uPAR, beyond regulating physiological functions, has orchestrated roles in cancer (Review)

LIANG WANG, XITE LIN and PENGMING SUN

Fujian Key Laboratory of Women and Children's Critical Diseases Research, Department of Gynecology, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, Fujian 350001, P.R. China

Received May 9, 2022; Accepted September 29, 2022

DOI: 10.3892/ijo.2022.5441

Abstract. Urokinase-type plasminogen activator receptor (uPAR) serves as the receptor for uPA and the uPA-uPAR complex initiates the extracellular matrix degradation cascade. In cancer, aberrantly elevated uPAR expression is associated with invasion and metastasis, as well as cancer proliferation and survival, thereby rendering uPAR an effective marker for prognosis and a target for therapy. Although uPAR is transiently expressed at limited amounts in normal tissues and certain non-cancer pathological processes, their underlying mechanisms do not overlap with those of tumorigenesis. The present review summarized the fundamental function, signaling pathways and targeted therapeutic strategies, particularly immunotherapy targeting uPAR, as well as its differential roles in non-cancer and cancer tissues, to objectively evaluate whether this classic molecular pathway is of enduring research value for future study.

Correspondence to: Dr Pengming Sun, Fujian Key Laboratory of Women and Children's Critical Diseases Research, Department of Gynecology, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, 18 Daoshan Road, Fuzhou, Fujian 350001, P.R. China
E-mail: sunfemy@hotmail.com

Abbreviations: uPAR, urokinase-type plasminogen activator receptor; ECM, extracellular matrix; GPI, glycosylphosphatidylinositol; PAI-1, plasminogen activator inhibitor type-1; TME, tumor microenvironment; FAK, focal adhesion kinase; HACMs, human adult cardiac myocytes; AECs, alveolar epithelial cells; EMT, epithelial-mesenchymal transition; HPV, human papillomavirus; EOC, epithelial ovarian cancer; CAR, chimeric antigen receptor

Key words: urokinase-type plasminogen activator receptor, extracellular matrix, tumor metastasis, cancer microenvironment, targeted therapy, gynecological cancer

Contents

1. Introduction

Urokinase-type plasminogen activator receptor (uPAR) was originally identified on the monocyte/macrophage-like human cell line U937 as the membrane receptor for the serine protease uPA in 1985 (1). The n9omenclature of uPAR reflects its primary function, where uPA binds to uPAR to activate the conversion of plasminogen into plasmin, followed by the mobilization of a proteolysis cascade to degrade the extracellular matrix (ECM), which provides structural support and an elaborate microenvironment for biological processes to occur within tissues (2). uPAR is also named CD87 in the clusters of differentiation classification, which is expressed by certain immune cell types (3,4). As uPAR is tethered to the cell surface by a glycosylphosphatidylinositol (GPI) anchor, it lacks a transcellular or intracellular framework. Furthermore, uPAR cooperates with lateral parts, mainly integrin, to assemble complexes and regulate signaling cascades, which are not restricted to proteolysis function.

In the first decade after the discovery of uPAR, researchers have attempted to decipher the molecular structures and functions of uPAR, uPA, plasmin, inhibitors plasminogen activator inhibitor type-1 (PAI-1) and PAI-2 (5-7). In the second decade, preclinical and clinical evidence demonstrated that uPAR is expressed at high levels in cancer tissues compared to its undetected expression level in para-cancer or normal tissues. Overexpression of uPAR promotes carcinogenesis by influencing proliferation, metastasis, invasion, apoptosis, dormancy, drug resistance

and recurrence of cancer cells, indicating that uPAR is a major biomarker for cancer invasion and metastasis (8-10). In the last decade, with the development of novel therapeutic methods, uPAR and the uPA-uPAR complex have been established as targets for therapeutic interventions (11,12). Numerous clinical trials pay attention to uPAR-specific drugs (13-15).

On the one hand, numerous studies have reported the construction of uPAR and signaling pathways associated with uPAR in detail (2,15). However, the non-specific expression of uPAR in certain normal tissues may discount the potential of uPAR as a clinically actionable therapeutic target. Cancer cells display heterogeneity depending on the tumor microenvironment (TME) and the interactions between stromal and cancer cells are dependent on the spatial and topographic distribution of uPAR in stromal and cancer cells, indicating that the functions of uPAR are not restricted to proteolysis (16-19). Therefore, to exploit whether uPAR may serve as an efficient therapeutic target, the functions of uPAR in metabolism, metastasis, invasion and inflammation require to be discussed.

2. Structure and function of uPAR and uPA in the plasminogen activator system

uPAR is located on the outer leaflet of the cell plasma membrane as a GPI-anchored cysteine-rich protein receptor. The primary ligand of uPAR is uPA and the binding of uPA to uPAR leads to the initiation of the plasminogen activation cascade and the regulation of pericellular proteolysis in cancer. Furthermore, uPAR mediates several biological processes, such as inflammation, cell migration, tissue remodeling, angiogenesis and cell adhesion in certain normal cells (14,20,21).

uPAR in the plasminogen activator system. The location of the uPAR gene (*PLAUR*) is chromosome 19q13.31 (Gene ID, 5329) comprising seven exons (22). Human uPAR cDNA encodes a polypeptide of 335 amino acids, including an N-terminal 22-residue secretion signal peptide and a C-terminal segment (30 amino acids) that is removed with the attachment of a GPI anchor. The mature protein (283 residues, 35 kDa) is highly glycosylated and is composed of three similar-sized (~90 residues each) homologous domains (herein referred to as DI, DII and DIII) without any transmembrane sequence (8,23). Since a GPI anchor does not completely penetrate the lipid bilayer, GPI-anchored protein is associated with the plasma membrane more loosely than transmembrane proteins (24). When uPAR is secreted from the plasma membrane by the proteolytic cleavage of the transmembrane domain or cleavage of the GPI anchor, soluble uPAR (suPAR) dissociates into extracellular fluids. Soluble and GPI-bound uPAR exists in different conformations, as the GPI regulates its molecular conformation (25). Full-length suPAR, which consists of all three domains without the GPI anchor, may be cleaved into two soluble forms, suPAR-DI and suPAR-DII-DIII, by numerous molecules, such as uPA, MMP, elastase, plasmin and cathepsin G. Serum or plasma levels of soluble uPAR may be used for diagnosis and prognosis of inflammation and cancer disease (26,27).

uPAR is a member of the lymphocyte antigen-6 (Ly6) superfamily and this superfamily is characterized by a three-finger Ly6 domain. Members of the human Ly6 family consist of 35 members, including uPAR, CD177, CD59 and prostate stem cell antigen. The Ly6 superfamily are involved in similar signaling cascades and biological functions, e.g. C4.4A, a structural uPAR homolog, which is also implicated in the invasion and metastasis of numerous cancer types (28-31).

uPA in the plasminogen activator system. uPA and its homolog tissue-type PA (tPA) cleave plasminogen to plasmin, thereby mediating the degradation of fibrin and other ECM proteins (32). tPA controls the degradation of intravascular fibrin, while uPA controls the production of plasmin during cell migration and invasion (33). Plasmin may degrade vitronectin, laminin, fibronectin, fibrin and proteoglycans (33).

In addition to the fundamental features of ligand-receptor binding, uPA-uPAR binding has four unique characteristics that facilitate several disease processes. First, the binding of uPA to uPAR has a topographical limitation. uPA is localized at the cell substratum and cell-cell contact sites through focal adhesions. When uPAR is occupied by uPA, its lateral mobility is restricted, but the unoccupied uPAR has relatively flexible mobility (34). This hallmark of uPAR facilitates active proteolysis within the cell-cell contact region. Therefore, the uPA-uPAR complex is not only an activation factor for proteolysis but also a platform for the actions of proteases. Furthermore, uPA binds to uPAR in a cell type-specific manner. The expression of uPAR is relatively specific to the cell type; uPAR is detected at high levels in cancer cells and cancer-associated stromal cells and moderate levels in monocytes, as well as certain endometrial cells, under physiological conditions. However, uPAR is barely detected in most normal tissues. Even though cells express uPAR, the formation of the uPA-uPAR complex depends on cellular functions. For instance, uPAR proteins on rhabdomyosarcoma cells are mostly occupied and confined to the cell adhesion sites, but uPAR proteins remain largely unoccupied on fibroblasts (HES cells) (34). Occupied uPAR promotes the neoplastic transformation of normal cells. In addition, the binding of uPA to uPAR is not necessary for uPAR to achieve its function. uPAR functions in downstream signaling without binding to its ligands. For instance, in estrogen receptor (ER)-positive breast cancer, but in the absence of estrogen, uPAR without binding to uPA may activate extracellular signal-regulated kinase (ERK)-epidermal growth factor receptor (EGFR) pathway depending on H-Ras and Rac-1 to facilitate cell proliferation (35). As another characteristic, although the uPA-uPAR protein-protein interaction is a tight high-affinity (dissociation constant K_D=1 nM) and stable interaction (dissociation rate constant $k_{off}=10^{-4}$ S^{-1}), the affinity depends not only on the binding site but also on the molecular integrity of uPAR (36). Although the functional binding site of the intact form of uPAR for uPA is DI, soluble uPAR DI binds to uPA with low affinity, indicating that the structure and integrity of the binding site are important for the effective binding of uPAR to uPA with high affinity (37). Of note, the binding site of uPAR for uPA is also the site where uPA cleaves uPAR into variant forms of suPAR. The affinity of uPAR for uPA and

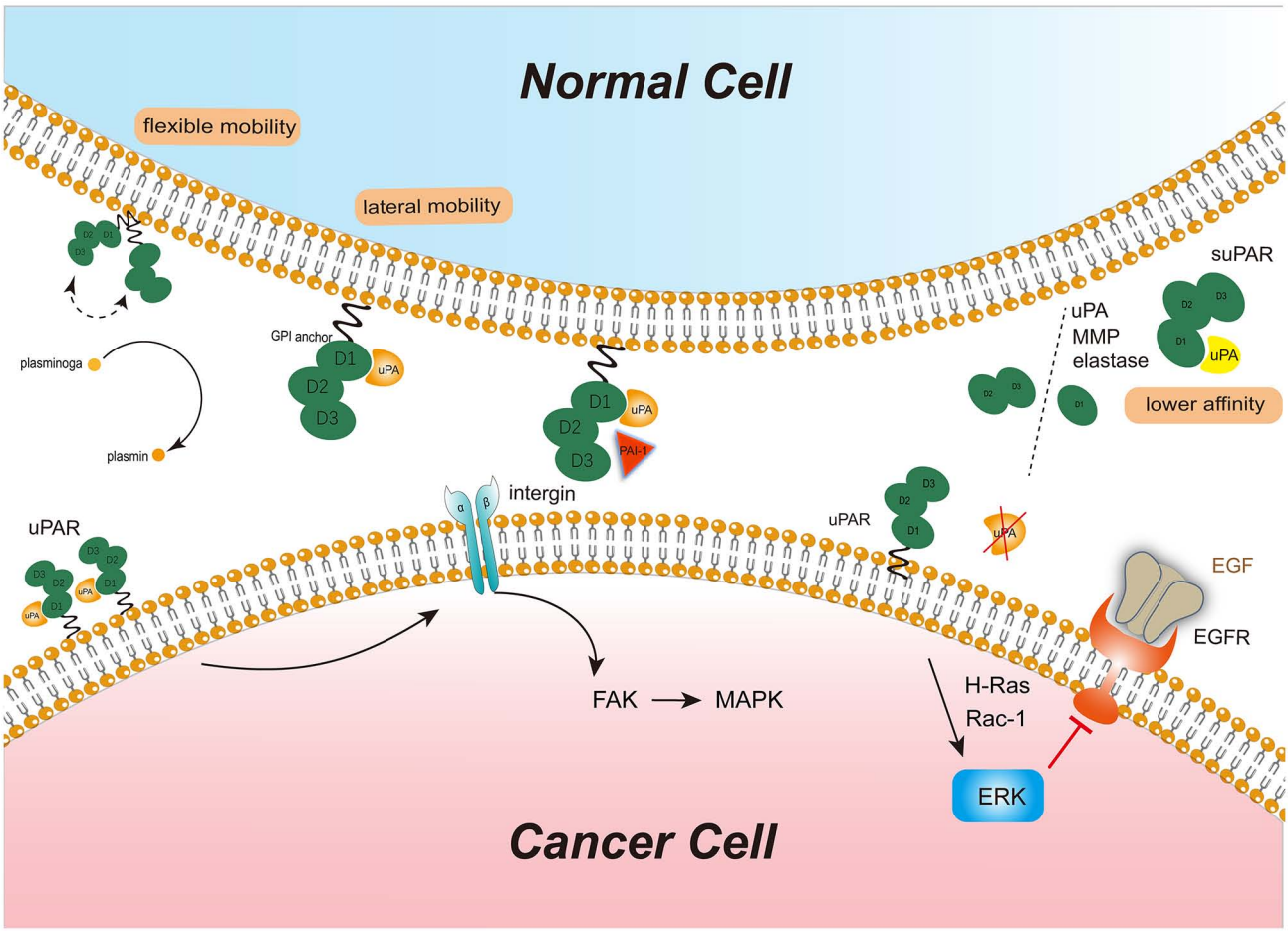

Figure 1. Schematic of the processes for uPAR to activate downstream signals. The four characteristics of uPA-uPAR binding. When uPA binds to uPAR, plasminogen transforms into plasmin. PAI-1 is an inhibitor of uPA-uPAR binding. uPAR without uPA has great flexibility, while uPAR binding with uPA has limited flexibility. More uPAR is occupied by uPA on tumor cells than on normal cells, and the occupied uPAR is conducive to further invasion. uPA-uPAR binding activates FAK and MAPK signaling via integrin. uPAR relies on H-Ras and RAC-1 to activate ERK and achieve co-expression with EGFR without the binding with uPA. uPAR is able to break off from GPI. Intact suPAR is able to fragment into DI and DII-DIII by binding with uPA, MMP, elastase and plasmin. The affinity of uPA and soluble uPAR decreased compared with membrane uPAR (IV). Free interceptive uPAR is usually found in tumors. uPAR, urokinase-type plasminogen activator receptor; FAK, focal adhesion kinase; suPAR, soluble uPAR; GPI, glycosylphosphatidylinositol; PAI-1, plasminogen activator inhibitor type-1.

the stability of the uPA-uPAR complex are dependent on the membrane localization of uPA. In healthy individuals, only intact suPAR may be detected in plasma and/or serum, while in patients with cancer, both intact and cleaved suPAR may be identified; thus, cleavage is unique for cancer (37).

Other important molecules associated with uPAR in the plasminogen activator system. Several ligands have been reported to bind to uPAR, out of which uPA is the most widely known ligand. The interaction of uPAR and integrin activates proteolytic cell signals and promotes the localization of proteases to the cell surface (38). In hepatocellular carcinoma cells, overexpressed uPAR, through interaction with α5β1 integrin, initiates an intracellular signaling cascade through the conversion of focal adhesion kinase (FAK) to active the MAPK ERK to induce cell growth (39). Blocking this pathway using FAK-related non-kinase resulted in cell dormancy without any changes in the apoptotic rate or the expression of proteins associated with the Akt signaling pathway (39). Furthermore, in ovarian cancer cells, the inhibition of the co-localization of α5 integrin and uPAR affects apoptosis but not angiogenesis (microvessel density) or proliferation (Ki-67) (40). α2β2 integrin (also known as MAC1) and uPAR co-localize on the surface of monocytes and neutrophils and induce leukocyte recruitment to the tumor environment in a uPA-independent manner (41,42). However, a study indicated that uPAR interacts with α5β6 integrin in ovarian and colorectal cancer cells to modulate cell migration, revealing that α5β6 integrin binds to the DII and DIII of uPAR (38).

The endogenous inhibitors of the uPA/uPAR system, namely PAI-1 and PAI-2, regulate the activity of uPA-uPAR through direct inhibition or their effect on cell surface expression of uPAR and internalization of uPA (43). uPAR-uPA-plasmin degrades ECM, mainly collagen, in homeostasis. Excessive PAI-1 results in the accumulation of collagen by inhibition of uPAR-uPA-plasmin to form fibrosis in ECM (44). Furthermore, PAI-1 has controversial roles in tumors: It inhibits the activation of uPA-uPAR to suppress invasion and metastasis, while on the other hand, it promotes angiogenesis and cancer growth (45). The processes of ligands binding with uPAR and activation of downstream signals are illustrated in Fig. 1.

3. Roles of uPAR in normal physiological functions

Although vast research focused on uPAR in cancer, uPAR and its ligands are not obsoletely exclusive to cancer. Its roles in non-cancer contexts should not be ignored and its functions in physiological processes should be explored to comprehensively appraise uPAR. Virtually, without any set standard for its expression levels, the uPA-uPAR system exists in every body system, such as the digestive and respiratory tracts, bones, skin, breast, genital organs and brain, as well as the urinary, central nervous, endocrine and hematopoietic systems (21). Within those systems, under physiological conditions, uPAR is expressed in dynamic biological processes, such as the migration of trophoblast cells and keratinocytes at the site of epidermal injury, and is expressed on cells with low numbers, and it mainly localizes at focal contacts and cell-cell contact sites (46). The activated plasmin-uPA-uPAR axis causes the retraction of endothelial cells, thereby exposing the basement membrane for its digestion and degradation (47). The in-depth understanding of the restricted expression of uPAR in non-cancerous tissues will facilitate the identification of malignancies.

Role of uPAR in nervous and cardiovascular systems. In the nervous system, uPAR is involved in both physiological and pathological processes. A mouse model deficient in uPA and uPAR indicated an aggravated form of autoimmune encephalomyelitis, proving that the uPA-uPAR complex is indispensable for central nervous system inflammation (48). Furthermore, the results suggested that T lymphocytes in those mice had reduced reactivity towards encephalitogenic antigens (48). Diaz *et al* (49) observed that neurons are able to release uPA and that astrocytes recruit uPAR to their plasma membrane during the recovery phase from a hypoxic injury. The binding of neuronal uPA to astrocytic uPAR induces astrocytic activation by a mechanism that does not require plasmin generation, but is mediated by the ERK1/2-regulated phosphorylation of the STAT3, astrocytic thrombospondin-1 and synaptic low-density lipoprotein receptor-related protein-1, demonstrating that the binding of uPA to uPAR initiates functions not limited to proteolysis (49).

In cardiac myocytes, the beneficial effects of uPA-uPAR binding are independent of the proteolytic function. For instance, in human adult cardiac myocytes (HACMs), both uPA and amino-terminal fragment (ATF) of uPA, which is devoid of the proteolytic domain but is able to bind to uPAR as uPA, may protect HACMs from oxidative damage by increasing the expression of 8-hydroxyguanine DNA glycosylase for DNA damage repair and inhibiting p53-induced apoptosis (50). In the hematological system, patients with paroxysmal nocturnal hemoglobinuria have decreased expression of GPI-anchored uPAR on granulocytes and platelets but exhibit increased suPAR in plasma. Somatic mutations in the gene encoding phosphatidylinositol-glycan biosynthesis class A protein result in the failure of synthesis of the GPI-moiety for protein anchoring and suPAR is not shed from the cell surface but secreted from leukocytes directly. The absence of membrane uPAR contributes to decreased activation of plasmin based on uPA-uPAR binding, giving rise to complications such as thromboembolism (51,52). In the immune response against pathogen infections, uPAR in monocytes and neutrophils is implicated in leukocyte recruitment, and is a potential maturation marker for leukocytes (29,41,42,53). For instance, when the lungs of uPAR-deficient mice were infected by *Pseudomonas aeruginosa*, there was no recruitment of neutrophils to the sites of infection. However, in wild-type mice, uPAR binding to β2 integrin induced neutrophil recruitment to the sites of infection in a uPA-and proteolysis-independent manner (54). Furthermore, during lung injury caused by the decreased expression of surfactant protein C, p53 directly bound to 3'UTR sequences of uPA, uPAR and PAI-1 and contributed to the apoptosis of alveolar epithelial cells (AECs). However, the suppressed expression of uPA and uPAR caused by p53 and the increased expression of PAI-1 indicated that the inhibition of the uPA system may induce apoptosis in AECs (55).

Roles of uPAR in respiratory, digestive and urinary systems. In airway epithelial cells, membrane-bound uPAR rather than suPAR orchestrates events such as proliferation, apoptosis and migration under normal conditions; however, the expression of uPAR alone is upregulated in the sputum of patients with asthma, chronic obstructive pulmonary disease and cystic fibrosis (56). In the bronchial epithelium, human airway trypsin-like protease (HAT) truncates full-length uPAR (DI-DII-DIII) into DII-DIII, which does not bind to its ligands-uPA and vitronectin. Therefore, uPAR is regulated by HAT in a ligand-independent manner, but the process involves the proteolytic function of uPAR in tissue remodeling (57). In normal lung epithelial cells, the uPA-uPAR-PAI-1 axis mediates fibrinolytic activity, while in acute lung injury and pulmonary fibrosis, all of the three components are active, which is similar to the scenario observed in cancer (58).

In the normal renal filtration barrier, uPAR is dispensable and the components of the plasminogen system, uPA, tPA and PAI-1, are expressed at relatively low levels. However, during podocyte damage, overexpression of uPA, uPAR and PAI-1 induces podocyte migration and podocyte apoptosis by plasminogen activation through the uPA-uPAR-α5β3 integrin axis (59). The levels of uPAR are also elevated in patients with kidney graft rejection (59). The expression of suPAR directly correlates with the degree of proteinuria and its interaction with apolipoprotein L1 serves as a strong predictor of kidney disease (60). In the digestive system, the upregulated uPA-uPAR pathway damages the epithelial barrier integrity of the intestinal mucosa, which is a cause of inflammatory bowel disease (61). In colonic crypt luminal surface epithelial cells, the expression of uPAR is regulated by Kruppel-like 4 transcription factor (62). The primary cause of liver fibrosis is cellular senescence and senescent cells exhibit upregulation of uPAR. Therefore, chimeric antigen receptor (CAR) T cells targeting uPAR have been proved to be suitable for the treatment of liver fibrosis (63).

Of note, uPAR is indispensable for the menstruation cycle and decidualization in the uterus; however, uPAR is also associated with poor prognosis for endometrial cancer (64,65). The expression of uPAR is always at moderate levels in non-cancerous tissues with certain beneficial effects, which are summarized in Table I.

Table I. Roles of uPAR in non-cancerous tissues or diseases.

Organ or system	Related molecules or pathways	Observed effect	Study type	(Refs.)
Nervous system	Plasmin-uPA-uPAR	Deficiency of uPA or uPAR in mice results in exacerbation of experimental autoimmune encephalomyelitis.	*In vivo*	(48)
Nervous system	uPA-uPAR-ERK1/2	Promotes the recovery of ischemic brain by activating astrocytes and recovering synapses.	*In vitro* and *in vivo*	(49)
Immune system	uPAR-β2 integrin	Deficiency of uPAR in mice results in failure recruitment of neutrophils in lung infected by *Pseudomonas aeruginosa*.	*In vivo*	(54)
Hematological system	uPA-uPAR-activated plasmin	In patients with paroxysmal nocturnal hemoglobinuria, the deficiency of GPI-uPAR on their granulocytes and platelets, contributes to decreased activated plasmin and thromboembolism.	*In vitro* and *in vivo*	(52)
Cardiovascular system	uPA-uPAR-hOOG1	uPA-uPAR binding protects cardiac myocytes from oxidative damage by increasing hOGG1 for DNA damage repair and inhibiting apoptosis.	*In vitro*	(50)
Urinary system	uPA-uPAR/suPAR-α5β3 integrin, PAI-1	The plasminogen system has no documented role in physiological development but activation of this system accelerates podocyte injury and kidney disease progression.	*In vitro* and *in vivo*	(59)
Digestive system	KLF4-uPAR-uPA	In colonic crypt luminal surface epithelial cells, the expression of uPAR is regulated by transcription factor KLF4.	*In vitro* and *in vivo*	(62)
Digestive system	uPA-uPAR	In inflammatory bowel disease, uPAR damages the epithelial barrier integrity of intestinal mucosa,	*In vivo*	(61)
Female reproductive system	Progesterone-uPA-uPAR-activated plasmin/PAI-1	Plasmin activated by increasing uPA-uPAR binding through degrading extracellular matrix regulates shedding in a menstruation cycle and is also affected by increasing PAI-1 under the stimulation of progesterone.	*In vivo*	(64)
			In vivo	(65)
Female reproductive system	Estrogen and progesterone-WNT pathway-uPAR	Estrogen and progesterone regulate the WNT pathway and uPAR is the target gene in the pathway to implement uterine stromal cell decidualization for reproduction.		

uPAR, urokinase-type plasminogen activator receptor; suPAR, soluble uPAR; GPI, glycosylphosphatidylinositol; PAI-1, plasminogen activator inhibitor type-1; KLF4, Kruppel-like factor 4; hOGG1, 8-hydroxyguanine DNA glycosylase.

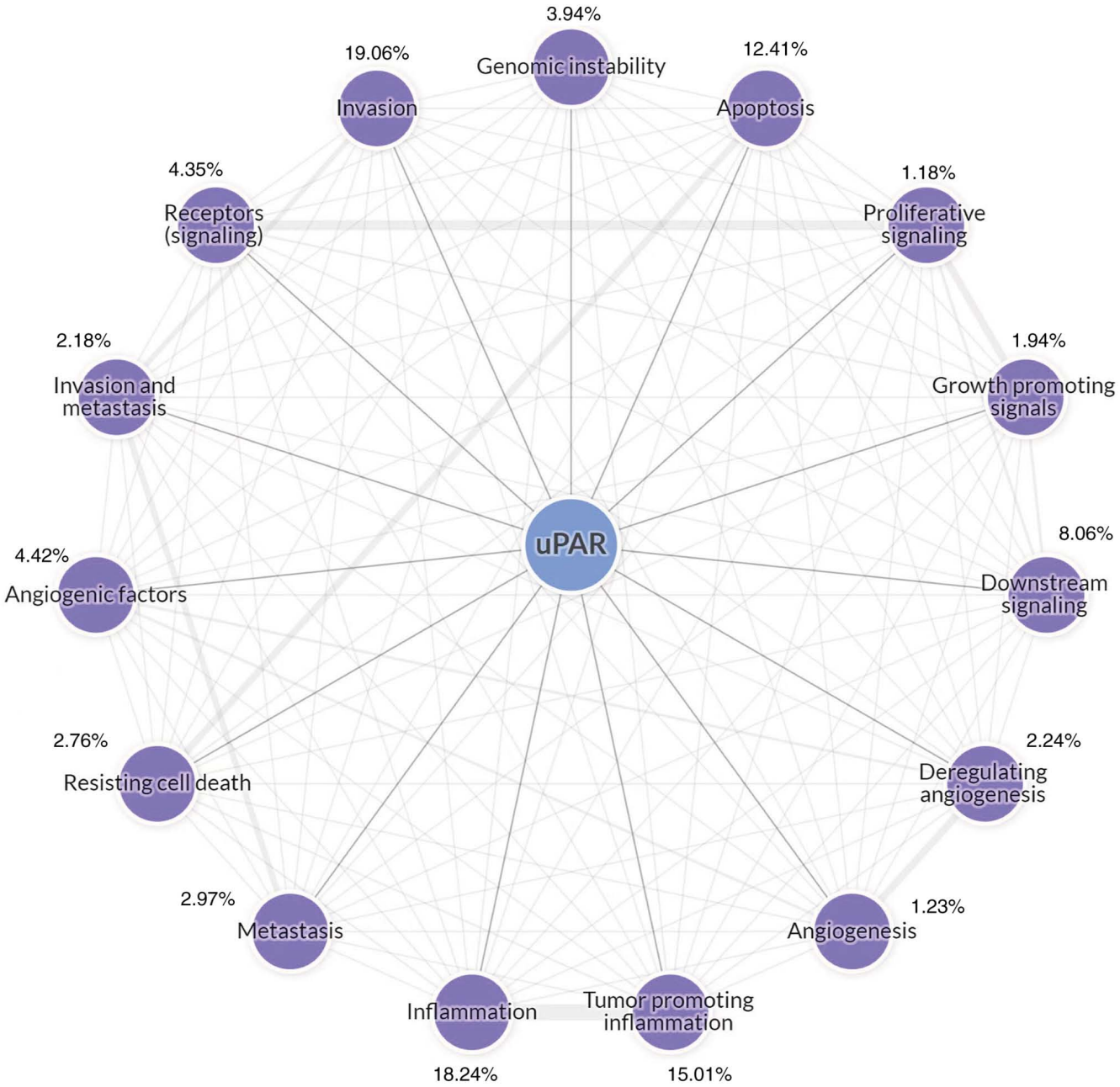

Figure 2. Network diagram of the functions of uPAR in cancer progression. Research on uPAR mainly focuses on invasion and metastasis, which makes it a classical biomarker for cancer invasion. However, in cellular energetics, research on uPAR is worthy of more attention, at least in the subjects of glycolysis and reactive oxygen species. The data were obtained with the Cancer Hallmarks Analytics Tool (https://lbd.lionproject.net/). uPAR, urokinase-type plasminogen activator receptor.

4. Pathological function of uPAR in cancer

The uPA system is involved in the proliferation, adhesion, migration and angiogenesis of tumor cells in common cancer types (22). Accumulating evidence has suggested that uPAR has a critical role in malignancies and the relatively specific functions of the uPA-uPAR complex include the regulation of cell metastasis, invasion and cell metabolism (64). The main functions of uPAR determined by most studies are presented in Fig. 2, which were collected by the Cancer Hallmarks Analytics Tool (http://chat.lionproject.net/). However, its role in cell energetics and expression in stromal cells have remained largely unexplored.

uPA-uPAR axis facilitates several processes in cancer progression. In cancer cell metabolism and energetics, as opposed to normal cells, cancer cells use glycolysis to produce ATP by a process called aerobic glycolysis or the Warburg effect (65). At present, cellular energetics is a minority field for uPAR, as indicated with the Cancer Hallmarks Analytics Tool (Fig. 2), but uPAR has been demonstrated to be involved in both glycolysis and reactive oxygen species (ROS). Laurenzana *et al* (65) reported that uPAR overexpression promotes glycolysis depending on the uPA-uPAR-a5b1 integrin axis connected with EGFR involved in the PI3K-mTOR-HIFα pathway in melanoma cells. In melanoma, the number of mitochondria in cancer cells increased when uPAR was knocked

out by CRISPR/Cas9 (66). High glucose and insulin levels increase the production of ROS to activate uPA-uPAR and PAI-1 proteolysis function in breast cancer (67). In cell metastasis and cell invasion, epithelial-mesenchymal transition (EMT) is a non-binary process where epithelial cells gradually acquire characteristics of mesenchymal cells, wherein cancer cells express markers with different types and levels (68). Highly activated plasmin-uPA-uPAR signaling induces increases in interleukin-like EMT inducer (ILEI) secretion and changes in the subcellular location of ILEI, which facilitates EMT to affect cancer progression in breast cancer (69). The crosstalk of uPAR with formyl peptide receptor type 1 (FPR1) through both autocrine and paracrine signaling induces invasion in melanoma cells (70). The 84-95 sequence of uPAR triggers the activation of FPR1 in a uPA-dependent manner (70). To inhibit invasiveness of glioblastoma cells, the solute carrier family 8 member 2 protein was utilized to inactivate the ERK1/2-NF-κB-MMPs/uPA-uPAR pathway (71). In hepatocellular carcinoma, PDZ-binding kinase enhanced *uPAR* expression by inducing the binding of ETS translocation variant 4 to the promoter region of uPAR, thus leading to cancer invasion and metastasis (72). In gastric cancer, overexpression of uPA and uPAR and knockdown of PAI-1 resulted in increased propensity for peritoneal metastasis in mice (73). Diallyl disulfide was reported to downregulate uPAR by inhibiting the ERK/Fra-1 pathway to suppress metastasis of gastric cancer cells (74). In addition, upregulation of uPAR may be an early marker from chronic inflammation to cancer in the stomach. uPAR was detected at high levels in gastric epithelial cells of mice during persistent infection with *Helicobacter pylori* (75). Of note, the baseline soluble uPAR level in serum prior to chemotherapy may predict adverse outcomes for patients; those cancers are types associated with an inflammatory state, such as lung and colon cancer (76).

Expression of uPAR in stromal cells in the TME. Increasing evidence indicates that stromal non-neoplastic cells have an important role in the TME; the interaction of stromal cells with tumor cells promotes tumor progression (22). uPAR has been reported to be abundantly expressed in stromal cells, including tumor fibroblasts, macrophages and endothelial cells, as well as tumor-infiltrating lymphocytes. uPAR expression in endothelial cells is involved in angiogenesis in cancer tissue. When the plasmin-uPA-uPAR axis is over-activated, endothelial cells undergo basement membrane degradation, migrate into the interstitial matrix and proliferate to form new vessels within the tumor tissue (77). In malignancies, uPAR may regulate angiogenic growth factor-induced endothelial cell migration and survival (78). uPAR uses the proteolytic activity of uPA on the endothelial cell surface to promote angiogenesis via the uPAR/uPA-plasmin-TGFβ1 positive feedback loop in a protease-dependent manner (79). Unseld *et al* (80) observed that uPAR cooperated with a5 integrin to activate FAK in an NF-κB-dependent manner, leading to downregulation of phosphatase and tensin homolog to promote angiogenesis in endothelial cells. However, in endothelial cells, suPAR may promote angiogenesis by its chemotactic sequence Ser88-Arg-Ser-Arg-Tyr92 via a direct mechanism involving the vitronectin receptor and G-protein-coupled formyl peptide receptor independent of uPAR proteolytic activity (77). Owing to the characteristics of expression of uPAR in stromal cells, selective targeting of uPAR in stromal cells may inhibit cancer progression (81,82). Stromal-targeting oncolytic measles virus, which was designed by exploiting the binding affinity of uPA for uPAR, induced apoptosis of breast cancer cells (82). This type of oncolytic virus is able to disintegrate tumor vasculature by targeting uPAR in epithelial cells. The addition of ATF to stromal uPAR-targeting oncolytic viruses is associated with increased apoptosis in breast cancer cells (82).

5. Pathological function of uPAR in gynecological and female breast cancers

Besides metabolism, metastasis, invasion and inflammation, uPAR has special functions for gynecological cancers and breast cancers in females beyond common cancer types. Those functions are related to the characteristics of each cancer type, which may provide a research direction or treatment approach for female cancers.

uPAR relates to specific biomarkers of breast cancer directly. Normal-appearing epithelium and normal female breast tissue were reported to be negative for uPAR (83). Of note, uPAR has special relations with the specific biomarkers HER2 and ER in breast cancer. First, HER2 has a strong co-expression with the level of uPAR. In a paraffin-embedded breast cancer tissue reverse-phase protein microarray containing 106 patient samples, uPAR was found to be significantly expressed and strongly correlated with HER2 overexpression; however, uPA expression was not correlated with HER2 (84). Gene amplification and overexpression of HER2 and uPAR occur in most cancers and decreased expression was induced by the other one being silenced by RNA interference. HER2 upregulates uPAR by activating Src and protein kinase C; furthermore, uPAR and HER2 may cooperate to activate ERK to induce cancer cell growth and to evade apoptosis in breast cancer (85). Second, the expression of ER is a major hallmark of most breast cancers, as breast cancer is a sex hormone-dependent tumor. uPA-uPAR performs functions depending on the ER and estrogen. In ER-positive breast cancer cells, the binding of uPA with uPAR in the presence of estrogen induces the activation of ERK to phospho-ERK, a cell survival factor; however, in ER-negative breast cancer cells, in the absence of estrogen, uPAR induces the activation of ERK without uPA through a partially different pathway (35).

uPAR indicates peritoneal metastasis and poor prognosis of ovarian cancer. Among gynecologic malignancies, ovarian cancer is the second most commonly diagnosed cancer and the second leading cause of cancer-related death; besides the high mortality, ovarian cancer, with large amounts of ascites, seriously affects the quality of life of patients (86,87). Approximately 70% of ovarian cancers are diagnosed at a terminal stage, and only 30% of patients with ovarian cancer may expect to survive for five years (88). uPAR has an integral role in promoting ovarian cancer proliferation, invasion and particularly metastasis. To reveal peritoneal metastasis, a study using $uPAR^{-/-}$ and $uPAR^{+/+}$ mice suggested that ablation of uPAR prevented tumor growth and peritoneal implants and also prolonged the survival, decreased ascitic fluid

accumulation and decreased macrophage infiltration in $uPAR^{-/-}$ mice compared with their $uPAR^{+/+}$ counterparts (89). The results indicated that uPAR has an important role in increasing vascular permeability and the formation of an inflammatory environment around ovarian cancer (89). Furthermore, uPAR was observed to be involved in a series of peritoneal metastatic cascade reactions. The host uPAR promotes ovarian cancer cell proliferation, mesothelial adhesion and invasion (89). To inhibit metastasis, humanized monoclonal antibody, ATN-658, which is an antibody against uPAR, may be used to inhibit metastasis and invasion of ovarian cancer cells (40).

The uPAR system has emerged as a biomarker for the diagnosis and poor prognosis of patients with ovarian cancer. The expression of uPAR was studied in 162 epithelial ovarian cancer tissues, which indicated that 92% of the ovarian tumors expressed uPAR (40). Chambers *et al* (90) measured the levels of uPAR, uPA, PAI-1 and PAI-2 in the ascites of patients with epithelial ovarian cancer (EOC) and indicated that the uPA/uPAR system affects the biology of ovarian cancer. Upregulation of uPA and PAI-1 has been found in >75% of primary ovarian carcinomas, most metastatic EOC samples and EOC cell lines (91). Patients with advanced ovarian carcinoma with elevated levels of uPA and PAI-1 are more prone to earlier disease recurrence and poorer survival outcomes compared with patients with low levels of these proteolytic factors in tumor tissues (92). The differential expression of uPA and PAI-1 has been detected between the stages of primary neoformation and omentum metastasis in patients with terminal ovarian cancer, indicating that high levels of uPA are associated with a larger volume of residual tumor after surgery (93).

uPAR is present in endometrial cancer and endometrium. Endometrial cancer is the most common gynecologic malignancy in developing countries, as well as in certain developed cities in China, such as Beijing and Shanghai (94). Most endometrial cancers are endometriosis adenocarcinomas, out of which 80% are type 1 endometrial carcinomas, which are estrogen-related and low-grade (International Federation of Gynecology and Obstetrics grades 1 and 2) with a better prognosis (95,96). However, patients with type 2 endometrial cancers do not respond to estrogen, thus exhibiting a poor prognosis (95,96). Abnormal uterine bleeding is an early symptom of endometrial cancer, which is often diagnosed at stage I with an endometrial biopsy, thereby facilitating the treatment of this cancer if detected (95,97). Studies on endometrial cancer pathogenesis mostly focus on the estrogen-stimulated carcinogenesis pathway, while the role of uPAR in carcinogenesis has not received much attention. Prifti *et al* (98) indicated that integrins $\alpha4\beta1$, $\alpha5\beta1$ and $\alpha6\beta1$ mediate adhesion and invasion of endometrial cancer cell lines. However, they did not detect any significant change in the expression of uPA, PAI-1 and uPAR after the addition of an anti-integrin antibody to endometrial cancer cells and they deduced that low levels of these proteins may be detected by sensitive methods such as ELISA (98). EMT is regulated by estrogen and progesterone through the PI3K/AKT, EGF, IL-6, PDGF, TGF-β, VEGF and Wnt/β-catenin signaling pathways in endometrial cancer (96). A study containing 54 samples of endometrial cancer tissues indicated that uPAR was not significantly related to clinical characteristics; however, a review on 65 endometrial cancer samples reported that uPAR is correlated with the disease stage, rate of recurrence and mortality, indicating that uPAR is a prognostic factor for endometrial cancer (99,100). Furthermore, the mRNA and protein levels of uPAR were indicated to be 33 times higher in advanced endometrial cancer than in normal endometrial tissues (99). In addition, a study on 293 patients with endometrial cancer suggested that PAI-1 and u-PA are promising prognostic factors and that active proteolysis facilitates endometrial cancer development (101).

As for normal endometrium, high amounts of plasmin are detected in the menstrual outflow during the shedding process to activate MMP in the endometrium. However, high levels of plasmin are not detected in cancers (102). Endometrial stromal cells express high levels of uPAR and PAI-1, and the internalization of uPA/PAI-1 complexes is enhanced under progesterone stimulation during the shedding process of the menstrual cycle, suggesting that uPA-uPAR/PAI-1 are activated under the effect of estrogen and progesterone (102). During the decidualization of uterine stromal cells, progesterone stimulates the activation of the Wnt pathway and the expression of uPAR, totally depending on estradiol, which proved that uPAR has a significant role in the menstrual cycle and successful reproduction in the uterine endometrium (103). The presence of uPAR in both normal endometrium and endometrial carcinoma revealed the difference between the normal physiological and carcinogenic effects of uPAR.

uPAR affects the pathogenesis and clinical prognosis of cervical cancer. Cervical cancer is the second most frequently diagnosed cancer type among females globally, mostly in developing countries. Persistent infection of keratinocytes with human papillomavirus (HPV) is associated with most cases, and most of them progress from cervical intraepithelial neoplasia (104). During the HPV infection process, the basement membrane and ECM have an important role in primary HPV infection and cancer initiation in the uterine cervix (104). The uPA/uPAR proteolysis system facilitates HPV-associated carcinogenesis by means of cell-derived MMP-9 (105).

At first, no uPAR expression is detected in normal cervical tissues (106). The prognostic value of uPAR in cervical cancer has been established preliminarily. uPAR was indicated to be related to the clinical classification, lymph node metastasis and degree of differentiation of cervical cancer in a clinical study from China (106). suPAR in serum was significantly decreased in patients post-surgery compared with that in patients pre-surgery (106). A retrospective study comprising 59 patients with cervical cancer in Japan suggested that uPAR was a poor prognostic factor related to shorter disease-free survival (107). However, the expression of other components of the uPA-uPAR system was not associated with poor prognosis (107). It was reported that HIF-1 transactivated the uPAR promoter under hypoxic conditions in cervical cancer (108). Hypoxic cells sorted from primary tumors and nodal metastases of cervical xenograft tumor models based on carbonic anhydrase-9 expression exhibited upregulated expression of metastasis-related genes, such as C-X-X motif chemokine receptor 4, uPAR, VEGFC, double minute 2 protein and encephalopsin (109). In addition, in cervical cancer stem cells sorted based on aldehyde dehydrogenase-1 expression, low

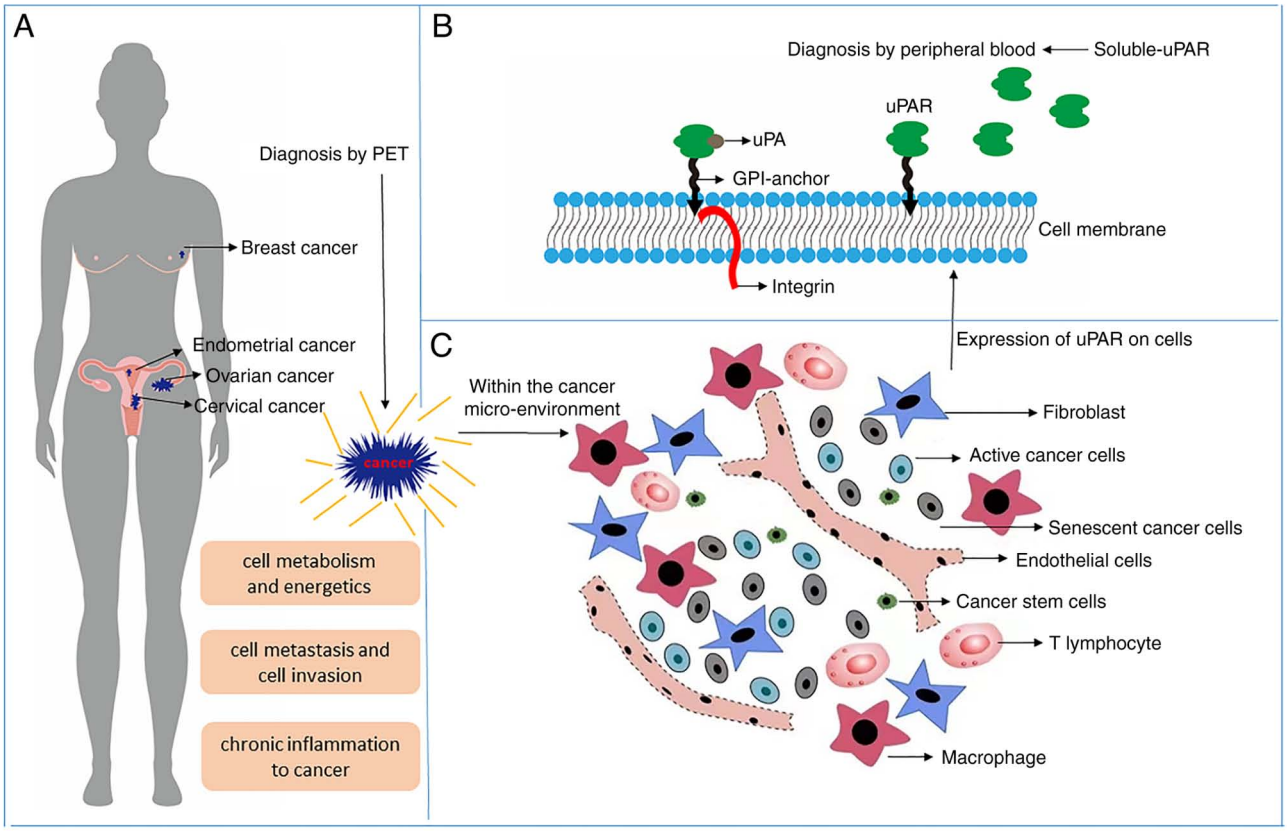

Figure 3. Mechanisms of the association of uPAR with cancer, particularly breast or gynecological cancers. (A) Cancers in females, including breast, cervical, endometrial and ovarian cancer, still have high morbidity and fatality. uPAR, as a classical metastasis marker, is involved in cell metabolism and energetics, as well as metastasis and invasion. By PET, cancers may be detected based on uPAR through radionuclide labeling. (B) On the cell membrane, with the expression of uPAR, it binds with uPA and connects with integrin for a cascade reaction. Soluble uPAR may shed off from the cancer cell membrane and this soluble form may be detected in peripheral blood for use as a prognosis marker. (C) Within the cancer micro-environment, uPAR may be expressed on multiple types of cells with different levels and stages, such as cancer cells both active or senescent, cancer stem cells, endothelial cells, lymphocytes, macrophages and fibroblasts. PET, positron emission tomography; uPAR, urokinase-type plasminogen activator receptor.

expression of PAI-1 and active uPA-uPAR proteolysis were detected, which resulted in an increased invasion tendency of cervical cancer stem cells (110).

In breast cancer and gynecological malignancies, uPAR is associated with clinical prognosis and characteristics; thus, exploration of the roles of uPAR in the pathogenetic mechanism is significant in the future. It has two forms, the soluble receptor and membrane receptor; they participate in unique malignant behaviors of various tumors and may be used as clinical indicators to guide prognosis. A schematic of the roles of uPAR in breast cancer and gynecologic tumors is provided in Fig. 3. The mechanisms by which uPAR contributes to pathogeneses in a proteolysis-independent manner require to be further explored.

6. Targeted therapy of uPAR implemented with both promise and limitations

To date, several experimental and preclinical studies have used uPAR as a target to inhibit cancer. First, regarding immunotherapy, the use of antibodies against uPAR is the main therapeutic strategy against tumors. A total of 12 unique human fragment of antigen bindings that target uPAR have been identified (111). Blocking the binding of uPA to uPAR and integrin to uPAR proved effective in inhibiting cell invasion (111). Monoclonal antibodies against uPAR, such as ANT-658 and ANT-615, have also been developed (112). ANT-658, which was demonstrated to have antitumor effects, was used to inhibit the growth of ovarian (40), liver (113) and prostate cancers (114). Of note, CAR T cells targeting uPAR proved beneficial for killing cancer cells in ovarian and lung cancer (63,115). Programmed death 1 (PD-1) antibody has been proven effective in the clinic and in a pre-clinical study, targeting uPAR potentiated anti-PD-1 efficacy in gastric cancer using uPAR antibody or uPAR CAR-T cells (116). Furthermore, bio-toxicity medicine and synthetic peptides that interfere with the binding of uPA to uPAR have been developed. A study exploited the specific binding of the EGF domain of uPA to uPAR and the antitumor effects of melittin to design and express a fusion protein in Pichia pastoris that contained uPA amino acids 1-43 and melittin (117). The fusion protein product, named rhupa1-43-melittin, resulted in cell cycle arrest, inhibited growth and induced apoptosis in ovarian cancer cells (117). Apart from this, the amino-terminal fragment (ATF) of uPA, which includes the uPAR-binding region but completely lacks the catalytic domain of uPA, has been used to design fusion proteins for the delivery of toxins, such as diphtheria toxin (118-120), the antiangiogenic domain of vasostatin (121), Kunitz-type protease inhibitor (122), ribosome-inactivating protein saporin (123) and scorpion toxin

Table II. Limitations of targeting uPAR in clinical anti-cancer therapies and potential solutions or strategies to be addressed by further research.

Limitation of preclinical pre-clinical research	Reasons for the limitation	Solutions to the limitation	(Refs.)
On-target, off-tumor	uPAR is expressed on both cancer cells and certain normal cells, so targeting uPAR may kill normal cells	The expression of uPAR in normal cells cannot be ignored, even in sensitive therapy. Regarding the administration route, intraperitoneal administration is safer than intravenous injection.	(125,127)
High but unregulated affinity	Targeting uPAR utilizes the affinity of uPA to uPAR. However, the unregulated affinity results in undifferentiated damage to both normal cells and cancer cells.	Regulating the affinity at a moderate level help the reagent or medicine attach to cells with high-level expression of uPAR, which is a safeguard for normal cells with lower expression of uPAR. Exploring antibodies is more significant than using uPA directly.	(109,110,119,121,122)
Expressed in cancer, but not all cancers	As for tumor heterogeneity, particularly in solid tumors, targeting uPAR cannot contain all cells in cancer	Combination of uPAR-targeting therapy with other therapies, or targeting uPAR and other molecules, may improve treatment effects. For instance, bispecific targeting of both uPAR and EGFR for solid cancer.	(128)
Within the tumor microenvironment, not only cells but also stroma	Most cancer therapies focus on cancer cells andignore the cancer stroma. uPAR may be expressed in certain stroma cells, making it a breakthrough point for cancer stoma	In cancer stroma, non-cellular components cannot be degraded, but stromal cells may be targeted if a suitable molecule is found.	(81)

uPAR, urokinase-type plasminogen activator receptor; uPA, urokinase-type plasminogen activator.

analgesic-antitumor peptide (124). Most of these toxin-delivery systems are efficient in cancer cell lines, but none of them are clinically applicable. A uPA-derived small-sized synthetic peptide (Å6) exerted a therapeutic effect by interfering with uPA/uPAR interaction in patients with advanced ovarian cancer (125). In non-cancer disease, a C-terminal domain of endostatin, known as E4, was able to bind to uPAR to exert antifibrotic effects in idiopathic pulmonary fibrosis and systemic sclerosis (126). In atomic medicine, uPAR has also been applied in positron emission tomography (PET) in non-invasive molecular imaging technology (127,128). The latest progress on uPAR in atomic medicine is a prospective phase II trial, which suggested that using 68Ga-NOTA-AE105 PET for imaging uPAR is relevant for risk stratification for patients with neuroendocrine neoplasms (129). Researchers are aware that single anti-uPAR therapy is not effective for cancer and combination therapy is widely studied, e.g., designed bi-specific anti-uPAR and EGFR toxins may kill solid tumor cells (130). Furthermore, naturopathy targeting uPAR has also been developed; photodynamic therapy and photothermal therapy essentially utilizes the binding of ATF to uPAR for capturing tumor cells (131). Overall, uPAR, a promising target for cancer therapy, has broad-anti-tumor applications. Inevitably, uPAR is expressed in numerous non-cancer tissues, as mentioned above in this review, and lessons learned from therapy failure and adverse reactions are that 'on-target off-tumor' effects should be avoided (132).

However, to date, no uPAR-targeted therapy has been approved in the clinic. The pre-clinical and clinical studies mentioned above implied that limitations of uPAR still represent a bottleneck to therapy. uPAR is not an exclusively-specific biomarker for cancer disease, which may cause on target-off tumor effects and different administration routes may have different degrees of this side effect (125,127). A higher affinity of uPAR-targeting is not directly linked to better efficacy. It is a challenge to control affinity at a moderate level to avoid unnecessary destruction of non-cancer cells (109,110,119,121,122). However, due to certain limitations, the untility of uPAR as an ideal biomarker for cancer is restricted. First, it is expressed in cancer, but not all cancers; furthermore, it is expressed not only in cancer cells but also stroma cells (81,128). Thus, novel modification strategies for uPAR targeting are indeed in need, such as those bispecific with other biomarkers such as EGFR (128). The limitations of uPAR in targeted therapy are summarized and corresponding possible solutions are suggested in Table II.

7. Conclusion

Virtually, elucidating the physiological roles of a molecule may help understand its function in cancer. Microscopically, within the TME, communications between cancers and stromal cells are orchestrated signals. Comparison of a molecule in both stromal cells and parenchymal cells may be an objective method. Furthermore, it is challenging to pinpoint a single molecule as a suppressor or promoter of a cancer. In physiological processes, uPAR is expressed at a moderate level, while in cancer, uPAR is usually overexpressed, which is associated with a malignant biological behavior. Therefore, it is important to study the function of uPAR under both physiological and pathological conditions to identify its particular role in tumorigenesis in the future.

Acknowledgements

Not applicable.

Funding

This study was supported by grants from the Natural Science Foundation of Fujian Province (grant no. 2021J05077), the Science and Technology Project of Fujian Provincial Health Commission (grant no. 2020GGB014) and the Fujian Provincial Health Commission (grant no. 2020J02059).

Availability of data and materials

Not applicable.

Authors' contributions

LW and XL performed the literature search. LW and PS conceived the study. LW, XL and PS were involved in writing the manuscript. LW, XL and PS read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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