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Teneurin-4 is frequently expressed in human ovarian carcinomas and is associated with tumor differentiation

Ziegler. A
Clínica Alemana-Universidad del Desarrollo, Chile

Teneurins are a family of highly conserved transmembrane proteins involved in embryonic development of the central nervous system. Using a chemoproteomic strategy, we recently identified teneurin-2 as a candidate biomarker of malignant pleural mesothelioma. In addition, expression of teneurins-2 and -4 was detected in breast and ovarian cancer cell lines. The role of teneurins in human carcinogenesis is currently unknown.

Purpose: We analyzed human ovarian tumors to assess teneurin-2 and teneurin-4 expression. The mechanisms involved in control of teneurin expression were examined in ovarian and breast cancer cell lines. Loss of function studies were performed using siRNAs directed against teneurin-2 and teneurin-4.

Methods and Patients: Abundance of teneurin mRNA in frozen tumors and control biopsies was determined by comparative real-time RT-PCR. The study was approved by the participating institutions' Ethical Committees, and tissues were obtained with informed consent of patients. The effect of siRNAs was assessed by measurement of proliferation rates, and by real-time PCR of teneurins and selected genes related to apoptosis and angiogenesis. The role of DNA methylation on teneurin-expression was determined in tumor cell lines using 5-Aza-Cytidine.

Results: Teneurin-2 and teneurin-4 mRNA could be detected by real-time PCR in all tumor samples but at varying levels. Relative mRNA levels were higher for teneurin-4 than for teneurin-2. Tumor differentiation data was available for 27 serous carcinomas and revealed that teneurin-4 mRNA was significantly lower (P<0,001, Students t-test) in poorly and undifferentiated tumors as compared to well and moderately differentiated tumors. Demethylating treatment with 5-Aza-Cytidine failed to induce teneurin expression in cell lines. Treatment with siRNAs directed at teneurins-2 or -4 did not affect proliferation or mRNA abundance of genes related to angiogenesis (VEGFA) and apoptosis (BCL2, BIRC5, CASP3, and ASP8).

Conclusions: We report the frequent expression of teneurin-2 and 4- mRNA in human ovarian tumors. Teneurin-4 levels were significantly associated with tumor differentiation. Expression of teneurin-2 and -4 genes does not appear to be controlled by DNA methylation in ovarian cancer cells, and no functional effect was observed by teneurin depletion on cell proliferation or apoptosis. We are currently evaluating the participation of teneurins in drug resistance and invasion.

aziegler@udd.cl