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INVITED COMMENTARY

Sperm Biology

Teasing apart the multiple roles of Shp2 (*Ptpn11*) in spermatogenesis

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Male germ cells are the only adult cells to undergo the intricate process of meiosis, which is preceded by the complex molecular transition from mitotic spermatogonia to spermatocytes. Recent single-cell transcriptomic studies have shown that this transition involves differential expression of thousands of genes.[1,2] Pinpointing the specific roles played by key regulators of this process is crucial to further our understanding of male fertility and, in the long-term, to support the development of infertility therapy and *in vitro* spermatogenesis.

The tyrosine phosphatase Shp2 (encoded by the gene *Ptpn11*) has previously been shown to have multiple roles during mouse spermatogenesis: loss of Shp2 expression in Sertoli cells disrupts the integrity of the blood–testis barrier and also results in a reduction of spermatogonia number and increased expression of differentiation-promoting factors.[3] Knockout of Shp2 in the embryonic precursor germ cells (gonocytes) demonstrated that this protein is essential for the production of undifferentiated spermatogonia.[4] However, although both Shp2 inhibition or global knockout suggested a role in adult germ cells,[5] its specific function in this cell population has yet to be established.

In *Asian Journal of Andrology*, Li *et al.*[6] address this aspect by investigating the role of Shp2 in the postnatal germ cells using a Stra8-Cre driver strain. They show that this germ cell-specific knockout causes increased differentiation of spermatogonia and reduced numbers of meiotic cells. Abnormal expression of numerous genes/proteins associated with meiotic recombination and synapsis was also identified, consistent with a role for Shp2 in the transition from spermatogonia to spermatocytes.

In humans, a role for SHP2 in spermatogenesis has previously been inferred from genetic studies which revealed that pathogenic gain-of-function mutations in *PTPN11* are associated with conferring a "selfish" selective advantage to spermatogonia. This results in the formation of mutant clones that spread within seminiferous tubules with age.[7] If passed on to progeny, these mutations cause the developmental disorder Noonan syndrome. Given this, it would be interesting to assess the effects of *Ptpn11* gain-of-function mutations in murine adult spermatogonia – which may provide further clues on the role of SHP2 in spermatogenesis and human disease.

Although Li *et al.*[6] propose that activation of SHP2 could be a potential target for the treatment of male infertility, given that *PTPN11* is a known oncogene, implementing such an approach could carry some risks. On the other hand, data from Li *et al.*[6] and from previous studies[5] suggest that permanent infertility could be a side effect of therapies being developed to inhibit SHP2.[8]

Delineating the role of *Ptpn11*/Shp2 in adult spermatogenesis provides a valuable insight into the multifaceted functions of this key disease gene.

COMPETING INTERESTS

Both authors declare no competing interests.

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