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Review Article

Cellular effects of factor VII activating protease (FSAP)

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ABSTRACT

Factor VII activating protease (FSAP) is a circulating serine protease of broad specificity that is likely to be involved in many pathophysiological processes. The activation of the circulating zymogen form of FSAP by histones, released from damaged cells, underlines its roles in regulating host responses to tissue damage and inflammation. Some of the direct cellular effects of FSAP are mediated through protease-activated receptors (PARs). Knock-down of each one of the four PARs in endothelial cells indicated that PAR-1 and -3 are involved in regulating endothelial permeability in response to FSAP. Overexpression of PARs in cell lines led to the conclusion that PAR-2 and -1 were the main receptors for FSAP. Studies with synthetic peptides and receptor mutants demonstrate that FSAP cleaves PAR-1 and -2 at their canonical cleavage site. However, PAR-1 is not activated by FSAP in all cells, which may be related to other, as yet, undefined factors. Inhibition of apoptosis by FSAP is mediated through PAR-1 and was observed in neurons, astrocytes and A549 cells. FSAP also mediates cellular effects by modulating the activity of growth factors, generation of bradykinin, C5a and C3a generation or histone inactivation. These cellular effects need to be further investigated at the *in vivo* level.

1. Introduction

Factor VII activating protease (FSAP), the official gene name is *hyaluronic acid binding protein 2* (*HABP2*), is a circulating plasma serine protease. FSAP has diverse effects in haemostasis [1], vascular biology [2], inflammation [3] and cancer [4]. FSAP is secreted by hepatocytes in its zymogen form, called pro-FSAP, at a concentration of 180 nM [5]. Activation of pro-FSAP is mediated by a variety of positively and negatively charged natural and synthetic polymers [6,7] as well as positively charged surfaces [8]. Of these, histones can activate pro-FSAP *in vivo* and are likely to be a key activator of pro-FSAP [9]. In mice, up to 40% of the circulating FSAP is activated after application of histones [9]. An autocatalytic mechanism for the activation of pro-FSAP is proposed, which is based on the dimerization of pro-FSAP molecules [9]. Once activated, FSAP cleaves various substrates [10] and it is inhibited by a number of circulating protease inhibitors [11]. Thus, tissue injury-, apoptosis- or inflammation-induced release of histones activates pro-FSAP. Activated FSAP in turn cleaves substrates to activate a number of responses in the organism that collectively orchestrate the response to injury (Fig. 1).

The Marburg I (MI) single nucleotide polymorphism in the FSAP-encoding gene leads to an amino acid exchange in the serine protease domain of FSAP and inactivation of the enzyme [12]. This may be due to a defect in the conversion from the zymogen to the active enzyme [13,14]. This polymorphism is a risk factor for carotid stenosis [15], stroke [16] as well as liver fibrosis [17]. There have been contradictory findings in relation to its association with venous thrombosis [18–22] and thyroid cancer [4,23]. In one genome wide association study (GWAS) the FSAP-expressing gene locus was found to be a risk factor for stroke in the young [24].

FSAP deficient mice do not show any phenotype under standard breeding conditions but do show exaggerated responses when challenged with different forms of injury. In a model of stroke, where clot formation was induced with the direct injection of thrombin in the middle cerebral artery, infarct size was larger and there was increased leukocyte infiltration and increased apoptosis in FSAP-deficient mice [25]. In a model of mechanical endothelial injury to the femoral artery, the neointima was bigger in FSAP-deficient mice compared to wild-type mice, again coinciding with increased leukocyte infiltration [2]. Similarly, liver fibrosis was enhanced after carbon tetrachloride application or bile duct ligation [26] and there was increased remodeling in the hind limb after induction of permanent ischemia [27]. Both thrombosis and haemostasis were suppressed in FSAP-deficient mice [1]. This indicates that FSAP is likely to influence cellular phenotypes in addition to exerting proteolytic effects in the extracellular environment relating to haemostasis.

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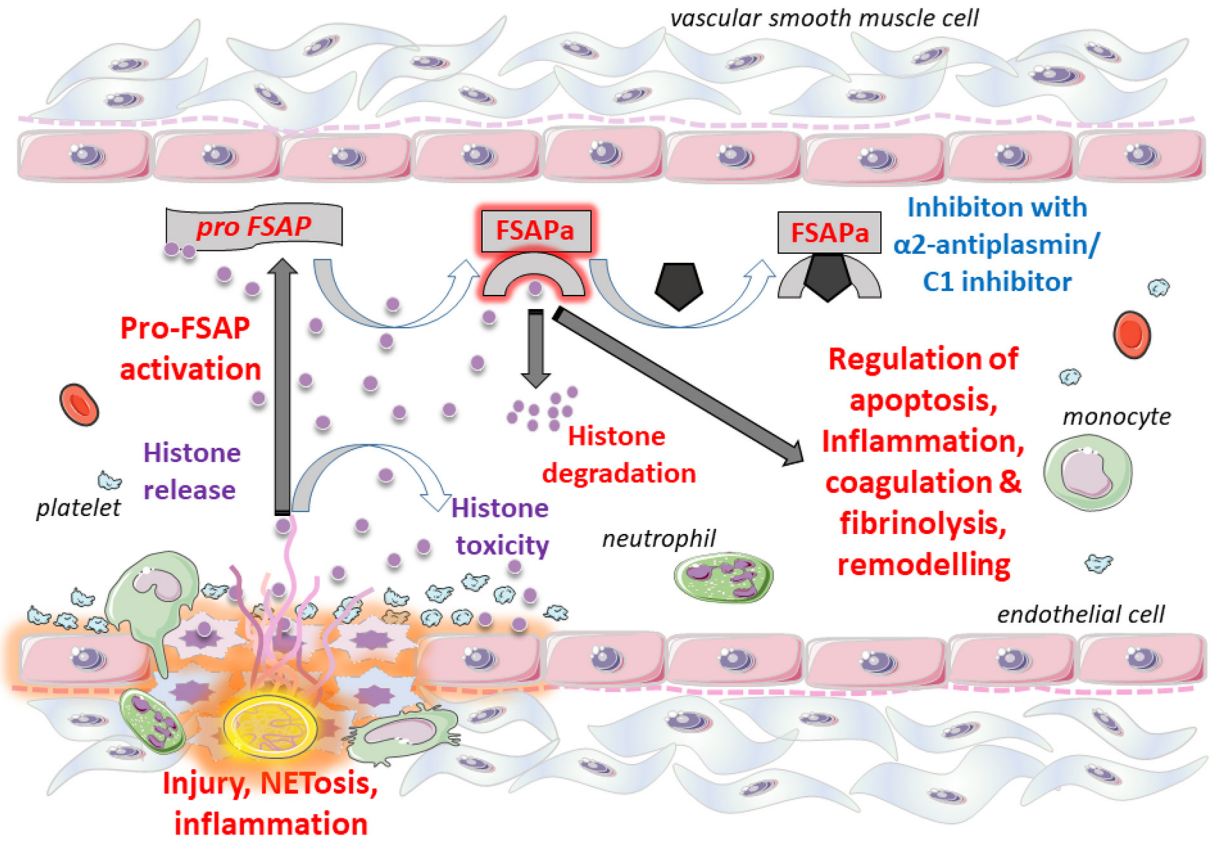

Fig. 1. Activation, inhibition and activity of FSAP: Histones released after injury, inflammation or NETosis activate pro-FSAP. Activated FSAP (FSAPa) cleaves histones and decreases their cellular toxicity. FSAPa also cleaves other circulating and cellular proteins to regulate apoptosis, inflammation, haemostasis, and tissue remodeling. Plasma inhibitors such as C1 inhibitor and α2-antiplasmin inhibit FSAPa.

2. Activation of protease activated receptors

Protease activated receptors (PARs) are a family of four G-protein coupled receptors that are activated in an irreversible manner by proteolytic cleavage and subsequent exposure of a tethered ligand at the N-terminus end. This tethered ligand folds back into the active site to mediate signaling [28]. PARs are expressed to varying degree in all cell types and many circulating proteases *e.g.*, thrombin, activated protein C (APC), FVIIa, FXa, elastase, cathepsin G, kallikrein, plasmin and matrix metalloproteinases (MMPs) can cleave these receptors (Fig. 2) [29]. The extent of cleavage depends on the concentration of the protease, its affinity for the receptor, the time of exposure, the preference for the cleavage site, localization of receptor in the plasma membrane as well as the presence or absence of co-receptors. Cleavage can lead to activation, biased activation or even inhibition of cell signaling [29]. In PARs the cleavage site defined by the first protease is called the canonical cleavage site. Furthermore, cell context-dependent signaling mechanisms depending on heterodimer formation, interactions with different isoforms of G-proteins and β-arrestins as well as calcium signaling have been described in detail [30–34].

In the vascular context, both PAR-1 and PAR-2 are ubiquitously expressed on endothelial cells, smooth muscle cells and leukocytes, whereas platelets do not express PAR-2. Canonical cleavage of PAR-1 at Arg41 by thrombin, FXa and plasmin and at a non-canonical site, Arg46, by activated protein C (APC) has been observed [35] (Fig. 2). Thrombin-mediated receptor activation has a pro-inflammatory and pro-apoptotic effect whereas APC-mediated receptor activation is responsible for a variety of cyto-protective, neuroprotective and anti-inflammatory effects and is of considerable therapeutic interest [31]. Canonical cleavage of PAR-2 at Arg36 by trypsin, FXa and tryptase as well as non-canonical cleavage by elastase and plasma kallikrein has been reported [36] (Fig. 2). PARs are involved in a variety of processes ranging from platelet aggregation, blood pressure, inflammation, thrombosis, atherosclerosis, sepsis and cancer and effective antagonists with clinical utility have been developed [35,36]. PAR-1 is a major target for drug development as it is likely to be beneficial in patients with cardiovascular diseases [30]. Thus, PARs represent obvious candidate receptors for FSAP.

The first study to indicate that PARs are involved in regulating microvascular permeability by FSAP was reported by Singleton and colleagues [37]. Silencing of PAR-1 and -3 attenuated LPS-, hyaluronic acid-, and FSAP-mediated endothelial barrier disruption. In a murine model of acute lung injury, LPS- and ventilator-induced pulmonary vascular hyperpermeability was significantly reduced by silencing FSAP expression with siRNA. These results suggest a causative link between FSAP and PARs, but this study did not provide any evidence for a direct cleavage of PARs by FSAP.

We have recently characterized the interaction between PARs and FSAP in HEK293T and A549 cells [38] that, both, express PAR-1 and PAR-2 mRNA. HEK293T cells did not show any FSAP-mediated activation of the ERK pathway, whereas ERK activation in A549 cells was dependent on PAR-2. Exogenous overexpression of N-terminal secreted alkaline phosphatase (SEAP)-PAR fusion proteins in HEK293T and A549 cells was used to determine cleavage of PARs and release of SEAP in the supernatants. FSAP cleaved PAR-2 in both cell types, whereas PAR-1 cleavage was only observed in A549 cells to a minor extent. Only the wild type enzymatically active serine protease domain of FSAP showed activity but not the MI isoform. Mutating various potential cleavage sites in PAR-1 and -2 confirmed FSAP-mediated cleavage at the canonical cleavage site; this finding was further confirmed by the use of synthetic N-terminal receptor peptides as substrates [38]. Although PAR-2 was identified as the receptor that is cleaved and

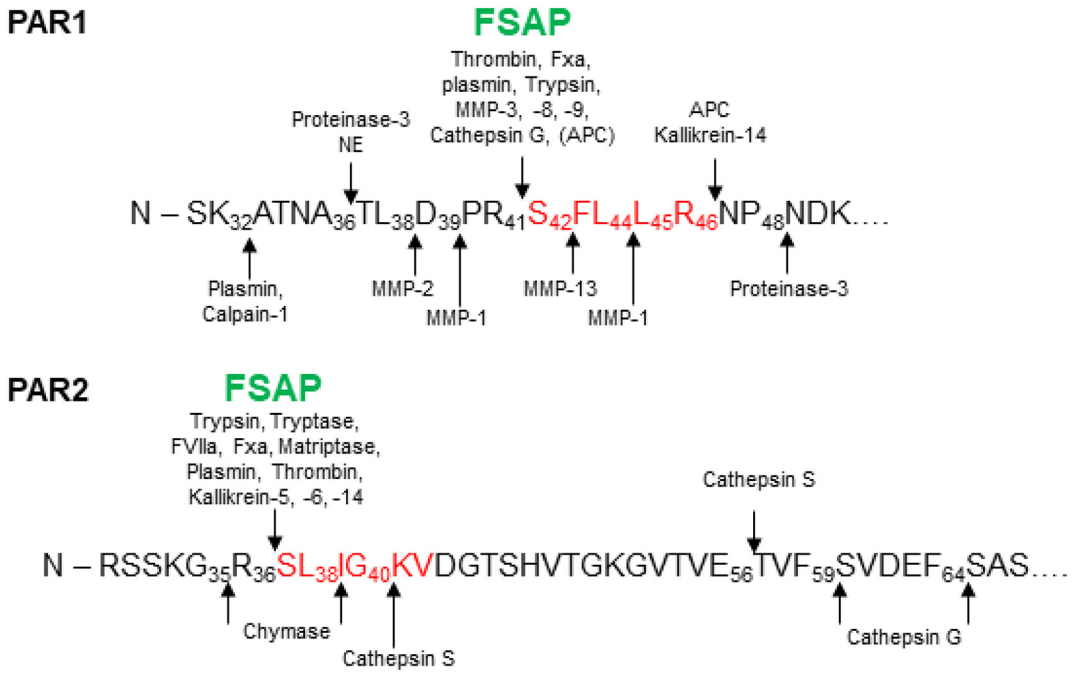

Fig. 2. Cleavage sites for FSAP in PAR-1 and -2 in comparison to other proteases. Cleavage sites for other proteases were taken from a review by Heuberger and Schuepbach [29].

activated most effectively by FSAP, the biological consequences of FSAP-mediated activation of PAR-2 need to be studied further. The overexpression strategy used here has a disadvantage in that, both cell lines used have a basal complement of endogenously expressed PARs that can influence the conclusions due to possible homo- or hetero-dimerization between the receptors.

FSAP activates a gene expression profile in endothelial cells (EC) and vascular smooth muscle cells (VSMC) that was related to inflammation, apoptosis and cell growth. In VSMC a PAR-1-dependent mechanism was evident, but this was not the case in EC [39]. We observed an anti-apoptotic effect of FSAP on neuronal cells and astrocytes when these cells were subjected to oxygen/glucose deprivation or oxidative stress mimicking ischemia reperfusion injury. These effects were abolished in the presence of a PAR-1 antagonist [25]. These studies were recapitulated in model of staurosporine-mediated apoptosis in A549 cells where FSAP was also anti-apoptotic in a PAR-1-dependent manner [38]. Our unpublished studies show that FSAP does not activate platelet aggregation, thus a universal activation of PAR-1 in all cell types is unlikely. Because of the hirudin-like sequence in PAR-1, thrombin has very high processivity for PAR-1, something that FSAP is lacking. Thus, whether PAR-1 functions as a receptor for FSAP or not, depends on additional cell-specific factors that remain to be defined.

3. Regulation of the activity of growth factors

While studying the effects of FSAP on VSMC it was noticed that FSAP prevented PDGF-BB-stimulated cell proliferation but exhibited no inhibitory effect on other growth factors. This was due to cleavage and inactivation of PDGF-BB [40]. PDGF-AA, -CC and -DD were not inhibited and mutating the cleavage site in PDGF-BB abolished this cleavage and inhibition of activity. The FSAP cleavage site was in the receptors binding region of PDGF-BB. In spite of this high selectivity and specificity *in vitro*, a difference in PDGF-BB levels in FSAP-knockout mice was not observed [2]. VEGF belongs to the same family of growth factors as PDGF and shares many structural features like the cysteine knot. VEGF-A_{165} was cleaved in its heparin/neuropilin binding domain and not in the receptor-binding domain as for PDGF-BB [41]. This did not directly disturb the binding and activation of cells with VEGF and endothelial cell migration, proliferation and signal transduction was unaltered. However, FSAP potently inhibited angiogenesis in an *in vivo* assay based on the formation of blood vessels in VEGF165-supplemented matrigel [41]. Activity of basic fibroblast growth factor (FGF2) on EC was inhibited by FSAP [42], but in the presence of heparin or heparin sulphate proteoglycans the activity of bFGF was either inhibited, enhanced or not affected by FSAP [43]. In the matrigel model, bFGF-mediated angiogenesis was also inhibited by FSAP [41] *in vivo*.

Growth factors of the PDGF and transforming growth factor β (TGF-β) family are secreted partially as pro-growth factors and cleaved into their mature form by extracellular proteases. Although no cleavage and activation of pro-TGFβ or mature TGFβ was observed, the activity of related factor, BMP-2 and pro-BMP-2, was elevated by FSAP [44]. Mutating the cleavage sites blocked both cleavage and activation of pro-BMP-2 by FSAP and the proliferative and osteogenic activity of BMP-2 was enhanced by this modification.

Over-expression of WT- and MI-FSAP in thyroid cancer cell lines, HEK293 cells and fibroblasts led to increased cell migration and colony formation. The effect of the MI isoform was stronger than that of WT-FSAP and a dominant effect of the MI-FSAP was observed upon co-transfection of MI and WT-FSAP. The mechanisms responsible for these effects were not characterized further [4]. This indicates that non-proteolytic mechanisms of action of MI-FSAP are also possible. Similarly, the down regulation of FSAP expression in lung cancer cell lines reduced cell migration, endothelial transmigration as well as the development of metastasis [45]. The development of metastasis *in vivo* was promoted by the overexpression of FSAP but further mechanisms were not characterized [45]. These intriguing studies suggest a strong cellular activation mechanism of FSAP that is relevant for tumor growth and metastasis.

4. FSAP in relation to inflammation

The primary site of expression of FSAP in the body is the liver parenchyma. However, FSAP can also be expressed in other cell types *e.g.*, monocyte-derived macrophages [46], lung carcinoma cells [45], lung endothelial, epithelial and macrophages from patients with the acute respiratory distress syndrome (ARDS) [37,47]. Patients with

sepsis also exhibit higher levels of circulating FSAP-inhibitor complexes, a marker of systemic FSAP activation [48]. Furthermore, pro-inflammatory mediators like IL-1, -6 and -8, TNFα and lipopolysaccharides (LPS) can trigger FSAP expression in cells like monocyte-derived macrophages [49], lung microvascular endothelial [37,47] and in human trophoblasts [50]. Whereas the liver expression maintains circulating FSAP levels, the local expression could be related to the regulation of tissue inflammation.

Tissue injury, inflammation and sepsis have been shown to be associated with the release of free histones in the plasma, the inhibition of which reduces their pathological effects strongly [51]. Two articles, recently, showed that the histone toxicity towards cells could be effectively inhibited by FSAP [52,53] (Fig. 2). While histone neutralization can be classified as an anti-inflammatory effect of FSAP, it also promotes a pro-inflammatory response in various cells. In monocyte-derived macrophages, FSAP activates a pro-inflammatory response by increasing MMP9, IL-6 and MCP-1 as well as VCAM-1 and ICAM-1 expression [46]. FSAP-mediated up-regulation of inflammation-related genes in endothelial and smooth muscle cells [39], together with a strong involvement of PAR-1 and PAR-2 in inflammatory diseases [36], suggests that this interaction may be of particular significance. FSAP also releases bradykinin from cell surface-bound kininogen and stimulates the phosphorylation of the transcription factor cAMP responsive element binding protein (CREB) [43]. Similarly, in histone-treated plasma, the activation of pro-FSAP was mirrored by the increase in the concentration of bradykinin [9]. Anaphylatoxins C5a and C3a were generated by FSAP in a purified system, but only C5a was produced in histone-activated plasma [3].

5. Conclusions

Tissue injury not only initiates haemostasis but also inflammation as well as remodeling and repair. Haemostasis factors play a major role in regulating all of these pathways, as illustrated by the effects of thrombin, plasmin, urokinase and FXIIa. Although these factors have diverse mechanisms of action, some mediate cellular responses *via* PARs. FSAP fits well into this pattern since it is also activated by tissue injury, through the release of extracellular histones (Fig. 1), and activates PAR-1 and -2 (Fig. 2). Known consequences include increased vascular permeability, inhibition of apoptosis and altered gene expression profiles. PAR activation, growth factor activity regulation or histone inactivation need to be confirmed *in vivo*. Taken together, these cellular actions of FSAP can account for the response to injury in the context of vascular remodeling [2,27], stroke [25], thrombosis [1] and liver fibrosis [26].

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Declaration of competing interest

None.

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