Infertility with defective spermatogenesis and steroidogenesis in male mice lacking androgen receptor in Leydig cells

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摘要

Abstract

Androgen and the androgen receptor (AR) have been shown to play critical roles in male fertility. Our previous data demonstrated that mice lacking AR (AR−/y) revealed incomplete germ cell development and lowered serum testosterone levels, which resulted in azoospermia and infertility. However, the consequences of AR loss in Leydig cells remain largely unknown. Using a Cre-LoxP conditional knockout strategy, we generated a tissue-specific knockout mouse (L-AR−/y) with the AR gene deleted by the anti-Müllerian hormone receptor-2 (Amhr2) promoter driven Cre expressed in Leydig cells. Phenotype analyses show that the outside appearance of L-AR−/y mice was indistinguishable from wild type mice (AR+/y), but with atrophied testes and epididymis. L-AR−/y mice were infertile, with spermatogenic arrest predominately at the round spermatid stage and no sperm could be detected in the epididymis. L-AR−/y mice also have lower serum testosterone concentrations and higher serum leuteinizing hormone and follicle-stimulating hormone concentrations than AR+/y mice. Further mechanistic studies demonstrated that hypotestosteronemia in L-AR−/y mice is not caused by reducing numbers of Leydig cells, but instead by the alterations of several key steroidogenic enzymes, including 17β-HSD3, 3β-HSD6, and P450c17. Together, L-AR−/y mice provide in vivo evidence that functional AR in Leydig cells is essential to maintain normal spermatogenesis, testosterone production, and required for normal male fertility