

TIGHT JUNCTION IN OVARIAN SURFACE EPITHELIUM AND EPITHELIAL OVARIAN TUMORS

Akademisk avhandling

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av

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- I. Formation and barrier function of tight junctions in human ovarian surface epithelium.
Zhu Y, Maric J, Nilsson M, Brannstrom M, Janson PO, Sundfeldt K.
Biol Reprod. 2004 Jul;71(1):53-9.
- II. Differences in expression patterns of the tight junction proteins claudin 1, 3, 4 and 5, in human ovarian surface epithelium as compared to epithelia in inclusion cysts and epithelial ovarian tumors.
Zhu Y, Brannstrom M, Janson PO, Sundfeldt K.
Int J Cancer. 2006 Apr 15;118(8):1884-91.
- III. Tight junction formation and function in serous epithelial ovarian adenocarcinoma.
Zhu Y, Sundfeldt K.
Manuscript.
- IV. TGF- β 1 modulates tight junction and the expression of cadherins in cultured ovarian surface epithelium and epithelial ovarian cancer cells.
Zhu Y, Nilsson M, Sundfeldt K.
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ABSTRACT

Zhu, Yihong. 2007. **Tight Junction in Ovarian Surface Epithelium and Epithelial Ovarian Tumors**. Department of Obstetrics and Gynecology, Sahlgrenska Academy at Göteborg University, Sahlgrenska University Hospital SE-413 45 Göteborg, Sweden.

Epithelial ovarian cancer originating from ovarian surface epithelium (OSE) is the most lethal type of gynecological cancer among women worldwide. The poor understanding of the cellular and molecular events associated with ovarian carcinogenesis leads to difficulties in early diagnosis and in efficient treatment. Recently, much evidence has implicated that tight junction (TJ) could play a role in signaling pathways that regulate cell proliferation, polarization, and differentiation. Moreover, altered expression of TJ proteins have been discovered in many types of human epithelial tumors.

The general aims of this thesis were to investigate the expression, localization, function and modulation of TJ in normal OSE and epithelial ovarian tumors (EOT). Moreover, a further understanding of the possible roles of TJ in transformation of OSE towards EOT and in tumor progression was sought.

The studies were approved by the human Ethics committee of Sahlgrenska Academy, Göteborg University. Informed written consent was obtained from all women participating in the study.

Cultured OSE, EOT biopsies and cell lines were used in the studies. Formation of TJ was investigated by electron microscopy observation, immunofluorescence and western blot with semi-quantitative densitometry analysis. Ion-barrier function of TJ was evaluated by trans-epithelial resistance (TER) measurement. The results showed that: 1. TJ proteins ZO-1, occludin and claudin-1 are expressed in normal OSE cells *in situ* and *in vitro*. TJ structure was confirmed by electron microscopy observation in early passage of cultured OSE. During culture of normal OSE, a low TER value was built up and could be interfered with by a Ca²⁺ chelator. 2. Claudin-3 and -4 were *de novo* expressed or up-regulated in ovarian epithelial inclusion cysts and EOT compared with normal OSE. Moreover, in ovarian serous and mucinous tumors, claudin-4 was significantly increased in borderline-type tumors and adenocarcinomas compared with benign tumors. Claudin-3 was significantly increased in adenocarcinomas compared with borderline-type and benign tumors; whereas no changes were found for claudin-1 or -5. 3. In the study of four ovarian cancer cell lines, ZO-1, claudin-1, -3, -4 and E-cadherin were found to be expressed along the entire cells periphery in serous adenocarcinoma cells concomitant with high TER value, while clear-cell and endometrioid adenocarcinoma cell lines did not express claudin-4 and E-cadherin, concomitant with minimal TER values. 4. When transforming growth factor (TGF)- β 1 was added to cultured OSE and OVCAR-3 ovarian cancer cell line, the expression levels of TJ and adherens junction (AJ) proteins and TER values were changed. Furthermore, treatment with TGF- β 1 also induced EMT-like morphological change in cultured OSE.

It is concluded that normal OSE forms TJ with a weak ion-barrier function. The TJ proteins claudin-3 and -4 are up-regulated in EOT. Specific function of TJ might depend on and differ in between various histological subtypes of ovarian cancer. TGF- β 1 can modulate the formation of TJ and AJ, and the ion-barrier function of TJ in both OSE and epithelial ovarian cancer cells in culture. These findings suggest a potential role of TGF- β 1 in epithelial ovarian tumorigenesis.

Key words: tight junction, claudin, ovarian surface epithelium, epithelial ovarian tumor, TGF- β 1

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