulmonary vessel wall (92). In PAH, pulmonary vascular remodeling is caused by endothelial cell proliferation and dysfunction, SMC proliferation and migration, and fibroblast proliferation and differentiation into SMC (93). The presence of thrombi in the lungs might also contribute to the vasoconstriction and increased pulmonary vascular resistance (86). The increased pulmonary artery pressure and workload on the heart causes patients to develop progressive RV hypertrophy and eventual RV failure. A direct role for TF in PAH has yet to be established, however several animal models have implicated the TF-dependent pathways in pulmonary vascular remodeling, vasoconstriction, and RV hypertrophy. The emerging hypothesis is that FXa and thrombin may exert these effects by activating PAR-2 and PAR-1 on pulmonary vascular cells.

Overexpression of tissue factor pathway inhibitor on pulmonary SMCs attenuated pulmonary vascular remodeling, RV hypertrophy and heart function in the mouse model of PAH induced by chronic hypoxia (94). FXa inhibition with rivaroxaban significantly reduced RV hypertrophy and function in the rat monocrotaline model of PAH (95). Interestingly, FXa inhibition had no effect on pulmonary artery muscularization (95). FXa can activate PAR-2, the expression of which is increased in the pulmonary arteries of patients with PAH and in rodent models (96). A recent study by Kwapiszewska and colleagues demonstrated that PAR-2 deficient mice were protected from chronic hypoxia-mediated remodeling of the pulmonary artery and RV hypertrophy and dysfunction (96). In vitro studies demonstrated that proliferation of pulmonary artery SMCs was mediated by mast cell tryptase-dependent PAR-2 activation, suggesting that mast cell tryptase may be another ligand activating PAR-2 during PAH (96).

Vasoconstriction that results from dysregulation of the nitric oxide-cGMP pathway is implicated in the pathogenesis of PAH (97). *In vitro* experiments using human pulmonary artery endothelial cells revealed that thrombin treatment dose-dependently decreased expression of endothelial nitric oxide synthase, guanyl cyclase and phosphodiesterase 5. The effects of thrombin on the nitric oxide-cGMP pathway were PAR-1 dependent (98). Moreover, the direct thrombin inhibitor dabigatran prevented RV remodeling and hypertrophy in monocrotaline-treated rats (98). These data suggest that thrombin-dependent activation of PAR-1 might contribute to PAH by downregulating nitric oxide-cGMP pathway and causing vasoconstriction. Thrombin might also contribute to excessive vasoconstriction in PAH by directly activating vascular smooth muscle cell contraction via PAR-1. In endothelial cell-denuded porcine pulmonary arteries, thrombin increased intracellular calcium and caused phosphorylation of myosin light chain 20 (MLC20), which lead to a sustained contraction of the vessel that was attenuated by PAR-1 antagonism (99, 100). The use of PAR-1 agonist peptide had similar effects as thrombin (99, 100). PAR-1 and PAR-2 can also be activated by the TF:FVIIa:FXa ternary complex on endothelial cells

(4) but a direct link between ternary complex-dependent PAR activation and PAH has yet to be established.

Summary

TF plays an important role in the heart during both physiologic and pathologic conditions. Under normal conditions, TF is required to maintain heart hemostasis and protect this vital organ from bleeding. Furthermore, TF-thrombin-PAR-1 pathway also plays an important role in protecting the heart against pathologic remodeling induced by viral myocarditis. The effects are mediated by enhancing anti-viral innate immune response at the initial phase of infection, reducing the viral load in the heart and minimizing an inflammation-mediated damage of myocardial tissue. In contrast, PAR-2 signaling seems to enhance viral myocarditis and heart damage (Figure 1).

During myocardial infarction-induced heart remodeling, TF dependent activation of coagulation and activation of PARs contribute to both initial size of the infarct as well as cellular process associated with pathologic heart remodeling including hypertrophic growth of cardiomyocytes and fibrosis (Figure 1).

TF-dependent activation of coagulation may also contribute to the heart remodeling associated with hypertension. Activation of PAR-1 and PAR-2 promote fibrosis, loss of heart function, and vasodilation caused by Ang II and isoproterenol. Similarly, PAR-1 and PAR-2 contribute to PAH via endothelial and smooth muscle cell-mediated vasoconstriction of pulmonary arteries. More studies are required to investigate if coagulation proteases and PARs can directly contribute to the remodeling of RV during PAH via affecting cardiomyocytes and cardiac fibroblast responses (Figure 2).

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Figure 1. Role of TF and coagulation proteases in the heart hemostasis and heart remodeling after the myocardial infarction and myocarditis

Abbreviations: FIIa – thrombin, VP – vascular permeability, P1 – PAR-1, P2 – PAR2, EM – extracellular matrix

Figure 2. Contribution of TF and coagulation protease to the heart remodeling induced by systemic and pulmonary hypertension

Abbreviations: Iso – Isoproterenol, FIIa – thrombin, VP – vascular permeability, P1 – PAR-1, P2 – PAR2, EM – extracellular matrix