

functional relationships between variants of *FTO* and the regulation of energy metabolism and conservation elucidated, then it may be possible to design agents that can be directed to sites of *FTO* action that will ultimately lead to improved methods of weight control.

Interestingly, the presence or absence of the *A* allele was not associated with birth weight.

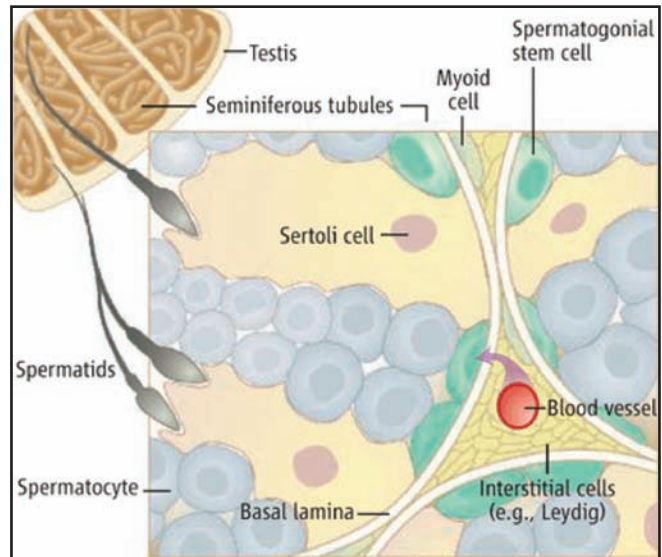
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Reference

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A Niche for Undifferentiated Spermatogonia

In human males, spermatogenesis proceeds over several decades. Scattered throughout the spermatogenic tubules of mammalian testes are spermatogenic stem cells (cells that are able to self-renew and to differentiate into cells with more specialized functions) that appear to be localized to specific regions within the tubule (Figure). In mice, undifferentiated spermatogenic stem cells constitute less than 1% of testicular cells and periodically differentiate into primitive type A single (As) spermatogonia that then give rise to daughter cells—A paired (Apr) and A aligned (Aal)—chains of 4 to 32 cells—that in turn evolve into more mature spermatogenic cells.¹ The tubular regions that harbor the most primitive and undifferentiated spermatogenic stem cells are termed “niches” and are deemed important because of the environment provided therein that enables the undifferentiated A cells to survive and from which daughter cells migrate and populate the spermatogenic tubules permitting the decades-long process of spermatogenesis. Yoshida and co-workers have identified the sites of As localization by labeling undifferentiated A cells with green fluorescent protein (GFP) expressed in response to a regulatory sequence of a gene (*Ngn3*) expressed in spermatogenic cells. Utilizing time-lapse imaging to follow the course of GFP cellular expression in intact mouse testes, they localized the earliest mouse spermatogenic stem cells (As) to specific regions in spermatogenic tubules; these cells reside in a basal tubular compartment adjacent to the interstitium and across from blood vessels that are surrounded by interstitial cells (including Leydig cells); these sites are characterized by turns in the spermatogenic tubule and by branching of their associated blood vessels. As As cells transitioned to Apr and Aal cells, they migrated from the site of origin and spread throughout the basal tubular compartment giving rise to more differentiated spermatogonia, spermatocytes, spermatids, and sperm. The investigators confirmed these observations by transplantation of testicular fragments from donor testes that had been cleansed of vessels and interstitium to sites beneath the tunica albuginea of recipient testes in vivo. Three months later, the grafts had revascularized, the interstitium had been reconstituted, and spermatogenesis was normal; As cells were again localized to turns in the tubules across from branch points of the blood vessels that were themselves encased in interstitial cells. The authors suggested that the niche for As cells by proximity of the tubular basal compartment to the branch point of blood vessels and to abundant interstitial cells provides



At home, in small narrow places. Spermatogonial stem cells localize to interstitial regions between seminiferous tubules in the mouse testis. This implies that interstitial cells and branching blood vessels secrete factors (arrow) that influence stem cell fate.

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a microenvironment in which “signals” from these cells recruit, nourish, and stimulate differentiation of spermatogenic stem cells. The biochemical nature of these signals is unknown but likely include testosterone, a factor known to be important for the earliest stages of spermatogonial differentiation, as well as products of the Sertoli cells. That niches can be reconstituted (as demonstrated by the testicular graft experiments) indicates that new niches can be developed, a process that would support long-term spermatogenesis.

Yoshida S, Sukeno M, Nabeshima Y-I. A vasculature-associated niche for undifferentiated spermatogonia in the mouse testis. *Science.* 2007;317:1722-6.

Editor’s Comment: Identification of the sites within the spermatogenic tubule that harbor undifferentiated spermatogenic stem cells may prove beneficial in isolating such cells. Inasmuch as these are cells with the diploid number of chromosomes (ie, prior to the first meiotic division), spermatogenic stem cells may ultimately provide a source of pluripotential stem cells.¹

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Reference

1. DiNardo S, Braun RE. *Science.* 2007;317:1696-7.