*Section A -Research paper*

# Role of Soluble Urokinase Plasminogen Activator Receptor in Contrast-Induced Acute Kidney Injury

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**Abstract:**

Although major advancements in the field of contrast radiology procedures, contrast-induced acute kidney injury (CI-AKI) continues to be a serious complication among patients receiving intravascular contrast media. Routine serum creatinine does not offer precise way to predict whom patient is likely to suffer from CI-AKI. Serum Urokinase -Type Plasminogen Activator Receptor may play a role in prediction of CI-AKI before serum rise of creatinine.

**Keywords:** Urokinase Plasminogen Activator Receptor, AKI, contrast-induced acute kidney injury.

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## Introduction:

The urokinase-type plasminogen activator (uPA) system consists of a proteinase (the uPA), its receptor (the urokinase-type plasminogen activator receptor – uPAR or CD87) and two major inhibitors, the plasminogen activator inhibitor 1 (PAI 1) and PAI 2. The uPA is a specific serine protease, which converts plasminogen into its active form, plasmin, a broad-spectrum serine protease involved in the digestion of basement membranes and of various protein substrates in the extracellular matrix ***(1).***

Therefore, it plays a crucial role in cell migration and extravasation. Two major functional domains have been identified in the uPA molecule: an N-terminal domain also known as 'growth factor domain' due to its homology with the epidermal growth factor and a C- terminal domain that displays protease activity. The N-terminal domain has no enzymatic activity but binds with high affinity to the cell-surface uPA receptor, uPAR or CD87 ***(2).***

The uPAR is a heavily glycosylated glycosyl-phosphatidylinositol (GPI)-anchored cell-surface receptor, composed of 274 amino acid residues, which binds uPA produced endogenously or released from surrounding cells, and focuses plasmin proteolytic activity on the relevant cell's surface. The uPAR belongs to the Ly6/

neurotoxin receptor family and consists of three internally disulfide-bonded domains (D1, D2 and D3). It is attached to the cell surface by a GPI anchor (Figure 1) ***(3).***

The receptor has neither transmembrane nor cytoplasmic domains. The ligand-binding activity resides in the N-terminal domain, but all three domains are necessary to achieve a high-affinity binding of uPA. By binding to uPAR through its N-terminal domain, the catalytic C- terminal domain of (pro)-uPA gets close to membrane-bound plasminogen ***(4).***

This process results in the enzymatic activation of (pro)-uPA into uPA, which subsequently activates more plasminogen to generate additional plasmin in a mechanism that is referred to as 'reciprocal zymogen activation'. Vitronectin represents another important ligand for uPAR; the binding of uPA and vitronectin to uPAR is not mutually exclusive and uPA stimulates the vitronectin binding to uPAR ***(1).***

uPA and uPAR functions are modulated by the two specific inhibitors, PAI 1 and PAI 2. These two proteins belong to the serpin family, and they bind and inhibit both free and receptor-bound uPA. The binding of PAI 1 to uPAR changes the properties of the receptor ***(4).***

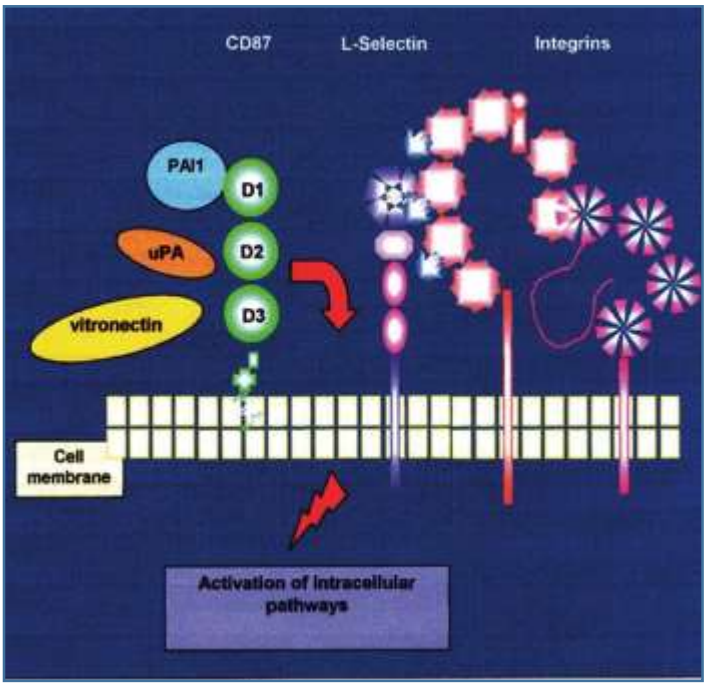


**Figure (1):** The urokinase-type plasminogen activator (uPA) system ***(5).***

Indeed, the uPAR–uPA–PAI 1 complex displays a binding site for the alpha-2-macroglobulin receptor, leading to an increased rate of internalization and degradation of this complex. uPAR is then recycled to the cell surface while the uPA–PAI 1 pair is degraded. Therefore, PAI 1 controls both the cell-surface proteolytic

activity and the cellular distribution of uPAR in the plasma membrane ***(2).***

**uPAR-related cell functions:**

uPAR exerts multiple regulatory effects on cell migration, leukocyte adhesion, chemotaxis and signal transduction during leukocyte recruitment from the circulation to extravascular sites of inflammation ***(3).***

- **Migration:**

The uPAR expression is strictly linked to cellular migration through its capacity to promote pericellular proteolysis. In response to uPA binding, the uPAR–uPA complex has been shown to `cluster and polarize at focal sites of the cell-substratum or intercellular contacts.the uPAR clustering favors the concentration of uPA and plasmin activity on the cell surface, a property likely to facilitate pericellular proteolysis and cell movement across tissue barriers ***(4).***

- **Chemotaxis:**

The uPAR is directly involved in the chemotaxis of monocytes and neutrophils. Chemotaxis is induced through a uPA-dependent conformational change of uPAR, which uncovers very potent chemotactic sequences residing in the linker connecting domains D1 and D2; such a chemotactic role of uPA may also be independent of uPA activity ***(1).***

- **Adhesion:**

Apart from inducing cell migration, uPA and uPAR can regulate cell adhesion to extracellular matrix proteins including vitronectin and fibronectin. The adhesion of myeloid cells to vitronectin might relate to uPAR occupancy, since uPAR itself binds vitronectin and mediates adhesion processes***(2).***

The binding of uPAR to vitronectin also inhibits adhesion to other proteins, such as fibronectin or fibrinogen, and inhibits fibrinogen internalization via the CD11b/CD18 integrin. This suggests that uPAR competition is involved in adhesion as well as in internalization/degradation processes ***(3).***

- **Signal transduction:**

It has been documented that uPAR, in spite of lacking an intracytoplasmic domain, is involved in signal transduction pathways. uPAR aggregation triggers activation signals through its association with such membrane spanning proteins as b1, b2 and b3 integrins, specialized in relating the intracellular and extracellular environments of the cells. It has been suggested that uPAR may act as a ligand rather than as an integrin-associated protein ***(4).***

- **Tissue remodeling:**

Recent results indicate that the activation of plasminogen into plasmin focuses the proteolytic activity on the surface of multiple myeloma (MM) plasma cells and may contribute to the removal of bone matrix noncollagenous proteins in this disease. In addition, plasmin can be involved in the activation of latent MMPs, which, by degrading type I collagen, may also participate in bone remodeling ***(3).***

The uPA system is also involved in the activation of prohepatocyte growth factor into its active form, which in turn induces the secretion of IL-11 by osteoblasts, a cytokine

with a potent stimulatory effect on osteoclastogenesis. The expression of uPA and uPAR could therefore represent a pathway by which normal and MM plasma cells interact with the bone marrow (BM) structure and might influence or trigger biological events such as bone matrix degradation, plasma cell invasion and homing, and potentially disease progression, in MM ***(4).***

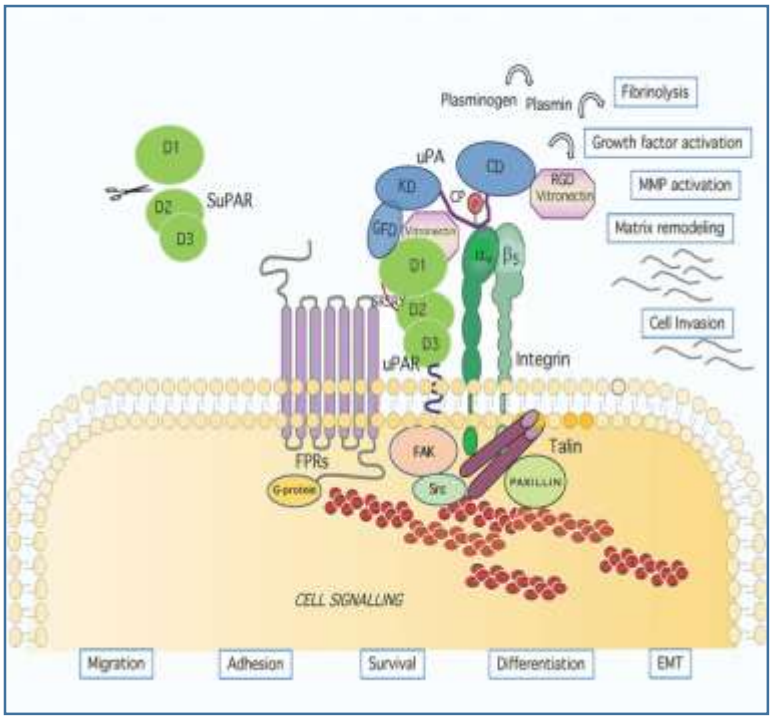


**Figure (2):** Graphic representation of the suPAR system on cell surface and related cell function ***(1).***

**Soluble uPAR (suPAR):**

A suPAR has been characterized in the plasma of normal healthy subjects as well as in the plasma and body fluids of cancer patients. suPAR is released from the plasma membrane by cleavage of the GPI anchor. suPAR can be further cleaved in the region that links domain D1 to domain D2 to yield two fragments, respectively, composed of D1 and D2D3 ***(1).***

The latter exhibits direct chemotactic activity. Cleaved uPAR is unable to bind uPA/PAI 1 complexes, neither is it internalized, nor does it have high affinity for vitronectin, and may be unable to act as a mediator of cell adhesion. It has been suggested that in cancer patients, peripheral blood levels of suPAR confer a poor prognosis ***(4).***

In fact, although suPAR is actively released from cancer cells, the rate of receptor shedding does not correlate with the intensity of uPAR expression or with the amount of tumor cells in the BM. Recent observations suggest that suPAR fragments display chemokine-like activities, and that, in vitro, suPAR could be capable of modulating

different processes such as cell adhesion, migration and proliferation ***(2).***

**SuPAR: a potential predictive biomarker for acute kidney injury:**

New data suggest that plasma soluble urokinase receptor (suPAR) might be a predictive biomarker and potential therapeutic target for acute kidney injury (AKI). However, many questions remain regarding the potential of suPAR to inform clinical decision making, identify patients for enrolment in clinical trials and add to the understanding of AKI pathogenesis ***(6).***

Increased plasma levels of soluble urokinase receptor (suPAR) are associated with the development of acute kidney injury (AKI) in different patient cohorts. Furthermore, murine experiments demonstrated that suPAR might sensitize the kidney to the deleterious effects of nephrotoxic insults ***(7).***

These findings suggest that suPAR could represent a new category of AKI biomarker that is increased prior to AKI, predicts increased risk of AKI has a pathogenic role in the development of AKI. The development of AKI biomarkers has been a translational research priority for the past 15 years owing to the limitations of serum creatinine levels in identifying patients with AKI in a timely and reliable fashion, particularly as creatinine levels may not rise until 24–72 h after AKI onset ***(8).***

The limitations of serum creatinine as a biomarker for AKI were highlighted by a series of negative clinical trials in which therapies that showed promise in preclinical studies were tested late in the course of AKI (that is, several days after onset). These findings led to the suggestion that if patients could be identified and enrolled within hours of developing AKI, such therapies might have a greater likelihood of being effective ***(1).***

Thus, efforts to identify biomarkers that appeared early in the course of AKI commenced in earnest. Among the hundreds of candidate AKI biomarkers that have been identified, only a few hold promise for continued development, including urine tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7) ([TIMP2]*[IGFBP7]), urine and plasma neutrophil gelatinase-associated lipocalin (NGAL), urine kidney injury molecule 1 , urine IL-18 and plasma cystatin C ***(6).***

Although use of early-recognition biomarkers to enroll patients in clinical trials has been limited, several studies have demonstrated that use of these biomarkers coupled with the implementation of recommended AKI care practices (for example, avoidance of nephrotoxins and optimization of hemodynamics) can improve patient outcomes ***(8).***

In many countries, platforms to measure urine [TIMP2] *[IGFBP7], urine NGAL and plasma cystatin-C are clinically available and being used in some centers to inform real-time decisions regarding patient care. Thus, the greatest success of these early-recognition AKI biomarkers is their use to

improve clinical care and outcomes, despite the lack of a specific therapeutic agent ***(7).***

In terms of clinical trial enrolment, the advantage of a biomarker such as suPAR that can potentially predict AKI rather than identify it at an early stage is substantial. Most importantly, if AKI can be predicted the number of testable therapeutic agents is much greater because the vast majority of interventions for AKI that have been identified in preclinical studies are only successful when administered before the induction of injury ***(8).***

As suPAR seems to be pathogenic, targeting suPAR itself might also have therapeutic potential. In addition to enriching clinical trials for patients who are most likely to develop AKI, a prediction biomarker such as suPAR has the potential to inform clinical decision making and care with pre-procedural risk stratification ***(6).***

However, a number of questions remain before suPAR can be used for clinical trial enrolment or risk stratification. Most importantly, a cut point for suPAR levels that can reliably predict AKI needs to be determined. Successful clinical application of suPAR will ultimately rely on a clear understanding of the pathophysiology behind its regulation and the mechanisms by which it might predispose to AKI ***(1).***

Together, these data suggest that suPAR might sensitize the kidney to subsequent injury by altering proximal tubular mitochondrial energy metabolism (towards increased energy production and oxygen consumption) and increasing oxidative stress***(6).***

**References:**

1. Alfano, D., Franco, P., & Stoppelli, M. P. (2022). Modulation of cellular function by the urokinase receptor signalling: A mechanistic view. Frontiers in Cell and Developmental Biology, 705.

2. Rasmussen, L. J. H., Petersen, J. E. V., & Eugen-Olsen, J. (2021). Soluble urokinase plasminogen activator receptor (suPAR) as a biomarker of systemic chronic inflammation. Frontiers in immunology, 12, 780641.

3. Bourassa, K. J., Rasmussen, L. J., Danese, A., Eugen-Olsen, J., Harrington, H., Houts, R., ... & Caspi, A. (2021). Linking stressful life events and chronic inflammation using suPAR (soluble urokinase plasminogen activator receptor). Brain, Behavior, and Immunity, 97, 79-88.

4. Chalkias, A., Mouzarou, A., Samara, E., Xanthos, T., Ischaki, E., & Pantazopoulos, I. (2020). Soluble urokinase plasminogen activator receptor: a biomarker for predicting complications and critical care admission of COVID-19 patients. Molecular Diagnosis & Therapy, 24, 517-521.

5. Bene, M. C., Castoldi, G., Knapp, W., Rigolin, G. M., Escribano, L., Lemez, P., ... & Van't Veer, M. (2004). CD87 (urokinase-type plasminogen activator receptor), function and pathology in hematological disorders: a review. Leukemia, 18(3), 394-400.

6. Reisinger, A. C., Niedrist, T., Posch, F., Hatzl, S., Hackl, G., Prattes, J., ... & Eller, P. (2021). Soluble urokinase plasminogen activator receptor (suPAR) predicts critical illness and kidney failure in patients admitted to the intensive care unit. Scientific Reports, 11(1), 17476.

7. Nusshag, C., Rupp, C., Schmitt, F., Krautkraemer, E., Speer, C., Kaelble, F., ... & Brenner, T. (2019). Cell cycle biomarkers and soluble urokinase-type plasminogen activator receptor for the prediction of sepsis-induced acute kidney injury requiring renal replacement therapy: a prospective, exploratory study. Critical Care Medicine, 47(12), e999.

8. Hayek, S. S., Leaf, D. E., Samman Tahhan, A., Raad, M., Sharma, S., Waikar, S. S., ... & Reiser, J. (2020). Soluble urokinase receptor and acute kidney injury. New England Journal of Medicine, 382(5), 416-426.