1 Role of Urokinase-Type Plasminogen Activator in Malignancy – General Introduction

Plasminogen activator of the urokinase type (uPA) has been shown to be overexpressed in most experimental malignant tumors and human cancers (DANO et al. 1985; DEBRUIN et al. 1987; SAPPINO et al. 1987; MARKUS 1988; SIM et al. 1988; DUFFY et al. 1990; JANICKE et al. 1990; TESTA and QUIGLEY 1990; SAPPINO et al. 1991; MIGNATTI and RIFKIN 1993). The overproduction of uPA by tumor cells was detected in primary cultures, organ cultures, and cancer cell lines. However, examination by in situ analyses (both immunocytochemistry and in situ hybridization) of sections of human tumors consisting of multiple cell types identified in some instances cells other than cancer cells as the uPA producers. Depending on the type of cancer, and in some instances the laboratory and the reagents used to perform the analysis, tumor, stromal, and sometimes infiltrating macrophages were found to be the main source of uPA and/or its receptor (GONDAHL-HANSEN et al. 1991; PYKE et al. 1991, 1993; BIANCHI et al. 1994; CARRIERE et al. 1994). Regardless of its source, however, it has been firmly established in several human cancers that high levels of uPA are predictive of more aggressive disease.

Two additional components of the plasminogen activation system, the uPA receptor (uPAR) and a specific inhibitor of plasminogen activators, PAI-1, display a distribution similar to that of uPA in human and animal cancers and have also been found to be reliable as independent predictors of the disease-free survival (Janicke et al. 1991; Grondahl-Hansen et al. 1993; Kobayashi et al. 1994).

The discovery of uPA overproduction by tumors led to a flurry of experiments in which its role as a determinant of the invasive phenotype of cancer cells has been shown in numerous in vitro and in vivo models (Ossowski and Reich 1983; Mignatti et al. 1986; Reich et al. 1988; Ossowski 1988a; Hearing et al. 1988; Axelrod et al. 1989; Yu and Schultz 1990). The existing evidence points to uPA as a crucial initiator of a proteolytic cascade leading to the generation of active plasmin and collagenases, which by degrading biological barriers remove the impediment to tumor cell spread. With the discovery of a specific cell surface receptor (Vassalli et al. 1985; Stoppelli et al. 1985), it was shown that receptor-bound uPA can remain active on the cell surface for several hours and that the bound form of uPA is more efficient in matrix degradation and invasion (Ossowski 1988b; Schlechte et al. 1989; Ossowski et al. 1991; Quax et al. 1991; Liu et al. 1995). Surface-bound uPA was shown to be protected from its physiological inhibitors in macrophages (Kirchheimer and Remold 1989), but this was not confirmed in any other cell types (Cubellis et al. 1989). The reason for this discrepancy remains unknown.

In addition to its matrix-degrading function, the binding of uPA or pro-uPA to its receptor has been shown to stimulate chemotaxis and/or chemokinesis in a variety of cell type such as neutrophils, tumor cells, and endothelium (Gudevicz and Gilboa 1987; Fibbi et al. 1988; Odekton et al. 1992; Del Rosso et al. 1993; Busso et al. 1994; Stahl and Muller 1994). The fascinating observation (Wei et al. 1994) that binding of uPA to its receptor confers vitronectin-binding specificity on uPAR suggests that tumor-secreted uPA, by binding to uPAR on endothelial cells and affecting their adhesion and migration, may lead to enhanced angiogenesis. In addition, not unlike the case for other glycoprophatidylinositol (GPI)-linked proteins, which are known to transduce signals through as yet unidentified pathways, the possibility of several signal transduction pathways through this receptor has also been considered. These involve tyrosine phosphorylation, protein kinase C (PKC), de novo diacylglycerol (DAG) generation etc. (Del Rosso et al. 1993; Duimizer et al. 1993, 1994; Anchini et al. 1994; Busso et al. 1994).

2 Experimental Approaches Aimed at Interfering with the Interaction of Urokinase-Type Plasminogen Activator with Its Receptor

The evidence cited above links two important functions of cancer cells, migration and invasion, with the cell surface-bound uPA activity. It is not surprising,