CHAPTER 23

GENETICS OF TESTICULAR TUMORS

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Testicular cancer (TC) has been reported to be the most common solid malignancy in young males. The risk factors are reported to be; hypospadias, cryptorchidism, impaired spermatogenesis. The family history of testicular cancer in first degree relative may increase the risk of testicular tumors. The predominant histological type has been reported to be Germ Cell Tumor (90–95%) and the prognosis is good with chemosensitivity to cisplatin-based therapy(1,2).

Testicular germ cell tumors (TGCT) are known to be the most common tumor in young white men with having a high heritability estimated to be 37–49%, and family history and cryptorchidism reported to be the strongest known risk factors, whereas no evidence regarding environmental risk factors have been defined(3).

The TGCTs can be divided into two main groups (i) tumors derived from germ cell neoplasia in situ (GCNIS); and (ii) tumors considered not to be derived from GCNIS(4). Basically cytogenetic aberrations associated with TGCTs are polyploidization and chromosome 12 amplification (isochromosome 12p). The other secondary chromosomal abnormalities are reported to be gain of genetic material on chromosomes 1, 2p, 7, 8, 12, 14q, 15q, 17q, 21q, and X with the deletion of genetic material from chromosomes 4, 5, 11q, 13q, and 18q (5). Also, genome-wide sequencing studies (GWAS) demonstrate secondary somatic gain/amplification of 12p in the most of patients with gain in 12q, 8q, 22q, and less frequently deletion/loss of 11q, 18q, 18p, 9p, 4q, 10q, 5q, 16q, and 19q (6). Other

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associated with distinct TGCT subtypes or poor prognosis (27). Also, hypermethylation of TGCTs reported to be associated with cisplatin resistance (28). The epigenetic states of TGCTs may be accepted as therapeutic targets such as DNA methyltransferase inhibitors (7).

Conversley DNA methylation, less is known regarding histone modifications in TGCTs. TGCTs have been reported to have high levels of bivalent histone marks H3K27me3 and H3K4me3 (29). Similarly with DNA methylation inhibitors, there is evidence that TGCT cells may be especially sensitive to histone targeting drugs (7).

Another epigenetic pathway; non-coding RNA, is a largely unexplored area in TGCT but reported to have the potential to provide potential therapeutic target. miR371a-3p has been reported to be pathognomonic for TGCTs, shown to be used as a plasma biomarker of TGCT burden compared to standard-of-care serum biomarkers AFP and hCG (7,30).

The other more direct mechanisms reported to be involved in epigenetic regulation of components of the DNA repair and DNA damage response pathways. The DNA promoter methylation of *BRCA1*, *RAD51*, *MLH1*, and *MGMT* has been shown to occur in and to influence chemosensitivity and progression in TGCTs (26).

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