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Regulation of the blood-testis barrier

Peter G. Stanton[a,b,*]

[a] Hudson Institute of Medical Research, Clayton, Victoria, Australia
[b] Dept. of Molecular and Translational Sciences, Monash University, Clayton, Victoria, Australia

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ABSTRACT

The purpose of this review is to describe the endocrine and local testicular factors that contribute to the regulation of the blood-testis barrier (BTB), using information gained from in vivo and in vitro models of BTB formation during/after puberty, and from the maintenance of BTB function during adulthood. In vivo the BTB, in part comprised of tight junctions between adjacent somatic Sertoli cells, compartmentalizes meiotic spermatocytes and post-meiotic spermatids away from the vasculature, and therefore prevents autoantibody production by the immune system against these immunogenic germ cells. This adluminal compartment also features a unique biochemical milieu required for the completion of germ cell development. During the normal process of spermatogenesis, earlier germ cells continually cross into the adluminal compartment, but the regulatory mechanisms and changes in junctional proteins that allow this translocation step without causing a 'leak' remain poorly understood. Recent data describing the roles of FSH and androgen on the regulation of Sertoli cell tight junctions and tight junction proteins will be discussed, followed by an examination of the role of paracrine factors, including members of the TGFβ superfamily (TGFβ3, activin A) and retinoid signalling, as potential mediators of junction assembly and disassembly during the translocation process.

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1. Introduction

Sperm production is absolutely dependent on a testicular structure called the **blood-testis barrier** (**BTB**, Fig. 1), which separates advanced germ cells within the testis from the immune system, that would otherwise see them as 'foreign'. While a complete loss of BTB function leads directly to infertility, during normal spermatogenesis this structure must transiently 'open' and 'close' to allow immature germ cells to cross into the immune-privileged environment. However, the mechanisms that control this process without causing a 'leak' in the healthy adult are poorly understood; similarly the extent to which disturbances in BTB regulation contribute to testicular disease and infertility in men remains unknown. Several reviews have recently examined in detail the molecular components [1–3] and architecture [4–6] of the cell junctions that comprise the BTB, but the endocrine and paracrine regulation of BTB function has received less attention. As we begin to understand more closely the complex molecular and cellular interactions and regulatory events that together comprise spermatogenesis [7–10], the time is now suitable for a re-examination of the mechanisms that control BTB function. In particular, this review will look for insights about BTB regulation that can be gained from in vivo and in vitro models of BTB formation during/after puberty, and from the maintenance of BTB function during adulthood.

* Correspondence address: Hudson Institute of Medical Research, 27-31 Wright St., Clayton, Victoria 3168, Australia.
E-mail address: peter.stanton@hudson.org.au

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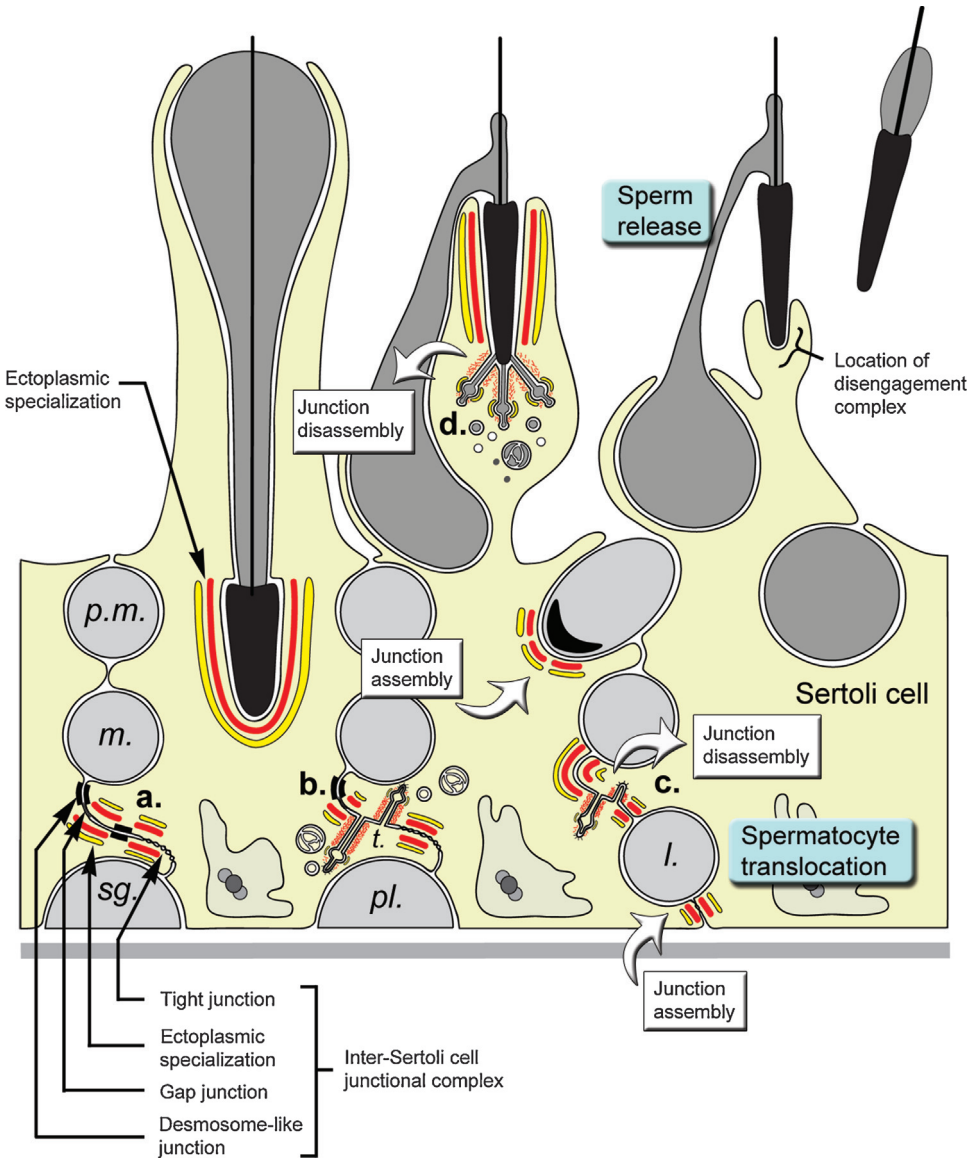

Fig. 1. Schematic diagram illustrating the positions of intercellular junctions in the mammalian seminiferous epithelium. The inter-Sertoli cell junctional complex (a) is comprised of tight junctions, gap junctions, a testis-specific adhesion junction called the ectoplasmic specialisation, and desmosome-like junctions. This junctional complex seals adjacent Sertoli cells creating an adluminal region in which meiotic (*m.*) and post-meiotic (*p.m.*) germ cells reside, whilst earlier germ cells (spermatogonia, *sg.*) reside in the basal compartment with free access to blood and lymphatic factors. These tight junctions (TJs) contain claudin-11, occludin and other TJ proteins (*see text*). At the beginning (b) of the process of spermatocyte translocation (stage VII in the rat), tubulobulbar complexes (*t.*) appear in the junctional complex, and will become involved in the endocytic removal of TJ proteins during junction disassembly. At this point, the spermatogonia has progressed to become a preleptotene spermatocyte (*pl.*) but is still located in the basal compartment. In late stage VIII/early stage IX spermatocyte translocation (c) occurs; the preleptotene spermatocyte moves off the basement membrane and becomes a leptotene spermatocyte (*l.*), while 'new' Sertoli cell TJs and other junction types are assembled below it, thus temporarily encasing the leptotene spermatocyte in an intermediate compartment between 'new' and 'old' TJs. These new TJs contain claudin-3 and potentially other TJ proteins yet to be found. 'Old' TJs are then disassembled and TJ proteins recycled to the new TJ to form the mature Sertoli cell junctional complex. It is worth noting that the Sertoli cell also co-ordinates other junction assembly and disassembly roles at the same time that spermatocyte translocation is happening; this involves formation of ectoplasmic specialisations adjacent to round spermatids which are later removed by tubulobulbar complexes (d) prior to sperm release. Figure modified and reprinted from [6], with permission from Elsevier.

2. General aspects of blood-testis barrier organisation

Experimental data confirming the existence of the BTB first appeared in the mid-1960s from Chiquoine [11] and Kormano [12], with the latter showing that vascular permeability tracers readily appeared in the pre-pubertal rat testis but not in the adult seminiferous epithelium (for reviews see [3,13]). Today, it is recognised that the BTB is comprised of three major components, being a physical barrier contributed by Sertoli cell junctions, a physiological barrier made up of Sertoli cell transporters that control movement of substances to- and from- the lumen, and an immunological barrier contributed by immunoregulatory factors and tolerance mechanisms [14–16]. All three components act in concert in the functional adult BTB, with the net result being the provision of an environment within the adluminal region that is both immunoprotective and of a controlled biochemical nature to allow meiotic and post-meiotic germ cell maturation to proceed. This review will primarily focus on the regulation of Sertoli cell junctions representing the physical barrier, but as will become evident, all three components are likely interlinked by common regulatory factors.

Sertoli cell tight junctions (TJs) are part of a larger inter-Sertoli cell junctional complex made up of TJs, gap junctions, a testis-specific adhesion junction called the ectoplasmic specialisation, and desmosome-like junctions (see Fig. 1) (for reviews see [2,5,6]).