Titel	The uPA receptor in ovarian cancer. Regulation by EGF and the estrogen responsive membrane receptor GPR30. Soluble uPAR in diagnosis and prognosis.
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Fulltext	Fulltext är ej tillgängligt i detta arkiv
Disputationsdatum	2008-11-14

Cell migration is the first step of the invasive process, which is part of the malignant phenotype, and the uPA receptor (uPAR) plays a central role in cell migration. We studied the role of EGF and estrogen on cell migration and uPAR expression in ovarian cancer cell lines. We also analyzed the diagnostic and prognostic value of cleaved forms of the uPAR in plasma from patients with ovarian tumors. EGF stimulates cell migration by up-regulation of cell surface uPAR in ovarian cancer cells via three distinct mechanisms: mobilization of uPAR from detergent resistant domains, which occurs within minutes of EGF stimulation, increased expression of uPAR mRNA, and decreased internalization and degradation of uPAR. Furthermore, EGF stimulated shedding of uPAR from the cell surface, and this was secondary to accumulation of uPAR on cell surface but independent of cell migration. Furthermore, we found that an anti-uPAR antibody R3, which prevents binding of uPA to uPAR, as well as Iressa that inhibits phosphorylation of EGFR, inhibited migration in response to each uPA and EGF. This supports the idea that uPAR and EGF receptor engage in the same multi-protein signaling complex on the cell membrane. Estradiol attenuates EGF-induced rapid uPAR mobilization and thus also cell migration, but it influences neither the level of uPAR mRNA, nor internalization and degradation of uPAR protein. In further experiments with OVCAR-3 cells, we showed that this effect of E2 was mimicked by tamoxifen and ICI 182780, two antagonists to nuclear ER, as well as G-1, a specific agonist to the membrane receptor GPR30. These results strongly suggest that the response to estradiol involved GPR30, but not ERalpha or ERbeta. Seven ovarian cancer cell lines and 44 ovarian tumor tissue samples expressed GPR30 mRNA. Expression was lower in poorly differentiated malignant tumors than in benign tumors. However, the levels of GPR30 mRNA and GPR30 protein did not correlate, since Western blot analysis showed that poorly differentiated tumors contained considerably more GPR30 protein than benign tumors. We measured the levels of intact and cleaved forms of suPAR (suPAR I-III, II-III, and I) in preoperative plasma samples from 335 patients with ovarian tumors using time-resolved fluorescence immune assays. We found that the levels of all suPAR forms differed between benign, borderline, and invasive tumors. In particular, the combination of suPAR(I-III + II-III) and CA125 gave better discrimination between benign and invasive tumors (AUC 0.94) than either marker alone. Moreover, a high preoperative level of uPAR(I) was an independent predictor of poor prognosis. Thus, suPAR forms can both serve as markers for early diagnosis and for poor prognosis in patients with ovarian cancer.