Effect of Wild-Type and Mutant E-Cadherin on Cell Proliferation and Responsiveness to the Chemotherapeutic Agents Cisplatin, Etoposide, and 5-Fluorouracil

Abstract:
Objectives: The cell adhesion molecule E-cadherin acts as a tumor and invasion suppressor and regulates cell proliferation. The aim of the present study was to investigate the impact of wild-type (wt) E-cadherin and tumor-derived mutant E-cadherin variants on the proliferation rate of MDA-MB-435S mammary carcinoma cells and the sensitivity of the cells to the chemotherapeutic drugs cisplatin, etoposide and 5-fluorouracil (5-FU) and whether p53 is involved in the chemotherapeutic response.

Methods: Proliferation rate was measured by XTT cell viability assay in the presence or absence of chemotherapeutics. Chemosensitivity was also measured by colony formation assay. Expression of p53 was investigated by immunoblot analysis. The mutational hot spot region exon 5–8 of p53 was analyzed for mutations by denaturing high-performance liquid chromatography. Results: The growth rate of MDA-MB-435S cells transfected with wt E-cadherin was reduced as compared with the parental cell line. In contrast, tumor-associated mutations of exons 8 or 9 of the E-cadherin gene interfere with the growth-suppressive function of E-cadherin. Cisplatin sensitivity of wt and mutant
E-cadherin-expressing MDA-MB-435S cells was reduced as compared with E-cadherin-negative, parental MDA-MB-435S cells. In contrast, chemosensitivity of parental, wt or mutant E-cadherin-expressing MDA-MB-435S cells measured after etoposide or 5-FU exposure was found to be similar in all tested cell lines. Since p53 influences the sensitivity of cells to chemotherapeutic agents, we investigated whether the p53 expression level or mutation status were different in the nontransfected or E-cadherin-transfected MDA-MB-435S cell lines. We found that the p53 expression pattern and genomic background were similar in all cell lines and not affected by cisplatin.

Conclusion: The results obtained in this study suggest that the expression and/or mutation of the E-cadherin gene influence the proliferation rate and drug sensitivity of tumor cells.

Stichworte: E-cadherin mutations; Cell growth; Chemosensitivity

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