# Biology of Germ Cell Tumors

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**KEYWORDS**

• Testicular • Germ cell tumors • Biology • Cisplatin resistance

Germ cell tumors are derived from cells belonging to the germ cell lineage. They occur primarily in the gonads, and less than 10% arise in specific extragonadal sites along the midline of the body. This pattern of distribution is thought to reflect the migration route of the primordial germ cells (PGCs) during embryogenesis—from the yolk sac to the genital ridges.[1]

Germ cell tumors of the testis (TGCTs) account for more than 95% of all testicular tumors, and they are the most common solid malignancies to affect young white men.[1] Histologically, TGCTs comprise 2 major subgroups: seminomas and nonseminomatous germ cell tumors (NSGCTs). Seminomas are composed of uniform tumor cells that resemble PGCs/gonocytes. In contrast, NSGCTs may contain one or more histologic subtypes that represent different differentiation lineages and stages of embryonic development—embryonal carcinoma, choriocarcinoma, yolk sac carcinoma, and teratoma.[1] Ten percent of TGCTs comprise elements of both seminomas and NSGCTs.

TGCTs are characterized by extreme sensitivity to chemotherapy. Despite this, approximately 20% of patients with metastatic TGCTs fail to achieve a complete response or relapse from complete remission; this is due to intrinsic cisplatin resistance or acquired resistance after an initial response. Understanding the molecular biology of TGCTs may thus allow the development of new therapies for the small subset of patients with a poor prognosis.

## PREINVASIVE DISEASE

Despite the clinical and histologic differences between seminomas and NSGCTs, all TGCTs are thought to arise from a common precursor lesion, carcinoma in situ, first

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described by Skakkebaek in 1972.[2] This hypothesis is supported by the frequent observation of carcinoma in situ in the testicular tissue adjacent to TGCTs as well as the development of TGCTs in patients previously diagnosed with carcinoma in situ.[3,4] Due to the absence of epithelial differentiation in these precursors, the term, *intratubular germ cell neoplasia, unclassified (ITGCNU)*, is now more commonly used. Spontaneous regression of ITGCNU does not seem to occur and eventually all ITGCNUs progress to TGCTs. The median time to the development of invasive disease is 5 years.[5]

ITGCNUs are thought to be derived from transformation of a PGC or gonocyte during fetal development.[6] Evidence supporting this includes the morphologic similarities and the presence of overlapping developmental immunohistochemical markers (PLAP, KIT, and OCT3/4) between ITGCNUs and PGCs and early gonocytes.[6–12] In addition, biallelic expression of the imprinted genes, *H19* and *IGF2*, has been reported in TGCTs, indicating again that these tumors may have arisen from PGCs, where genomic imprinting is temporarily erased.[13] More recently, gene expression profiling studies have revealed a substantial overlap between the expression profile of ITGCNUs and that of embryonic stem cells, providing further evidence of the fetal origin of ITGCNUs.[14,15]

The precise molecular events underlying the initiation of malignant transformation from gonocyte to ITGCNU remains poorly understood; 2 theories have been put forward. Skakkebaek and colleagues[6] proposed that the origins of ITGCNU are fetal gonocytes that are unable to develop into normal spermatogonia.[16] These arrested germ cells are thought to be susceptible to postnatal or pubertal gonadotrophin stimulation, which may lead to further malignant progression later in development.[16,17] This model is supported by extensive data suggesting ITGCNU cells are transformed gonocytes. In the second model, Chaganti and Houldsworth postulated that transformation occurs after the onset of spermatogenesis, involving the zygotene-pachytene spermatocyte.[18] These cells contain replicated DNA, express wild-type p53 temporarily, and seem to be associated with a recombination checkpoint. Furthermore, aberrant chromatid exchange events associated with crossing-over during this stage may lead to increased copy number of the short arm of chromosome 12 (12p), consequential cyclin D2 (*CCND2*) overexpression, and aberrant reinitiation of the cell cycle. This model cannot explain, however, the development of ITGCNU in the gonads of children with sexual differentiation disorders.

Two models have also been proposed to explain the subsequent progression of ITGCNU into seminomas and NSGCTs.[19] In the linear progression model, TGCTs progress along a single pathway, from ITGCNU through seminomas to NSGCTs. Alternatively, the independent progression model postulates that ITGCNU progresses along independent pathways to produce both seminomas and NSGCTs.[19] Considerable evidence exists to support both models and it is likely that both pathways exist.

## GENETIC CHANGES

TGCTs are characterized by the invariable gain of material from chromosome 12p.[20–24] In the majority of cases, this is due to an isochromosome of 12p, i(12p), first reported by Atkin and Baker in 1982.[20] This abnormal chromosome comprises 2 fused short arms of chromosome 12 and is common to both seminomas and NSGCTs. The remaining i(12p)-negative TGCTs have also been shown to contain gain of chromosome 12p sequences, either as tandem duplications located in situ or transposed elsewhere in the genome.[21,22]