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Survey

Cytokines and junction restructuring during spermatogenesis—a lesson to learn from the testis

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Abstract

In the mammalian testis, preleptotene and leptotene spermatocytes residing in the basal compartment of the seminiferous epithelium must traverse the blood-testis barrier (BTB) at late stage VIII through early stage IX of the epithelial cycle during spermatogenesis, entering the adluminal compartment for further development. However, until recently the regulatory mechanisms that regulate BTB dynamics remained largely unknown. We provide a critical review regarding the significance of cytokines in regulating the 'opening' and 'closing' of the BTB. We also discuss how cytokines may be working in concert with adaptors that selectively govern the downstream signaling pathways. This process, in turn, regulates the dynamics of either Sertoli–Sertoli tight junction (TJ), Sertoli–germ cell adherens junction (AJ), or both junction types in the epithelium, thereby permitting TJ opening without compromising AJs, and vice versa. We also discuss how adaptors alter their protein–protein association with the integral membrane proteins at the cell–cell interface via changes in their phosphorylation status, thereby altering adhesion function at AJ. These findings illustrate that the testis is a novel in vivo model to study the biology of junction restructuring. Furthermore, a molecular model is presented regarding how cytokines selectively regulate TJ/AJ restructuring in the epithelium during spermatogenesis.

Keywords: Spermatogenesis; Testis; Junction restructuring; Cytokines; TGF-β3; TNFα; p38 MAPK; ERK; JNK; Blood-testis barrier; Adherens junction; Tight junction; Adaptors; Ectoplasmic specialization

Contents

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1. Introduction

The production of mature spermatozoa (haploid, 1*n*) from spermatogonia (diploid, 2*n*) is essential for the perpetuation of all mammalian species. Such event, known as spermatogenesis in the male, takes places in the functional unit of the testis called the seminiferous tubule. Seminiferous tubules, in turn, coordinate with Leydig cells in the interstitium and the brain via the hypothalamic-pituitary-testicular axis to regulate spermatogenesis [1,2]. Although spermatogenesis varies in detail in different species (e.g., minks are seasonal breeders exhibiting seasonally or environmentally responsive phases in this process whereas spermatogenesis continues throughout the entire life span in humans and rodents), the cellular constituents and the basic physiology of the testes are rather similar [3]. We limit our discussion largely in rats, mice and/or men since most studies were conducted in these species.

Spermatogenesis can be divided into three distinct phases which provide an upward of 150×10^6 spermatozoa per day per man [1,3]. The germline stem cells (spermatogonia) can either self-proliferate (phase 1) or differentiate into primary spermatocytes, which then undergo meiosis and differentiate into secondary spermatocytes and eventually haploid spermatids (phase 2). These cells, in turn, differentiate morphologically and functionally to spermatozoa via spermiogenesis (phase 3), which are released into the tubule lumen at spermiation [1,3]. This entire process of germ cell development in the seminiferous epithelium is dependent on temporal and spatial expression of unique sets of genes and proteins. In the rat testis, an epithelial cycle (∼12–14 days duration) can be divided into 14 stages which are classified according to the unique germ cell types that associate with Sertoli cells in the epithelium [3,4]. It takes ∼58 days for a single spermatogonium to fully differentiate and develop into 256 spermatozoa. As such, it takes ∼4.5 epithelial cycles for one spermatogonium to differentiate into 256 spermatids. For each stage, at least four germ cell types are present in the epithelium that are organized spatially into layers from the base to the lumen of the seminiferous tubule [3,4]. Furthermore, spermatogenesis cannot complete without the support of Sertoli cells, which are the only other cell type in the seminiferous epithelium behind the BTB besides germ cells (note: the BTB has physically divided the epithelium into the basal and adluminal compartment, see Fig. 1) [5–7]. Except for the spermatogonia, developing germ cells move progressively toward the lumen [8]. For instance, preleptotene and leptotene spermatocytes that lie at the periphery of the tubule and outside the BTB must traverse the BTB at late stages VIII and early IX of the epithelial cycle [8].

It is conceivable that enormous Sertoli–germ cell interactions take place in the seminiferous epithelium throughout spermatogenesis [1–4,6,9,10]. If one views spermatogenesis as a voyage of a germ cell that moves from the basal to the adluminal compartment while developing to a mature spermatozoon, this process involves numerous decision makings and executions. It also requires signalings in and out of germ and sertoli cells to facilitate this event. Although it is not entirely clear regarding the sequence of these signals, there are at least two sources: external signals from outside the tubule (e.g., via Leydig cells, peritubular myoid cells, and both paracrine and hormonal factors including those from the pituitary gland), and internal crosstalks between germ and Sertoli cells (e.g., integrin-mediated signalings) [5,6,11,12]. The phenotypic consequence of these signalings is manifested, at least in part, via the constant remodeling at the Sertoli–Sertoli and Sertoli–germ cell interface where different cell junction types are present [1,2].

The identities of these signals and the details of the remodeling events have become increasingly clear in recent years [1,2]. For instance, there is accumulating evidence that illustrates the crucial roles of cytokines pertinent to spermatogenesis and junction restructuring [2]. In this review, we first give an update on the junction complexes that are found in the testis, highlighting how cytokines (e.g., TGF-β3, TNFα) can affect junction dynamics and how these signals are being fine-tuned to allow their regulation of a particular junction type.

2. The seminiferous epithelium: Sertoli–germ cell junctions and spermatogenesis

2.1. Seminiferous epithelium

The seminiferous epithelium is composed of Sertoli and germ cells (see Fig. 1). The Sertoli cell is by and large a tall