Nature Reviews Urology | Published online 6 Dec 2016; doi:10.1038/nrurol.2016.255

Brilly/DigitalVision/Getty

TESTICULAR CANCER

Origin and evolution of TGCTs

> a unique pattern of highly recurrent reciprocal copy number alterations is present in TGCTs

New data published in *Nature* has revealed distinct genomic features that are associated with the origin of testicular germ cell tumours (TGCTs), and the chemosensitivity and progression to chemoresistance of this disease. These results could be used to help improve the efficacy of chemotherapy.

To identify genomic features of TGCTs that are associated with disease origin and progression, Amaro Taylor-Weiner and colleagues undertook clinically integrated molecular analysis of 59 germline-matched tumour samples from 47 men with TGCTs and two patients with primary mediastinal germ cell tumours (PMGCTs).

Mutational significance analysis revealed that the most significantly mutated gene was *KRAS*, and only one other gene — *RPL5* — was observed to be significantly mutated. Phylogenetic analysis of whole-exome sequencing data from patient-matched germ cell neoplasia *in situ* showed that both tumour types had chromosome arm 12p gain but the only putative driver mutation that distinguished the two tumours was a *KRAS* mutation in TGCT. These results suggest that these two processes could be separate events in TGCT evolution, with mutation of *KRAS* occurring after chromosome 12p arm-level gain.

Absolute copy number analysis showed frequent arm-level and chromosome-level gains of one parent allele accompanied by loss of the other parent allele, resulting in loss of heterozygosity (LOH). These reciprocal (R)LOH events often resulted in copy-neutral LOH and, frequently, the remaining parent allele was amplified. The mean number of chromosome arm-level amplifications across the cohort was 28.3 and 45% of arm-level deletions harboured a reciprocal amplification — considerably more than have been observed in other types of cancer. Additionally, significantly more RLOH events than would be expected by chance were observed in analysis of whole-exome sequencing data from a cohort of separate fresh-frozen primary TGCTs. These data show a unique pattern of highly recurrent reciprocal copy number alterations is present in TGCTs.

Transcriptome profiling of a subset of tumour samples showed that wild-type *TP53* is expressed in primary TGCTs, metastatic TGCTs, and PMGCTs. Overall, the genomic changes observed in TCGT tumours are similar to the adaptive changes that occur in human embryonic kidney cells when they undergo prolonged passaging *in vitro*. These cells and tumours also have similar characteristics, including sensitivity to chemotherapy-induced DNA damage, which has been shown to be the result of intact p53 status and high mitochondrial priming. Thus, the researchers investigated whether fundamental apoptotic propensity caused by increased mitochondrial priming resulted in chemosensitivity in TGCTs with wild-type *TP53* and RLOH. Dynamic BH3 profiling of samples from tumours and adjacent normal tissue demonstrated significantly increased BIM BH3-induced mitochondrial depolarization in tumours. These results suggest that the foundation of chemosensitivity in TGCTs could be intact *TP53* status, RLOH, and high mitochondrial priming.

Phylogenetic analysis of whole-exome sequencing data from 13 samples from five patients acquired both before and after chemotherapy showed that chromosome arm 12p truncation was shared across all samples. Chemotherapy-resistant tumours that arose after first-line or second-line treatment accumulated further copy number events, including reciprocal deletions. Furthermore, pluripotency and apoptosis regulators that are expressed in TGCTs (*NANOG* and *POU5F1*) were not present in resistant metastatic tumours. These data suggest that resistance is associated with continued RLOH copy number events and loss of pluripotency markers.

Eliezer M. Van Allen, a corresponding author for the paper, explained "This study provides insight into unique genomic features that are present in germ cell tumours, and sheds light on how these processes evolve as the tumours become chemoresistant. Furthermore, this investigation highlights the role of apoptotic priming of germ cell tumours for chemosensitivity." He concluded "This study sets the stage for functional interrogation of RLOH drivers, as well as epigenetic investigation for the role of pluripotency mediators in contributing to chemoresistance in this disease."

Louise Stone

ORIGINAL ARTICLE Taylor-Weiner, A. *et al.* Genomic evolution and chemoresistance in germ cell tumours. *Nature* http://dx.doi.org/10.1038/nature20596 (2016)