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The urokinase-receptor in infectious diseases

Il recettore dell'urochinasi nelle infezioni

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INTRODUCTION

Plasminogen is a zymogen circulating in plasma, mostly synthesized as a single chain in the liver; it is converted to the two-chain active plasmin by a single cleavage, catalyzed by two specific activators, the urokinase-type plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA). Plasmin is a broad-spectrum protease. It binds and degrades fibrin; thus, a primary *in vivo* function of plasmin is the regulation of fibrinolysis. Fibrin can be bound also by plasminogen and tPA; since the assembly of plasminogen and its activator at the surface of fibrin results in a very efficient fibrin degradation, tPA plays a key role in fibrinolysis [1].

Plasminogen/plasmin also bind to the cell surface, as well as uPA. Plasminogen/plasmin cellular binding sites are low-affinity heterogeneous receptors whereas the uPA receptor (uPAR) binds its ligand with high affinity and specificity. Both receptors are expressed on a variety of cell types; the assembly on the cell surface of both plasminogen and its urokinase-type activator strongly enhances plasminogen activation, as it occurs for plasminogen and tPA on the fibrin clot [2]. Plasmin is able to promote, beside fibrinolysis, the degradation of various components of the extracellular matrix (ECM); its localized activity on the cell surface allows the cells to degrade the surrounding ECM and to move across physical barriers. Thus, the uPA-mediated plasminogen activation has been implicated in biological processes requiring cell migration [1, 2]. Cell migration is a basic event in various physiological and pathological processes, including cell recruitment in innate and adaptive immunologic response, wound healing, angiogenesis.

The activity of the plasminogen activation system is regulated by specific inhibitors, such as the α2-antiplasmin for plasmin, and the type 1 (PAI1) and type 2 (PAI2) inhibitor for uPA and tPA [1, 2].

uPAR plays a central role in cell migration by regulating cell-associated plasmin activity; however, a large body of evidence has clearly shown that it is involved in cell migration, as well in cell adhesion, survival and proliferation, even independently of the proteolytic activity of its ligand, likely by interacting with other extracellular and/or cell-surface ligands [3].

uPAR is expressed on most of leukocytes, including monocytes/macrophages, granulocytes, immature dendritic cells, and is involved in their migration across the blood barrier and into tissues, crucial events in inflammation, immune response against infection, cancer invasiveness and tissue remodeling following injury [4, 5]. Further, uPAR can be released from the cell surface in soluble forms; increased suPAR levels have been reported in individuals suffering from viral, bacterial or parasitical infections as well as autoimmune diseases and cancer [5]. suPAR levels are thought to reflect the state of immune activation of the individual. Interestingly, in all of these conditions the higher concentration of serum suPAR correlates with a worse prognosis of the disease.

Here, we will review uPAR structure and functions and its involvement in infectious diseases.

THE uPA RECEPTOR

The uPA receptor was identified in 1985 and its cDNA sequenced in 1990 [6, 7]. The cDNA sequencing showed the absence of a obvious

transmembrane sequence. In fact, uPAR is anchored to the cell membrane by a glycosylphosphatidylinositol (GPI) tail, which is attached to the C-terminus after removal of a signal sequence [8]. The GPI-anchor confers extreme mobility to uPAR along the cell-membrane and enables the receptor to associate to specialized microdomains of the plasma membrane (lipid rafts) [9]. Mature uPAR is a heavily glycosylated protein consisting in three homologous domains termed DI, DII and DIII from the N-terminus. DI is mainly involved in uPA binding, even if the full-length molecule is required for an efficient binding. The solved crystal structure of the soluble form of uPAR, bound to an antagonist peptide or to the amino-terminal fragment (ATF) of uPA, has shown that the three domains delimit a central cavity accomodating the ligand peptide [10]. uPAR, beside uPA, binds with high affinity vitronectin (VN), thus acting as a non-integrin ECM receptor [11]. The DI-DII linker region of uPAR is extremely sensitive to the action of various proteases, including plasmin and uPA. The proteolytic cleavage in the uPAR DI-DII linker region promotes the release of the uPA-binding DI domain, thus leaving on the cell surface truncated forms of GPI-uPAR (DII-DIII uPAR), detected in various cell types [1, 3, 12]. These DII-DIII uPAR forms can expose at the N-terminus, according to the cleavage site, the sequence SRSRY, corresponding to amino acids 88-92, that is involved in cell migration [3, 13].

Both full-length and cleaved forms of uPAR can be shed from the cell surface by the action of phospholipases or proteases, generating soluble uPAR forms (suPAR and DII-DIII suPAR). uPAR soluble forms have been detected *in vitro*, in supernatant from cultured cells, and, *in vivo*, in body fluids as plasma, urine and cerebrospinal fluid [1, 3]. The cleaved suPAR form exposing the sequence SRSRY (aa 88-92) is a ligand of the G-Protein Coupled Receptors (GPCRs) for the fMet-Leu-Phe peptide (fMLF) [14]. fMLF is a peptide of bacterial origin that is a strong leukocyte chemoattractant. fMLF receptors (fMLF-Rs) were firstly identified in leukocytes, and, subsequently, in several different cell types. The fMLF-R family comprises the high affinity fMLF-R (FPR1) and its homologues FPR2 and FPR3. FPR2 has a much lower affinity for fMLF, whereas it is efficiently activated by several other molecules, including lipoxin A_4, serum amyloid A, HIV derived peptides. FPR3 shows a high homology with the other two fMLF-Rs but does not bind fMLF and shares few ligands with FPR2, including DII-DIII suPAR [15]. Cell-surface uPAR is present in various immunologically active cells including monocytes, activated T-lymphocytes and macrophages, but also endothelial cells, keratinocytes, fibroblasts, smooth muscle cells, megakaryocytes, epithelial cells [5].

uPAR FUNCTIONS

The primary GPI-uPAR functions are strictly related to its extracellular ligands. uPAR regulates extracellular proteolysis by binding uPA and cell adhesion to ECM by binding VN. However, uPAR is able to regulate cell adhesion, migration and proliferation, protects from apoptosis and anoikys and induces epithelial mesenchymal transition (EMT), independently of uPA enzymatic activity [1, 3]. These multiple uPAR activities implicates that the GPI-uPAR, even devoid of a transmembrane and cytosolic region, is able to activate intracellular signalling pathways. To this end, its interaction with cell-surface molecules, provided with signalling capability, is required. uPAR interactions with molecules other than uPA is consistent with the solved crystal uPAR structure, which shows a large external surface of the receptor, well separated from the central urokinase-binding cavity, that is available for the binding to other molecules [10]. In fact, uPAR can associate to integrins of the beta1, beta2 and beta3 families; integrins represent the main uPAR partner in cell signalling [16, 17]. uPAR binding sites have been identified in integrins and integrin binding sites have been identified in uPAR domains DII and DIII. uPAR association to integrins, beside allowing uPAR-dependent signalling, also regulates integrin activity [1, 3].

The capability of the DII-DIII suPAR to bind the fMLF-Rs and functional interactions of the full-length GPI-uPAR with these chemotaxis receptors, observed in various cell types [18-20], have suggested that also the fMLF-Rs could associate to uPAR on the cell membrane and contribute to its signalling activities [1, 3].

uPAR also cross-talks with growth-factor receptors, such as the epidermal growth factor receptor (EGFR) and the platelet derived growth factor receptor (PDGFR) beta, and, as recently shown, with CXCR4, the receptor for the stromal-derived factor 1 (SDF1) chemokine, through the involvement of fMLF-Rs [3, 21].

Full-length GPI-uPAR and suPAR have a similar conformation, except in the DI-DII linker; in fact, an antibody raised to a peptide comprising residues 84-94, which constitutes a part of the linker-region, recognizes uPAR but not suPAR [22]. uPAR retains its ligand-binding capability in the full-length soluble form, suggesting that suPAR may act as a ligand-scavenger molecule able of inhibiting uPA-dependent cell-associated proteolysis and cell adhesion to VN [1, 3].
The cleavage abolishes uPAR binding to all its extracellular and cell-membrane ligands. However, the DII-DIII suPAR, exposing the SRSRY sequence, exerts a novel activity, since it binds and activates the fMLF-Rs [14]. In fact, the cleaved suPAR is a potent chemoattractant for cells expressing these GPC receptors, including leukocytes. Interestingly, DII-DIII suPAR acts *in vivo* as an efficient mobilizing agent for leukocytes and hematopoietic stem cells [23].

uPAR IN INFECTIOUS DISEASES

uPA and uPAR are expressed by a variety of cells of hematopoietic origin and the levels of various components of the PA system are up-regulated during several infections, suggesting a role for this system in the development of both innate and adaptive immune responses [24]. In fact, bacterial products, such as endotoxin, and proinflammatory cytokines, such as IL-1 and TNF-α, released upon infection, increase the expression and secretion of uPA by several cells, including monocytes and neutrophils. The local release of uPA potentiates neutrophil activation, superoxide production and migration by either uPAR-dependent or -independent pathways [24].
Membrane-bound and soluble uPAR are capable of modulating mononuclear cell adhesion and migration *in vitro*. In addition, the cleaved soluble form of uPAR may contribute to the recruitment of inflammatory cells through fMLF-Rs stimulation. In fact, *in vivo*, macrophages and neutrophils of uPAR-deficient mice fail to infiltrate the lungs after infection with *Streptococcus pneumoniae* or *Pseudomonas aeruginosa* [25, 26]. Further, migration of inflammatory cells into peritoneal cavity of thioglycollate-treated uPAR (-/-) mice resulted impaired [27]. By contrast, uPA-deficient mice showed similar or enhanced host defense to both *S. pneumoniae* or *P. aeruginosa* as compared to wild type mice [25, 26]. The finding that uPAR- and uPA-knockout mice have different susceptibilities to several pathogen infections and that PAI1- or plasminogen-knockout mice show optimal inflammatory cell migration and host defense during *S. pneumoniae* infection indicate that uPA and uPAR contribute to innate immune responses also independently of proteolytic activities [28].
Exposure to the spirochete Borrelia burgdorferi, the causative agent of Lyme borreliosis, induces up-regulation of uPAR expression on murine and human leukocytes. B. burgdorferi-inoculated uPAR (-/-) mice harbored significantly higher Borrelia numbers compared to wild type controls. This was associated with impaired phagocytotic capacity of B. burgdorferi by uPAR (-/-) leukocytes *in vitro* [29].
In addition to modulating the development of innate immune responses, uPA and uPAR may also participate in the initiation of adaptive immune responses. Both uPA and uPAR are rapidly upregulated during T-cell activation. Further, uPAR is expressed by antigen-presenting cells (APCs), such as dendritic cells (DCs), monocytes and macrophages [4,5]. T-cell recruitment to the lung is defective in uPAR (-/-) mice [30].
The discovery of the soluble receptor in plasma from healthy individuals initially suggested that suPAR levels reflected the overall level of cell-surface uPAR. Indeed, suPAR levels are thought to reflect the state of immune activation of the individual; in fact, increased suPAR levels have been reported in patients with viral, bacterial or parasitical infections as well as autoimmune diseases [5]. A higher level of serum suPAR correlates with a worse prognosis in several infectious diseases, including Human immunodeficiency virus-1 (HIV-1) infection, tuberculosis (TB) and malaria [5].
suPAR level is elevated by active TB disease and, at time of TB treatment initiation, is prognostic for survival during the treatment period. In the patients who successfully complete the treatment, suPAR levels decrease to the level of non-infected individuals. Thus, suPAR seems a very promising biomarker in TB [31].
HIV-1 infection has been shown to result in uPAR up-regulation on leukocytes *in vitro* and *in vivo* [32]. The level of suPAR was measured retrospectively in serum samples from 314 patients with HIV-1 infection [33]. Serum suPAR levels were correlated to survival with AIDS-related death as the end point. High levels of serum suPAR (greater than median) were associated with poor overall survival, and Kaplan-Meier analysis on patients stratified by suPAR

level demonstrated a continuous increase in mortality rates with higher suPAR levels. After adjustment for accepted prognostic markers, the prognostic strength of suPAR remained highly significant, indicating that the serum suPAR level was a novel, strong, and independent predictor of survival in HIV-1 infection [33]. suPAR was shown to be a strong predictor of immunologic failure and mortality in highly active antiretroviral therapy (HAART) patients with HIV-1 infection, with a prognostic strength similar to that of CD4+ T-cell count and viremia. Combining prognostic value of suPAR and CD4 added clinical value on the risk of mortality in non- antiretroviral therapy treated HIV-1 patients [5].

suPAR plasma level has been recently proposed as a predictor of disease severity and case fatality in patients with bacteraemia in a prospective cohort study. Plasma suPAR levels were measured in 132 patients with bacteraemia caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, β-haemolytic streptococci or *Escherichia coli* [34]. suPAR values were examined on days 1-4 after a positive blood culture, on days 13-18 and on recovery. The maximum suPAR values on days 1-4 were markedly higher in nonsurvivors compared to survivors. At a cut-off level of 11.0 ng mL(-1) , the sensitivity and specificity of suPAR for fatal disease was 83% and 76%, respectively. A high level of suPAR (≥11 ng mL(-1)) was associated with hypotension and high sequential organ failure assessment score (≥4). A high suPAR level remained an independent risk factor for case fatality in a logistic regression model adjusted for potential confounders. On these basis authors proposed plasma suPAR level as a sensitive and specific independent prognostic biomarker in patients with bacteraemia.

CONCLUSIONS

uPAR is expressed by a variety of hematopoietic cells and its expression is up-regulated during various bacterial, viral and parasitic infections, suggesting a role for uPAR in the development of an efficient innate and/or adaptive immune response [4, 5, 23, 35]. uPAR modulates mononuclear cell adhesion and migration *in vitro*; its absence in knock-out mice impairs a correct immune response to various infective agents. *In vivo*, uPAR might favor recruitment, activation and phagocytic activity of cells belonging to the innate immune response. In the peripheral lymphoid organs, uPAR might then favor T-cell activation, proliferation and differentiation, and in this way contribute to the development of adaptive immunity. Cell-surface uPAR can be released in soluble forms (suPAR). Serum suPAR level is related to the overall level of cell-surface uPAR expression and seems to reflect the activation state of the immune system. Thus, suPAR appears to be a stable marker of immune activation with a strong prognostic value in various infectious diseases [36].

Keywords: urokinase, urokinase-receptor, uPA, uPAR

Conflict of interest disclosure
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SUMMARY

Cell migration through the extracellular matrix (ECM) or endothelial cells is a basic process in several physiological and pathological events, including the immune host response to pathogens, both in the case of innate and adaptive immunity. The urokinase-type plasminogen activator (uPA) receptor (uPAR) is a GPI-anchored cell-surface receptor largely expressed on most of leukocytes, including monocytes/macrophages, granulocytes, immature dendritic cells. uPAR has been detected also in soluble and cleaved forms, which are increased in several pathologies. uPAR focuses the proteolytic activity of its ligand, the serine-protease uPA, on the cell membrane, thus promoting localized plasminogen activation and allowing the cell to degrade surrounding ECM and to move across physical barriers. However, the discovery that uPAR can bind with high affinity a component of the ECM, vitronectin (VN), and associates to cell surface molecules to activate signalling pathways inside the cells, largely expanded the role that uPAR can play in cell proliferation/survival and adhesion/migration, which are crucial events for an efficient immune response to infectious agents. This review is focused on the expression and possible functions of the various forms of uPAR in infectious diseases.

RIASSUNTO

La capacità delle cellule di migrare attraverso la matrice extracellulare (ECM) o attraverso la barriera endoteliale è fondamentale in vari eventi fisiologici e patologici, inclusa la risposta del sistema immunitario ai patogeni. Il recettore (uPAR) dell'attivatore del plasminogeno di tipo urochinasico (uPA) è un recettore ancorato alla superficie cellulare tramite una coda glicosfingolipidica ed è espresso nella maggior parte dei leucociti, inclusi i monociti/macrofagi, i granulociti, le cellule dendritiche. L'uPAR è presente anche in forme tronche e/o solubili; i livelli di tali forme risultano incrementati in numerose patologie.

L'uPAR focalizza l'attività proteolitica del suo ligando, la serin-proteasi uPA, sulla superficie cellulare, promuovendo l'attivazione localizzata del plasminogeno a plasmina, permettendo così alla cellula di degradare la matrice extracellulare circostante e di attraversarla. Tuttavia la scoperta che l'uPAR può legare con alta affinità un componente dell'ECM, la vitronectina, ed è in grado di associarsi a molecole della superficie cellulare per attivare vie di segnalazione intracellulari, ha contribuito ad ipotizzare un ruolo più ampio per l'uPAR nella proliferazione, sopravvivenza, adesione e migrazione cellulare, processi fondamentali per una efficiente risposta immunitaria alle infezioni.

Saranno quindi analizzate l'espressione e le possibili funzioni delle varie forme dell'uPAR nelle malattie infettive.

REFERENCES

[1] Ragno P. The urokinase receptor: a ligand or a receptor? Story of a sociable molecule.*Cell Mol. Life Sci.* 63, 1028-1037, 2006.

[2] Rijken D.C., Lijnen H.R. New insights into the molecular mechanisms of the fibrinolytic system. *J. Thromb. Haemost.* 7, 4-13, 2009.

[3] Montuori N., Ragno P. Multiple activities of a multifaceted receptor: roles of cleaved and soluble uPAR. *Front. Biosci.* 14, 2494-2503, 2009.

[4] Plesner T., Behrendt N., Ploug M. Structure, function and expression on blood and bone marrow cells of the urokinase-type plasminogen activator receptor, uPAR. *Stem Cells.* 15, 398-408, 1997.

[5] Thunø M., Macho B., Eugen-Olsen J. suPAR the molecular crystal ball. *Dis Markers.* 27, 157-172, 2009.

[6] Vassalli J.D., Baccino D., Belin D. A cellular binding site for the Mr 55,000 form of the human plasminogen activator, urokinase. *J. Cell Biol.* 100, 86-92, 1985.

[7] Roldan A.L., Cubellis M.V., Masucci M.T., et al. Cloning and expression of the receptor for human urokinase plasminogen activator, a central molecule in cell surface, plasmin dependent proteolysis. *EMBO J.* 9, 467-474, 1990.

[8] Ploug M., Rønne E., Behrendt N., Jensen A.L., Blasi F., Danø K. Cellular receptor for urokinase plasminogen activator. Carboxyl-terminal processing and membrane anchoring by glycosyl-phosphatidylinositol. *J. Biol. Chem.* 266, 1926-1933, 1991.

[9] Sitrin R.G., Johnson D.R., Pan P.M., et al. Lipid raft compartmentalization of urokinase receptor signaling in human neutrophils. *Am. J. Respir. Cell Mol. Biol.* 30, 233-241, 2004.

[10] Kjaergaard M., Hansen L.V., Jacobsen B., Gardsvoll H., Ploug M. Structure and ligand interactions of the urokinase receptor (uPAR). *Front. Biosci.* 13, 5441-5461, 2008.

[11] Wei Y., Waltz D.A., Rao N., Drummond R.J., Rosenberg S., Chapman H.A. Identification of the urokinase receptor as an adhesion receptor for vitronectin. *J. Biol. Chem.* 269, 32380-32388, 1994.

[12] Ragno P., Montuori N., Covelli B., Hoyer-Hansen G., Rossi G. Differential expression of a truncated form of the urokinase-type plasminogen-activator receptor in normal and tumor thyroid cells. *Cancer Res.* 58, 1315-1319, 1998.

[13] Høyer-Hansen G., Ploug M., Behrendt N., Rønne E., Danø K. Cell-surface acceleration of urokinase-catalyzed receptor cleavage. *Eur. J. Biochem.* 243, 21-26, 1997.

[14] Resnati M., Pallavicini I., Wang J.M., et al. The fibrinolytic receptor for urokinase activates the G protein-coupled chemotactic receptor FPRL1 /LXA4R. *Proc. Natl. Acad. Sci.* USA. 99, 1359-1364, 2002.

[15] Le Y., Murphy P.M., Wang J.M. Formyl-peptide receptors revisited. *Trends Immunol.* 23, 541-548, 2002.

[16] Smith H.W., Marshall C.J. Regulation of cell signalling by uPAR. *Nat. Rev. Mol. Cell Biol.* 11, 23-36, 2010.

[17] Alfano D., Ragno P., Stoppelli M.P., Ridley A.J. RhoB regulates uPAR signalling. *J. Cell Sci.* 125, 2369-2380, 2012.

[18] Fazioli F., Resnati M., Sidenius N., Higashimoto Y., Appella E., Blasi F. A urokinase-sensitive region of the human urokinase receptor is responsible for its chemotactic activity. *EMBO J.* 16, 7279-7286, 1997.

[19] Montuori N., Carriero M.V., Salzano S., Rossi G., Ragno P. The cleavage of the urokinase receptor regulates its multiple functions. *J. Biol. Chem.* 277, 46932-46939, 2002.

[20] De Paulis A., Montuori N., Prevete N., et al. Urokinase induces basophil chemotaxis through a urokinase receptor epitope that is an endogenous ligand for formyl peptide receptor-like 1 and -like 2. *J. Immunol.* 173, 5739-57348, 2004.

[21] Montuori N., Bifulco K., Carriero M.V., et al.

The cross-talk between the urokinase receptor and fMLP receptors regulates the activity of the CXCR4 chemokine receptor. *Cell. Mol. Life Sci.* 68, 2453-2467, 2011.
[22] Høyer-Hansen G., Pessara U., Holm A., et al. Urokinase-catalysed cleavage of the urokinase receptor requires an intact glycolipid anchor. *Biochem. J.* 358, 673-679, 2001.
[23] Selleri C., Montuori N., Ricci P., et al. In vivo activity of the cleaved form of soluble urokinase receptor: a new hematopoietic stem/progenitor cell mobilizer. *Cancer Res.* 66, 10885-10890, 2006.
[24] Mondino A, Blasi F. uPA and uPAR in fibrinolysis, immunity and pathology. *Trends Immunol.* 25, 450-455, 2004.
[25] Rijneveld A.W., Levi M., Florquin S., Speelman P., Carmeliet P., van Der Poll T. Urokinase receptor is necessary for adequate host defense against pneumococcal pneumonia. *J. Immunol.* 168, 3507-3511, 2002.
[26] Gyetko M.R., Sud S., Kendall T., Fuller J.A., Newstead M.W., Standiford T.J. Urokinase receptor-deficient mice have impaired neutrophil recruitment in response to pulmonary Pseudomonas aeruginosa infection. *J. Immunol.* 165, 1513-1519, 2000.
[27] May A.E., Kanse S.M., Lund L.R., Gisler R.H., Imhof B.A., Preissner K.T. Urokinase receptor (CD87) regulates leukocyte recruitment via beta 2 integrins in vivo. *J. Exp. Med.* 188, 1029-1037, 1998.
[28] Rijneveld A.W., Florquin S., Bresser P., et al. Plasminogen activator inhibitor type-1 deficiency does not influence the outcome of murine pneumococcal pneumonia. *Blood* 102, 934-939, 2003.
[29] Hovius J.W., Bijlsma M.F., van der Windt G.J., et al. The urokinase receptor (uPAR) facilitates clearance of Borrelia burgdorferi. *PLoS Pathog.* 5, e1000447, 2009.
[30] Gyetko M.R., Sud S., Sonstein J., Polak T., Sud A., Curtis J.L. Antigen-driven lymphocyte recruitment to the lung is diminished in the absence of urokinase-type plasminogen activator (uPA) receptor, but is independent of uPA. *J. Immunol.* 167, 5539-5542, 2001.
[31] Eugen-Olsen J., Gustafson P., Sidenius N., et al. The serum level of soluble urokinase receptor is elevated in tuberculosis patients and predicts mortality during treatment: a community study from Guinea-Bissau. *Int. J Tuberc. Lung Dis.* 6, 686-692, 2002.
[32] Alfano M., Sidenius N., Blasi F., Poli G. The role of urokinase-type plasminogen activator (uPA)/uPA receptor in HIV-1 infection. *J. Leukoc. Biol.* 74, 750-756, 2003.
[33] Sidenius N., Sier C.F., Ullum H., et al. Serum level of soluble urokinase-type plasminogen activator receptor is a strong and independent predictor of survival in human immunodeficiency virus infection. *Blood*. 96, 4091-4995, 2000.
[34] Huttunen R., Syrjänen J., Vuento R., et al. Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteraemia: a prospective cohort study. *J. Intern. Med.* 270, 32-40, 2011.
[35] Selleri C., Montuori N., Ricci P., et al. Involvement of the urokinase-type plasminogen activator receptor in hematopoietic stem cell mobilization. *Blood* 105, 2198-2205, 2005.
[36] Eugen-Olsen J. suPAR - a future risk marker in bacteremia. *J. Intern. Med.* 270, 29-31, 2011.