B7-H4 (DD-O110) is overexpressed in early stage ovarian cancer

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Abstract

B7-H4 (DD-O110), a novel membrane protein that functions as a negative regulator of T-cell response. We have developed a sensitive ELISA for B7-H4 and have previously shown that the B7-H4 levels in serum are elevated in ovarian cancer patients compared to normal controls and patients with benign gynecological diseases. To further characterize the overexpression of B7-H4 in ovarian cancer, we evaluated the expression of B7-H4 with CA125 proteins in tissue lysates from ovarian cancers of various histological types and stages.

Ovarian tissue lysates from 255 patients with ovarian carcinomas were assessed for the levels of B7-H4 and CA125. Patients were diagnosed with either early stage cancer (n=169) or late stage cancer (n=86). For comparison, ovarian tissue from patients with benign gynecological diseases (n=152) and from normal controls (n=152) were tested. The concentrations of B7-H4 and CA125 in ovarian tissue extracts were correlated with clinicopathological variables documented at the time of surgical excision and with patient outcome.

Methods & Materials

Patient Population

Ovarian tissue lysates from 255 patients (median age 56 years, range 23-99 years) with ovarian carcinomas were assessed for the levels of B7-H4 and CA125. Fifty-seven patients were diagnosed with early stage cancer, 169 patients had late stage cancer. For comparison, ovarian tissue from patients with benign gynecological diseases (n=152) and from normal controls (n=152) were tested. The concentrations of B7-H4 and CA125 in ovarian tissue extracts were correlated with clinicopathological variables documented at the time of surgical excision and with patient outcome.

Expression by histological types

Statistical Analysis

The B7-H4 and CA125 concentration in the control group (normal and benign tissue) was selected as the cutoff values for B7-H4 CA125 positive or negative. Kaplan-Meier analyses were performed based on binary categorizations (positive if above cut-off values for B7-H4 and CA125) and the results of log rank tests for time to relapse or death were determined. For Kaplan-Meier analyses, 101 patients still alive at the end of the study were censored. All statistical analyses were performed using SPSS v14.0 (SAIS edition). Cox RC index was used to assess distributions of values, to perform Wilcoxon Rank Sum tests, correlation and multivariate logistic regressions based on continuous variables, and Kaplan-Meier survival analyses.

Summary

- B7-H4 (DD-O110) was over-expressed in 73% of undifferentiated carcinomas, 67% of serous adenocarcinomas, 63% of endometrioid cancer, 45% of mucinous carcinoma and 26% of non-epithelial carcinomas.
- B7-H4 expression was low in normal ovaries and ovaries from patients with benign gynecological diseases. B7-H4 expression was also low or undetectable in other normal tissues.
- In early stage cancers, 48% of patients with stage I cancer, 57% of patients with stage II cancer, and 67% of patients with late stage cancer had B7-H4 values higher than normal controls or benign diseases.
- B7-H4 was elevated in 42 patients with early stage cancer, and CA125 was elevated in 16 patients. When the two markers were combined, 50% of patients with early stage disease were positive for B7-H4 or CA125.
- The survival analysis showed that neither B7-H4 nor CA125 were markers for the prognosis of relapse or survival of patients when the data were analyzed for stage subgroups. The multivariate Cox regression analysis considered B7-H4 and CA125 as categorical variables, which were increased with stage but not with expression of either B7-H4 or CA125.
- The data demonstrate elevation of B7-H4 expression in early stage ovarian cancer tissues, and support the potential utility of measuring B7-H4 levels in serum for the detection of early stage ovarian cancer.

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