

## Acute Pancreatitis: Proteinase-Activated Receptor-2 as Dr. Jekyll and Mr. Hyde

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### Summary

„Proteinase-activated“ receptor-2 (PAR-2) is a G protein-coupled transmembrane receptor with seven transmembrane domains activated by trypsin. It has been shown in the pancreatic tissue that PAR-2 is involved in duct/acinary cells secretion, arterial tonus regulation and capillary liquid content turnover under physiological conditions. These above mentioned structures play an important role during the development of acute pancreatitis and are profoundly influenced by a high concentration of trypsin enzyme after its secretion into the interstitial tissue from the basolateral aspect of acinar cells. Among the other factors, it is the increase of interstitial trypsin concentration followed rapidly by PAR-2 action on pancreatic vascular smooth muscle cells that initiates ischemic changes in pancreatic parenchyma and that finally leads to necrosis of the pancreas. Consequent reperfusion perpetuates changes leading to the acute pancreatitis development. On the contrary, PAR-2 action on both exocrine and duct structures seems to play locally a protective role during acute pancreatitis development. Moreover, PAR-2 action is not confined to the pancreas but it contributes to the systemic vascular endothelium and immune cell activation that triggers the systemic inflammatory response syndrome (SIRS) contributing to an early high mortality rate in severe disease.

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### Key words

PAR-2 • Acute pancreatitis • Trypsin

### Acute pancreatitis

Depending on the severity, cytologic changes ranging from apoptosis (Bhatia 2004) to necrosis of parenchyma and/or fatty tissue caused by digestive enzymes and subsequent local disturbances of blood supply are the major signs of severe “acute pancreatitis”.

Grossly, edema, focal necrosis, and hemorrhage are observed in the fully developed disease in the pancreatic region during surgery or autopsy. Microscopically, there is necrosis of the parenchyma and fatty tissue of the pancreas visible together with the remnants of necrotic fatty cells and a pale eosinophilic (light pink) material in fatty tissue. In these foci, fatty acid crystals and

hematoidin pigment may appear as a sign of hemorrhage. Necrosis of glandular parenchyma is at first characterized as coagulation necrosis circumscribed by the edge of polynuclear leukocytes (Thomas 1989). Nevertheless, the disease is not confined to the pancreas alone but is always accompanied with pulmonary, renal, cardiovascular, central nervous and coagulation system injury potentially resulting in a multiorgan dysfunction syndrome (MODS) with a high mortality rate.

It is known from experimental studies in animal models of acute pancreatitis that axial trans-Golgi transport of proenzymes into the acinary lumen fails and basolateral secretion into the interstitium of pancreatic gland increases (Rattner 1996). This failure can be induced by obstruction (bile stones, spasm of papilla Vateri, etc.), toxic substances (alcohol) or by ischemia (vasospasm, shock, severe atherosclerosis). Morphologically, this axial transport failure appears as dilatation of the Golgi complex (Cook *et al.* 1996). The extent of organ damage depends on the activated enzymes in the interstitium of the gland. On the other hand, the drainage of the region mediated by lymphatic vessels is important in the development of the disease. In the organ as a whole, lymphatic drainage depends on the local blood circulation, status of the vascular barrier and capillary turnover including the quality of lymphatic vessels.

In the past, intracellular premature activation of trypsin protease leading to acinary cell necrosis was discussed as a causative agent of acute pancreatitis, however, this theory failed to explain coagulation necrosis of cells related much more to the organ ischemic injury.  $\alpha 1$  anti-trypsin deficiency was suspected mainly as a cause of chronic pancreatitis and a link to the acute disease can be found in the literature (Novis *et al.* 1975). However, other studies have not proved any correlation between pancreatitis and  $\alpha 1$  anti-trypsin deficiency (Braxel *et al.* 1982, Witt *et al.* 2002). The mast cell activation could also be involved in the initiation of AP and the early phase of AP-induced MODS, but the mechanisms seem to be complex and remain still to be elucidated (Dib *et al.* 2002). Apoptotic cell death together with caspase-cascade activation and cytochrome c release from mitochondria, related to mild or moderate pancreatitis, is also currently discussed (Bhatia 2004, Gukovskaya and Pandol 2004). Nevertheless, ischemic changes by themselves do not result in AP, but consequent reperfusion of an organ accompanied with free radical release is necessary for inducing acute

pancreatitis.

The following systemic inflammatory responses are caused by inflammatory mediators (IL-1, IL-4, IL-6, IL-8, IL-10, TNF- $\alpha$  and others) produced in damaged pancreas (McKay *et al.* 1996a,b, Scholmerich 1996). Increased density of adhesion molecules (CD54, CD62E, CD62L) on the surface of endothelial cells closes the vicious circle of inflammatory response. Production of inflammatory substances is related to oxidative stress (Sweiry and Mann 1996) but also to certain pancreatic enzymes activation in the interstitium. The role of trypsin was investigated in relation to mediation of a local and systemic mediated inflammatory response (Hartwig *et al.* 2004).

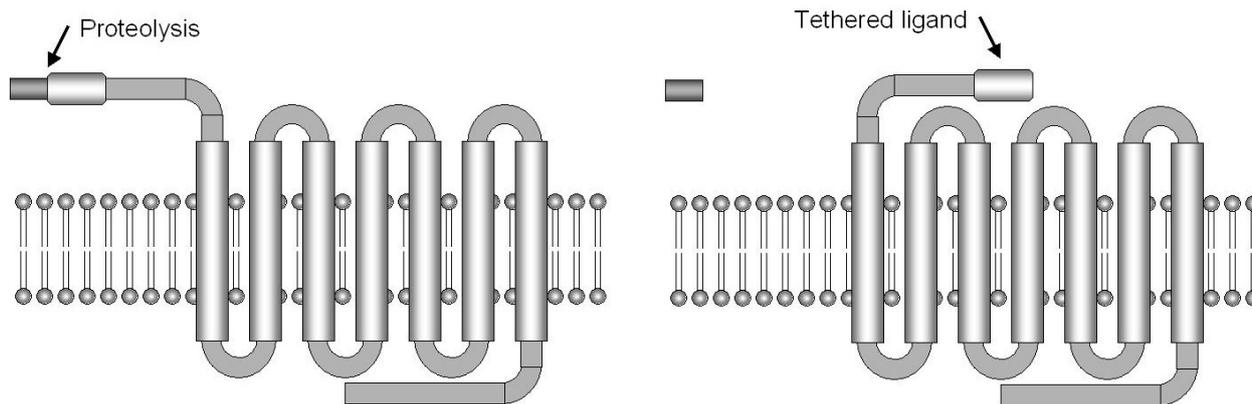
### Proteinase-activated receptor-2

It is known that one of the pancreatic enzymes, trypsin, modulates many biological processes by acting on specific proteinase-activated receptor-2 (PAR-2). PAR-2 belongs to a family of G protein-coupled receptors activated by tethered ligand sequences within the N-terminal that is made accessible after the site-specific cleavage of the protein (Bohm *et al.* 1996).

Trypsin activates PAR-2 by the mediation of a unique process based on the recognition of the receptor by the enzyme, subsequent cleavage at the specific site of NH<sub>2</sub> terminal and presentation of a new NH<sub>2</sub> terminal, which behaves as a tethered ligand (Fig. 1). This ligand interacts with the extracellular domain of the receptor molecule. Thus, PAR-2 is a receptor, whose ligand is a physical part of the receptor molecule (Dery *et al.* 1998). This receptor was previously described on normal and malignant immunocompetent cells as well as on endothelial and muscle cells of both major and minor vessels. Its presence was also immunohistochemically demonstrated on intestinal epithelial cells, epithelial cells of exocrine organs (including the pancreatic duct and acinary cells or pancreatic tumor cells) (Kaufmann *et al.* 1998), keratinocytes, fibroblasts and further cells of stomach, small intestine, colon, liver and kidney (Nystedt *et al.* 1995).

### General function of proteinase-activated receptor-2

As mentioned above, PAR-2 is expressed on variety of cells with a wide spectrum of cellular responses after activation. The function and biology of PAR-2 is



**Fig. 1.** Schematic description of PAR-2 activation. In the first phase, the specific oligopeptide is cleaved from the N-terminal part of the receptor and tethered ligand is expressed. In the second phase, the tethered ligand activates the receptor in the reaction with its 1st and 2nd extracellular domain.

reviewed in detail elsewhere (Dery *et al.* 1998, Cottrell *et al.* 2003, Steinhoff *et al.* 2005).

### How trypsin acts on pancreatic structures and the role of PAR-2 in physiological conditions and during acute pancreatitis development

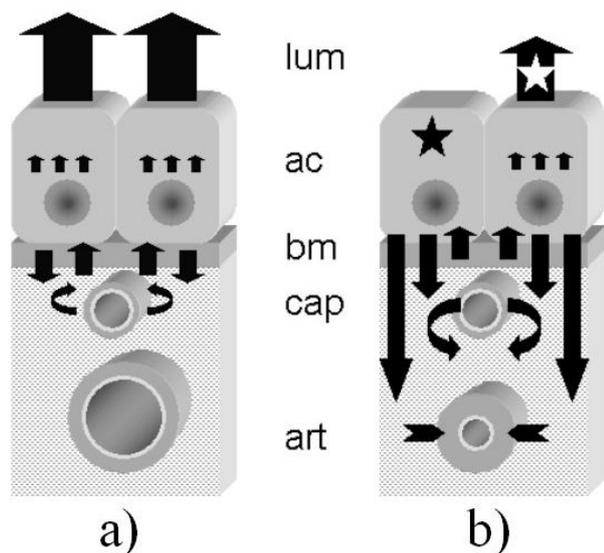
#### *Vascular effect of proteinase-activated receptor-2 activation*

PAR-2 is strongly activated during AP development (Olejár *et al.* 2001). PAR-2 presence on endothelial cells and mainly on smooth muscle vascular cells suggests that the activation of PAR-2 receptors after increased basolateral secretion of trypsin might contribute to one of the most discussed causal mechanism in acute pancreatitis development – ischemic-reperfusion injury (Toyama *et al.* 1996). Thus, PAR-2 activation on smooth muscle cells causes vasoconstriction (Moffatt and Cocks 1998). However, vasoconstriction and ischemia does not cause AP by itself, as already mentioned above. On the contrary, PAR-2 activation on endothelial cells causes pronounced vasodilatation *via* nitric oxide release (Cheung *et al.* 1998). We hypothesize that the vascular effect of PAR-2 in vessels of different diameter leading to constriction or dilatation could be the major point starting the cascade of changes resulting finally, depending on the severity, in pancreatic cell apoptosis/necrosis *via* the above mentioned ischemia-reperfusion mechanism (Fig. 2). Furthermore, PAR-2 activation primarily increases vascular permeability in general which could also be linked to edematous changes at the beginning of AP development (Kawabata *et al.* 1998). High concentrations and PAR-2 activation on vessels might be

the leading mechanism causing pancreatic ischemia during AP initiation. Attacks of pain during chronic pancreatitis exacerbation could also be related to simple organ ischemia, probably without a reperfusion mechanism leading to major necrosis as during AP. PAR-2 activation also increases IL-6 production (Chi *et al.* 2001), induces von Willebrand factor release, and serves as a mitogen for human umbilical vein endothelial cells (Mirza *et al.* 1996, Nystedt *et al.* 1996, Storck *et al.* 1996).

#### *Epithelial effect of proteinase-activated receptor-2 activation*

PAR-2 seems to confer a surprisingly protective effect on acinar cells during bile-induced cell damage and on the pancreatic ducts, acting therefore as a double-edged sword both in inducing and attenuating cellular damage (Kong *et al.* 1997). However, trypsin in the circulation of rats with taurocholate-induced severe acute pancreatitis reached levels sufficient to activate endothelial and immune cells to stimulate nitric oxide and interleukin-8 production, respectively. The activation of systemic protease-activated receptor-2 by its circulating agonists induced a hemodynamic response similar to that observed in rats with severe acute pancreatitis. Furthermore, some authors hypothesize that trypsin, acting *via* PAR-2, might regulate the severity of this disease. They found that experimental acute pancreatitis is more severe in PAR-2(-/-) than in *wild* mice and that *in vivo* activation of PAR-2, achieved by parenteral administration of the PAR-2 activating peptide SLIGRL-NH<sub>2</sub>, reduces the severity of pancreatitis. This indicates that PAR-2 exerts also a protective effect in pancreatitis development and that activation of PAR-2 ameliorates



**Fig. 2.** Schematic description of acute pancreatitis development. **a)** Physiologically, the majority of acinary cells proenzyme/enzyme production after stimulation is secreted intraluminally. These enzymes go from acini to duodenum *via ductus choledochus*. Only a small part of proenzymes/enzymes enters interstitium. Enzymes secreted basolaterally are reinternalized together with nutrients into the acinary cells. Internalisation is also regulated by PAR-2 stimulation by interstitially activated trypsin. **b)** During pathological conditions (cholelithiasis, ethanol abusus, etc.), the physiological transport of proenzymes is blocked at different levels. Basolateral secretion of enzymes is markedly enhanced over their internalisation. Pronounced stimulation of PAR-2 on capillary cells by activated trypsin causes edema formation. Activation of PAR-2 on smooth muscle cells causes marked vasoconstriction, whereas activation of PAR-2 on endothelial cell leads to vasodilation. Abbreviations: lum – acinary lumen, ac – acinary cells, bm – basal membrane, cap – capillary, art – artery, asterisk presents block of transcellular enzymatic transport.

pancreatitis with regard to its potential therapeutic use (Sharma *et al.* 2005).

Some authors, who investigated pancreatic duct cells *in vitro*, proposed that activation of intracellular biochemical processes in these cells by trypsin could also participate in tissue debris elimination in AP (Nguyen *et al.* 1999, Kawabata *et al.* 2000). It is suggested that duct epithelium participates in the disappearance of interstitial edema by activation of PAR-2. In pancreatic acinal cells, the intake of trypsin from interstitium and its transcellular transport are physiologically involved in an entero-pancreatic circuit of trypsin (Beynon and Kay 1976). However, this circuit is not important under physiological circumstances because only a small amount of serum trypsin is secreted by the exocrine part of the pancreas. In pathologic conditions (during AP), the intake of trypsin-rich fluid and its enhanced transcellular transport after PAR-2 stimulation is obvious. A similar pattern of

cytoplasmatic positivity (mainly basolateral) of PAR-1 (similar receptor activated by another proteolytic enzyme thrombin) can also be seen in other cells during inflammation (in proximal tubular cells of the kidney) (Grandaliano *et al.* 2000). The role of PAR-1 in the development of AP and its relation to the thrombin content in interstitial edematous fluid during AP development will be the aim of further studies. However, from the available data we may conclude comprehensive action of PARs (Macfarlane *et al.* 2001). In general, PAR-2 participates on different intracellular responses including the phosphatidylinositol system activation in intestinal epithelial cells, which results in the intracellular utilization of arachidonic acid and secretion of prostaglandins (Kong *et al.* 1997). It is suggested that PAR-2 activation by trypsin contributes to the absorption in nutritional process. From this point of view, the major function of PARs in the digestive system seems to be the stimulation of nutritional transport.

### Lectures from knock-out models: proteinase-activated receptor-2 in general immunology

Variety of PAR-2-deficient murine models have been investigated under different conditions to unravel putative physiological roles of PAR-2. The effect of PAR-2 comprises an amazing amount of effects on different functions of the organism. Kawagoe *et al.* (2002) found that PAR-2 might play a significant role in type IV allergic dermatitis as PAR-2 deficient mouse ear treated with hypersensitivity-inducing topical agents showed attenuated signs of inflammation as compared with the wild type. Partially overlapping work of Seeliger *et al.* (2003) confirmed the previous results. Allergic airway inflammation was used by Schmidlin *et al.* (2002) to show a diminished eosinophil infiltration in mice lacking PAR-2. Ferrel *et al.* (2003) demonstrated a role for PAR-2 in mediating chronic inflammation in monoarthritis model with a significant reduction of joint swelling and no signs of articular destruction even at the microscopical level. Noorbakhsh *et al.* (2005) described more severe neuroinflammation and neuronal loss in PAR-2 null animals in their work on HIV associated dementia. Lindner *et al.* (2000) showed a delayed onset of inflammation as examined by leukocyte rolling. Another work on ischemic brain injury (Jin *et al.* 2005) revealed the greater size of infarction focus and TUNNEL counted cells in knockout mice.

**Table 1.** Involvement of pancreatic and systemic structures in pathological processes during acute pancreatitis development

Effect	Structure	Reference
<i>Vascular effect of PAR-2</i>		
vasoconstriction	muscularis propria	Moffatt et al. (1998)
vasodilatation/ hypotension	endothelium (systemic)	Cheung et al. (1998)
edema formation	lymphatics	Kawabata et al. (1998)
hypotension	endothelium ? (systemic)	Cicala et al. (1999)
<i>Nociceptive effect of PAR-2</i>		
pain induction	duct cells (intraductal activation of PAR-2)	Hoogerwerf et al. (2001, 2004)
<i>Secretion (protective) effect of PAR-2</i>		
increase of pancreatic exocrine secretion	acinary cells	Kawabata et al. (2000)
clearance of toxins and debris	duct cells (basolateral activation)	Nguyen et al. (1999)
<i>Proinflammatory role of PAR-2</i>		
NO and IL-8 production	systemic effect	Namkung et al. (2004)

### Proteinase-activate receptor-2: direct link between enzymatic digestion and immune system

Presence of PAR-2 in inflammatory cells was also demonstrated in the past. It causes intracellular  $Ca^{2+}$  mobilization, prostaglandin and cytokine synthesis in Jurkat T-cells (Mari *et al.* 1996) or intracellular  $Ca^{2+}$  mobilization in human granulocytes isolated *ex vivo* (Howells *et al.* 1997). As discussed above, in the rat model of acute pancreatitis, trypsin in the circulation of rats with taurocholate-induced severe acute pancreatitis reached levels sufficient to activate endothelial and immune cells to stimulate nitric oxide and interleukin-8 production (Namkung *et al.* 2004). It is suggested that high amounts of cytokines produced in AP (McKay *et al.* 1996a,b) are also induced by PAR-2 activation. PAR-2 also plays an important role in the genesis of hypotension associated with endotoxic shock (Cicala *et al.* 1999).

PAR-2 is present also on fibroblasts. It is known that PAR-2 action on fibroblasts causes a mitotic response, collagen synthesis and scar formation (Akers *et al.* 2000). As fibrosis and reparation changes are obvious in chronic pancreatitis histologic samples, PAR-2 action may contribute to this effect as well.

Link between inflammation and pain *via* PAR-2 activation is also suggested, but the PAR-2-mediated

role for trypsin in the pathogenesis of pancreatic pain is independent of its inflammatory effect (Hoogerwerf *et al.* 2001, 2004).

### Conclusions

The presence of PAR-2 expression on both vascular structures, as well as acinary and duct epithelium in acute pancreatitis was described in the past. This suggests an important role of trypsin-activated receptors in induction/development and/or regeneration/repair/cellular protection in acute pancreatitis. Recently published data show that PAR-2 plays both a beneficial and a harmful effect in AP development. Moreover, PARs contribute to systemic changes in AP development and leads to multiple organ dysfunction syndrome and eventual death. Local and systemic structures influenced by the PAR-2 activation during acute pancreatitis are summarized in Table 1. Despite all the above described effect of PAR-2 activation, the vascular action leading to the pancreatic ischemic disturbance could be the principal mechanism starting consequent local changes resulting in acute pancreatitis development.

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