

Factor VII-Activating Protease Latest Presentations GTH 2010



Factor VII activating protease in inflammatory disease-a sensor for cell death in circulation?

Zeerleder S., Hämostaseologie (GTH) 2010 30 1: Abstract SY04-02

Summary:

In-vitro FSAP activates coagulation as well as fibrinolysis, but the in-vivo relevance of these findings is still under debate. Recently the authors observed that FSAP interacts with apoptotic cells leading to the release of nucleosomes. FSAP binds abundantly to both apoptotic and necrotic cells but not to living cells. FSAP activation in plasma is indicated by complex formation of FSAP with its target serpin Inhibitors C1-inhibitor and α 2-antiplasmin: FSAP is activated by apoptotic and to a lesser extent by necrotic cells and not by living cells. Interestingly, no evidence for FSAP activation upon coagulation activation was found.

Since FSAP is activated by dead cells the authors analyzed whether FSAP serpin complexes are formed in inflammatory diseases and might serve as an indicator of in vivo cell death. FSAP was activated in different inflammatory conditions in animals and humans, respectively.

Taken together the data propose that FSAP is a sensor for in vivo cell death and therefore might constitute a new link to innate immunity.

No activation of Factor VII-activating protease upon coagulation

Stephan F et al., Hämostaseologie (GTH) 2010 30 1: Abstract P15-04

Summary:

FSAP activates factor VII independently of tissue factor in vitro, however it's in vivo role in coagulation is not known. FSAP circulates in plasma as an inactive single-chain proenzyme and becomes activated (cleaved) upon contact with apoptotic cells. Active FSAP can form complexes with C1-inhibitor (C1Inh) and α 2-antiplasmin (AP) in plasma which is a measure of in vivo FSAP activation.

The authors compared FSAP activation in the presence of apoptotic vs. non-apoptotic cells. FSAP in plasma was activated upon incubation with apoptotic cells as shown by appearance of two-chain FSAP on western blots. No FSAP activation was observed upon incubation of plasma with living cells. FSAP activation by apoptotic cells was also indicated by complex formation of FSAP with C1Inh and AP, whereas no such complexes could be detected after incubation with living cells. Notably, no coagulation activation could be detected in these samples. No differences in FSAP levels and no FSAP complexes could be measured before and after clot formation in serum. Incorporation of FSAP complexes in the formed clot could be excluded. Moreover no FSAP activation could be detected upon coagulation activation via the extrinsic or intrinsic pathway, respectively.

Taken together measurement of FSAP complexes with its inhibitors by ELISA is a useful tool to measure FSAP activation. The authors demonstrate that FSAP is not activated during coagulation via the extrinsic or intrinsic pathway.

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Factor seven activating protease (FSAP) is activated massively in multiple trauma patients and in turn activates complement factors

Kanse SM et al., Hämostaseologie (GTH) 2010 30 1: Abstract P15-03

Summary:

Tissue injury leads to the activation of FSAP which not only mobilizes the coagulation system but also triggers the complement system. The authors addressed the possible role of FSAP as a marker and/or a therapeutic target for managing the treatment of patients with trauma. They measured FSAP antigen and activity by ELISA and western blot at various time points in plasma from polytrauma patients. Activation of complement factors was determined by ELISA and complement haemolytic activity assays.

Early after trauma there was a 9-fold increase in FSAP activity that returned to baseline level after 24-48 h. High activity coincided with 3-fold lower FSAP antigen that was normalized after 5 days. High levels of FSAP-inhibitor complexes immediately after trauma were detected. Significantly enhanced serum levels of C3a and C5a were found in polytrauma patients, which were associated with a reduction in complement haemolytic activity.

In view of these findings, in vitro activation of C3 and C5 by FSAP was investigated. Both, C3 and C5 were cleaved by FSAP in a dose- and time-dependent manner to generate C3a and C5a, respectively that exhibited biological activity as determined by chemotactic activity towards neutrophils and HMC-1 cells.

The authors suggest that FSAP might serve as a marker and/or a therapeutic target for managing the treatment of patients with trauma.

Factor seven activating protease (FSAP) inhibits the activity of platelet derived growth factor-BB (PDGF-BB)

Hersemeyer K et al, Hämostaseologie (GTH) 2010 30 1: Abstract FC1-05

Summary:

The authors provide evidence that FSAP regulates the activity of platelet-derived growth factor (PDGF-BB) in vivo. FSAP inhibits PDGF-BB mediated vascular smooth muscle (VSMC) proliferation and migration. This is due to cleavage of a specific site (amino acid sequence RKK) of PDGF-BB, which is important for receptor binding and activation.

The authors investigated the consequences of altering this sequence with respect to its interaction with FSAP. They also determined the role of the PDGF-BB-FSAP axis in vivo by using the injury-induced neointima formation model.

Wild type PDGF-BB was cleaved by FSAP and this was associated with reduced proliferation towards VSMC. The mutant (RKK-EEE) was not cleaved by FSAP and its activity remained unchanged after treatment with FSAP. Application of exogenous FSAP in the mouse vascular injury model reduced neointima formation that was associated with reduced vascular smooth muscle cell (VSMC) proliferation and migration. Compared to wild-type mice FSAP^{-/-} mice showed enhanced neointima formation after vascular injury.

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Factor seven activating protease (FSAP) can activate members of the transforming growth factor (TGF) family of growth factors

Rödel E et al., Hämostaseologie (GTH) 2010 30 1: Abstract P18-12

Summary:

Rödel and colleagues provide evidence that FSAP can activate the latent growth factors pro-GDF-5 and pro-BMP-2. The activation of these factors can contribute to remodeling processes in various organs and diseases.

Previously it was found that FSAP can inactivate heparin binding growth factors such as platelet derived growth factor-BB. The authors analyzed whether FSAP is involved in the activation of transforming growth factors (TGFs) and bone morphogenetic proteins (BMPs). Latent TGF-beta could be activated by low pH but not by FSAP, pro-GDF-5 was cleaved by FSAP in a time and concentration-dependent manner, which was inhibited by aprotinin. The GDF-5 generated by pretreatment with FSAP was of a smaller molecular weight than the known mature GDF-5. However in functional assays it was biologically active. Similarly, pro-BMP-2 was also activated by FSAP.

Circulating factor seven activating protease (FSAP) is associated with clinical outcome in acute coronary syndrome

Parahuleva M et al., Hämostaseologie (GTH) 2010 30 1: Abstract P18-23

Summary:

Parahuleva and colleagues provide evidence that plasma FSAP activity is increased in patients with Acute Coronary Syndrome (ACS). The plasma FSAP levels were an independent prognostic marker for future cardiovascular events, suggesting its potential role in risk stratification and clinical management of stable Coronary Artery Disease (CAD).

Previously it was found that FSAP is present in unstable atherosclerotic lesions and is a risk factor for late complications of carotid stenosis. The present study was performed (i) to examine the relation between plasma concentration and activity of FSAP and clinical instability of CAD and (ii) to investigate the FSAP expression in monocytes and activated platelets in patients with CAD.

Circulating FSAP concentration and activity as well as FSAP expression in monocytes and activated platelets were assessed in patients with different stage of CAD (n=545). The median FSAP activity in control non-coronary subjects was significantly different from those in patients with stable angina. In the group of patients with unstable angina, the median FSAP activity was significantly higher than in the control group. In the group of patients with ACS, the median FSAP activity was also significantly higher than in the control group or the group with stable angina.

Elevated FSAP levels indicated a significantly increased risk of death or non-fatal myocardial infarction during one year of follow-up. Furthermore, there were no significant changes in the FSAP expression in monocytes and activated platelets in the groups.

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Factor seven activating protease (FSAP): a link between inflammation and coagulation in coronary artery disease

Parahuleva M et al., Hämostaseologie (GTH) 2010 30 1: Abstract P18-17

Summary:

Parahuleva and colleagues provide evidence that FSAP may play a role in atherosclerosis by enhancing the inflammatory response of human macrophages as a novel activator of NF-kappaB.

FSAP may be involved in the progression of atherosclerosis and the development of associated clinical events. It is present in unstable atherosclerosis lesions and its plasma level and activity are increased in patients with coronary artery disease (CAD). However, the molecular mechanism by which circulating FSAP influences the progression of CAD is unclear. The present study was performed to examine the relation between FSAP and the pro-inflammatory activation of monocytes/ macrophages.

FSAP induces IkappaB-dependent NF-kappaB activation in a time-dependent fashion. FSAP induces the phosphorylation and proteolytic degradation of the inhibitor protein IkappaB α and the phosphorylation of p65, which contributes to the enhancement of DNA-binding activity of NF-kappaB. In parallel, FSAP induced the expression of ICAM, IL-6, and TF, genes known to be under the control of NF-kappaB. Aprotinin, a pharmacological inhibitor of FSAP, blocks The FSAP-induced gene expression indicating that the proteolytic activity of FSAP was required.

Factor seven activating protease (FSAP); a regulator of pericellular proteolysis?

Daniel JM et al., Hämostaseologie (GTH) 2010 30 1: Abstract P18-03

Summary:

FSAP can specifically activate pro-urokinase (pro-uPA). This in turn leads to increased activation of plasminogen as well as matrix metalloproteases (MMPs). The authors analyzed the influence of FSAP on the pericellular proteolysis system in the mouse vascular injury model.

Application of exogenous FSAP in the mouse vascular injury model reduced neointima formation that is associated with reduced vascular smooth muscle cell (VSMC) proliferation and migration. PA activity was decreased after exogenous application of FSAP. This activity was blocked with the uPA inhibitor amiloride and there was very low activity in uPA -/- mice. On the other hand gelatinase activity was increased after application of FSAP and this could be blocked by the MMP inhibitor captopril. Compared to wild-type mice FSAP-/- mice showed enhanced neointima formation after vascular injury. However, there was no difference between WT and FSAP -/- mice with respect to the changes in PA and gelatinase activity.

The authors conclude that although the local application of exogenous FSAP *in vivo* alters the pericellular proteolysis balance in the vessel wall and can contribute to vascular remodeling processes the same was not observed in FSAP -/- mice. Enhanced neointima formation in FSAP -/- mice is likely to be due to other factors unrelated to the differential regulation of pericellular proteolysis.

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The Marburg I polymorphism (G534E) of Factor VII activating protease (FSAP) prevents FVII activation, but retains a thrombotic risk due to FVIII activation

Etscheid M et al., Hämostaseologie (GTH) 2010 30 1: Abstract SY11-05

Summary:

Etscheid and colleagues provide evidence that the loss of fibrinolytic potential in combination with a higher Factor VIII activation capacity may contribute to a prothrombotic state in carrier of the MI variant.

FSAP can activate Factor VII, uPA, tPA, and kininogen, and inactivates Factor V and Factor VIII. A sequence variant of FSAP termed Marburg I (MI), shows diminished uPA activation but supposedly retains full Factor VII activation capacity, leading to haemostatic imbalance in MI carriers. Accordingly, the FSAP-MI variant was found to be an independent risk factor in late carotid stenosis and was associated with increased risk of venous thromboembolism.

FSAP from genotyped individuals was incubated with purified plasma proteins. Subsequently the activation of those proteins was analyzed. pro-uPA is cleaved by FSAP much more efficiently than Factor VII, indicating a clear preference of FSAP for the fibrinolytic system. Unlike wild type FSAP, MI-FSAP is a very weak activator of Factor VII, uPA, and kininogen. Most interestingly, MI-FSAP lead to increased FVIII:C activity, whereas WT-FSAP reduced FVIII:C activity.

Taken together homozygous MI-carriers lack relevant FSAP activity against Factor VII, uPA and kininogen, this is in contrast to earlier reports that MI-FSAP and WT-FSAP are equally effective Factor VII activators. A significant change in specificity of MI compared to wild type is seen in FVIII processing, causing a prothrombotic tendency in MI-carriers. A haemostatic imbalance in MI-carriers due to reduced uPA activation but unchanged Factor VII activation needs a revision, taking into consideration elevated FVIII:C levels.

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Factor VII-Activating Protease Latest Presentations ISTH 2009



FACTOR SEVEN ACTIVATING PROTEASE (FSAP) – INFLAMMATION AND COAGULATION CROSS-TALK IN PATIENTS WITH CORONARY ARTERY DISEASE

M Parahuleva, R Maj, A Staubitz, H Hoelscherman, H Tillmanns, A Erdogan, **SM Kanse**
ISTH 2009: OC-WE-128

Summary:

Factor VII-Activating Protease (FSAP) has been implied in the progression of atherosclerosis, and particularly in coronary artery disease, and the development of associated clinical events.

Along these lines Parahuleva and colleagues examined the relation between plasma concentration of FSAP and pro-inflammatory activation of macrophages and the signalling pathways induced by FSAP. FSAP treatment induced I κ B-dependent NF- κ B activation in freshly isolated human monocytes. FSAP also induced the phosphorylation and proteolytic degradation of the inhibitor I κ B α . Moreover, the phosphorylation of p65, which is known to contribute to the enhancement of DNA-binding activity of NF- κ B, was induced by FSAP. Expression of NF- κ B, ICAM, IL-6, and tissue factor, all of which under the control of NF- κ B, was increased by FSAP.

The authors conclude that FSAP may play a novel role in atherosclerosis by enhancing the inflammatory response of human monocytes/macrophages via NF- κ B activation.

THE EFFECT OF MONOPHASIC ORAL CONTRACEPTIVE REGIMENS ON FACTOR VII-ACTIVATING PROTEASE - A RANDOMIZED MULTICENTRE STUDY

JJ Sidelmann, SO Skouby, C Klufft, U Winkler, F Vitzthum, H Schwarz, J Jespersen
ISTH 2009: OC-MO-090

Summary:

Oral contraceptives (OCs) affect plasma levels of haemostatic factors and the use of OC is a risk factor for development of cardiovascular disease. This study addressed the effect of OCs on FSAP in human blood.

Women were analysed that took oral contraceptives with different estrogen and progestin dosage. Marburg I variant, FSAP antigen and FSAP activity was measured at the start and after 6 cycles of OC. Marburg I was found to be present in 49 (8.4%) of the women, in all three treatment groups ($P=0.44$). Marburg I was associated with significantly reduced levels of FSAP ($P<0.001$). OC use increased the median plasma concentration of FSAP antigen by 25% and FSAP activity by 58% ($P<0.001$). The relative increase in FSAP activity was significantly higher in women carrying the wild type genotype (63%) than in women carrying the Marburg I variant (50%) ($P=0.01$). The increase in FSAP was independent of the estrogen dosage and progestin ($P>0.1$).

In conclusion, OCs increased FSAP in plasma independent of the estrogen dosage and the progestin component but with less significance in women carrying Marburg I genotype than in women with the wild type genotype.

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Factor VII-Activating Protease Latest Presentations ISTH 2009



THE MARBURG I POLYMORPHISM (G534E) OF FACTOR VII ACTIVATING PROTEASE (FSAP) PREVENTS FVII ACTIVATION, BUT CONTRIBUTES TO THROMBOEMBOLIC RISK DUE TO FVIII ACTIVATION.

M Etscheid, L Muhl, D Pons, KT Preissner, W Ruf, W Jukema, SM Kanse
ISTH 2009: OC-TH-110

Summary:

Etscheid and colleagues have further addressed the dual role of FSAP in hemostasis and fibrinolysis. With refined methods they compared the activities of wild-type FSAP (wt-FSAP) vs. Marburg I FSAP (MI-FSAP).

pro-uPA was found to be cleaved much more efficiently and at lower concentrations than FVII, indicating a preference of FSAP for the fibrinolytic system. Purified MI-FSAP activated FVII much less efficient than wt-FSAP. This was confirmed with FSAP from plasma of 5 individuals homozygous for the MI-FSAP allele. Pro-uPA was only weakly processed by FSAP from homozygous Marburg I carriers.

However, the central finding was on Factor VIII (FVIII) processing: wt-FSAP caused inactivation of FVIII, whereas MI-FSAP caused activation.

The authors conclude that the hypothesis of a haemostatic imbalance and increased athero-thrombotic risk in Marburg I-carriers due to reduced uPA but unchanged FVII activation capacity needs a revision and should take into consideration circulating FVIII levels.

FACTOR VII-ACTIVATING PROTEASE (FSAP): DOES IT ACTIVATE FACTOR VII?

F Stavenuiter, E Sellink, HJM Brinkman, AB Meijer, K Mertens
ISTH 2009: OC-WE-084

Summary:

Stavenuiter and colleagues produced recombinant FSAP (recFSAP) and analysed its suitability for functional studies.

In the recFSAP, the natural activation site (R313-I314) was replaced by a cleavage site for the bacterial protease thermolysin, which prevented the problem of autoactivation and autodegradation observed in natural FSAP. This allowed to obtain purified intact FSAP.

Thermolysin activated recFSAP displayed the same affinity for chromogenic peptide substrates as pdFSAP and retained its capability to activate pro-uPA. recFSAP interacted with negatively charged surfaces but did not have FVII-cleaving activity, even in the presence of calcium-ions and lipid vesicles of varying composition. Only on membranes of 100% cardiolipin FVII cleavage did occur, but this resulted in transient activation and rapid degradation.

While recFSAP indeed activates pro-uPA, it does not activate FVII. Whether or not the effect of cardiolipin, which is an intracellular lipid, has any physiological significance remains to be explored.

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Factor VII-Activating Protease Latest Presentations ISTH 2009



FACTOR VII-ACTIVATING PROTEASE IS ACTIVATED IN SEPSIS

S Zeerleder, I Bulder, F Stephan, M de Kruif, J Hoogerwerf, T van der Poll, L Aarden
ISTH 2009: PP-TH-153

Summary:

Factor VII-activating protease (FSAP) removes nucleosomes from apoptotic cells and is inhibited by C1-inhibitor (C1Inh) and α 2-antiplasmin (AP).

The authors compared FSAP activation in the presence of apoptotic vs. non-apoptotic cells. FSAP in plasma was found to be activated upon incubation with apoptotic cells as evidenced by appearance of two-chain FSAP on western blots. No FSAP activation was observed upon incubation of plasma with living cells. FSAP activation by apoptotic cells was also indicated by complex formation of FSAP with C1Inh and AP, whereas no such complexes could be detected after incubation with living cells.

Moreover, the authors asked, whether a similar mechanism can also be expected in vivo and they analysed plasmas from cases of sepsis, during which the formation of apoptotic cells is a hallmark. They found elevated levels of FSAP/C1Inh complexes in plasma of baboons with lethal sepsis and in plasmas from 8 out of 16 patients suffering from severe sepsis.

In conclusion the authors demonstrate that FSAP is activated upon contact with apoptotic cells and forms complexes with C1Inh and AP. They suggest that determination of complexes between FSAP and C1Inh or AP in plasma is tool to study FSAP activation in vivo.

FACTOR SEVEN ACTIVATING PROTEASE (FSAP); A KEY REGULATOR OF PERICELLULAR PROTEOLYSIS.

J Daniel, O Uslu, K Hersemeyer, O Rannou, L Muhl, KT Preissner, D Sedding, **SM Kanse**
ISTH 2009: AS-TH-058

Summary:

Daniel and colleagues asked whether FSAP may influence factors involved in pericellular proteolysis. They studied the influence of FSAP on the expression of uPA, tPA, MMP-2 and -9 (gelatinases) in cultured endothelial cells (EC) and vascular smooth muscle cells (VSMC). Studies were also performed in the mouse vascular injury model.

FSAP was found to activate pro-uPA to uPA but, over time, to decrease the activity of uPA in cultured EC and VSMC. Protein levels of uPA were reduced and the enzymatic activity of FSAP was required for this. In contrast, an increase in the gelatinase activity (MMP-2 and -9) was observed, without changes in the levels of individual proteins. FSAP caused this through a non-proteolytic mechanism. However, there was no regulation of the mRNA levels for uPA, tPA, MMP-2 and -9. Also the levels of the gelatinase inhibitors, i.e. the tissue inhibitors of matrix metalloproteinases (TIMPs), were not affected. In a similar manner as in vitro, FSAP reduced uPA activity and increased gelatinase activity in vessel walls in the mouse vascular injury model.

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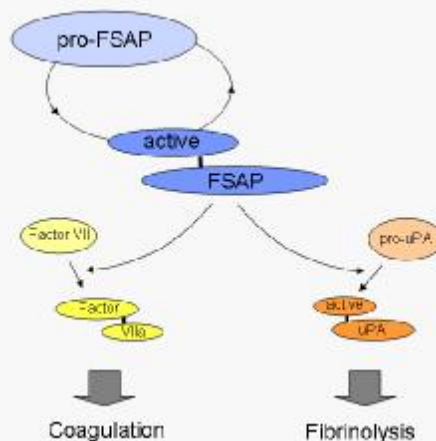
Factor VII-activating protease (FSAP)



Diagnostic relevance

Factor VII-activating protease (FSAP) is a serine-protease present in human plasma as a single-chain pro-enzyme (64 kDa) at a concentration of 12 µg/ml. The pro-enzyme can be activated by an autocatalytic mechanism or by urokinase generating the active two-chain form (40 and 30 kDa). The activity of FSAP is strongly dependent on Ca²⁺ ions and is efficiently inhibited by α₂-antiplasmin and aprotinin.

FSAP has the ability to activate both coagulation factor VII (independent of tissue factor) and pro-urokinase. Thus, FSAP has a dual function as a potent pro-coagulant and a pro-fibrinolytic agent.



Indication

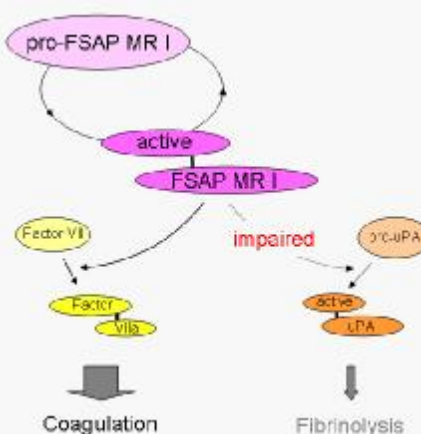
- Thromboembolic diseases
- Risk predictor of carotid stenosis

Aliases

- Plasma hyaluronan binding protein (PHBP)
- Hyaluronan-binding protein 2 (HABP2)

Pathophysiology

Recently a frequent (5 - 10% of healthy subjects) variant of FSAP with a single nucleotide polymorphism (SNP) has been identified, termed "Marburg I" (FSAP-MI). The FSAP-MI variant shows diminished activity in pro-urokinase activation, whereas the capacity to activate Factor VII is normal. It seems likely that FSAP-MI, due to the resulting hemostatic imbalance, may promote the development of thromboembolic diseases. Accordingly, the FSAP-MI variant was found to be a significant risk predictor for the evolution and progression of carotid stenosis.



Method

ELISA

Sample

Citrated plasma

Preanalytics

Heparanized plasma is not suitable

References

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FSAP assays and antibodies



ASSAYS	Assay Type	Format	Product #
IMUBIND® FSAP kit	ELISA	96 tests	876
IMUBIND® FSAP Marburg I kit	ELISA	96 tests	878

ANTIBODIES	Known Applications	Amount	Product #
anti-human FSAP mAb	ELISA, Western blot, Immunohistochemistry	250 µg	4601
anti-human FSAP mAb	ELISA, Immunoprecipitation	250 µg	4602
anti-human FSAP mAb	ELISA, Western blot	250 µg	4603
anti-human FSAP Marburg I mAb	ELISA	250 µg	4611

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