REVIEW

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Pathophysiological actions of protease activated receptors (PARs)

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Serine proteases such as thrombin, mast cell tryptase, trypsin, or cathepsin G, for example, are highly active mediators with diverse biological activities. So far, proteases have been considered to act primarily as degradative enzymes in the extracellular space. However, their biological actions in tissues and cells suggest important roles as a part of the body's hormonal communication system during inflammation and immune response. These effects can be attributed to the activation of a new subfamily of G protein-coupled receptors, termed protease-activated receptors (PARs). Four members of the PAR family have been cloned so far. Thus, certain proteases act as signaling molecules that specifically regulate cells by activating PARs. After stimulation, PARs couple to various G proteins and activate signal transduction pathways resulting in the rapid transcription of genes that are involved in inflammation. For example, PARs are widely expressed by cells involved in immune responses and inflammation, regulate endothelial-leukocyte interactions, and modulate the secretion of inflammatory mediators or neuropeptides. Together, the PAR family necessitates a paradigm shift in thinking about hormone action, to include proteases as key modulators of biological function. Novel compounds that can modulate PAR function may be potent candidates for the treatment of inflammatory or immune diseases.

1. Introduction

PARs belong to a new subfamily of G protein coupled receptors (GPCRs) with seven transmembrane domains activated via proteolytic cleavage by serine proteases (Derry 1998; Coughlin 2000; Macfarlane 2001; Hollenberg 2002). PAR_1, PAR_3, and PAR_4 are targets for thrombin, trypsin, or cathepsin G (Vu 1991; Ishihara 1997; Kahn 1997; Xu 1998). In contrast, PAR_2 is resistant to thrombin, but can be activated by trypsin, mast cell tryptase, factor Xa, acrosin, gingipain, and neuronal serine proteases (Nystedt 1995a, b; Molino 1997; Lourbakos 1998; Steinhoff 1999; Camerer 2000; Smith 2000; Lourbakos 2001). Interestingly, PARs are activated by a unique mechanism: proteases activate PARs by proteolytic cleavage within the extracellular N-terminus of their receptors, thereby exposing a novel "cryptic" receptor-activating N-terminal sequence that, remaining tethered, binds to and activates the receptor within the same receptor (Vu 1991; Nystedt 1995a, b). Specific residues (about six amino acids) within this tethered ligand domain are believed to interact with extracellular loop 2 and other domains of the cleaved receptor (Verrall 1997), resulting in activation. This intramolecular activation process is followed by coupling to G proteins and the triggering of a variety of downstream signal transduction pathways (Dery 1998; Macfarlane 2001; Hollenberg 2002). Thus, PARs are not activated like "classical" receptors because the specific receptor-activating ligand is part of the receptor, whereas the circulating agonist is a relatively nonspecific serine protease that does not behave like a traditional hormonal regulator akin to insulin.

Taken together, data obtained using the enzyme activators themselves (trypsin, thrombin), and using PAR gene-deficient mice provide compelling evidence that PARs play a critical role in the regulation of various physiological and pathophysiological functions in mammals, including humans. This review focuses on the biology and signaling properties of PARs in various mammalian tissues and highlights the current knowledge about the role of PARs.

Protease signaling in tissues depends on the generation and release of proteases, availability of cofactors, presence of protease inhibitors, and activation and inactivation of PARs. Many proteases that activate PARs are produced during tissue damage, and PARs make important contributions to tissue responses to injury, including hemostasis, repair, cell survival, inflammation, and pain. Drugs that mimic or interfere with these processes are attractive therapies: selective agonists of PARs may facilitate healing, repair, and protection, whereas protease inhibitors and PAR antagonists can impede exacerbated inflammation and pain. Major future challenges will be to understand the

role of proteases and PARs in physiological control mechanisms and human diseases and to develop selective agonists and antagonists that can be used to probe function and treat disease.

2. PARs and wound healing

Several findings suggest that PAR_1 could play a role in wound healing. Activation of PAR_1 stimulates proliferation of keratinocytes (Thomas 1977; Corvera 1997) and fibroblasts (Noorbakhsh 2003) and also induces angiogenesis (Seeliger 2003). Plasmin, thrombin, and PAR_1 AP (protease activated receptor 1 activated protein) induce expression of cysteine-rich angiogenic protein Cyr-61, a growth factor-like gene implicated in angiogenesis and wound healing, in fibroblasts from wild type but not PAR_1-deficient mice (Minami 2004). Moreover, the topical application of thrombin and PAR_1 AP to incisional wounds in rats improves wound strength and increases angiogenesis, thereby promoting wound healing (Andrede-Gorden 1999).

3. PARs and cardiovascular disease

The inappropriate aggregation of platelets makes an important contribution to occlusive vascular disorders such as stroke, angina, and myocardial infarction, where accumulation of atherosclerotic plaques promotes platelet-mediated thrombus formation. Thrombin is a major mediator of platelet aggregation and fibrin deposition, and thrombin inhibitors are useful antithrombotic agents. One drawback of such inhibitors is their disruption of the normal hemostatic mechanism, and a selective suppression of the effects of thrombin on platelets may be advantageous. A difficulty of studying the role of PARs in thrombus formation is that platelets express several thrombin receptors, which vary among species. However, despite the redundancy and interspecies differences, recent observations in cynomologus monkeys, whose platelets, like those of humans, express PAR_1 and PAR_4, suggest that PAR_1 antagonists may be useful therapeutic agents in humans (Carmeliet 2001). Thus the PAR_1 antagonist RWJ-58259 markedly inhibits thrombus formation and vessel occlusion in a model of electrolytic injury of the carotid artery in cynomologus monkeys. Despite the fact that platelets from these animals possess the dual PAR_1/PAR_4 system, antagonism of a single receptor is effective, raising the possibility that antagonism of a PAR_1 may be of use for treatment of thrombosis disorders in humans.

PAR antagonists may also be of interest in treating vascular injury. In addition to its role in thrombus formation, thrombin is also implicated in restenosis of the blood vessels after vascular injury. Thus a PAR_1 blocking antibody or a PAR_1 antagonist attenuates thickening of the neointima of the rat carotid artery, initiated by damage to the endothelium by balloon angioplasty (Muehlenweg 2000). Similarly, vascular injury is attenuated in PAR_1-deficient mice (Kaufmann 1999). The protective effect of PAR_1 antagonism or deletion occurs even though rat and mouse platelets do not express PAR_1 and thus exhibit normal aggregation in the absence of functional PAR_1. These effects of thrombin on restenosis are therefore dependent on the proliferative or proinflammatory effects of PAR_1 on vascular smooth muscle.

PAR_2 may contribute to injury that follows ischaemia and reperfusion of tissues (Ohmori 1999). Ischaemia and reperfusion of the heart induces injury that is characterized by generalized inflammation and necrosis. PAR_2 is up regulated in a model of coronary ischaemia and reperfusion injury in rats, and administration of a PAR_2 AP markedly protects the heart from injury. PAR_2 activation also improves efficiency of ischaemic preconditioning and reduces cardiac inflammation in the rat heart (Zhang 1995).

4. PARs and cancer

The microenvironment of tumors is replete with proteases that can activate PARs, and tumor cells themselves express PARs. Malignant cells secrete thrombin and trypsin, which can affect proliferation and mediate metastatic processes such as cellular invasion, extracellular matrix degradation, angiogenesis, and tissue remodeling.

PAR_1 and PAR_2 are expressed by a wide range of tumor cells (Schultheiss 1997; Steinhoff 1999; Naldini 2000; Covic 2000; Hirano 2002). In breast tumor tissues, PAR_1 and PAR_2 are expressed in the tumor cells, mast cells, macrophages, endothelial cells, and vascular smooth muscle cells of the metastatic tumor microenvironment (Hirano 2002). In particular, there is an up-regulation of PAR_1 and PAR_2 in proliferating stromal fibroblasts surrounding the carcinoma cells. In pulmonary tumor alveolar walls, the expression of PAR_1 and PAR_2 mRNA is increased by 10- and 16-fold, respectively, compared with normal alveolar tissues (Suidan 1996). Expression of trypsin is also detected in this tumor tissue. Exposure of certain tumor cells to thrombin and PAR_1 AP also enhances their adhesion to platelets, fibronectin, and von Willebrand factor *in vitro* and promotes pulmonary metastasis when cells are administered to mice *in vivo* (Shapiro 2000; Wang 2003). Moreover, over expression of PAR_1 in certain tumor cells can enhance their metastatic potential in animal models. In colon cancer cell lines, activation of PAR_1 induces a marked mitogenic response, which is dependent on activation of MAP kinase ERK1/2, and also stimulate motility of wounded cells (Riewald 2002). Together, these results suggest that antagonists of PAR_1 may be useful treatments for proliferation and metastasis of certain tumors. However, PAR_1 AP has also reported to inhibit migration and invasion of breast cancer cell lines when applied as a concentration gradient in the direction of movement (Macey 1998). PAR_2 may also contribute to tumor formation and metastasis since PAR_2 AP stimulates proliferation of colon tumor cell lines (Naldini 2000).

5. PARs and blood vessels

PAR_1 can potentially regulate vascular function under both physiological as well as pathophysiological conditions (Coughlin 2000, 2001). A number of studies have revealed that thrombin and other agonists of PAR_1 can affect the vascular tone. Before the discovery of PAR_1, it was observed that thrombin could regulate vascular tone by an endothelial-dependent mechanism involving the release of nitric oxide (NO) (Muramatsu 1992). It is now recognized that this effect of thrombin is due to the activation of PAR_1. Moreover, thrombin and PAR_1 agonists can contract vascular smooth muscle cells (VSMC) by a direct effect that requires extracellular Ca^{2+}. Thus, in isolated coronary artery and aorta preparations, PAR_1 mediates relaxation (Ku 1986; Muramatsu 1992).

Recent observations support a role of thrombin and PAR_1 in regulation of normal functions (Weksler 1978; Kameda 1997; Kaplanski 1997, 1998) and atherosclerotic endothe-

lium (Nelken 1992). In normal human arteries, PAR_1 is mostly confined to the endothelium, whereas during atherogenesis, its expression is enhanced in regions of inflammation associated with macrophage influx, smooth muscle cell proliferation, and an increase in mesenchymal-like intimal cells.

These data suggest that PAR_1 regulates proliferation and accumulation of neointimal smooth muscle cells during tissue repair (Takada 1998). Vascular wall cells respond to the procoagulant factor Xa by an increase in intracellular Ca^{2+} ($[Ca^{2+}]_i$) and by assembly of this factor into prothrombinase complexes that even enhance this effect. Additionally, factor Xa stimulation of PAR_1 leads to an increased production of tissue factor, a prothrombotic agent, underlining the important role of PAR_1 for thrombosis (Mclean 2001). Together, these results point to a pivotal role of PAR_1 in vascular homeostasis and thrombosis.

PAR_1 agonists are also mitogenic, stimulating proliferation of endothelial cells (Mirza 1996; Schaeffer 1997), mediating endothelium-dependent relaxation to thrombin and trypsin in human pulmonary arteries (Hamilton 2001), and causing the release of IL-6 from human microvascular endothelial cells (HMEC) (Chi 2001). Because PAR_1 up-regulates α-1(I)-procollagen synthesis in VSMC, one may speculate that PAR_1 plays a role in vascular wound healing (Dabbagh 1998).

6. PARs and platelets

Activation of platelets by thrombin or activating proteins (APs) specific for PAR_1 is characterized by calcium influx; cytoskeletal reorganization; platelet aggregation; degranulation (Vu 1991; Hung 1992; Vassallo 1992); thromboxane production (Ma 2001); mobilization of the adhesion molecule P-selectin and the CD40 ligand to the platelet surface (Henn 1998); stimulation of serotonin and epinephrine release (Smith 1986); enhanced expression of CD62, PDGF (AB) and PDGF (BB) (Graff 2002); and exposure of anionic phospholipids (phosphatidylserine, phosphatidylethanolamine) that support blood clotting (Anderson 1999).

7. PARs and immune cells

It is well documented that PARs influence monocyte motility and chemotaxis, modulate pleiotropic cytokine responses, contribute to mononuclear cell proliferation, and induce apoptosis in various immune cells (Naldini 1998; Szaba 2002). Recently, it has been shown that PAR_1 is capable of stimulating elastase secretion from macrophages (Raza 2000). Moreover, functional thrombin receptors are expressed on human T lymphoblastoid cells (Tordai 1993).

PAR_1 modulates chemotaxis in inflammatory cells. Besides IL-8 secretion (Kaplanski 1997), thrombin induces production of monocyte chemoattractant protein-1 (MCP-1) in monocytes, probably via PAR_1 (Colotta 1994).

Furthermore, PAR_1 is capable of inducing IL-1 as well as IL-6 production in monocytes (Naldini 2000). These cytokines are known to be proangiogenic, implicating PAR_1 in angiogenesis and tissue repair.

8. PARs and nervous system

Recent studies are in favor of an important role of thrombin and PARs in the brain under normal and pathophysiological conditions such as trauma, inflammation, or tumorigenesis (Festoff 1996; Grand 1996). Under pathophysiological conditions, i.e., during breakdown of the blood-brain barrier, circulating thrombin in the bloodstream may enter the central nervous system (CNS), leading to activation of PAR_1 or PAR_4. In human brain, PAR_1 is expressed in neurons and astrocytes (Striggow 2001).

Moreover, PAR_1 agonists induce up-regulation of inducible NO synthase (iNOS) in these cells and promote neuronal survival after ischaemia (Striggow 2000) or brain trauma (Xi 1999). PAR_1 also protects astrocytes and neurons from apoptosis induced by hypoglycemia and oxidative stress during inflammation (Vaughan 1995). In contrast, thrombin may also exert cytotoxic effects on neurons and induce neurite retraction (Gurwitz 1988; Suidan 1992), which may be at least in part due to PAR_1. Functional studies further revealed that PAR_1 agonists cause retraction of neurites by neuroblastoma cells and induce Ca^{2+} mobilization by hippocampal neurons (Striggow 2000).

In astrocytes, thrombin stimulates aggregation, morphological changes, and proliferation via PAR_1 and induces intracellular caspase pathways leading to apoptosis in a cultured motor neuron cell line (NSC19) (Donovan 1997; Smirnova 1998). Both PAR_1 and PAR_2 stimulate enhanced proliferation of astrocytes (Wang 2002). It is now well accepted that NMDA receptor over activation plays a role in expanding the region of neuronal injury after experimental ischaemia (Whetsell 1996; Dirnagl 1999; Lee 1999). Thus, it is possible that thrombin entry into the brain during hemorrhagic stroke and penetrating head wound may contribute to neuronal damage through potentiation of NMDA receptor function.

The recent demonstration that thrombin entry into the brain can evoke seizures (Lee 1997) together with the thrombin-mediated potentiation of NMDA receptor responses described here suggests that thrombin together with heme-derived iron (Willmore 1978) could be a contributing factor to post-traumatic seizures. Data showing thrombin potentiation of NMDA receptor function plus plasmin-induced reductions in GABAergic transmission (Mizutani 1997) are consistent with the idea that serine proteases can control neuronal excitability (Luthi 1997).

Taken together, these data clearly indicate a functional role of PAR_1 during inflammation and injury in the CNS. Thus, future studies taking into account all CNS-derived PARs, their proteases, and protease inhibitors are necessary to fully explore the role of PARs in the brain.

9. PARs and interstitial fibrosis

An increasing body of evidence suggests that proteases may play a key role in the pathogenesis of tissue fibrosis. Several of these enzymes, including metalloproteases, collagenases, gelatinases, plasmin, and plasminogen activators (PA), can directly catalyze the degradation of extracellular matrix (ECM) components (Kotani 1995; Norman 1996; Heidland 1997). Thus, an imbalance between these proteases and their specific inhibitors may promote ECM deposition. In the large family of protease inhibitors, plasminogen activator inhibitor-1 (PAI-1) is the most heavily involved in tissue fibrosis (Rerolle 2000). PAI-1 gene expression is strikingly induced by TGF-β and may play a key role in the powerful profibrotic action of this growth factor. Interestingly, an increased expression of this inhibitor of plasminogen activation has been demonstrated in several progressive renal diseases, including IgA nephropathy (IgAN) (Yamamoto 1996, Wang 1997, Grandaliano 2000).

Recently, different investigators reported that PAR-2 might also represent the cell-surface receptor for activated coagulation factor X (FXa) (Bono 2000; Kawabata 2001). Coagulation cascade activation is a prominent feature of both acute and chronic inflammatory processes. Several reports support the hypothesis of a key role for coagulation factors in the pathogenesis of tissue fibrosis, particularly within the kidney (Grandaliano 2000). Interestingly, earlier works suggested that FXa, the enzymatically active constituent of the prothrombinase complex, triggers complex pathways involved in the regulation of cellular growth (Ko 1996; Camerer 1999). Binding of FXa to vascular endothelial cells induces the release of PDGF-like molecules, thus providing a paracrine mechanism for cell proliferation (Gajdusek 1986). Moreover, we have recently demonstrated that FXa directly stimulates proliferation of human mesengial cells, an event that has been shown to precede the development of glomerulosclerosis (Monno 2001).
However, recent observations would support the hypothesis that coagulation factor Xa (FXa) may induce cell activation primarily through the interaction with PAR-2 (Camerer 2002; Koo 2002). It has been observed for the first time that activation of PAR-2 by FXa as well as trypsin could induce a significant increase in PAI-1 gene expression. An increasing body of evidence suggests that inhibition of plasminogen activator by plasminogen activator inhibitor-1 (PAI-1) may play a central role not only in preserving fibrin deposits, but also in the development of interstitial fibrosis and glomerular sclerosis (Rerolle 2000). Indeed, plasmin as well as plasminogen activators can induce extracellular matrix (ECM) degradation directly or through the activation of metalloproteases. Thus, an increased PAI-1 expression reducing the turnover of ECM components may cause their abnormal accumulation, leading to tissue fibrosis. Disruption of the PAI-1 gene was shown to decrease the accumulation of fibrin in the lungs of experimental animals and to prevent most of the pulmonary fibrosis (Eitzmen 1996).
Several groups of investigators reported the ability of thrombin to cause an increased PAI-1 gene expression in a variety of cell lines, potentially reducing the activity of the fibrinolytic system (Villamediana 1990; He 1991). However, thrombin was reported to increase also the expression of plasminogen activators (Wojta 1993; Hayakawa 1995). Indeed, it has been observed that thrombin induced urinary plasminogen activator (u-PA) gene expression in proximal tubular cells, respectively, confirming previous observations. On the other hand, it was demonstrated for the first time that PAR-2 activation caused a marked increase in PAI-1 mRNA levels without modifying the expression level of u-PA. Thus, it is conceivable that the overall effect might be an inhibition of fibrinolysis as well as of the physiologic ECM turnover significantly stronger than the one induced by thrombin. In addition, the different expression profile induced by thrombin and FXa rules out the possibility, recently suggested, that FXa may interact and cause the activation of PAR-1, the main known thrombin receptor. Indeed, FXa effects were reproduced by direct PAR-2 activation by its specific agonist peptide
Finally, a significant increase in TGF-β gene and protein expression in proximal tubular cells exposed to PAR-2 agonists has been reported. Because TGF-β is the well-established mediator of interstitial fibrosis, observation strongly supports the hypothesis that activation of PAR-2 may play a pathogenic role in the progression of renal damage in IgAN. Interestingly, this powerful profibrotic factor can induce PAI-1 gene expression in several cell lines (Rerolle 2000). However, PAI-1 gene expression induced by PAR-2 activation in tubular cells does not depend on the autocrine effect of TGF-β. Indeed, the time courses for PAI-1 and TGF-β gene expression do not differ significantly, suggesting that newly synthesized TGF-β cannot play a significant role in the PAI-1 gene expression induced by PAR-2 activation. In addition, trypsin-induced PAI-1 gene expression was not inhibited by preincubation with a specific neutralizing anti-TGF-β antibody.
In conclusion, we can suggest that PAR-2 expressed by renal resident cells and activated either by mast cell tryptase or by FXa may induce an increased ECM deposition modifying the PAI-1/PA balance and inducing TGF-β expression. These molecular mechanisms may underlie interstitial fibrosis and renal damage progression in IgAN.

10. PARs and inflammation

Mast cells release tryptase as part of an inflammatory response and PAR2 is up regulated by several inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), PAR2 has been suggested to participate in inflammatory responses (Nystedt 1996).
PAR2 is expressed in vascular endothelial cells, where it mediates proliferation (Mirza 1997) and nitric oxide (NO) release and in vascular smooth muscle cells (Saiffedine 1996), where it appears to induce proliferation (Bono 1997). Moreover, the accumulation of mast cells in human atherosclerotic lesions (Kaartinen 1994; Jeziorska 1997) may activate these vascular PAR2 receptors, suggesting a potential role for this receptor in vascular injury and inflammatory responses.

11. PARs and blood pressure

Studies in rats (Hwa 1996; Emilsson 1997) and mice (Cheung 1998) have shown that activation of PAR2 decreases arterial pressure, presumably as a result of arterial vasodilatation. This *in vivo* response is similar to that caused by PAR1 activation *in vivo*. However, the PAR1 response is more complex, consisting of an initial arterial pressure decrease followed by an arterial pressure increase.
Using mouse strains deficient in PAR1 or PAR2, it has been found that PAR2 activation results exclusively in hypotension without consistent changes in heart rate. The hypotension is presumably mediated by vasodilatation. In contrast, PAR1 activation induces both an initial hypotensive response and heart rate decrease followed by hypertension. These changes in arterial pressure reflect both vasodilatation and vasoconstriction. Furthermore, the accentuated PAR1 response in PAR2 deficient mice suggests possible compensatory changes in PAR1 expression or intracellular signaling, or other changes downstream from PAR1 receptor activation. It suggests that PARs play a significant role in regulating blood pressure.

12. PARs and respiratory system

It has been demonstrated that both thrombin and trypsin induced both time and concentration dependent cytokine release. Exposure of cells to increasing concentrations of peptidases resulted in diminished cytokine release, suggests susceptibility of individual cytokines to proteolysis (Ruef 1993; King 1998). Both thrombin and the trypsin related mast cell peptidase, tryptase, have been shown to

be elevated in sputum from asthmatic patients compared with controls and, in the case of tryptase, enzyme concentration correlated with disease severity (Gabazza 1999; Louis 2000). Similarly, protease inhibitors have been shown to modulate bronchial activity, suggests that proteases *per se* are important in the pathogenesis of this disease (Forteza 2001).

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