ERK1/2, PI3K AND p70S6K ARE IMPORTANT MEDIATORS FOR HGF-INDUCED MIGRATION AND INVASION IN HUMAN OVARIAN CANCER CELLS

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INTRODUCTION. Ovarian carcinoma is a fast developing and invasive cancer type. This neoplasm arises from the ovarian surface epithelium (OSE). Hepatocyte growth factor (HGF) has been suggested as an ovarian promoting cytokine and the Met tyrosine kinase, a high affinity receptor for HGF, is often overexpressed in ovarian cancer [reviewed in 1]. This study investigated the Met-dependent signaling required for cell scattering (dissociation) and invasive growth of OSE cells at different stages of neoplastic transformation. Two experimental culture models were used: (1) non-tumorigenic IOSE-29, tumorigenic IOSE-Ov29 and the tumor-derived, more highly malignant IOSE-Ov29/T4, which were generated by multiple genetic manipulations [2-4]; and (2) established human ovarian cancer cell lines, SKOV-3 and CaOV-3.

METHODS. The level of Met receptor expression was analyzed by Western blots. The scattering assay and collagen gel invasion assay were performed to measure HGF-induced cell motility and invasiveness, respectively. To investigate the signaling pathways activated by HGF, cells were incubated with or without HGF and various inhibitors including PD98059, LY294002, SB203580, and rapamycin. Specific activation of ERK1/2, Akt and p70S6K will be determined by immunoblotting using specific antibodies against active, phosphorylated forms of these protein kinases. In parallel experiments, scattering assay and collagen gel invasion assay were performed to investigate whether disruption of these pathways would substantially impair cell motility and invasion by human ovarian cancer cells.

RESULTS. Compared to nontumorigenic IOSE-29, tumorigenic IOSE-Ov29, IOSE-Ov29/T4 and human ovarian cancer cell lines SKOV-3 and CaOV-3 exhibited high levels of Met (Fig. 1). HGF activated Met signaling in all lines but elicited different responses: HGF-induced scattering and collagen gel invasion in malignant OSE but did not alter the growth pattern of IOSE-29. Inhibition with PD98059 (PD), LY294002 (LY) and rapamycin (Rp) independently prevented...
HGF-induced invasive growth, whereas treatment of cells with SB203580 (SB) had no effect (Fig. 2).

Fig. 1. Western blot analysis of the Met receptor of lane 1, OSE; lane 2, IOSE-29; lane 3, IOSE-Ov29; lane 4, IOSE-Ov29/T4; and lane 5, ovarian cancer cell line.

DISCUSSION. Our data correlate specific responses to HGF-mediated signaling with specific signaling pathways and with progressive neoplastic changes. Furthermore, these data emphasize the potential role of overexpression of Met receptor in promoting cellular migration and extracellular matrix degrading activities, suggesting targeting Met-dependent signaling is likely to be a promising therapeutic modality to limit ovarian cancer progression.

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REFERENCES


