Commentary

Noncanonical Wnt Signaling in the Integrity of the Blood-Testis Barrier and Sperm Release

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The mammalian testis is formed by 2 morphologically and functionally distinct compartments: the seminiferous tubules and the interstitial tissue. The seminiferous tubules contain the germ cell population, originating the male gametes in the adult, and the somatic Sertoli cell lineage. In the interstitial tissue lies the Leydig cell population, responsible for androgen secretion, amid connective tissue with blood vessels and nerves. The structure and function of the testes show remarkable changes during postnatal life, especially during pubertal maturation, driven by androgens (1). One notorious transformation occurs within the seminiferous tubules: prepubertal spermatogenesis, limited to spermatogonial mitoses, switches to adult spermatogenesis, where spermatogonial proliferation is followed by 2 successive meiotic divisions and spermatid maturation leading to the production and release of spermatozoa. This gonad-specific biologic process depends essentially on the support given by mature Sertoli cells. While molecules coming from the blood vessels present in the interstitial tissue have free access to spermatogonia, meiotic and postmeiotic germ cells are completely isolated from blood-borne substances. This is mainly due to the development of the blood-testis barrier (BTB) during pubertal maturation (2).

The BTB divides the seminiferous tubules into 2 compartments, basal and adluminal, each featuring a specific microenvironment. Although tight, the BTB is a dynamic structure allowing germ cell translocation from the basal to the adluminal compartment in adult spermatogenesis (3). The BTB is essentially formed by inter-Sertoli cell junctions, namely tight junctions, basal ectoplasmic specializations, gap junctions, and desmosomes (4). Germ cells occur in species-specific cyclic associations during spermatogenesis; in the rat testis, there are 14 stages in a seminiferous epithelial cycle. The passage of germ cells across the BTB takes place during stage VIII, when opening and subsequent closing allow preleptotene spermatocyte translocation from the basal to the adluminal compartment. Special junctions exist between Sertoli cells and elongated spermatids at the apical compartment of the seminiferous epithelium, called apical ectoplasmic specializations (ES), which are involved in maintaining spermatid polarity, as well as in spermatid adhesion to the seminiferous epithelium and sperm release occurring at stage VIII of the epithelial cycle. During the opening of the BTB and the apical ES at stage VIII and their subsequent closing, there are significant changes in the expression of actin binding proteins, such as

Arp3 and Eps8 (5); however, their regulatory mechanisms remained ill defined.

Yan Fu and colleagues have explored the involvement of Wnt5a in Sertoli cell junctions through the planar cell polarity signaling pathway (6). The authors first showed in adult rat testes that Wnt5a was highly expressed in the BTB at stages VII and VIII of the seminiferous epithelium cycle and in the apical ES at stage VII. Dual-label immunofluorescence studies demonstrated a colocalization of Wnt5a with F-actin, ZO-1, N-cadherin, β-catenin, and Cx43, all of them components of the BTB junctional complexes.

The role of Wnt signaling in the junctional function of Sertoli cells was supported by the observation that Wnt5a expression was decreased after treatment with $CdCl_2$, a BTB toxicant, and adjudin, an apical ES-disrupting chemical (6). Furthermore, elegant in vivo studies inducing a specific knockdown of Wnt5a by small interfering RNA testicular injection showed that elongated spermatids remained trapped within the seminiferous epithelium at stage VIII, with no sperm release, indicating an apical ES disturbance. These observations were coincident with decreased expression of the BTB components ZO-1, occludin, N-cadherin, β-catenin, and Cx43. In addition, significant changes were observed in actin-binding proteins. For instance, Arp3 expression that normally occurs on spermatid concave side at stage VII was abolished following Wnt5a knockdown. On the other hand, Eps8 expression in the BTB, which is high at stage VII and significantly wanes at stage VIII in normal conditions, showed a decreased expression level at stage VII with no decrease at stage VIII in Wnt5a-knockdown animals. Concomitantly, the structure of F-actin was disturbed. Altogether, a severe functional disruption of the BTB integrity was evidenced.

Finally, Fu and colleagues explored the molecular pathway involved in Wnt5a signaling in Sertoli cell junctions (6). Wnt signaling, also involved in cell proliferation, survival, differentiation, polarization, and migration, may follow a canonical or a noncanonical pathway. The latter includes the planar cell polarity pathway and the Wnt/Ca^{2+} pathway (7). The observation that the receptor-tyrosine kinase-like orphan receptor 2 (ROR2) expression was impaired following Wnt5a knockdown suggested that Wnt5a regulated BTB dynamics through the planar cell polarity pathway. Additionally, Wnt5a can modulate the mTOR pathway, which in turn regulates BTB integrity through mechanistic target of rapamycin complex 1 (mTORC1) and mTORC2: mTORC1 promotes whereas mTORC2 disturbs

BTB integrity (8). The work by Fu et al (6) clearly shows that Wnt5a knockdown disrupts the balance between mTORC1 and mTORC2 in rat Sertoli cells.

In summary, the results of the elegant study performed by Fu and colleagues (6) provide novel insight into the Wnt5a signaling pathway involved in the regulation of the BTB and apical ES integrity through ROR2, and the balance between mTORC1 and mTORC2, involved in the actin-dependent processes that maintain the BTB and apical ES dynamics. The understanding of the precise mechanisms underlying the BTB physiology is a clue to the approach of male fertility disorders derived from congenital or acquired defects.

Additional Information

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Disclosures: The author has nothing to disclose.

Data Availability: Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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