<Further Development 6_06>

Descent of the Testes

Spermatogenesis in mammals is a heat-sensitive process that breaks down at the normal human body temperature of 37°C. In mice, heating the testes to normal body temperature (38°C) prevents the spermatogonia from repairing double-stranded DNA breaks during the first meiotic prophase (Hirano et al 2022). It is generally thought that this is why the testes of most mammals hang in a scrotal sac, outside the body, where they function at a temperature hovering around 34°C (Moore 1924; Setchell 1998; Hadziselimovic 2022). Thus, the scrotum is thermoregulatory sac that houses the testes at a lower temperature than that of the body.

Indeed, one of the differences between the testes and the ovaries is their position within the body. The ovaries are located near the kidneys, well within the body. The testes, however, have descended such that they are outside the main body, residing in the scrotum. The testes descend in two steps, the first step is within the abdomen, and the second step is from the abdomen to the scrotum. This sexual dimorphic position of the gonads in mammals is dependent on differential development of two ligaments, the cranial suspensory ligament (CSL) and the gubernaculum. During male embryogenesis, the gubernaculum grows and the CSL regresses. This results in the transabdominal descent of the testes. In the female, CSL develops while the gubernaculum regresses. The CSL holds the ovaries in a position lateral to the kidneys.

Recent evidence suggests that the regression of the CSL and the induction of gubernaculum development are mediated by testosterone and Insl-3, respectively. The *Insl3* gene (insulin-like hormone-3; originally designated Ley I-L), a member of the insulin-like superfamily, is specifically expressed in Leydig cells of the fetal and postnatal testis. When male mice were made homozygous for a targeted deletion of the *Insl3* locus (Nef and Parada, 1999; Zimmerman et al., 1999), the testes failed to descend, remaining freely floating in the abdominal cavity. These malformations were due to failure of gubernaculum development during embryogenesis. The deficiency of *Insl3* appeared to stop gubernaculum growth, while testosterone inhibited the CSL growth. There was no ligament to hold the testes. In double-mutant male mice lacking both the *Insl3* and androgen receptor genes, the testes were positioned adjacent to the kidneys and steadied in the abdomen by the CSL, just like ovaries. These findings demonstrate that *Insl3* induces gubernaculum development in an androgen-independent way, while androgen-mediated regression of the CSL occurs independently from *Insl3.* Therefore, in addition to producing testosterone and anti-Müllerian duct hormone, the testes also produce insulin-like hormone-3, a hormone necessary for a part of the secondary male phenotype.

While the knockout mice show that these two testicular hormones are necessary for testes descent within the abdomen, mutations in the *Insl-3* gene may not be that important for human conditions where the testes fail to descend (Krausz et al., 2000). In a study of 31 men with undescended testes, none of them showed any mutations in their *Insl-3* genes.

Hutson and colleagues (2015) have written a comprehensive review of testes descent, and an excellent depiction of the descent of the human testes can be found at http://www.embryology.ch/anglais/ugenital/diffmorpho04.html.

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