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Affiliations of authors: E. Taioli, Department of Environmental Medicine and Kaplan Cancer Center, New York University Medical Center, NY, and IRCCS-Ospedale Maggiore di Milano; H. L. Bradlow, D. W. Sepkovic, M. P. Osborne, Strang Cancer Research Laboratory, Rockefeller University, New York; S. Garbers, Department of Environmental Medicine, New York University Medical Center; S. J. Gate, Department of Environmental Medicine and Kaplan Cancer Center, New York University Medical Center.

Correspondence to: Emanuela Taioli, M.D., Department of Environmental Medicine, Epidemiology Program, New York University Medical Center, 341 E. 25th St., New York, NY 10010.

Re: Urokinase and Urokinase Receptor: Association With In Vitro Invasiveness of Human Bladder Cancer Cell Lines

Urokinase-type plasminogen activator (uPA) is a serine protease causally involved in cancer invasion and metastasis [reviewed in (1,2)]. It is now generally believed that uPA mediates metastasis by attaching to a membrane-bound receptor termed uPAR (1,2). Consistent with their role in experimental metastasis, high levels of these molecules have been found to associate with poor prognosis in a variety of human cancers (2,3). In a recent report, Hudson and McReynolds (4) concluded that both uPA and its receptor were necessary for in vitro invasion by bladder tumor cells. In an accompanying editorial, Hasui and Osada (5) stated that further work was necessary to establish the relative prognostic strengths of uPA and uPAR in different human cancers.

Following extraction with 1% Triton X-100, we have used an enzyme-linked immunosorbent assay (American Diagnostica, Greenwich, CT) to measure both uPA and its receptor in 134 human breast cancers (6). With the use of optimum cutoff points, uPA was a stronger prognostic marker than uPAR for both disease-free interval (uPA—\( P = .0005, \chi^2 = 8.9 \); uPAR—\( P = .05, \chi^2 = 4.4 \)) and overall survival (uPA—\( P = .0005, \chi^2 = 9.1 \); and uPAR—\( P = .025, \chi^2 = 5.4 \)). P values were derived using Cox Proportional Hazards Regression Analysis and are two-sided). However, if median values were used as cutoff points, uPA levels, but not receptor levels, were significantly associated with patient outcome (6). As shown in Fig. 1, combining uPA with uPAR gave

Fig. 1. Effect of combining urokinase-type plasminogen activator (uPA) and urokinase receptor (uPAR) levels on disease-free interval (upper diagram) and overall survival (lower diagram) in patients with breast cancer. Optimum cutoff points were used for both uPA and uPAR (6). Since only four patients had high uPA and low uPAR levels, this group was excluded from the figure.
enhanced prognostic information over that supplied by either protease or receptor alone.

Consistent with our findings, Grøndahl-Hansen et al. (7) also found no significant association between detergent-extracted uPAR levels and patient outcome in breast cancer if the median value was used as the cutoff point. In contrast, assay of uPAR in a cytosol extract (i.e., no detergent was used) led to a significant association between receptor levels and overall survival but not between receptor levels and disease-free survival. In this study, the relative prognostic strengths of the protease and receptor were not compared in the total population of patients used. However, in the postmenopausal node-positive subgroup, uPAR, but not uPA, was an independent indicator of outcome.

uPA and uPAR have also been compared for relative prognostic impact in other cancers. Thus, in both squamous cell carcinoma of the lung (8) and renal carcinomas (9), uPAR has been shown to be a stronger marker of aggressiveness than uPA. In colorectal cancers, although uPA (10–12) and receptor (13) have been shown to be prognostic, no study has directly compared their relative impact on patient outcome.

These findings from human cancers are consistent with the data from model systems, indicating that both uPA and its receptor are involved in invasion and metastasis. Additional work with larger numbers of patients is required to establish whether uPA or uPAR is the stronger prognostic factor. Finally, our preliminary results from breast cancer shown above suggest that the combined measurement of both uPA and its receptor may supply enhanced prognostic information over that obtained with either protein alone.

MICHAEL J. DUFFY
CATHERINE DUGGAN

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Affiliation of authors: Department of Nuclear Medicine, St. Vincent’s Hospital, Dublin, Ireland. Correspondence to: Michael J. Duffy, M.D., Department of Nuclear Medicine, St. Vincent’s Hospital, Dublin 4, Ireland. E-mail: mjduffy@SVHERC.ucd.ie

Responses

The urokinase-type plasminogen activator receptor (uPAR) focuses urokinase-type PA (uPA) proteolytic activity at the cell surface to facilitate tumor invasion. Our work (1) suggested that in vitro invasion of extracellular matrix by bladder cancer cells requires both a source of uPA and its receptor. Two additional studies (2,3) support this hypothesis. In a study of four human gastric cancer cell lines, the cell line expressing both uPA and its receptor (II746T) showed the highest invasive potential on modified chorioallantoic membranes (CAMs) of chick embryos. T-Lymphoblastic leukemia cells able to transmigrate through an extracellular matrix barrier were observed to express uPA and high levels of uPAR (3). Inhibition of uPA/uPAR interaction reduced the invasive potential of tumor cells in vitro in all three studies. An additional recent observation (4) showed that clones of Hep3 cells transfected with a vector expressing uPAR antisense RNA reduced cell surface uPAR levels. Low cell-surface uPAR expression was associated directly with significantly reduced invasiveness on CAMs of chick embryos, and cells appeared dormant for up to 5 months. Thus, a synergistic action between two components of the PA system appears to enhance invasion in laboratory studies. Inhibition of invasion and tumorigenicity can be affected through alteration of the uPA/uPAR interaction.

Translation of this idea into the clinical setting was made when Duffy and Duggan showed that both uPA and the uPAR can be used as prognostic markers in patients with breast cancer. The combination of the two enhanced prognostic information in their series of patients over either marker alone. Hoffman et al. (4) found uPA levels in patients with muscle-invasive bladder cancer to be a stronger independent prognostic marker for patient survival than lymph node status or tumor grade. uPAR and PAI-1 levels did not show any significant association with survival in these patients with bladder cancer. Combinations of markers were not studied. As suggested, further clinical studies correlating uPA and uPAR with clinical outcome may prove to be useful in other tumor types.

With further confirmation of this hypothesis clinically, the development of novel therapies to inactivate or remove the uPAR on the cell surface may be a new strategy for cancer therapy.

Questions remain regarding the potential roles, alone and in combination, of other components of the PA system in tumor invasion and metastasis. All three