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Review

Diversity and functional evolution of the plasminogen activator system

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ABSTRACT

The urokinase plasminogen activator system is a family of serine proteases which consists of uPA (urokinase plasminogen activator), uPAR (urokinase type plasminogen activator receptor) and PAI-1 (plasminogen activator inhibitor 1). In addition to their significant roles in activation, these proteases act as key regulators of the tumor microenvironment and are involved in the metastatic process in many cancers. High levels of uPA system proteases in many human cancer predicts poor patient prognosis and strongly indicated a key role of uPA system in cancer metastasis. Individual components of uPA system are found to be differentially expressed in cancer cells compared to normal cells and therefore are potential therapeutic targets. In this review, we present the molecular and cellular mechanisms underlying the role of uPA system in cancer progression. Epithelial to mesenchymal transitions (EMT) is the main cause of the cancer cell metastasis. We have also attempted to relate the role of uPA signaling in EMT of cancer cells.

1. Introduction

Urokinase type plasminogen activator (PLAU or uPA), and its receptor (uPAR), the substrate plasminogen (Plg), and the plasminogen activator inhibitor 1 and 2 (PAI1 and PAI2) also known as serpine 1 and serpine 2 together make the plasminogen activator system [1]. This system is a major regulator of the tumor microenvironment and is crucially involved in the metastatic process in many cancers. uPA system has a wide range of targets along with prominent location in the proteolytic network of tumors and that's why this system attracted attention of many research groups [1]. The plasminogen activator systems are involved in various physiological processes like tissue remodeling [2], but in addition to this, uPA system is involved in pathogenesis of vascular diseases such as atherosclerosis, thromboembolic disorders and stroke [3]. Research on plasminogen system intensified after urokinase was found in the urine of cancer patients in 1960 [4]. Moreover, another study in 1988 in breast cancer patients for the first time revealed uPA as a prognostic marker for survival in cancer [5]. The receptor of uPA i.e. uPAR was discovered by Vassalli et al in 1985 and its association with cancer was established in 1991 by Ossowski et al [6,7]. Since then extensive research has been undertaken on its role in cancer invasion and metastasis. Two types of plasminogen activator are found in plasminogen activator system viz., tissue type plasminogen activator (tPA) and urokinase type plasminogen activator (uPA). The former is present in both normal and some malignant tissues and is mainly involved in conversion of plasminogen to plasmin during dissolution of blood clot, while uPA is mainly associated with malignancy of cancer and plays role in pericellular proteolysis during cell migration and tissue remodeling [8]. Furthermore, it is well established now that higher expression level of both uPA and uPAR enhance tumor growth and metastasis and correlated with poor prognosis [9,10]. Though both tPA and uPA can activate inactive plasminogen to active plasmin, uPA has been extensively studied in cancer metastasis.

2. Constituents of the plasminogen activator system: uPA, uPAR, and Plg

2.1. uPA is a multifaceted protein

uPA is a serine protease with molecular weight of approximately 50,000 Da which is released from the cells as a single chain zymogen pro-uPA, a non-active 411 amino acid glycoprotein which after cleavage at K158–I159 forms two-chain high molecular weight uPA (HMW uPA) [11]. This conversion is catalyzed by plasmin, blood coagulation factor XIIa, plasma kallikrein, cathepsin B, cathepsin L, T cell–associated serine proteinase, nerve growth factor-γ and prostate specific antigen [12–16]. This high molecular weight uPA undergoes additional proteolytic cleavage and is converted into three functionally independent regions: the amino terminal fragment which contains growth factor domain (GFD) and has high affinity to bind with uPAR, the kringle domain involved in intracellular signaling and cell migration and a carboxyl terminal proteolytically active serine protease domain which retains its plasminogen activator function [17,18]. The serine protease domain of uPA has high affinity for its substrate which

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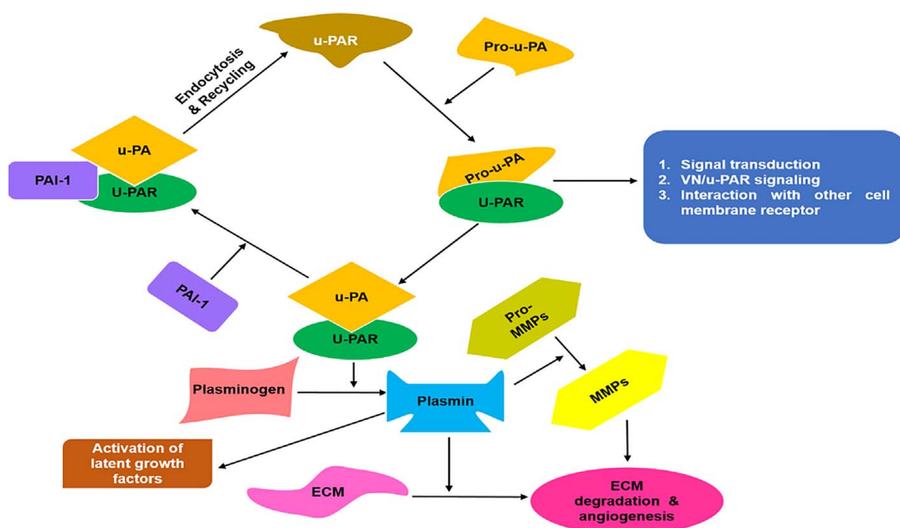

Fig. 1. The urokinase-type plasminogen activator (uPA) system in cancer. Inactive urokinsae type plasminogen activator (uPA) binds with the urokinsae type plasminogen activator receptor (uPAR) and cleaves the plasminogen into active plasmin. Activated plasmin then breaks extracellular matrix (ECM) components and helps in cell migration and invasion. Active plasmin can subsequently activate pro-MMPs into MMPs that also degrade ECM. For intracellular signaling uPA-uPAR complex interacts with other cell surface receptors such as integrin and EGFR. uPAR also interacts with vitronectin to regulate cell adhesion and cell migration. Plasmin activation by uPA-uPAR system is inhibited by PAI-1. The binding of PAI-1 forms a trimeric complex PAI-1-uPA-uPAR which is recognized by lipoprotein related protein and internalized for endocytosis.

generate activated protease plasmin by cleaving inactive zymogen plasminogen [Fig. 1]. Activated plasmin degrades various components of ECM resulting in its pro-invasive and pro-metastatic effects [19,20]. The concentration of uPA in blood plasma is around 20 pM and most of it forms complex with PAI-1 while rest is present in the pro-uPA form [21]. uPA is quite restricted in terms of its substrate specificity and plasminogen is its main substrate [12,22]. However, there is evidence that uPA may also have other substrates such as macrophage stimulating protein (MSP) and hepatocyte growth factor/scatter factor; these substrates have high sequence similarity with plasmin but lack proteolytic activity. They are also secreted as inactive zymogen and become active after undergoing proteolytic cleavage [23]. Various cytokines and growth factors, such as TNF-α, EGF and VEGF can induce release of uPA. However, there is speculation about the enzyme responsible for activation of pro-uPA to uPA. Plasmin may be the activator of pro-uPA but then the question arises as to which one of these molecules is activated first uPA or plasmin and how [24]. As mentioned earlier, there are many other activators of pro-uPA such as kallikreins and cathepsins, and they can also be first activator of pro-uPA [25]. Additionally, in vitro experiments have proved that binding of pro-uPA to uPAR facilitates the activation of plasminogen to plasmin without the activation of pro-uPA. This is not completely surprising because it is already known that uPA plasminogen conversion activity increases by as much as 50 fold after binding with uPAR [26]. It is believed that after binding with pro-uPA, uPAR undergoes some conformational changes that confer protease abilities to the single-chain molecule [27]. It is well established that tumor tissues have elevated expression of uPA than normal tissues [28–30]. uPA is present at invading front of the cancer cells and facilitates cell invasion and migration in both primary and metastatic tumors [31]. uPA is also found to play role in angiogenesis investigated in models of corneal vascularization [32]. It is demonstrated that proteolytic activity of uPA is needed for the migration of endothelial cells which is one of the earliest steps in angiogenesis and is also necessary for the earliest stages in tube formation [33,34].

2.2. Transcriptional regulation of uPA

Development of cancer and its progression towards the metastatic stage involves the deactivation and activation of many specific genes. Earlier it was believed that cancer is a genetic disease and mutation in the DNA sequence is the sole cause of change in gene expression during cancer progression. However, now it is very well established that epigenetic changes also play a significant role in change in gene expression including those involved in cancer development and progression [35]. Dynamic epigenome is observed by many researchers with some parts of epigenome in a state of flux throughout life while others are inherited or established during embryonic development [36,37]. There are various mechanisms by which epigenetic modifications are effected such as DNA methylation, post-translational modification of histone tails, nucleosome positioning, and non-coding RNA [38]. These epigenetic modifications are brought in by protein machinery which consists of histone modifiers, chromatin remodeling complexes, DNA methyltransferases (DNMTs) and methyl-DNA binding proteins (MBDs), proteins which interact with histone modifications [36]. Epigenetic modification of uPA is demonstrated in early stage hormone-responsive breast cancer cell lines (MCF-7 and T-47D), late stage hormone-insensitive breast cancer cells and normal human mammary epithelial cells (HMEC) by exploring the correlation between expression of uPA and hormone (estrogen) sensitivity [39]. The expression of uPA is conspicuous only in the highly invasive MDA-MB-231 cells [39]. Catherine Leurer et al demonstrated DNA methylation status of the uPA gene by performing southern blot analysis. They observed that CpG islands of uPA gene of highly invasive breast cancer cell lines are hypomethylated while CpG islands of uPA gene of normal breast cells and early stage breast cancer cells are methylated [39]. To examine the methylation status of CpG islands in the uPA promoter methylation sensitive PCR yielded similar results showing that CpG islands in the uPA promoter of MCF-7 were around 90% methylated while highly invasive MDA-MB-231 cells had fully demethylated CpGs in the same region [39]. An analysis of DNA methylation machinery showed that MDA-MB-231 cells have low DNMT1 activity and high DMase activity while MCF-7 cells had reduced DMase activity and high DNMT1 activity confirming their previous data on demethylated uPA promoter in MDA-MB-231 cells and partially hypomethylated promoter in MCF-7 cells [39]. Additionally, DNA methylation was found as the dominant mechanism for uPA gene silencing because when inhibitor of histone deacetylase i.e., Trichostatin A was added, it did not induce uPA expression in MCF-7 cells while uPA expression in MDA-MB-231 was enhanced [40]. The uPA and PAI-1 expression in gastric cancer, meningioma, laryngeal squamous cell carcinoma and prostate cancer were also found to be regulated by DNA methylation where both uPA and PAI-1 were also recognized as epigenetic based prognostic and therapeutic targets [41,42]. However, to observe the impact of uPA-PAI-1 methylation in cancer, there is only scanty results based on clinical studies.

2.3. Characteristics and biological functions of uPAR

uPAR was discovered by Stoppelli et al and Vassalli et al in the year 1985 [6,43]. This is a cell surface receptor which has very high affinity

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