Chapter 2

ROLE OF SERINE PROTEASES AND THEIR INHIBITORS IN TUMOR GROWTH AND ANGIOGENESIS

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Abstract
Acquisition of invasive/metastatic potential through protease expression is a key event in tumor progression. The proteolytic enzyme plasmin is generated from the precursor plasminogen by the action of urokinase-type plasminogen activator (urokinase, uPA) or tissue-type plasminogen activator (tPA) under the control of plasminogen activator inhibitor-1 or PAI-1. High levels of components of this proteolytic system including uPA, its cell surface receptor (uPAR) and its inhibitor PAI-1 have been correlated with a poor prognosis for different cancers. The initial concept for the implication of serine proteases during cancer progression is that proteases degrade extracellular matrix components, a prerequisite for endothelial, inflammatory or tumor cell migration to distant sites. They have also been implicated in the activation of cytokines or other proteinases, as well as in the release of growth factors sequestered within the extracellular matrix. Recent information have underlined the importance of cell-surface proteases, their receptors/activators or their inhibitors in cell migration. This review focuses on the emerging roles of the plasminogen/plasmin system during cancer growth and angiogenesis with a special emphasis on PAI-1.

1. INTRODUCTION

The invasive process by which malignant tumors disseminate can be considered as an unregulated tissue remodeling process which progressively involves both cancer and normal cells. Recruitment and reorganization of the normal host cells lead progressively to the development of a supporting stroma infiltrated by a new blood capillary network (Noël et al, 1998). Tumor cell invasion and metastatic processes require the coordinated and temporal regulation of a series of adhesive, proteolytic and migratory events (Noël et al, 1997; Reuning et al, 1998). Extracellular proteinases, i.e. serine protease and matrix metalloproteinases have been implicated in cancer metastasis.

The plasminogen system is composed of an inactive proenzyme plasminogen (Plg) that can be converted to plasmin by either of two plasminogen activators
urokinase-type (uPA) and tissue-type (tPA) plasminogen activators which are serine proteinases (Andreasen et al, 1997; Carmeliet et al, 1998; Dano et al, 1999). Their activity is controlled by plasminogen activator inhibitors, PAI-1 and PAI-2 (plasminogen activator inhibitor-type 1 and type 2), belonging to the serine proteinase inhibitor (serpin) family. Having a broad substrate specificity, plasmin is able to degrade many extracellular matrix components, to activate other proteases such as pro-metalloproteinases, and to activate or release growth factors from the extracellular matrix (Rifkin et al, 1999).

The growth factor domain of pro-uPA or uPA binds a specific, high affinity cell-surface receptor (the urokinase receptor or uPAR) increasing uPA activity and directing plasmin activity to the cell surface (Figure 1). The uPAR is a glycosylphosphatidylinositol (GPI)-linked surface receptor (Blasi, 1997, 1999). While the plasma inhibitor α₂ macroglobulin inactivates soluble uPA relatively slowly, uPA bound to uPAR appears to be protected by a steric effect (Stephens et al, 1991), thus allowing plasminogen activation to occur on the cell surface even in the presence of serum. Interaction between PAI-1 and uPA on the cell surface leads to internalization of the uPAR/uPA/PAI-1 complex and drives uPAR cycling through the endosomal compartment back to the cell surface (Andreasen et al, 1997; Blasi, 1999). The uPA activity may also be lost from the cell surface by proteolytic cleavage, leaving the so-called amino-terminal fragment (ATF) bound on the cell surface. Besides its interaction with uPA, uPAR also binds to the extracellular matrix protein vitronectin and cooperates with some integrins to modulate cell adhesion and migration (Chapman et al, 1999). Recent data suggest that uPAR is an integrin ligand rather than, or in addition to, an integrin-associated protein (Tarui et al, 2001).

2. CLINICAL RELEVANCE OF THE PLASMINOGEN/PLASMIN SYSTEM

Many studies have shown that upregulation of uPA, uPAR and PAI-1 in malignant tumors is associated with increased malignancy [for review, see (Reuning et al, 1998; Andreasen et al, 1997; Frankenne et al, 1999; Brunner et al, 1999; Schmitt et al, 2000). These proteolytic factors are very good prognostic markers, suited to identify cancer patients at risk to develop metastases (Schmitt et al, 2000). Initial studies performed on breast tumors (Duffy et al, 1988; Jaenicke et al, 1989) were extended to a variety of cancers such as ovarian, cervix, bladder, kidney, brain, lung, gastric, colon, pancreas, esophagus and liver cancers (Schmitt et al, 2000). High tumor tissue concentrations of uPA and PAI-1 were also associated to poor prognosis in early stage endometrial cancer.