

Urokinase Plasminogen Activator Receptor (CD87): Something Old, Something New

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Received April 1, 2003; accepted April 2, 2003

ABSTRACT

CD87 is a widely expressed receptor for urokinase plasminogen activator (uPA) and plays a critical role in regulation of cell-surface plasminogen activation. An expanding body of evidence suggests that CD87 is involved in regulation of diverse physiological and pathological processes, including cellular adhesion, cell motility, angiogenesis, tumor invasion, and tumor metastasis. These data characterize CD87 as a pleiotropic molecule that mediates a wide range of events beyond plasminogen activation through extensive and complex interactions with other cell-surface molecules, such as integrins and L-selectin. The association of CD87 overexpression in tumor cells with tumor invasion has attracted many researchers to exploration of the potential therapeutic utility of CD87 by targeting binding of CD87 to uPA, the interactions between CD87 and other surface and matrix molecules, CD87 gene expression, and posttranscriptional modification. Therapeutic strategies targeting CD87 as a key molecule of tumor invasion and metastasis have great potential for becoming valuable assets in therapy for malignant tumors. *Lab Hematol.* 2003;9:67-71.

KEY WORDS: CD87 · Urokinase plasminogen activator receptor · Granulocytes

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INTRODUCTION

The urokinase plasminogen activator (uPA) system participates in a broad array of cell functions, such as extracellular proteolysis, chemotaxis, adherence, proliferation, neutrophil priming for oxidant production, and cytokine release, which variously contribute to implantation, development, angiogenesis, inflammation, and metastasis of tumors. Since its discovery less than 2 decades ago [1], the uPA receptor (uPAR, CD87) has been identified as a critical protein in regulation of fibrinolysis through cell surface plasminogen activation in physiological and pathological conditions. Moreover, expanding evidence indicates that CD87 also is involved in processes not related to plasminogen activation, including cellular adhesion, transmission of extracellular signals across the plasma membrane, and subsequent regulation of gene expression. In this review, we discuss the molecular structure, tissue distribution, and functions of CD87 with a focus on the role of this receptor in regulation of cell motility and tumor invasion, and the potential impact of this new knowledge in devising new therapeutic strategies for malignant tumors.

STRUCTURE

Purified human CD87 is a single-chain, highly glycosylated, extracellular protein with a heterogeneous molecular mass of 50 to 60 kd [2,3]. The human gene for CD87 has been mapped to chromosome 19q13. UPAR is a cysteine-rich molecule with 3 homologous 80-residue domains and 2 short linker regions. The amino terminal domain D1 is endowed with uPA binding activity, whereas domains D2 and D3 host receptors for vitronectin and a high-molecular-weight form of kininogen [4].

The COOH terminal is anchored to the plasma membrane by glycosylphosphatidylinositol (GPI). The GPI anchoring moiety is added during posttranslational processing [5]. Soluble variants of CD87 have been demonstrated in healthy individuals [6].

TISSUE DISTRIBUTION

CD87 is a broadly expressed multifunctional protein. On hematopoietic cells, CD87 is normally expressed on monocytes, eosinophils, neutrophilic granulocytes, skin mast cells, and dendritic cells [7-10]. CD87 is not expressed on CD34⁺ bone marrow cells [10]. The exact stage of neutrophilic maturation at which CD87 begins to be expressed has been controversial [11]. However, results of a recent study by our group suggested that CD87 is a marker of terminal neutrophilic maturation expressed at the band and segmented stages of neutrophilic maturation [12]. CD87 is not expressed on erythrocytes, platelets, or resting B- and T-lymphocytes. However, activated T-lymphocytes and natural killer cells express this antigen [3]. Granulocytes have an intracellular storage pool of CD87, which has been recently mapped to the primary rather than the secondary neutrophilic granules [13]. The presence of storage pool may explain the enhanced expression of surface CD87 on neutrophils after stimulation. Nonhematopoietic cells, such as endothelial cells, hepatocytes, fibroblasts, keratinocytes, smooth muscle cells, and placental trophoblasts, also express CD87 [14-18].

PHYSIOLOGIC FUNCTIONS

As the receptor for uPA, CD87 has the principle function of retaining and concentrating uPA at the cell surface for local conversion of plasminogen to plasmin, which exerts its primary role of pericellular proteolysis by activating several metalloproteinases [19]. This process is critical for chemotaxis and cell migration, which are necessary for cells of the immune system to migrate effectively to sites of infection and inflammation. The process relies on the presence of CD87 on activated leukocytes, macrophages, endothelial cells, and fibroblasts [20]. It has been demonstrated that CD87 is capable of localizing and anchoring uPA at the leading edge of cell migration [21]. The effect is blocked by specific CD87 antibody and recovered on CD87 complementary DNA transfection [22]. In vivo studies have indicated that migration of leukocytes into inflamed peritoneum is reduced in CD87^{-/-} knock-out mice (CD87^{-/-}) compared with wild-type mice [23]. Moreover, neutrophil recruitment to the lung in response to pulmonary *Pseudomonas aeruginosa* infection was dramatically reduced in CD87-deficient mice [24]. Therefore CD87 is now considered an integral element of immune response because it regulates chemotaxis and cell migration.

Although the essential role of CD87 in regulating cell motility has been partially attributed to its capacity to local-

ize proteolytic activity on the cell surface by binding of uPA, there is accumulating evidence that CD87 also is involved in motility control through mechanisms independent of proteolytic activity of uPA. These mechanisms may include induction of signal transduction events, binding to the extracellular matrix molecule vitronectin, and association with other transmembrane molecules [25,26]. As mentioned earlier, CD87 is a GPI-linked protein that lacks transmembrane and cytoplasmic domains. Therefore CD87 is incapable of eliciting transmembrane signals in the absence of other contributing factors. However, CD87 can mediate several intracellular signals and cell functions because of its ability to interact with other transmembrane molecules, such as integrins, complement receptors, and L-selectin [25,27]. Ultimately, integration of the signals forms the intracellular signaling network, which is essential for cell motility through reorganization of the actin cytoskeleton and adhesion [26]. Although the mechanism of the CD87 signaling system is still under investigation, changes in CD87 signaling are thought to contribute to the functional alterations coordinating the temporal engagement of adhesive/detachment interactions during the process of cell migration.

CD87 IN NONNEOPLASTIC CONDITIONS

Paroxysmal nocturnal hemoglobinuria (PNH) is a stem cell disorder characterized by defective GPI anchor on the cell membrane with subsequent deficiency of proteins that are GPI anchored. PNH cells have been shown to lack CD87, and the deficiency may contribute to severe transmigration impairment of neutrophils over an endothelial barrier observed in these patients [28]. In addition, neutrophils and monocytes secrete a truncated form of uPAR in PNH [3].

CD87 expression is up-regulated in various tissues under pathological conditions, including arthritis, cerebral malaria, and Alzheimer's disease [29-31]. Levels of soluble CD87 are elevated in patients with PNH and in patients with tuberculosis, inflammatory rheumatic disease, and malignant tumors [6,32,33]. Some investigators have proposed the use of soluble CD87 for monitoring clinical activity and therapeutic response in some of these conditions [32].

CD87 AND HEMATOLOGIC MALIGNANCIES

Chronic lymphocytic leukemia and Hodgkin's and non-Hodgkin's lymphomas usually are negative for CD87 [10]. Fewer than 10% of patients with acute lymphoblastic leukemia express CD87 [10,34]. However, most patients with acute myeloid leukemia have CD87⁺ blasts, the strongest expression occurring in acute monocytic leukemia. Expression of CD87 on leukemic blasts has been correlated with clinical bleeding [35]. Histiocytic malignancies usually are CD87⁺ [10]. A recent study showed that plasma cells in multiple myeloma express CD87 [36].

CD87, NONHEMATOLOGIC MALIGNANCIES, AND TUMOR INVASION

The critical steps involved in tumor invasion and metastasis include intravasation, extravasation, and migration of tumor cells. A prerequisite for these steps is the ability of tumor cells to degrade the extracellular matrix surrounding the primary tumor. Results of numerous studies over the past decade have indicated that the uPA/uPAR (CD87) system plays an essential role in this process [37]. Extensive evaluation of CD87 expression in human cancer tissue has shown increased expression in malignant tumors of various organs, including colon, stomach, breast, bladder, and endometrium [38-44]. Furthermore, increased CD87 expression has been correlated with distant metastasis, tumor recurrence, and poor prognosis of a variety of cancers [39,41-44].

In addition to the tumor cells, other types of tumor-associated cells express CD87. These cells include macrophages and endothelial cells in cancers of the breast, colon, and liver [45,46]. Tumor-associated macrophages are thought to stimulate tumor angiogenesis by producing angiogenic factors such as vascular endothelial growth factor (VEGF) and interleukin 8 [47,48], whereas CD87 may regulate tumor angiogenesis indirectly by mediating macrophage invasion and adhesion in tumors. In colon cancer specimens, both CD87 and VEGF were found more highly expressed in tumors with increased blood vessel invasion than in tumors lacking vascularity [38]. In an *in vitro* model, tumor necrosis factor- α stimulated tube formation by human endothelial cells, an effect that was completely blocked by CD87 monoclonal antibody [49]. In addition, hypoxia stimulated high expression of CD87 on breast cancer cells, a phenomenon associated with increased surface uPA activity and invasiveness of tumor cells. Of interest was that the effect of hypoxia was abrogated by anti-CD87 antibody [50]. The strong association of CD87 with tumor invasion and metastasis has attracted many researchers to explore the potential clinical value of CD87 as a diagnostic and therapeutic target.

A NEW THERAPEUTIC TARGET FOR MALIGNANT TUMORS?

CD87 has been exploited as a target for cancer therapy. The major focus has been on assessing the effect of blocking the uPA-uPAR (CD87) interaction. Many studies have focused on peptides because of the sequence of the growth factor domain of uPA, which mediates its binding to uPAR. These peptides have been demonstrated to be effective in inhibiting laminin degradation by cancer cells and limiting metastasis in several animal models [51]. However, use of these peptides had several drawbacks, including poor bioavailability and susceptibility to protease degradation in plasma. Recently, several high-affinity peptide ligands of CD87 have been produced in an attempt to circumvent the previously encountered problems. *In vitro*

studies demonstrated that these potent peptide ligands were capable of inhibiting binding of uPA to CD87 and of inhibiting cancer cell intravasation [52]. A recent study by Sato et al showed effective reduction of tumor growth and spread of human ovarian cancer cells in nude mice through use of high-affinity uPA-derived cyclic peptides [53]. Although the initial tests were encouraging, more animal studies are needed for further assessment of effectiveness *in vivo*.

Another approach is designed to block the nonproteolytic effects of CD87 mediated by interaction of the receptor with other molecules on the cell membrane or extracellular matrix. One of the targets is CD87-integrin interaction, which has been implicated in mediation of cellular signaling and regulation of cell adhesion and motility. Studies showed that a peptide (M25) was able to bind to CD87 and inhibit cellular adhesion to fibronectin, fibrinogen, vitronectin, and cytokine-stimulated endothelial cells [54]. This peptide did not inhibit binding of CD87 to uPA and, more interestingly, did not have homology to the integrin α_M [54].

Gene therapy with vector delivery of antisense gene to uPAR has been successfully used in down-regulation of CD87 expression in several preclinical studies. The results have been increased tumor dormancy, decreased tumor growth, inhibition of angiogenesis in tumor, and increased survival [55,56]. Introduction of CD87 antisense oligodeoxynucleotide into tumor cells has been shown to switch off CD87 gene expression and to abolish invasive properties of the cells [57]. Decreased CD87 expression also was achieved at the posttranscriptional level through interaction of CD87 messenger RNA (mRNA) with a specific CD87 mRNA binding protein [58]. Clinical utilization of these approaches relies on overcoming the difficulty in delivery of these therapeutic vectors or compounds.

Targeting CD87 on tumor cells may represent a specific way for selective delivery of therapeutic agents to tumor cells. Several fusion proteins of the amino terminal fragment of uPA and the toxin derived from *Pseudomonas* exotoxin have been described as cytotoxic to several tumor cells at low concentration [59]. Several recent studies have demonstrated that diphtheria toxin-urokinase fusion protein is selectively toxic to CD87⁺ leukemic cells from patients with acute myeloid leukemia [60,61]. Similar approaches could be used to deliver radiotherapeutic and radiodiagnostic moieties to tumor cells that overexpress CD87.

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