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Editor

Encyclopedia of Signaling Molecules

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With 1893 Figures and 247 Tables

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Plasminogen Activator Inhibitor-2

► Plasminogen Activator Inhibitor-1

Plasminogen Activator, Urokinase Receptor

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Synonyms

CD87; Monocyte activation antigen Mo3; PLAUR; uPAR; u-PAR; U-Plasminogen Activator Receptor from 2; URKR; Urokinase plasminogen activator surface receptor

Historical Background

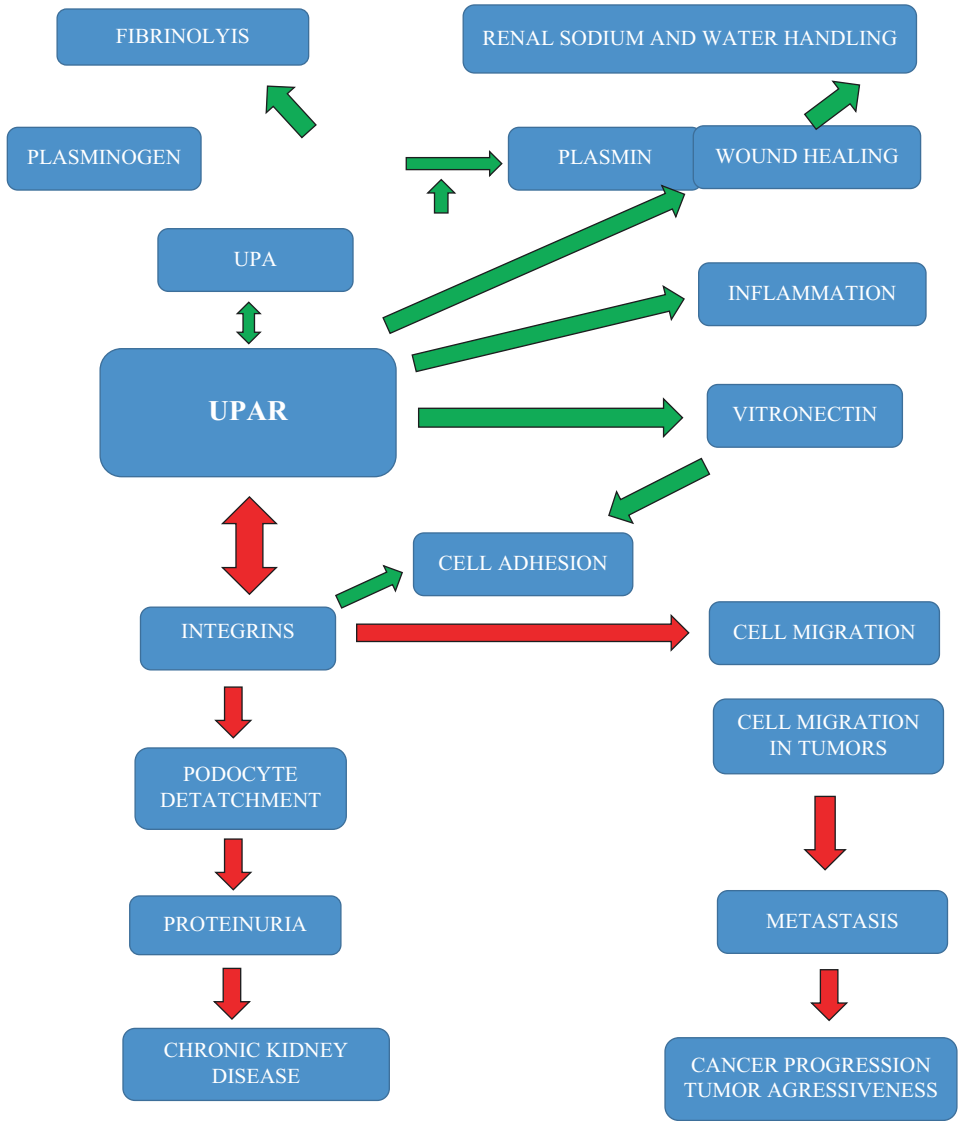
In 1988 and 1989, respectively, Nielsen et al. and Estreicher et al. reported that the cell surface urokinase-type plasminogen activator (UPA) receptor was a 40- to 60-kD protein (Nielsen et al. 1988; Estreicher et al. 1989). Subsequent cloning of the human UPA receptor (uPAR) cDNA in 1990 showed that the primary structure of this receptor consists of 313 amino acid residues (Roldan et al. 1990). The entire uPAR sequence was found to be a triplicate of a cysteine-rich consensus sequence of about 90 amino acid residues suggesting that the origin of the uPAR might be an internal triplication of an ancestral gene (Behrendt et al. 1990, 1991).

uPAR is a receptor located in the plasma membrane of cells. However, one unusual feature of uPAR is its linkage to the plasma membrane via a glycosylphosphatidylinositol membrane anchor (Behrendt et al. 1991; Ploug et al. 1991). Interestingly, the ligand-binding domain of the receptor can be proteolytically cleaved by its own ligand, uPA (Hoyer-Hansen et al. 1992). This unusual phenomenon may represent an additional regulatory step in the plasminogen activation process, which is mainly involved in the fibrinolytic system (Bu et al. 1994).

General Aspects

As mentioned above, uPAR is an extensively N-glycosylated membrane receptor tethered to the plasma membrane by a glycosylphosphatidylinositol lipid anchor. uPAR orchestrates a wide variety of cellular processes, including extracellular proteolysis, cell migration, adhesion, signaling, and proliferation, both under physiologic and pathologic conditions (Sarra-Ferraris and Sidenius 2013) (Fig. 1). Moreover, uPAR has important roles in wound healing, inflammation, and stem cell mobilization as well as in severe pathological conditions such as HIV-1 infection, tumor invasion, and metastasis (Alfano et al. 2002) (Fig. 1). This ample variety of actions positions uPAR as a receptor that is structurally devoted to mainly command regulatory processes between the cell and the surrounding environment.

On the plasma membrane, uPAR acts as the high-affinity binding site for uPA, thus promoting plasmin generation at the cell surface.



Plasminogen Activator, Urokinase Receptor, Fig. 1 Main functions of uPAR and its agonists. *Green arrow*, physiologic actions; *red arrows*, pathologic actions

The activation of proteolytic cascades after uPA-uPAR interaction is widely believed to be responsible for the biologic activity of uPAR; however, further studies have extensively documented the existence of a variety of biologic activities induced solely by overexpression of the receptor or by the binding of catalytically inactive uPA derivatives. These effects, referred to as the "non-proteolytic" functions of uPAR, rely on direct and functional interaction with other proteins on the plasma membrane or in the pericellular environment. The absence of a cytoplasmic tail makes uPAR unable to directly contact signaling molecules in the cytoplasm, and the signaling activity of uPAR has therefore been ascribed to interactions with a growing number of signaling receptors. It has indeed been shown that uPAR regulates signaling downstream of tyrosine kinase receptors, integrins, and G protein-coupled receptors. In addition, non-proteolytic

uPAR functions include the direct effect exerted by uPAR on cell adhesion through its specific interaction with the extracellular matrix protein vitronectin, classifying uPAR also as a non-integrin cell adhesion receptor. The importance of the uPAR-vitronectin interaction in the modulation of cell adhesion is becoming more and more compelling because it seems to be intimately connected to most of uPAR's non-proteolytic functions. Therefore, uPAR is a molecule that is involved in a wide variety of physiological pathways that range from fibrinolysis to cell adhesion, migration, and also water and sodium handling and proteinuria (Sarra-Ferraris and Sidenius 2013; Trimarchi 2015).

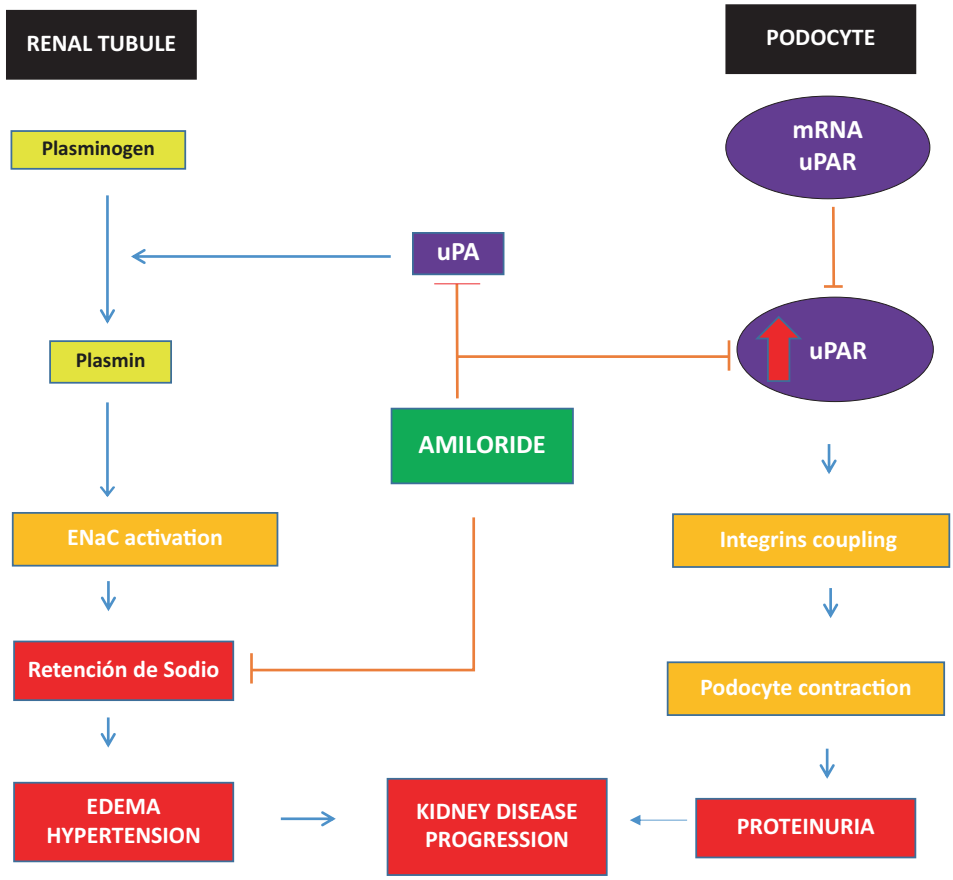
In this regard, it has been shown that uPAR interacts with several integrins that modulate their ligand-binding activities (Chapman and Wei 2001). Normally, certain integrins anchor podocytes to the glomerular basement membrane (Figs. 1 and 2). Under pathological situations, lipid raft-associated uPAR placed in podocytes forms a complex with the β3 subunit of certain integrins as αvβ3, thereby causing its activation. It is a key signal that mediates uPAR-induced cellular events leading to podocyte detachment and proteinuria when coupled to αVβ3 integrin, located at the basal side of the podocyte (Zhang et al. 2012) (Fig. 2).

Clinical Relevance

The participation of uPAR in the fibrinolytic system is probably the best known action of the receptor. uPAR's plasmatic agonist uPA converts plasminogen to plasmin, a protease that functions as an anti-thrombotic molecule (Loof et al. 2014) (Fig. 1).

Cell line data and analysis of tumor samples have demonstrated that uPAR plays a role in a number of different processes critical to tumor progression including angiogenesis (Binder et al. 2007), tumor growth (Hildenbrabd et al. 2008), and metastasis (Sidenius and Blasi 2003). uPAR is expressed in most solid cancers as well as in several hematologic malignancies including myeloproliferative disorders, acute leukemias, and multiple myeloma (Mustjoki et al. 1999; Béné et al. 2004; Hjertner et al. 2000). In cancer, uPAR expression appears to be constitutive and associated with disease aggressiveness (Aguirre Ghiso et al. 1999; Forbes et al. 2004). uPAR is expressed by multiple tumor cell types found in tumors including endothelial cells and infiltrating inflammatory cells such as neutrophils and macrophages. Expression of uPAR is further upregulated by hypoxia and may facilitate the epithelial-mesenchymal transition hypothesized to occur as a tumor acquires an invasive phenotype (Lester et al. 2007). In general, the uPAR expression pattern in tumors falls into two categories: tumors in which uPAR is expressed by both tumor and tumor-associated cells (e.g., pancreatic cancer (Cantero et al. 1997), bladder cancer (Bhuvarahamurthy et al. 2004), and renal cell carcinoma (Bhuvarahamurthy et al. 2005) and tumors in which uPAR is expressed on tumor-associated cells but not on the tumor cells themselves, e.g., colon cancer (Pyke et al. 1994; Mazar et al. 2011).

Another route of interest is the activation of proteolytic cascades after uPA–uPAR interactions, believed to be responsible for the biologic activity of uPAR. uPAR appears to play a critical role at least in two different ways. The first one is by its agonist, UPA, participating in the activation of distal tubular $ENa^{+}C$ via conversion of plasminogen to plasmin by and contributing to the generation of edema in glomerulopathies and the nephrotic syndrome (Svenningsen et al. 2009; Wei et al. 2008) (Fig. 2). Noteworthy, it has been reported that both plasminogen and plasmin are present in the urine of proteinuric rats with the metabolic syndrome and heavy proteinuria but not in control rats (Hamm et al. 2010; Ma and Eaton 2005). Svenningsen et al. have shown that plasmin present in the urine of nephrotic rats and humans can activate $ENa^{+}C$ (Svenningsen et al. 2009). Additionally, they showed that uPA present in the rat and human kidney can convert inactive plasminogen (which is filtered by the nephrotic kidney) to the active-form plasmin (Trimarchi 2015). The second one is that it has been demonstrated the role uPAR plays at the basal side of podocytes (Figs. 1 and 2). In this



Plasminogen Activator, Urokinase Receptor, Fig. 2 The role of uPAR and amiloride in the kidney

respect, integrins play a critical role in the attachment of podocytes to the glomerular basement membrane. The coupling of uPAR to integrins αvβ3 and α1β3 can activate intracellular actin and the contraction of podocytes. This phenomenon results in proteinuria and can precipitate podocyte detachment, a phenomenon named podocyturia, an irreversible event that leads to chronic renal disease and eventually to end-stage renal disease (Trimarchi 2015) (Fig. 2).

Therapeutic Implications

uPAR is an attractive target for the treatment of cancer not only because it seems to have multiple functional roles associated with tumor progression but also because its expression is restricted quite tightly to tumor tissue and it is rarely expressed in adjacent normal tissues (Li and Cozzi 2007). uPAR expression is transiently upregulated during several physiological processes, such as during wound healing and inflammatory response to infection (Xia et al. 2003; Gyetko et al. 2000; Schnaper et al. 1995). Targeting uPAR expressed on tumor-associated cells may be as important as targeting uPAR expressed on tumor cells and may lead to enhanced antitumor activity especially in those tumor types expressing uPAR on both types of cells. uPAR expression is upregulated on macrophages associated with a tumor compared with monocytes circulating in the blood or their counterparts residing within normal tissue (DanØ et al. 1999). uPAR expression is also observed on angiogenic endothelium (Yamamoto et al. 1994).

A corollary of these observations is that uPAR expression appears to increase with grade or stage (i.e., aggressiveness) of the tumor and may be enriched in metastatic lesions (Suzuki et al. 1998). These recent studies emphasize the importance of targeting tumor-associated cells in addition to the tumor cells themselves and provide a strong rationale for the discovery and development of uPAR-targeted therapeutics. Also, uPAR-UPA interaction is another site to intervene, as well as downstream UPA actions and plasmin itself (Figs. 1 and 2) (Mazar et al. 2011).

This interaction is blocked by amiloride, but tPA action is not modified by amiloride (Jankun and Skrzypczak-Jankun 1999). A recent study has shown that podocyte uPAR expression can be reduced using amiloride (Zhang et al. 2012). Amiloride plays a significant role in reducing podocyte cell motility in vitro and proteinuria in mice (Pyke et al. 1994). Amiloride inhibits the synthesis of uPAR and uPAR mRNA and consequently the podocyte αvβ3 integrin activation mediated by uPAR on αvβ3 integrin (Fig. 2). Amiloride capacity to inhibit uPAR synthesis by T lymphocytes should be of particular interest in different causes of nephrotic syndrome, because blocking their activation would inhibit αvβ3 integrin activation and the development of proteinuria with final renal dysfunction (Zhang et al. 2012; Trimarchi et al. 2014; 2016; Trimarchi 2015).

Summary

The urokinase plasminogen activator receptor (uPAR) is a cell surface receptor involved in a multitude of physiologic and pathologic processes. uPAR regulates simultaneously the plasminogen activator system and modulates cell adhesion and intracellular signaling by interacting with extracellular matrix components and signaling receptors. The multiple uPAR functions are deeply interconnected, and their integration determines the effects that uPAR expression triggers in different contexts. The proteolytic function of uPAR affects both the signaling and the adhesive functions of the receptor. These functions position uPAR as a molecule that plays important roles in tissue repair and fibrosis, in cell adhesion and migration, and in cell signaling and inflammation. Finally, recently, uPAR has been implicated in salt and water handling and in the pathophysiology of proteinuria.

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