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An oncofetal and developmental perspective on testicular germ cell cancer

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ABSTRACT

Germ cell tumors (GCTs) represent a diverse group of tumors presumably originating from (early fetal) developing germ cells. Most frequent are the testicular germ cell cancers (TGCC). Overall, TGCC is the most frequent malignancy in Caucasian males (20–40 years) and remains an important cause of (treatment related) mortality in these young men. The strong association between the phenotype of TGCC stem cell components and their totipotent ancestor (fetal primordial germ cell or gonocyte) makes these tumors highly relevant from an onco-fetal point of view. This review subsequently discusses the evidence for the early embryonic origin of TGCCs, followed by an overview of the crucial association between TGCC pathogenesis, genetics, environmental exposure and the (fetal) testicular micro-environment (genvironment). This culminates in an evaluation of three genvironmentally modulated hallmarks of TGCC directly related to the oncofetal pathogenesis of TGCC: (1) maintenance of pluripotency, (2) cell cycle control/cisplatin sensitivity and (3) regulation of proliferation/migration/apoptosis by KIT-KITL mediated receptor tyrosine kinase signaling. Briefly, TGCC exhibit identifiable stem cell components (seminoma and embryonal carcinoma) and progenitors that show large and consistent similarities to primordial/embryonic germ cells, their presumed totipotent cells of origin. TGCC pathogenesis depends crucially on a complex interaction of genetic and (micro-)environmental, i.e. genvironmental risk factors that have only been partly elucidated despite significant effort. TGCC stem cell components also show a high degree of similarity with embryonic stem/germ cells (ES) in the regulation of pluripotency and cell cycle control, directly related to their exquisite sensitivity to DNA damaging agents (e.g. cisplatin). Of note, (ES specific) micro-RNAs play a pivotal role in the crossover between cell cycle control, pluripotency and chemosensitivity. Moreover, multiple consistent observations reported TGCC to be associated with KIT-KITL mediated receptor tyrosine kinase signaling, a pathway crucially implicated in proliferation, migration and survival during embryogenesis including germ cell development. In conclusion, TGCCs are a fascinating model for onco-fetal developmental processes especially with regard to studying cell cycle control, pluripotency maintenance and KIT-KITL signaling. The knowledge presented here contributes to better understanding of the molecular characteristics of TGCC pathogenesis, translating to identification of at risk individuals and enhanced quality of care for TGCC patients (diagnosis, treatment and follow-up).

1. Introduction

Germ cell tumors (GCTs) represent a diverse group of tumors presumably originating from (early fetal) developing germ cells. Five GCT subtypes can be defined based on different stages in germ cell maturation. Most frequent are the (testicular) germ cell cancers ((T)GCC, type II GCTs). TGCC accounts for ≈1% of all solid cancers in Caucasian males. In contrast to other solid cancers, TGCC occurs in adolescents and young adults, accounting for 60% of all malignancies diagnosed in men between 20 and 40 years of age [1–3]. In the Netherlands, TGCC incidence in 2012 was 9.43/100,000 (European standardized rate), an increase of 45% since 2002 (Dutch Caner Registration (IKNL), www.cijfersoverkanker.nl) which is consistent with increasing incidence outside The Netherlands (+3–6%/year) [4]. 5-year survival rates under current treatment regiments exceed 96% (IKNL). Prognosis depends strongly on the composition/location of the tumor and patient characteristics [1,2]. In spite of the overall success of treatment, TGCC remains an important cause of (treatment related) mortality in these young men [5,6].

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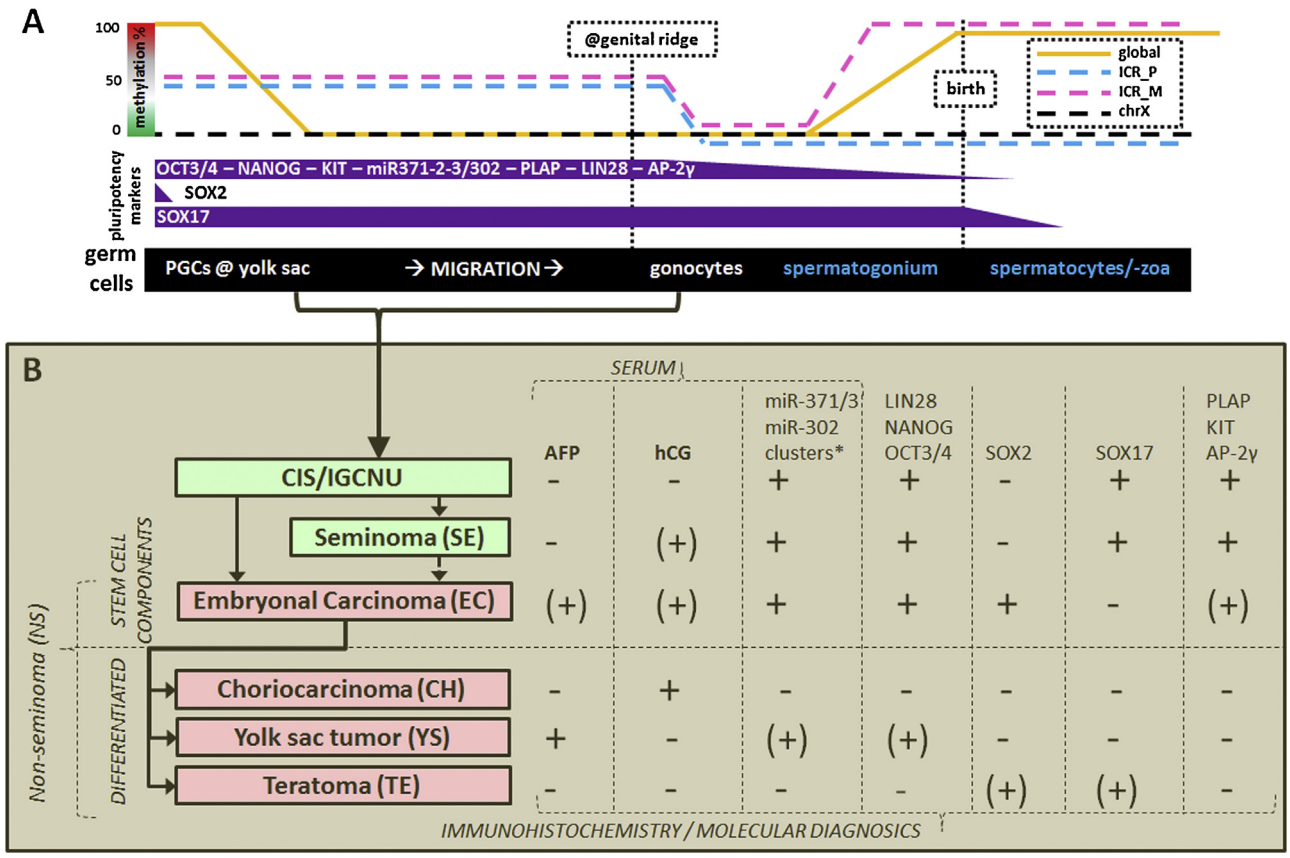

Fig. 1. Placing the TGCC cell of origin in an onco-fetal perspective as related to early embryonic germ cell development. The figure summarizes the observations reviewed in the main text. Panel A illustrates the physiological epigenetic reset and expression of core pluripotency markers during fetal germ cell development and the process of migration and maturation. Based on the reviewed evidence and anatomical localizations, the cell of origin of (T)GCC is positioned between the early PGC (extragonadal seminomas/germinomas) and gonocyte stage (testicular seminoma in the case of a male patient). ICR_P/M: imprinting control regions regulating expression of the paternal/maternal allele. Panel B summarizes the interrelation between the various types of TGCC and illustrates their totipotent potential. The methylation status and profile of mainstream diagnostic/onco-fetal markers is displayed as reviewed in the main text. * = miR-371/372/373 cluster and miR-302abcd/267 cluster.

A common precursor lesion called carcinoma-in situ (CIS) or intratubular germ cell neoplasia unclassified (IGCNU, WHO definition [7]) precedes TGCC [1,2,8,9]. Because of the non-epithelial origin of TGCC, CIS is technically not a proper term but will be used throughout this review in the interest of consistency with existing literature. At least 70% of all CIS progresses into TGCC within 7 years and the prevalence of CIS in autopsies was comparable to the lifetime risk of TGCC. This suggests that all patients with CIS eventually develop TGCC [10,11], which has however not yet been proven conclusively. Invasive TGCCs are divided into seminoma (SE) and non-seminoma (NS, stem cell component embryonal carcinoma (EC)). ECs can differentiate into all somatic (teratoma) and extra-embryonic (yolk sac tumor and choriocarcinoma) lineages including germ cells, hence exhibiting the totipotent potential of TGCC [1,2,7,12] (Fig. 1). TGCC subtypes have distinct histopathological and molecular marker profiles used in research and diagnosis [1,2,13–27]. For follow-up, serum markers Alpha Feto-Protein (AFP), human Chorionic Gonadotrophine (hCG) and in a limited fashion Lactate DeHydrogenase 1 (LDH-1) are currently used, although they have limited specificity and are not sensitive for detecting TGCC stem cell components (SE or EC) or their precursor lesion CIS [4,28–30]. Novel diagnostic strategies include immunohistochemical analysis of semen in search of CIS which has shown high specificity, but low sensitivity, warranting further investigation and optimization [31–34]. Quantifying the methylation status of specific regions (XIST promoter) of serum cell free DNA has been suggested as follow-up marker, but has so far not been validated [35,36]. Very recently, a number of independent studies showed that serum levels of embryonic micro-RNA (miR) clusters 371-3 and 302abc/367 are predictive for the presence of TGCC. This tool proved especially sensitive for identifying the SE and EC components which are indeed known to express these miRs [13,14,37–41]. Many (suggested) TGCC markers are functionally related to the unique fetal origin and pluripotent biology of these tumors as will be reviewed below (Fig. 1).

The strong association between TGCC and their totipotent ancestor (fetal primordial germ cell or gonocyte) makes these tumors highly relevant from an onco-fetal point of view, especially since a number of animal and cell line models are available for functional studies (supplementary data). Here, the fetal origin and intrinsic pluripotent oncofetal properties of TGCC cells are reviewed, especially with regard to their stem cell components SE and EC. Risk factors that might trigger malignant transformation of embryonic germ cells and disease progression are also discussed.

2. From fetal germ cells to CIS and beyond

2.1. Normal germ cell development

Embryonic germ cells or primordial germ cells (PGC) are detected in the proximal epiblast at week 5–6 gestational age in humans (E6.5 in mice). During fetal development these cells migrate along the midline of the body, where GCTs are also located: from the yolk sac, via the hindgut to the genital ridge. These cells are characterized by positive immunohistochemical staining for a number of pluripotency/germ cell markers: e.g.