Newly discovered immunohistochemical markers and micro-RNAs detected in testicular germ–cell tumors

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Testicular germ–cell tumors (TGCTs) are the most frequent malignant tumors in men 20–40 years of age and the most frequent cause of death from solid tumors in this age group. TGCTs consist of two major histological groups: seminomas and nonseminomatous germ–cell tumors (NSGCTs). NSGCTs can be further divided into embryonic carcinoma, teratoma, yolk sac tumor, and choriocarcinoma, which differ in therapy, prognosis, but all show characteristics of the primordial germ cells. New biomarkers – OCT3/4, SOX2, SOX17, HMGAI, Nek2, GPR30 – represent novel molecular targets for antineoplastic strategies. The role of micro-RNA is highlighted as molecular prognostic factor in patients with TGCT.

Key words: immunohistochemical markers, micro-RNA, germ–cell tumors.

Testicular germ–cell tumors (TGCTs) are the most frequent solid malignant tumors in men 20–40 years of age and the most frequent cause of death from solid tumors in this age group. TGCTs comprise two major histological groups: seminomas and nonseminomatous germ–cell tumors (NSGCTs). NSGCTs can be further divided into embryonic carcinoma, teratoma, yolk sac tumor, and choriocarcinoma. Seminomas and NSGCTs significantly differ in clinical features, therapy, and prognosis, but both show characteristics of the primordial germ cells. Many new biomarkers – OCT3/4, SOX2, SOX17, HMGAI, Nek2, GPR30 – represent novel molecular targets for antineoplastic strategies.

Three serum tumor markers (alpha fetoprotein, chorionic gonadotropin and lactate dehydrogenase) are currently used for prognostic purposes. AFP is a serum protein produced by the fetal yolk sac, liver, and gastrointestinal tract. The highest concentrations observed during 12–14 weeks of gestation and decline 1 year after birth. AFP is secreted by embryonic carcinoma and yolk sac tumor, but not by pure choriocarcinoma or pure seminoma. Elevated AFP can be seen after treatment in patients with liver disease, and several malignancies including hepatocellular carcinoma, lung, pancreatic, colon, and gastric cancers. During pregnancy, hCG is produced by the syncytiotrophoblastic cells of the placenta. In TGCTs, syncytiotrophoblastic cells are also responsible for production of hCG. All patients with choriocarcinoma and 40–60% of patients with embryonic cell carcinoma have elevated hCG and 20% of patients with pure seminoma have elevated serum hCG. LDH is an enzyme found in all cells and represent a nonspecific marker for the burden of disease, and can be elevated in many malignancies and chronic disease (liver and heart failure, pancreatitis, hemolytic anemia and collagen disorders).

Nowadays the testing serum for tumor markers (AFP, hCG, LDH) is a standard diagnostic procedure in managing patients with germ cell testicular tumors, although highest prognostic value is seen in nonseminomatous malignancies. Historically, these serum markers were one of major tests to differentiate seminoma, nonseminomatous or mixed primary tumors [1–5].

Elevation of “classic” tumor markers is usually seen in 60% of pts with germ cell testicular tumors. This justifies further search of newer molecular, genetic and immunohistochemical markers [6].

Review of literature yields new immunohistochemical markers, which help in diagnosis of different types of GCT, and present a potential targets for developing new pharmaceutical agents.

To name, CD117 (C-kit or KIT–marker of tyrosine kinase transmembrane receptors and stem cells growth marker) and D2-40 (marker of lymphatic vessels endothelium, used to study lymphovascular invasion and lymphangiogenesis in tumors) can be used to differentiate atypical seminoma and embryonic carcinoma.

CD117 and D2-40 are being detected in cells of seminoma, and their expression is absent in embryonic carcinoma [7].

Study of the multifunctional nonhistone high mobility proteins (HMGAI) (high mobility group, isoforms 1 and 2), which take part in transcription in nonseminomatous tumors demonstrate their higher expression compared to seminoma tumors. Hyperexpression of HMGAI speaks for malignant phenotype, resistance to chemotherapy drugs, early and fast metastases and unfavorable prognosis [8–11].

NEK2 – belongs to centrosomal serine/threoninkinases engaged in correct split of chromosomes in G2/M stage of cell cycles (the gene is located on 20q13). Many factors affect the activity of these proteininkinases, such as damage to DNA. Higher expression of this gene causes anomaly of centrosome and chromosome instability, which leads to abort of signal to apoptosis and preservation of genetically changed cells. Abrupt expression of NEK2 is found in seminoma cellular nuclei and in cellular line TCam-2 and correlates with level of expression of stem cell markers (pluripotency) – PLZF and OCT4 [12]. It was discovered that NEK2 plays a role of modulating factor for alternative splicing, which is key event in regulation of gene expression and most frequently is damaged in cancer cell [13]. (Alternative splicing is a process which allows generation of different mRNA transcripts from same gene, and different proteins, respectively. This allows for diversity of final proteins considering limited amount of genes. Up to 94% of human genes adopt alternative splicing).

OCT3/4 – is one of transcription factors from POU family, controls mRNA synthesis through binding with specific site on DNA. Transcription factors may be oncogenic and oncosuppressive, their mutation or changes in their regulation may start the cancerogenesis. Study on cell lines demonstrated that OCT3/4 was a key factor in a process of self-renewal of nondifferentiated embryonic stem cells, thus maintaining pluripotency potential. OCT3/4 can be used as a marker or non-differentiated cells. The expression of its gene is finely regulated; because even slight changes (up- or down-regulation) cause the differentiation of cells. Normally OCT3/4 is being activated in oocyte and stays activated until its implantation. Knockdown of OCT3/4 gene causes differentiation of cells, which proves the role of this factor in maintenance of self-renewal of embryonic stem cells. It is known, that mice embryos with low level of OCT3/4 protein do not build up the cellular population and differentiate into trophoectoderm. The main function of OCT3/4 is restraining stem cells from differentiation. As per Looijenga L.H. et al. [14], beside some types of germ-cell tumors (seminoma, germinoma, dysgerminoma), the embryonic carcinoma cells hold pluripotency potential (ability to differentiate). They are considered as stem cell component in non-germ cell tumors. The cells of seminoma, TIN, germinoma and dysgerminoma hold phenotype of early embryonic stem cells. It is known, that mice embryos with low level of OCT3/4 protein do not build up the cellular population and differentiate into trophoectoderm.
А К Т У А Л Ь Н Ы Е Т Е М Ь

Современные иммуногистохимические маркеры и микро-РНК при герминогенных опухолях яичка

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Герминогенные опухоли яичка чаще встречаются в возрасте 20–40 лет и являются одной из основных причин смертности от онкологических заболеваний в указанной возрастной группе. В статье рассмотрены новые иммуногистохимические маркеры OCT3/4, SOX2, SOX17, HMGA1, Nek2, GPR30. Также освещена роль исследования микро-РНК в качестве молекулярного прогностического маркера герминогенных опухолей яичка.

Ключевые слова: иммуногистохимические маркеры, микро-РНК, опухоли яичка.

Сучасні імуноістокхімічні маркери та мікро-РНК
при гірміногенніх пухлинах яєчка

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Герміногенні пухлини яєчка найчастіше зустрічаються у віці 20–40 років та є одним з основних причин смертності серед чоловіків молодого віку. У статті розглянути імуноістокхімічні маркери OCT3/4, SOX2, SOX17, HMGA1, Nek2, GPR30. Також висвітлено значення дослідження мікро-РНК у якості молекулярного фактора прогнозування перебігу захворювання при герміногенніх пухлинах яєчка.

Ключові слова: імуногістохімічні маркери, мікро-РНК, пухлини яєчка.
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