Androgen Receptor Roles in Spermatogenesis and Fertility: Lessons from Testicular Cell-Specific Androgen Receptor Knockout Mice

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摘要

Abstract

Androgens are critical steroid hormones that determine the expression of the male phenotype, including the outward development of secondary sex characteristics as well as the initiation and maintenance of spermatogenesis. Their actions are mediated by the androgen receptor (AR), a member of the nuclear receptor superfamily. AR functions as a ligand-dependent transcription factor, regulating expression of an array of androgen-responsive genes. Androgen and the AR play important roles in male spermatogenesis and fertility. The recent generation and characterization of male total and conditional AR knockout mice from different laboratories demonstrated the necessity of AR signaling for both external and internal male phenotype development. As expected, the male total AR knockout mice exhibited female-typical external appearance (including a vagina with a blind end and a clitoris-like phallus), the testis was located abdominally, and germ cell development was severely disrupted, which was similar to a human complete androgen insensitivity syndrome or testicular feminization mouse. However, the process of spermatogenesis is highly dependent on autocrine and paracrine communication among testicular cell types, and the disruption of AR throughout an experimental animal cannot answer the question about how AR in each type of testicular cell can play roles in the process of spermatogenesis. In this review, we provide new insights by comparing the results of cell-specific AR knockout in germ cells, peritubular myoid cells, Leydig cells, and Sertoli cells mouse models that were generated by different laboratories to see the consequent defects in spermatogenesis due to AR loss in different testicular cell types in spermatogenesis. Briefly, this review summarizes these results as follows: 1)

the impact of lacking AR in Sertoli cells mainly affects Sertoli cell functions to support and nurture germ cells, leading to spermatogenesis arrest at the diplotene primary spermatocyte stage prior to the accomplishment of first meiotic division; 2) the impact of lacking AR in Leydig cells mainly affects steroidogenic functions leading to arrest of spermatogenesis at the round spermatid stage; 3) the impact of lacking AR in the smooth muscle cells and peritubular myoid cells in mice results in similar fertility despite decreased sperm output as compared to wild-type controls; and 4) the deletion of AR gene in mouse germ cells does not affect spermatogenesis and male fertility. This review tries to clarify the useful information regarding how androgen/AR functions in individual cells of the testis. The future studies of detailed molecular mechanisms in these in vivo animals with cell-specific AR knockout could possibly lead to useful insights for improvements in the treatment of male infertility, hypogonadism, and testicular dysgenesis syndrome, and in attempts to create safe as well as effective male contraceptive.