

## Sertoli Cells

### A. Pre-pubertal

- Fill seminiferous tubule – no lumen
- Secrete anti-Müllerian hormone in fetal life, are pre-Sertoli cells.
- Post-birth but pre-pubertal, there is a critical window, weeks to months depending on species, in which pre-Sertoli cells divide to form the number of Sertoli cells that will be present in adults.
- Numbers regulated by FSH secretion and FSH receptor numbers. Also need GNRH-LH-testosterone.
- If unilateral castration, compensatory hypertrophy – really mostly hyperplasia. Get nearly doubling of Sertoli number in remaining testis – mechanism FSH-inhibin driven. Only minor effect of unilateral castration in adult, and no increase in cell numbers.

- ### B. Testis size – genetic component, highly heritable, about 60% genetic, depends on FSH regulation of Sertoli cell numbers during the critical window. Female relatives have the same mechanism but different endpoint – larger testes = earlier puberty in female relatives.
- Sperm production directly correlated testis size, about 15 germ cells per Sertoli in adult.
  - After critical period pre-pubertal, Sertoli cells rarely divide if ever. Very resistant to irradiation, toxins; hard to kill; germ cells easy to kill, very susceptible to insults.

### C. Morphology

- Is an epithelium-basement membrane in seminiferous tubules, lumen into which fluids, sperm secreted. Without germ cells, Sertoli cells would fill seminiferous tubule.
- Myoid = smooth muscle-like cells around outside of tubule. Junctions between myoid cells. Big species differences in numbers of layers myoid.
- Leydig cells and infrastructure such as blood and lymph vessels between Sertoli cells.
- Sertoli cell structure
  - Euchromatic, pleiomorphic nucleus, much transcription
  - Some species lots of smooth endoplasmic reticulum.
  - Many lysosomes, vacuoles, lipofuscin accumulates in older males.
  - Very elaborate junctions between Sertoli cells.
  - At ends of S. tubules, specialized Sertoli cells form tubuli recti, valve-like entrance into rete testis.

#### D. Blood-testis barrier

- No blood cells get into S. tubules; in most species bathed in lymph.
- Large molecules perfused in blood to testis do not get into S. tubules.
- Some smaller molecules get by the myoid cell junctions but get stopped by Sertoli-Sertoli junctions.
- These junctions divide S. tubule into basal and adluminal compartments. Adluminal part completely protected from blood.
- Small molecules need to go through rather than between Sertoli cells to get from blood to adluminal compartment.

#### E. Slides of Sertoli cells

diagrams, light microscope, scanning and transmission electron microscope

#### F. Regulation of Sertoli cell function

- FSH-FSH receptor.
- Standard protein kinase A system – cyclic AMP, protein kinase A, phosphorylation of key proteins, regulation of transcription, enzymes, etc.
- Effects FSH different prepubertal than post
  - Pre -- stimulate mitosis, cell proliferation, differentiation
  - Post -- glucose uptake, metabolism  
protein synthesis, secretion  
physiological function
- Hypophysectomy, Sertoli cells and testis shrink
- Testosterone also key regulator, very high concentrations, androgen receptor
- $5\alpha$  reductase – converted to dihydrotestosterone
- Aromatase – converted to estradiol 17 beta
- Species differences how much DHT,  $E_2$
- Permissive stimulators
  - Vitamin A (retinol) is concentrated by Sertoli cells -- need retinol binding protein  
Vitamin E, absolutely essential in some species.
- Numerous autocrine and paracrine regulators.

- IGF-1 system, testis-specific and non-specific growth factors, 2-way communication Leydig and myoid cells, germ cells.

#### G. Sertoli cell secretions

- Over 100 proteins made and secreted; secreted as made, not stored, species differences
- Main protein secreted = androgen binding protein. 80% secreted lumen, 20% basal – possibly used Sertoli cell itself, goes into rete testis fluid – delivered to head of epididymis – may function to deliver androgens to epididymal epithelium in addition to transport. Synthesis and secretion very FSH-dependent.
- Inhibin – heterodimer of TGF-beta family. Negative feedback to gonadotrope in anterior pituitary for FSH secretion. Measurement confusing because homodimer is activin with opposite function – causes FSH secretion.
- Transferrin and ceruloplasmin – iron and copper binding proteins – needed for protein function
- Retinol binding protein – Vitamin A
- Plasminogen activator (urokinase type) – proteolysis for spermatid remodeling, release
- Most secretion into rete testis fluids – about 10  $\mu\text{l/h/gm}$  testis – fluid secretion also depends FSH.

#### H. Sertoli cell functions

Nurse cell – regulate spermatogenesis and spermiogenesis. Many genes are expressed only in the testis, have testicular versions of many non-testicular genes, e.g. testis-specific lactate dehydrogenase.

The haploid, late spermatid and sperm very dependent on Sertoli cell – can't synthesize their own proteins.

- Rete testis fluid more like intracellular than extracellular fluid very high potassium. This fluid also transports sperm which are non-motile when spermiation occurs.
- Maintain blood-testis barrier.
- Protection immune system – post-meiotic proteins not present when self – non-self established by immune system – sperm very antigenic, need protection from immune system – if breached, subfertility/sterility. This happens with testicular damage, vasectomy, some diseases.
- BT barrier also protects environmental toxins, diseases, etc., to great extent.

- Pre-meiotic cells in basal compartment; post-meiotic in adluminal junctions between Sertoli cells open and close to let germ cells pass – multiple, sequential junctions.

#### I. Sertoli cells in vitro

- Difficult to maintain appropriate geometry.
- Cells plate down and form flat layer unless extracellular matrix such as Matrigel – collagen, hyaluronic acid, etc.
- Much learned isolated Sertoli cells – beginning to have successful in vitro spermatogenesis, at least some steps.

#### J. Pathologies

- Any derangement in gonadotropin/testosterone secretion causes problem – genetic or otherwise.
- Injury, irradiation stop spermatogenesis.
- Sertoli cell tumors rare – typical of non-dividing cells.
  - Heat very damaging.