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Review

Cell polarity and planar cell polarity (PCP) in spermatogenesis

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ABSTRACT

In adult mammalian testes, spermatids, most notably step 17–19 spermatids in stage IV–VIII tubules, are aligned with their heads pointing toward the basement membrane and their tails toward the tubule lumen. On the other hand, these polarized spermatids also align across the plane of seminiferous epithelium, mimicking planar cell polarity (PCP) found in other hair cells in cochlea (inner ear). This orderly alignment of developing spermatids during spermiogenesis is important to support spermatogenesis, such that the maximal number of developing spermatids can be packed and supported by a fixed population of differentiated Sertoli cells in the limited space of the seminiferous epithelium in adult testes. In this review, we provide emerging evidence to demonstrate spermatid PCP in the seminiferous epithelium to support spermatogenesis. We also review findings in the field regarding the biology of spermatid cellular polarity (e.g., head-tail polarity and apico-basal polarity) and its inter-relationship to spermatid PCP. Furthermore, we also provide a hypothetical concept on the importance of PCP proteins in endocytic vesicle-mediated protein trafficking events to support spermatogenesis through protein endocytosis and recycling.

Contents

1. Introduction

Cell polarity plays a pivotal role in multiple cellular events to support tissues and organs during embryogenesis, post-natal development and cell homeostasis, including directional cell movement, cell proliferation, cell survival/apoptosis, and cell differentiation [1–6]. On the other hand, cell polarity is a distinguishable feature of highly differentiated cells in some organs, such as in elongating/elongated spermatids and spermatozoa in the testis. Elongated spermatids and spermatozoa are highly polarized cells with the head that contains the genetic materials in highly condensed chromosomes on one end, and a long tail constituted by actin- and microtubule (MT)-based cytoskeletal elements at the opposite end of the spermatid/sperm. The process from which spermatozoa are formed in the seminiferous epithelium of the seminiferous tubule is designated spermatogenesis. Spermatogenesis consists of three distinctive phases. Phase I includes the mitotic self-

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renewal and differentiation of spermatogonia stem cells at the stem cell niche located near the basement membrane of the seminiferous epithelium, at the site where seminiferous tubules meet, adjacent to the microvessels in the interstitium [7–9]. Phase II denotes development of spermatocytes, such as preleptotene spermatocytes derived from type B spermatogonia, which must be transported across the blood-testis barrier (BTB) to enter the adluminal compartment while differentiating into leptotene spermatocytes, and transform into zygote, pachytene and diplotene spermatocytes to undergo meiosis I and II to generate haploid spermatids [10]. In phase III, post-meiotic haploid spermatids undergo a series of morphological, molecular, and cellular differentiation to form elongated spermatids via spermiogenesis (including steps 1–16, 1–19 and 1–6 spermatids in mouse, rat and human testes, respectively [11–16]), to be accompanied by their transport across the adluminal compartment of the seminiferous epithelium, whereas fully developed spermatids (i.e., spermatozoa) line-up at the luminal edge and are eventually released into tubule lumen at spermiation [17–19]. It is of interest to note that during spermiogenesis, developing spermatids exhibit a unique dual-level cell polarity. On a single cell level, the seemingly symmetric round spermatids (steps 1–7 spermatids in the rat testis) initiate unique polarization in step 8–19 spermatids wherein the head at the proximal end containing the cell nucleus is accompanied by the elongating flagellar at the tail (i.e., distal growing end), exhibiting head-tail polarity. On the multi-cellular level, those elongating and elongated spermatids are uniquely oriented with their heads point basally towards the basement membrane of the seminiferous epithelium while their tails extend apically to the tubule lumen of the seminiferous tubule as groups of cells (such as in stage V tubules) or as an entire population of cells (such as in stage VIII tubules), displaying apico-basal polarity. These two levels of polarity thus guarantee functional specialization of the developing spermatids and to ensure that a maximal number of spermatids are packed in the limited space of the seminiferous epithelium along the seminiferous tubules. It is of interest to note that the length of all seminiferous tubules in an adult rat testis was estimated to be ~26-m when combined and each tubule has a diameter of ~280 μm [20,21], thereby capable of producing as much as ~70 million sperm daily per testis pair [22]. Without the highly polarized orientation of spermatids in the tubules, it is not possible to maintain such an enormous output in adult animals.

It is noted that the alignment of steps 17–19 spermatids during stage V–VIII of the epithelial cycle in the rat testis also reveal another type of polarity known as planar cell polarity (PCP), referring to the alignment of highly polarized cells (i.e., elongating/elongated spermatids) on the plane of seminiferous epithelium, analogous to cuticle cell hair or cell hair found in insects or inner ear (cochlea) of rodents and humans. Herein, we review some of the latest findings in the field, examining the functional relationship of PCP and spermatogenesis, including the likely underlying mechanism(s) that support PCP during spermiogenesis.

2. Planar cell polarity (PCP) of elongating/elongated spermatids during spermiogenesis

In adult rat testes, any typical cross-section of the seminiferous tubule along the longitudinal axis illustrates the alignment of polarized spermatids across the plane of polarized epithelial Sertoli cells which support spermatid development, differentiation, and transport across the epithelium, such as noted in Fig. 1. Due to the unique association of developing spermatids with Sertoli cells in the seminiferous epithelium, spermatogenesis has been divided into 6, 12 and 14 stages in the human, mouse and rat testes, in which unique stages of developing spermatids and cellular events are associated with Sertoli cells in the epithelium [11,13–15,23,24]. For instance, in the rat testis, spermiation takes place at stage VIII of the epithelial cycle with the concomitant appearance of step 8 spermatids, plus transport of preleptotene spermatocytes across the BTB; while meiosis I/II takes place in stage XIV tubules [13]. Furthermore, step 5 round spermatids and step 17 elongating spermatids are both found in stage V tubules, whereas step 19 elongated spermatids are seen in the stage VII and VIII tubules.

When the cross-section of a seminiferous tubule, such as the one at stage VIII of the seminiferous epithelial cycle, is closely examined, step 19 elongated spermatids exhibit typical apico-basal polarity in which their heads point basally to the basement membrane, whereas their tails extend apically to the tubule lumen (Fig. 1). Furthermore, spermatid heads containing the condensed genetic materials in rodents are not round- or oval- shaped as noted in human sperm, instead they are curve-shaped at the tip of the head, analogous to a hook-like structure, and the alignment of these hook-like structures are all uniform across the plane of Sertoli cell epithelium. We have used confocal microscopy and the Imaris software package (Version 9; Bitplane, Concord, MA) for subsequent 3D-reconstruction of the images obtained along the longitudinal axis of a stage V–VI (containing step 17 and 18 spermatids) (Fig. 1**A**) and stage VII–VIII (containing step 19 spermatids) (Fig. 1**B**) seminiferous tubule to assess the presence PCP regarding spermatid alignment across the seminiferous epithelium. It was noted that polarized step 17, 18 and 19 spermatids in stage V, VI and VII–VIII tubules, respectively, displaying PCP (Fig. 1**A**–**H**). Among step 17–19 spermatids, step 19 spermatid heads (Fig. 1**A**) were shown to align with strict and uniform PCP across the plane of the seminiferous epithelium (Fig. 1**B**, **D**, **E** & **H** *vs.* **A**, **C**, **F** & **G**). In short, polarized step 19 elongated spermatids in stage VII–VIII tubules display strict PCP by aligning onto the plane of the seminiferous epithelium, whereas PCP is also detected in stage V and VI tubules in step 17 and 18 spermatids as these spermatids progressively to assume their proper alignment to prepare for their release at spermiation.

In this context, it is of interest to note that step 19 spermatids displaying PCP are similar to other polarized epithelia. For instance, *Drosophila* wing hair also align and point strictly to a uniform direction along the tissue axis which is perpendicular to the apico-basal axis of the cell plane [25]. The cochlea (inner ear) in rodents and humans is another example of PCP in which the actin-based stereocilia on the apical surface of sensory hair cells are precisely oriented [26]. However, unlike *Drosophila* wing hair in wing cells, and the stereocilia of the sensory hair cells in cochlea, in which wing hair and stereocilia are integrated components of the corresponding hair cells, step 19 spermatids are not organelles of the Sertoli cells. Instead, spermatids are separate entities and independent cells *per se* even though they rely exclusively on Sertoli cells for nutritional, paracrine/hormonal and structural supports. Nonetheless, elongated spermatids exhibit PCP polarity and it is supported by the fact that numerous PCP proteins expressed by Sertoli and germ cells [27] across the plane of the seminiferous epithelium.

3. Regulation of spermatid head-tail and apico-basal polarity

As briefly discussed above, spermatids exhibit polarity on both single- and multi-cellular levels. These two levels of polarities emerge as early as in the step 1 round spermatids during the onset of spermiogenesis in which the genetic materials begin to undergo condensation and tightly pack into the head region to form the nucleus, concomitant with the preparations of the: (i) genesis of the acrosome located in front of the spermatid nucleus and (ii) elongation of the tail in which the spermatid head also begin to

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