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The interaction between urokinase receptor and vitronectin in cell adhesion and signalling

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Abstract

The extracellular matrix (ECM) is a complex structural entity surrounding and supporting cells present in all tissue and organs. Cell–matrix interactions play fundamental roles during embryonic development, morphogenesis, tissue homoeostasis, wound healing, and tumourigenesis. Cell–matrix communication is kept in balance by physical contact and by transmembrane integrin receptors providing the dynamic link between the extracellular and intracellular environments through bi-directional signalling. The urokinase-type plasminogen activator receptor (uPAR) is a plasma membrane receptor overexpressed during inflammation and in almost all human cancers. One of its functions is to endorse ECM remodelling through the activation of plasminogen and downstream proteases, including matrix-metalloproteases (MMPs). Beside its role in ECM degradation, uPAR modulates cell–matrix contact through a direct engagement with the ECM component, vitronectin (Vn), and by regulating the activity state of integrins thus promoting or inhibiting integrin signalling and integrin-mediated cell adhesion to other ECM components, like

fibronectin and collagen. In this review we have centred our attention on the non-proteolytic function of uPAR as a mediator of cell adhesion and downstream signalling.

Keywords: uPAR; Integrins; Vitronectin; Fibronectin; Cell adhesion; Cell migration; Integrin signalling

Introduction

Cell adhesion and migration are two tightly coupled processes decisive to normal development and physiology. In normal tissue, cells are structurally and functionally integrated with their surrounding extracellular matrix (ECM), and abnormality in ECM organisation and cell–ECM interactions contribute extensively to disease (De Wever and Mareel, 2003; Ross, 1995). Loss of tissue integrity, due to excessive proteolytic degradation of the ECM, and altered cell–ECM adhesion are defined characteristics of many diseases like chronic atherosclerosis, and during tumour invasion and dissemination of metastasis (Dano et al., 2005; De Wever and Mareel, 2003; Ross, 1995). Members of the integrin family execute cell–ECM communication across the plasma membrane by means of bidirectional signal transmission, resulting in a myriad of cellular functions. The urokinase-type plasminogen activator receptor (uPAR) is a cell surface

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receptor able to regulate extracellular proteolysis as well as integrin activity and signalling, thus contributing to the cell–ECM homoeostasis.

Urokinase plasminogen activator receptor

uPAR and its ligand, urokinase-type plasminogen activator (uPA), are involved in numerous physiological and pathological processes, such as pericellular proteolysis, wound healing, tissue regeneration, and tumour progression (Blasi and Carmeliet, 2002). uPAR expression is upregulated during inflammation and in many human diseases, including cancer, and its expression levels correlate with poor prognosis in patients (Sidenius and Blasi, 2003). uPAR is a GPI-anchored cell surface receptor expressed by many cell types, counting epithelial, endothelial, and most haematopoietic cells (Blasi and Carmeliet, 2002). uPAR contributes to the regulation of pericellular proteolysis through the binding of uPA. Active uPA converts the zymogen plasminogen into the active serine protease plasmin, a process tightly regulated by plasminogen activator inhibitors (PAI-1 and PAI-2). The generation of plasmin promotes the degradation of the ECM by direct digestion and by activation of pro-matrix metalloproteases (MMPs), including MMP-3, -9, -12 and -13 in vivo (Carmeliet et al., 1997). For that reason, it was initially believed that the primary function of uPAR in the leading edge of migrating cells was to regulate invasive cell migration by virtue of its ability to promote degradation of the ECM. Indeed, uPAR has been detected in invadopodia (Artym et al., 2002) and in the invasive front of many human tumours (Dano et al., 2005; Nielsen et al., 2007), and its expression on tumour cells strongly correlates with their migratory and invasive phenotype (Wang, 2001). However, it is becoming evident that uPAR also elicits a plethora of non-proteolytic functions, and its involvement in cell adhesion, migration, proliferation and differentiation is now well-documented (Blasi and Carmeliet, 2002).

Vitronectin

A second binding partner of uPAR is the ECM component, vitronectin (Vn) (Wei et al., 1994). Vn circulates in the blood as a monomer, but is converted into a multimeric form when incorporated into the ECM. Vn is found in loose connective tissue of many organs, blood vessel walls, lymph nodes, and in the stroma of lymphatic tissue (Hayman et al., 1983; Reilly and Nash, 1988). Increased Vn deposition is found in reactive and fibrotic tissue (Reilly and Nash, 1988), atherosclerotic plaques (Niculescu et al., 1989) and in several tumours (Gladson and Cheresh, 1991; Loridon-Rosa et al., 1988). Accordingly, Vn has been implicated in a variety of physiological and pathological processes, including haemostasis (Mohri and Ohkubo, 1991; Thiagarajan and Kelly, 1988), angiogenesis (Brooks et al., 1994a, b, 1995), rheumatoid arthritis (Tomasini-Johansson et al., 1998), and tumour cell invasion (Juliano and Varner, 1993; Nip et al., 1992). Vn also engages and activates members of the integrin family ($\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha IIb\beta 3$) (Hynes, 1992; Preissner, 1991). Integrin binding to Vn is mediated through the RGD motif in Vn (Pytela et al., 1985), and its interaction contributes to cell adhesion, migration and integrin-mediated signal transduction. A unique function of Vn is to bind and maintain PAI-1 in its active conformation (Declerck et al., 1988; Lindahl et al., 1989), thus keeping PAI-1 ready to inhibit further plasminogen activation and extracellular proteolysis. Vn therefore provides a template on which cells can coordinate pericellular proteolysis as well as integrin and uPAR-mediated cellular processes, such as cell adhesion and migration.

uPAR modulates integrin-based cell adhesion and activity

As cell adhesion molecules, integrins are unique in their bidirectional signalling capacity across the plasma membrane. Integrin adhesiveness can dynamically be regulated by a process, termed inside-out signalling, where external stimuli received by cell surface receptors for chemokines and cytokines initiate intracellular signals that eventually alter the affinity state of the integrins. On the contrary, direct integrin binding of extracellular ECM ligands sets off a complex series of molecular events, termed outside-in signalling, regulating cell shape, migration, growth, and survival.

The role of uPAR as a modulator of cell adhesion, signalling, and migration is becoming more and more compelling. uPAR is believed to regulate the activation state of integrins, thereby influencing their adhesive properties as well as their signalling capacities (Kugler et al., 2003). This is supported by various studies showing uPAR-dependent changes in integrin-mediated adhesion to fibrinogen, collagen (Col), fibronectin (Fn), and Vn (Simon et al., 2000; Wei et al., 1996, 2001).

In a series of studies by Ossowski and co-workers, it was demonstrated that high expression of uPAR induces $\alpha 5\beta 1$ integrin-mediated cell adhesion to Fn, which subsequently generated a persistent mitogenic signal that ends tumour dormancy and induces tumour growth in vivo. Conversely, reducing the uPAR levels, through antisense technology, forced these carcinoma cells back into a state of dormancy (Aguirre Ghiso et al., 1999, 2001; Chaurasia et al., 2006). Direct interaction between $\alpha 5\beta 1$ integrin and the Ser245 of uPAR was proposed to