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Molecular biology of testicular germ cell tumors: Unique features awaiting clinical application

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Contents

Abstract

Testicular germ cell tumors (TGCTs) are the most common solid tumors in young adult men characterized by distinct biologic features and clinical behavior. Both genetic predispositions and environmental factors probably play a substantial role in their etiology. TGTCs arise from a malignant transformation of primordial germ cells in a process that starts prenatally, is often associated with a certain degree of gonadal dysgenesis, and involves the acquirement of several specific aberrations, including activation of SCF–CKIT, amplification of 12p with up-regulation of stem cell genes, and subsequent genetic and epigenetic alterations. Their embryonic and germ origin determines the unique

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sensitivity of TGCTs to platinum-based chemotherapy. Contrary to the vast majority of other malignancies, no molecular prognostic/predictive factors nor targeted therapy is available for patients with these tumors. This review summarizes the principal molecular characteristics of TGCTs that could represent a potential basis for development of novel diagnostic and treatment approaches.

Keywords: Testicular germ cell tumor; Etiopathogenesis; Molecular aberration; Stem cell genes; p53; Chemotherapy resistance; Prognostic factor

1. Introduction

Though relatively rare, testicular (and extragonadal) germ cell tumors (TGCTs) are the most common solid tumors in young men aged 18–35 years, and represent the leading cause of cancer-related morbidity and mortality in this group. Their incidence is steadily increasing worldwide, ranging around 5–10/100,000 in developed countries and displaying profound ethnic and geographic differences (the highest incidence in Europe estimated for 2012 was in Denmark and Norway – over 12/100,000, in contrast to 5/100,000 in neighboring Finland or 3/100,000 in Spain). Their mortality has been slightly decreasing to 0.5/100,000 in developed countries, largely attributable to the platinum-based chemotherapy and multidisciplinary approach in their management [1–6]. The principal risk factors for TGCTs include the family history of testicular tumor (relative risk (RR) ≈ 4–6 for sons and 8–10 for brothers), cryptorchism (RR ≈ 4–8), and contralateral testicular tumor diagnosed previously (RR ≈ 25). The increasing incidence of TGCTs seems to correspond with decreasing fertility among men, male sub/infertility being also related to TCGTs (RR up to 20 for infertile men) [2,4,7,8].

Both genetic predispositions and environmental factors are thought to play a significant role in the etiopathogenesis of these tumors. Several gene loci with low penetrance probably contribute to the TGCT susceptibility (e.g. proposed gene TGCT1 on Xq27, also linked to cryptorchism; gr/gr deletion in AZFc region on Y chromosome; etc.) [6,8,9]. In recent genome-wide association studies, six gene loci were related to TGCT predisposition: KITLG, SPRY4, BAK1, DMRT1, TERT and ATF7IP [10–15]; and the International Testicular Cancer Linkage Consortium (ITCLC) continues to recruit participants for studies on genetics of familial TGCTs. Regarding environmental factors, increased exposure to estrogens (including xenoestrogens, endocrine disrupting chemicals – EDC) in prenatal and early postnatal period is hypothesized to contribute to the rising occurrence of TGCTs and sub/infertility. Among other environmental toxicants, phtalates and nanoparticles have been shown to affect both somatic and developing germ cells but their contribution to testicular problems such as infertility or tumors is unclear [16,17].

The traditional histologic classification of TGCTs is based on the type of their differentiation dividing them into two major groups: seminomas (typical, undifferentiated, spermatocytic) and non-seminomas (embryonal carcinoma, teratoma and teratocarcinoma, yolk sac tumor, choriocarcioma, mixed tumors). Their precursor lesion of carcinoma *in situ* (CIS) character is the intratubular germ cell neoplasm, unclassified (ITGCNU). TGCT cells express several characteristic antigens (SOX2 and 17, NANOG, OCT3/4, HMGA1 and 2, PATZ1, CKIT, Aurora-B, PLAP, etc.) that may help to identify the TGCT subtypes and distinguish TGCTs from other tumors [2,18]; they may also release proteins including human choriogonadotropin (HCG) and alpha-fetoprotein (AFP) useful as serum tumor markers for the disease monitoring [19–21].

Although in the clinical course TGCTs, particularly non-seminomas, tend to metastasize relatively early to lymph nodes (retroperitoneal, mediastinal, left supraclavicular) and other organs (lungs, liver, brain), due to their exceptional chemosensitivity to platinum derivates they are curable even in the stage of advanced metastatic disease – a characteristic which is unparalleled among any other solid tumors in adults. Seminomas differ from non-seminomas by their later onset (mostly during the fourth decade of life, about 10 years later than non-seminomas), usually slower growth and dissemination, and also very high radiosensitivity. Patients with TGCTs are stratified into risk groups according to the histology, TNM stage and serum markers (IGCCCG classification). Therapy of TGCTs is multimodal including surgery, platinum-based chemotherapy, and/or radiotherapy. The 5-year overall survival is estimated around 95% for good-prognosis, 80% for intermediate-prognosis, and 70% for poor-prognosis tumors. The overall cure rates of TGCTs approach 85%; over 95% for localized disease and approximately 80% for metastatic disease – the best response by any solid tumor [22–25]. Despite that, TGCTs still remain a significant cause of death in adult young men and the management and outcomes of TGCT patients have not changed much since the introduction of cisplatin into the clinical practice in the late 1970s, newer approaches (high-dose chemotherapy) or cytostatics (taxanes, gemcitabine) bringing rather modest improvement to patients' survival.

2. TGCT development

According to the cell of origin, genetic and other characteristics, human germ cell tumors (GCTs) have been recently divided by an alternative WHO classification system into five entities (Table 1) [26,27]. TGCTs of young adults that are in the focus of this review belong to WHO type II GCTs. Pediatric TGCTs (type I) and spermatocytic seminomas (type III) are rare, have different etiopathogenesis, biologic and