Inhibition of the tumor-associated urokinase-type plasminogen activation system: effects of high-level synthesis of soluble urokinase receptor in ovarian and breast cancer cells in vitro and in vivo.

Abstract:
Tumor cell invasion and metastasis depend on the coordinated and temporal expression of proteolytic enzymes to degrade the surrounding extracellular matrix and of adhesion molecules to remodel cell-cell and/or cell-matrix attachments. The tumor cell-associated urokinase-type plasminogen activator system, consisting of the serine protease uPA, its substrate plasminogen, its membrane-bound receptor uPAR, as well as its inhibitors PAI-1 and PAI-2, plays an important role in these pericellular processes. Especially, association of the proteolytic activity of uPA with the cell surface via interaction with uPAR significantly increases the invasive capacity of tumor cells. Consequently, various approaches have been pursued to interfere with the expression or activity of uPA and/or uPAR, including antisense strategies and the development of active-site inhibitors of uPA or inhibitors of uPA/uPAR interaction. In this review, we focus on the results obtained in vitro and in vivo with tumor cells producing high levels of a recombinant soluble form of uPAR, which efficiently inhibits uPA binding to cell surface-associated uPAR and, by this, acts as a scavenger for uPA.