Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Markers of Lymphocytic-Macrophagal Infiltration and Their Association With the Receptor Phenotype and Proliferative Activity of Tumor Tissue in Various Molecular-Biological Types of Endometrial Cancer

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Background and Aims: The last years were characterized by a shift from the former subdivision of endometrial cancer (EC) into two main types [1, 2] to modern molecular biological classifications of this disease [3-5]. The purpose of this investigation was an attempt to compare such prognostic indicators for EC as features of lymphocytic [6] and macrophage infiltration of tumor tissue with markers of its hormonal sensitivity (receptor phenotype) and the proliferation index Ki-67 [7], taking into account the molecular biological type of the disease. **Materials and Methods:** The study involved material from untreated patients with endometrial cancer (a total of 219 people). The average age of patients was close to 55-60 years. Using classification of Talhouk et al. [5] allowed to perform a search for POLE mutations, evaluate by IHC the expression of the oncoprotein p53 and MMR (mismatch-repair) proteins / MLH1, MSH2, MSH6 and PMS2/, and also identify the type of disease without a characteristic molecular profile (WCMP). The IHC method was also used to study the rate of estrogen (ER) and progesterone (PR) receptors, Ki-67 proliferative activity index, as well as the severity of macrophage-lymphocytic tissue infiltration of EC based on the analysis of the macrophage (CD68) and lymphocytic cells (cytotoxic CD8 and regulatory FoxP3) markers using reagents from Ventana and Dako. Statistical assessment of the relationships of the studied indicators was carried out by the Spearman rank correlation coefficient. **Results:** FoxP3 (in contrast to CD8 and CD68) positively and significantly correlates (ρ varies from 0.2895 to 0.3477) more often with ER, but not with PR. Ki-67 index in EC tissue positively and reliably correlates with FoxP3 both in the MMR-D and WCMP groups and in the combined cohort of EC patients. In the latter case, a similar relationship with Ki-67 extends to other studied markers of lymphocytic-macrophage infiltration, namely CD8 and CD68 (ρ 0,1746-0,3294). Only in the entire group of EC patients there is a positive rank correlation (0.4119!) between ER and PR expression. **Conclusions:** In patients with certain types of EC the connection between the estrogenic signal and PR induction is lost; it is especially noticeable in the MMR-D group, as exemplified by the negative correlation (-0.2951) of FoxP3 and PR expression. Taken together with existing data this indicates an important role of the endocrine component for differentiating separate groups of patients with EC, that may also be of practical importance. **References:** 1. Bokhman JV. *Gynecol Oncol* 1983; 15: 10-17. 2. Suarez AA et al. *Gynecol Oncol* 2017;144(2):243-249. 3. Murali R et al. *Lancet Oncol* 2014; 15: e268-278. 4.Berstein LM et al. *Future Oncol*. 2017 13(28):2593-2605. 5. Talhouk A. et al. *Cancer*. 2017;123(5):802-813. 6. Gargiulo P. et al. *Cancer Treat Rev*. 2016;48:61-8. 7. Kitson S. et al. *Mod Pathol*. 2017; 30(3): 459-468.

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Mechanism of Mutant p53 Using Three-Dimensional Culture on Breast Cancer Malignant Phenotype via SREBP-Dependent Cholesterol Synthesis Pathway

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In many cancers, including hormone sensitive tumors such as breast cancer, the "gain of function" caused by mutations in the tumor suppressor gene p53 plays an important role in the acquisition of malignant phenotypes and the regulation of cancer stem cell characteristics. However, its action of molecular mechanisms, particularly in vivo conditions, has not been fully clarified. Therefore, we focused on the "gain of function" of mutant p53 and the cholesterol biosynthesis pathway, especially the mevalonate(MVA) pathway, using breast cancer cells, and clarified the interaction between them and the relationship with cancer malignancy using 3D-culture. Here, we generated knock out and knock in breast cancer cell lines for p53 using CRISPR-Cas9 system, and then confirmed malignant morphological changes by 3D-culture model. We found that the introduction of mutant p53 was solely able to mediate the malignant transformation of cancer. Next, focusing on the relationship between cancer malignant transformation and lipid metabolism pathway, we investigated the role of the MVA pathway in malignant transformation by mutation p53. When investigating the effects of the addition of HMG-CoA inhibitors and isoprenoids, intermediate metabolites were important for malignant transformation during 3D culture. Furthermore, knockdown of SREBP2, which controls the MVA pathway, suppressed malignant phenotypes, so we proceeded with analysis of the interaction between mutant p53 and SREBP2. As the result, we found that mutant p53 and SREBP2 co-localize in the nucleus and consistently mutant p53 was associated with mevalonate pathway genes in parallel with binding pattern of SREBP2. Thus, our results provide the novel insight into the potential therapeutic targets for breast cancer with poor prognosis.

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Microtubule-Associated Protein 2 as a DHEA Binding Protein in Endometrial Cancer

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