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Review

Regulation of spermatid polarity by the actin- and microtubule (MT)-based cytoskeletons☆

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ABSTRACT

It is conceivable that spermatid apico-basal polarity and spermatid planar cell polarity (PCP) are utmost important to support spermatogenesis. The orderly arrangement of developing germ cells in particular spermatids during spermiogenesis are essential to obtain structural and nutrient supports from the fixed number of Sertoli cells across the limited space of seminiferous epithelium in the tubules following Sertoli cell differentiation by ~17 day postpartum (dpp) in rodents and ~12 years of age at puberty in humans. Yet few studies are found in the literature to investigate the role of these proteins to support spermatogenesis. Herein, we briefly summarize recent findings in the field, in particular emerging evidence that supports the concept that apico-basal polarity and PCP are conferred by the corresponding polarity proteins through their effects on the actin- and microtubule (MT)-based cytoskeletons. While much research is needed to bridge our gaps of understanding cell polarity, cytoskeletal function, and signaling proteins, a critical evaluation of some latest findings as summarized herein provides some important and also thought-provoking concepts to design better functional experiments to address this important, yet largely expored, research topic.

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1. Introduction

During spermatogenesis in the mammalian testis, including both rodents and humans, developing spermatids display unusual polarity to support the packaging of millions of spermatids across the seminiferous epithelium. Thus, millions of spermatozoa can be produced daily in the limited space of the seminiferous tubules tightly packed inside the testes [1–3]. Studies have shown that there are two types of spermatid polarity during the epithelial cycle to support spermatogenesis. The first type is the apico-basal polarity in which the heads of elongating/elongated spermatids in the testis are orientated by pointing to the basement membrane (i.e., individual cell polarity), which is supported by the partitioning defective (Par)- [4], the Scribble- [5], and the Crumbs (Crb)- [6] based polarity protein complexes that are found in virtually all mammalian cells including Sertoli and/or germ cells in the testis [7,8]. The second type is the spermatid planar cell polarity (PCP)

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in which polarized elongating/elongated spermatids are aligned across the plane of the Sertoli cell epithelium in the tubules by orientated unidirectionally, supported by PCP proteins such as Vangl2 [9,10]. Studies have shown that these polarity proteins and PCP proteins are working in concert with F-actin-based cytoskeleton to support spermatid polarity and PCP [2,11]. However, emerging evidence based on published findings in the testis has shown that the microtubule (MT)-based cytoskeleton is also involved in polarity protein- and PCP protein-mediated spermatid polarity. A recent review in this Special Issue [11] has summarized recent findings regarding the role of the Par-, the Scribble- and the Crumbs homolog 3 (Crb3)-based polarity protein complexes in the adult rat testis by working closely with the F-actin-based cytoskeleton to modulate spermatid polarity. As such, we do not include such discussion and pertinent findings herein to avoid redundancy. Instead, we focus more on latest findings using different animal models to assess the relationship between spermatid polarity/spermatid PCP and the organization of actin- and MT-based cytoskeletons. This information should provide insightful information regarding future experimental planning to better understand the integrated function of both cytoskeletons to support spermatid polarity and PCP.

2. Polarity proteins and planar cell polarity proteins

Studies in the rat testis have shown that, similar to other epithelial cells, the Par-based polarity complex is comprised of at least 4 proteins: Par3, Par6, aPKC (atypical protein kinase C), and Cdc42 which tightly associate with the integral membrane protein JAM-C (junctional adhesion molecule C, also known as JAM-1) (Table 1), predominantly expressed at the apical ES (ectoplasmic specialization) to modulate apico-basal spermatid polarity and adhesion [4] at the Sertoli cell-spermatid interface [4]. However, the Par-based proteins are also expressed at the basal ES at the Sertoli cell-cell interface near the basement membrane, consistent with its localization at the blood-testis barrier (BTB) [4]. In this context, it is of interest to note that the ES is a testis-specific and actin-rich adherens junction (AJ) type, restrictively expressed at the Sertoli-spermatid interface, limited to step 8–19 spermatids in the rat testis, whereas the basal ES is only found at the Sertoli cell-cell interface, coexisting with the tight junction (TJ) to create the Sertoli cell BTB [12–14]. The Par-based polarity complex is working closely with the Crb3-based polarity complex which is composed of Crb3 (an integral membrane protein), Pals1 (protein associated with Lin-7 1) and PatJ [6] to support apico-basal polarity as noted in other epithelia [15]. For instance, studies have shown that aPKC in the Par-based polarity protein can modulate Par3 or Crb3 function via phosphorylation, inducing the necessary cross-talk between these two polarity complex to modulate cell polarization [15–17]. On the other hand, the Scribble-based polarity complex that supports apico-basal polarity is composed of Scribble, Lgl2 (Lethal giant larvae 2) and Dlg1 (Discs large 1) in the rat testis [5], which is mutually exclusive regarding its function and also physical localization *vs.* the Par- and the Crb3-based polarity complexes [7,15]. In the

Table 1
Functions of different polarity proteins and PCP proteins in mammalian cells and tissues.

	Protein	Phenotype in rodents following deletion (knockout, KO) or knockdown (KD) in corresponding model	References	Mutation(s), deletion or changes in expression that lead to corresponding diseases in humans	References
Par3-Complex	Par3			Up-regulation in ovarian and prostate cancer, down-regulation in pancreatic cancer.	[40–42]
	Par6			Up-regulation in breast cancer and non-small-cell lung cancer, mutation inhibits heart development.	[43–45]
	Cdc42	Cdc42-deficiency causes forebrain malformation, failing to develop into two hemispheres, leading to holoprosencephaly.	[46]	Up-regulation in polycystic kidney disease, mutation leads to thrombocytopenia.	[47,48]
	PKC	PKCι knockout leads to embryonic fatality, conditional deletion of aPKCλ in differentiated neurons causes polarity complex disruption.	[49,50]	Mutation leads to Alzheimer's disease; Down-regulation in B-cell chronic lymphocytic leukemia.	[51,52]
Scribble- Complex	Scribble	Deletion leads to embryonic fatality, mutation leads to lung and prostate cancer.	[53–55]	Mutation leads to lung cancer, down-regulation in prostate cancer.	[54,55]
	Dlg1	Deletion leads to embryonic fatality, requires for development of respiratory, cardiovascular and urogenital systems.	[56–58]	Mutation leads to Crohn's disease, and schizophrenia.	[59,60]
	Lgl2			Mutation leads to Barrett gastric foveolar dysplasia, a congenital gastroesophageal reflux disease.	[61]
Crumbs-3- Complex	CRB3	Deletion leads to embryonic fatality, requires for the development of kidney and lung.	[62]		
	PALS1	PALS1 shRNA knockdown in developing brain leads to the presence of excessive neurons, and followed by massive apoptosis, causing abrogation of the entire cortical structure; conditional PALS1 knockdown in mouse E14 embryonic stem cells causes defects in retina.	[63,64]		
PCP Complex	Vangl2	Deletion in mice perturbs brain development, leading to embryonic fatality in some, but not all, mice.	[65]	Mutation leads to congenital heart defect and neural tube defects.	[66,67]
	Prickle1	Deletion leads to embryonic fatality due to failure of distal visceral endoderm migration.	[68]	Mutation leads to neural tube defects and type 2 diabetes.	[69,70]
	Dvl3	Deletion leads to embryonic fatality due to defects in heart formation.	[71]	Mutation leads to: (i) Robinow syndrome manifested by short-limbed dwarfism and abnormalities in the head, face and external genitalia; (ii) prostate cancer; (iii) leukemia; (iv) microcephaly; (v) depression; (vi) Hirschsprung's disease; or (vii) lung cancer.	[72–78]
	Fzd3	Embryonic fatality, essential for the brain development.	[79,80]	Mutation leads to schizophrenia, and Hirschsprung disease (due to the absence of nerve cells in colon, leading to chronic constipation); up-regulation in polycystic kidney disease.	[47,81,82]

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