Imaging of Prostate Cancer Using Urokinase-Type Plasminogen Activator Receptor PET

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KEYWORDS

• uPAR • PET • Prostate cancer • Radionuclide imaging • Theranostics • Molecular imaging

KEY POINTS

- Urokinase plasminogen activator receptor (uPAR) is a key component in proteolysis and extracellular matrix degradation during cancer invasion and metastasis.
- uPAR expression in prostate cancer provides independent prognostic information in addition to that contributed by PSA, Gleason score, and other clinicopathologic parameters.
- PET imaging of uPAR in prostate cancer is a new and clinically relevant diagnostic and prognostic biomarker.
- Two recent phase I uPAR PET studies including patients with prostate cancer have shown encouraging data and support large-scale clinical trials.

INTRODUCTION

The most commonly diagnosed malignancy among men in Western countries is prostate cancer (PC).[1] PC has a highly variable prognosis with some PCs remaining indolent and not causing any clinical symptoms or morbidity, whereas other PCs are or become aggressive and are associated with fast progression and high mortality.[1,2] Conventional anatomic imaging methods in PC—including MR imaging for primary disease and contrast-enhanced computed tomography (CT) and ^{99m}Tc-methylene diphosphonate–bone scintigraphy for metastatic disease—have several significant limitations, especially considering sensitivity and specificity.[3] These limitations and an increasing understanding of the complex nature and the underlying heterogeneity of PC have stimulated the development of new imaging approaches that allow direct visualization of the molecular pathology in malignant prostate tissue. These methods include multiparametric MR imaging and PET using radioligands, such as choline, gastrin-releasing peptide receptor, and prostate-specific membrane antigen-targeting ligands.[1] Indeed, functional and metabolic imaging techniques are gaining importance as the therapeutic paradigm has shifted from structural tumor detection alone

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to distinguishing patients with indolent tumors that are managed conservatively from patients with more aggressive tumors, which may require immediate treatment with surgery or radiation therapy. This has led to a search for upregulated tumor-specific markers that can serve as candidates for tumor imaging with the potential of identifying the aggressive tumor phenotype. Urokinase-type plasminogen activator receptor (uPAR) has recently been identified as a promising imaging target candidate for PC.[4] Several strategies to develop uPAR-targeting radiopharmaceuticals have been explored, using peptides, proteins, small molecules, antibodies, and nanoparticles.[5] We have recently successfully translated two of these radioligands, both based on the uPAR-targeting small linear peptide AE105, into the clinic with the first ever human studies of uPAR PET imaging in PC.[6,7]

This article focuses on PET imaging of uPAR in PC as a new and clinically relevant diagnostic and prognostic imaging biomarker technique. The potential use of uPAR PET to evaluate uPAR-directed anticancer therapy and the applicability of a uPAR-ligand for targeted radionuclide therapy are also discussed.

UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR IN PROSTATE CANCER

PC metastasizes from the prostate gland through pelvic lymphatic drainage and hematogenous routes resulting in a high prevalence of metastases to regional nodes and bones, particularly the spine. The exact mechanisms involved in PC progression remain unclear. A key requirement in the complex process of tumor invasion and metastasis is the ability of tumor cells to produce and recruit growth factors and proteolytic enzymes within the tumor cell environment to promote neovascularization, tumor growth, and extracellular matrix degradation to facilitate tumor metastasis.[8] A central player in this process is the uPAR system (**Fig. 1**). The plasminogen activator system consists of a serine protease urokinase-type plasminogen (uPA), its glycosylphosphatidylinositol-anchored cell membrane receptor (uPAR), and two specific inhibitors PAI-1 and PAI-2. uPA binds with high affinity to uPAR and subsequently converts plasminogen to active plasmin, which in turn activates several proteases related to the degradation of extracellular matrix proteins and basal membranes, thereby facilitating cancer cell invasion and metastasis.[2,5,9–13] In addition, uPA/uPAR binding affects multiple other aspects of the tumor progression and development by eliciting tumor-associated processes including cell proliferation, cell adhesion, and migration, through interactions with coreceptors, such as integrins, G-protein-coupled receptors, and growth factor receptors activating intracellular signaling pathways.[14,15] A particular high uPAR expression in cancer cells is found at the invasive

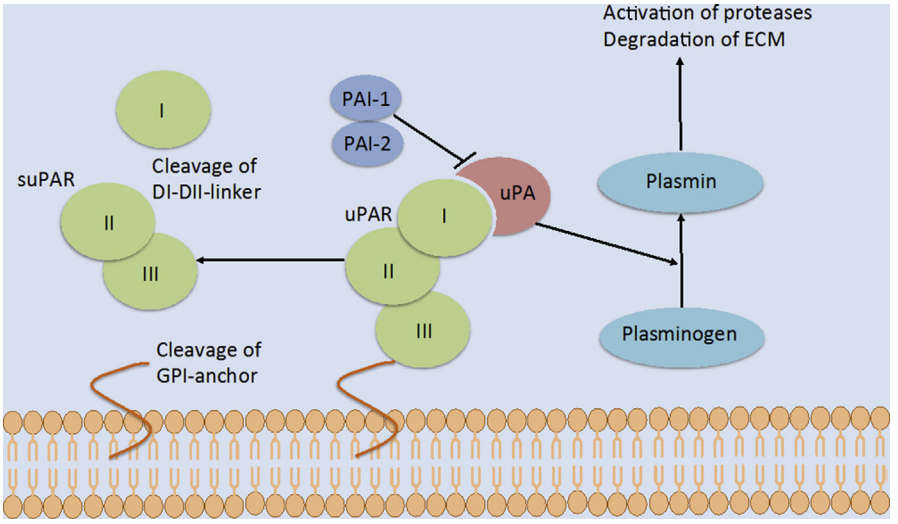

Fig. 1. Overview of the urokinase-type plasminogen (uPA)/uPAR system. uPAR consists of three domains (I, II, III) and is attached to the cell surface by a glycosyl phosphatidylinositol (GPI) anchor. uPA bound to uPAR cleaves plasminogen, generating the active protease plasmin. Plasmin activates matrix metalloproteases. Both plasmin and matrix metalloproteases degrade extracellular matrix (ECM) and thereby promote cancer invasion and metastasis. The proteolytic activities of uPA and plasmin are inhibited by PAI-1 and PAI-2. Soluble uPAR (suPAR) is released from the plasma membrane by cleavage of the GPI anchor. Both uPAR and suPAR can be cleaved in the region that links domains DI to DII to yield a DI and DIIDIII fragment.