Motor Proteins and Spermatogenesis

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Introduction

The blood-testis barrier (BTB) in the adult mammalian testis is a unique blood-tissue barrier which restricts paracellular (between cells; i.e., gate-keeper function of the BTB) and transcellular (across cells; i.e., fence function of the BTB) transport (or diffusion) of water, electrolytes, nutrients, cytokines and biomolecules including paracrine and autocrine factors between adjacent Sertoli cells at the base of the seminiferous tubules, also known as the Sertoli cell barrier [1–6] (Fig. 1). Interestingly,

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microvessels found in the interstitial space between seminiferous tubules contribute relatively little barrier function to the BTB in the testis of rodents, primates and humans (Fig. 1) [5, 9]. The BTB also divides the seminiferous epithelium into the basal and the adluminal (apical) compartments as noted in Fig. 1. As such, meiosis I/II and all the cellular events pertinent to post-meiotic development take place behind the BTB in a specialized microenvironment (Fig. 1), whereas mitotic proliferation of spermatogonia and differentiation/transformation of type A and type B spermatogonia to earlier spermatocytes take place in the basal compartment [10–12]. The BTB is a highly dynamic blood-tissue barrier since preleptotene spermatocytes, once derived from type B spermatogonia in the basal compartment rodents, are to be transported across the BTB in late Stage VII through early Stage IX of the epithelial cycle while differentiating into leptotene spermatocytes, which can be transformed into zygotene and pachytene spermatocytes to prepare for meiosis. Studies have shown that the BTB in the rodent testis is constituted by the actin-based tight junction (TJ) between adjacent Sertoli cells, reinforced by a testis-specific actin-rich adherens junction (AJ) type called basal ectoplasmic specialization (ES), and supported by the actin-based gap junction, but also intermediate filament-based desmosome [13–19]. Once haploid spermatids are formed through meiosis, they are also being transported across the seminiferous epithelium in the adluminal compartment before fully developed step 19, 16, and 12 spermatids in the testis of rats, mice, and humans, respectively, are transformed to spermatozoa via spermiogenesis [12, 14, 20] as these cells are lacking the ultrastructures found in motile

Fig. 1 (continued) BTB (for basal ES) but also spermatid transport across the epithelium (for apical ES). These germ cells, namely spermatocytes and developing spermatids are the cargoes which are to be transported "directionally", either to be base or to the adluminal edge of the seminiferous epithelium, due to the polarized nature of the actin- and MT-based cytoskeletons through the MT- or actin-dependent motor proteins. For instance, dynein 1 moves cargoes to the minus (−) end of MTs, and kinesin 15 to the plus (+) end of MTs; whereas myosin VIIa moves cargoes to the plus (+) end of actin filaments and myosin VI to the minus (−) end of actin filaments. In brief, the actin- and MT-based tracks found in Sertoli cells work in concert to support the directional\transport of germ cells across the seminiferous epithelium using the corresponding actin- and MT-based motor proteins. Even though germ cells located outside the Sertoli cell actin- and MT-cytoskeletons, the ES provides the means by which these germ cells anchor tightly onto the Sertoli cell cytoskeleton-based tracks to facilitate their transport across the epithelium. Through these actions of corresponding motor proteins, proper germ cell and cargo transports can take place across the seminiferous epithelium during the epithelial cycle to support spermatogenesis

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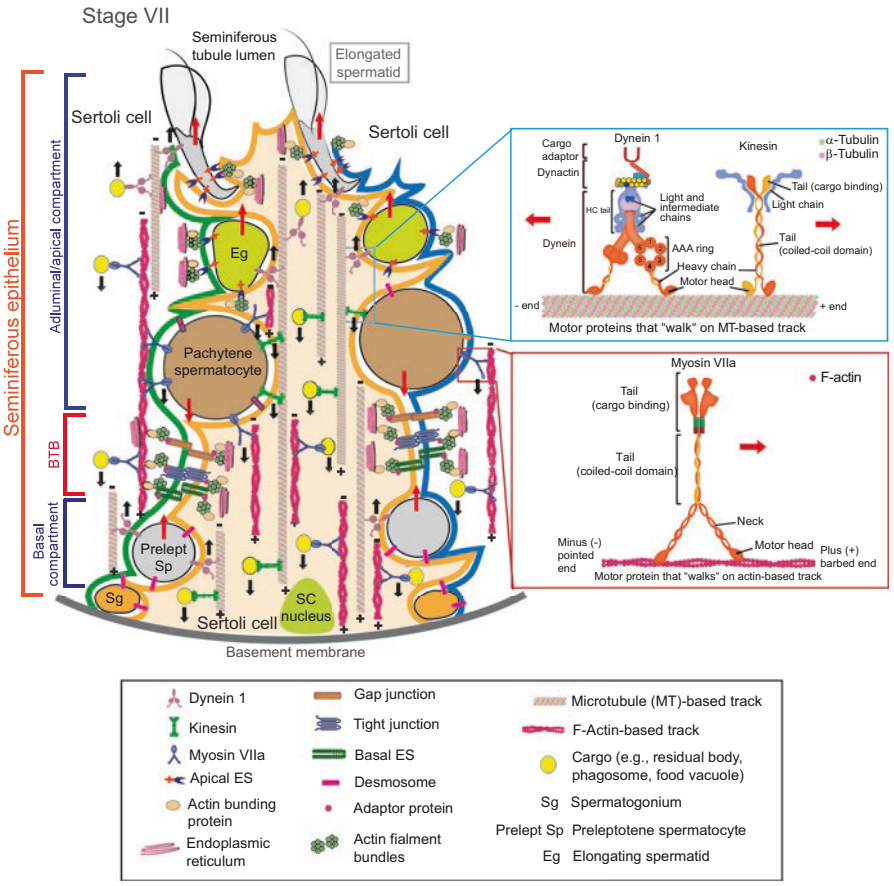

Fig. 1 Schematic drawing of the cross-section of a typical Stage VII seminiferous tubule from adult rat testes. The seminiferous epithelium across the tubule is constituted by adjacent Sertoli cells which, in turn, support germ cells at different stages of their development during spermatogenesis as noted herein with a Sertoli:germ ratio of about 1:30–50 [7, 8] (*left* panel). Between adjacent Sertoli cells near the basement membrane are the specialized junctions, namely the actin-based tight junction (TJ), basal ES (ectoplasmic specialization, a testis-specific adherens junction type) and gap junction, which together with the intermediate filament-based desmosome constitute the blood-testis barrier (BTB). The BTB also divides the seminiferous epithelium in the rat testis and other mammalian testes into the basal and the adluminal (apical) compartments, such that meiosis I/II and all subsequent events of post-meiotic spermatid development take place behind the BTB. The most notable structural features are the microtubule (MT)-based and actin-based tracks that stretch across the seminiferous epithelium. These tracks support the corresponding MT- and actin-based motor proteins (see the insets on the right panel) to provide cellular transport of cargoes as discussed in this review. For F-actin, besides serving as the track-like structures to support cellular transport, actin filaments that lay parallel to the Sertoli cell plasma membrane are assembled as bundles which appeared as aggregates of rod-like structures in cross-sections of the testis, both at the Sertoli-spermatid site called apical ES and also at the Sertoli cell-cell interface at the BTB called basal ES. The ES is not only an important ultrastructure to support spermatid and Sertoli cell adhesion, they are crucial to support preleptotene spermatocyte transport across the

cells, namely the lamellipodia and filopodia [21]. Spermatozoa are then line-up at the edge of the seminiferous tubule lumen to undergo spermiation in Stage VIII of the epithelial cycle in rodents versus VI in humans, respectively, which is composed of a tightly regulated series of biochemical and cellular events involving multiple signal and regulatory proteins [13, 22–24]. The testicular sperm emptied into the epididymis are then undergo another series of maturation processes, rendering them capable of fertilizing the egg.

Studies have shown that BTB dynamics that support preleptotene spermatocyte transport across the immunological barrier, and the subsequent haploid spermatid transport across the seminiferous epithelium, are tightly regulated cellular events. These involve several biologically active peptides released at the basement membrane but also at the Sertoli-spermatid adhesion site known as the apical ES via proteolytic cleavage of the structural proteins at these two sites, namely the F5-, the NC1- and the LG3/4/5-peptide [9, 25–27]. These bioactive peptides, in turn, are working in concert with a number of signaling proteins such as mTORC1/rpS6/Akt1/2 and FAK-Y407, and cytoskeletal regulatory proteins such as Arp3, Eps8, +TIPs and −TIPs to modulate BTB and ES dynamics [9, 27, 28]. The ultrastructures and the biomolecules that support germ cell transport are the actin- and MT-based cytoskeletons, as well as the corresponding actin- and MT-based motor proteins. In brief, motor proteins are the "vehicles" that carry the "cargoes", namely preleptotene spermatocytes and spermatids, utilizing the corresponding actin or microtubule (MT)-based cytoskeletons as tracks to transport developing germ cells and other organelles (e.g., residual bodies, phagosomes, cell vacuoles, endocytic vesicles) to their corresponding "destination" across the seminiferous epithelium (Fig. 1). Furthermore, this requires intricate involvement of both actin- and MT-based cytoskeletons to support cargo transport across the seminiferous epithelium. However, much of this information remains unknown. In this review, we provide a timely discussion on latest findings in this area of research regarding the role of motor proteins in supporting cargo transport across the seminiferous epithelium using the rat testis as a study model. We also highlight some of the specific research areas that deserve attentions in future studies, which should be helpful to understand the underlying mechanism(s) of idiopathic male infertility.

Sertoli Cell Cytoskeletons in the Testis

In the seminiferous epithelium of adult rodent testes, similar to other mammalian organs, the two prominent cytoskeletons are the intrinsically polarized actin- and microtubule (MT)-based cytoskeletons which are composed of globular subunits of actin and α-tubulin/β-tubulin oligomers, respectively (Fig. 1) [29–33]. These polarized structures also serve as tracks to support specific motor proteins for directional transport of cargoes across the seminiferous epithelium. On the other hand, the intermediate filament-based cytoskeleton constituted by vimentin [16, 34] and the septin-based cytoskeleton [35] are both apolar structures, thus, they do not support motor proteins for directional cargo transport along their filaments.

Actin-Based Cytoskeleton

A functional actin-based track is composed of linear actin filaments (i.e., filamentous actin, F-actin) derived from polymerized globulin (G)-actin subunits, with the fast-growing barbed (+) end near the base of the seminiferous epithelium, closest to the basement membrane, and the slow-growing pointed (−) end near the seminiferous tubule lumen (Fig. 1) [36, 37]. In brief, polymerization of a linear actin filament occurs by incoming ATP-bound G-actin subunits at the fast-growing barbed (+) end involving actin nucleation proteins (e.g., formin 1, spire 1). The ATP-bound G-actin subunits are rapidly dephosphorylated to ADP-bound G-actin and are all found at the slow-growing pointed (−) end near the tubule lumen (Fig. 1) [37, 38]. The actin-based tracks are most notable in late Stage VIII of the epithelial cycle that stretch across the seminiferous epithelium and align perpendicular to the basement membrane [38] (Fig. 1). However, F-actin are also prominently noted at the apical ES and basal ES/BTB wherein the actin filaments are aligned parallel to the Sertoli cell plasma membrane and appear as bundled structures in cross-sections of the tubules. As such, these actin filaments appear as "rod-like" structures in cross-sections of the tubules at the apical ES and basal ES/BTB sites, thereby reinforcing cell adhesion (Fig. 1). ES in the testis also plays a crucial role to support germ cell transport as preleptotene spermatocytes (at the basal ES) and developing spermatids (at the apical ES) tightly anchored onto the actin filament bundles at the ES, and with the MTs located nearby [18, 33], which are located in close proximity to the plasma membrane of the Sertoli cell. Thus, these cells are separated only by their apposing Sertoli cell-cell or Sertoli-germ cell plasma membranes [3, 39]. Thus, even though these germ cells, namely preleptotene spermatocytes or haploid elongate spermatids, are located "outside" the Sertoli actin filament and MT networks, they are anchor onto these cytoskeletons through the unusual adhesion of ES between these adjacent cells, which are considered as cargoes to the Sertoli cell at the site. Due to this intrinsic polarized nature of the actin filaments, the actin-based plus (+) end-directed motor protein myosin VIIa, and the actin-based minus (−) end-directed myosin VI are capable of moving cargoes either to the base or to the tubule lumen across the epithelium, respectively (Fig. 1).

MT-Based Cytoskeleton

Microtubules (MTs) are also polarized ultrastructures in which a microtubule is composed of 13 laterally associated protofilaments of α- and β-tubulin heterodimers, with a hollow lumen wherein the plus (+) fast growing end is near the basement membrane and the minus (−) slow growing end near the tubule lumen (Fig. 1) [40–43]. Due to the intrinsic polarized nature of MTs, the MT-based minus (−) end-directed motor protein dynein 1 and the plus (+) end-directed motor protein kinesins (e.g., kinesin 15) can move cargoes to the corresponding minus or plus end of MTs, respectively [44–47].

Motor Proteins

Motor proteins are a class of molecular motors that bind to either microtubule (MT)- or actin-based tracks. They are capable of converting chemical energy through the hydrolysis of ATP to generate the mechanical force necessary to transport cargoes along the track across cell cytoplasm. Herein, we discuss several motor proteins that have been studied in the testis pertinent to support spermatogenesis. Besides serving as an update, this summary also provides the basis for future studies regarding the role of motor proteins in supporting germ cell and cargo transport across the seminiferous epithelium.

MT-Based Motor Proteins: Dynein and Kinesin

Dynein

Dynein is a family of motor proteins that use MT-based track in retrograde sliding movement towards the minus (−) ends of microtubules [47, 48]. In brief, a dynein motor protein transports cargoes towards the center of the cell or seminiferous tubule lumen in the testis. There are two major classes of dyneins, cytoplasmic and axonemal dyneins, which are classified according to their function and structure differences. Dynein 1 is a cytoplasmic dynein of about 1.5 megadaltons (MDa) (Fig. 2; Fig. 3A), involved in intracellular transport, mitosis, cell polarization and directional cargo transport. For instance, dynein 1 carries the cargo (e.g., spermatid) by "walking" along the MT-track in the Sertoli cell. Even though spermatids locate outside the Sertoli cell, but they are tightly anchored onto the MT-track in the Sertoli cell at the apical ES (or preleptotene spermatocyte anchored onto the MT-track in the Sertoli cell at the basal ES), which is a known adhesion ultrastructure that supports spermatid or preleptotene spermatocyte transport [3, 17]. There are 15 types of axonemal dyneins to support ciliary (e.g., dynein 2) and flagellar movement [48–51] such as sperm flagella that confers sperm progressive motility. Axonemal dyneins support the beating of flagella and cilia through rapid and efficient sliding movements of MTs [52]. In this context, it is of interest to note that mechanical movement of hair cells in cochlea is supported by the motor protein prestin [53, 54] which is different from the dynein family motor proteins. A functional dynein motor protein is considerably larger and more complex than kinesin or myosin motors, and it is composed of two heavy chains and a variable number of associated intermediate chains, light intermediate chains and light chains (Fig. 3A). For instance, dynein 1 is a dimeric protein composed of two identical heavy chains with a large molecular mass (Mr) of 500 kDa each. Each HC, in turn, binds to a light intermediate chain (LIC), an intermediate chain (IC), and three light chains (LCs) of LC7, LC8, and Tctex 1 (Fig. 3A). Thus, dynein 1 is a dimer of dimers. Each heavy chain is composed of three functional domains: a coiled-coil stalk with MT binding domain (MTBD) containing a globular motor head at the C-terminus, an AAA+ ring containing six AAA+ modules that organized into a doughnut-like structure, and a

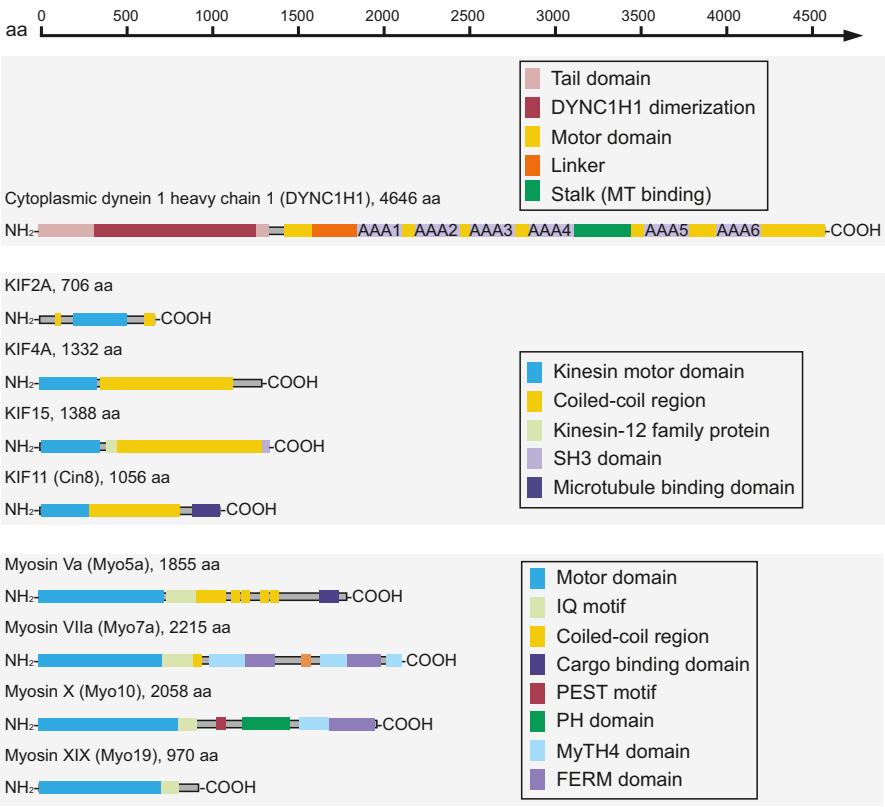

Fig. 2 Schematic illustration on the functional domains of the microtubule-based motor proteins dyneins and kinesins, and actin-based motor proteins myosins. The different functional domains of motor proteins dyneins, kinesins and myosins are noted in corresponding panels. This figure was prepared based on earlier reports [55–58]. Abbreviations: DYNC1H1, dynein cytoplasmic 1 heavy chain 1; KIF, kinesin; MT, microtubule; SH3, SRC homology 3 domain; IQ motif, isoleucine and glutamine motif is a basic unit containing about 23 amino acids; PEST motif, a motif rich in proline (P), glutamic acid (E), serine (S) and threonine (T); PH domain, pleckstrin homology domain; MyTH4 domain, Myosin Tail Homology 4 domain; FERM domain, F for 4.1 protein, E for ezrin, R for radixin and M for moesin

cargo-binding tail at by N-terminus (Figure 3A). The AAA+ ring can hydrolyze ATP hence converting chemical energy into mechanical force to support cargo transport [59]. In the testis, dynein 1 interacts with a protein complex called dynactin and cargo adaptor to form a functional motor protein called the dynein-dynactin-adaptor complex that supports spermatid transport on MT-based cytoskeleton. Dynein I also transports various cellular cargoes along MT towards the minus (−) end of MT tracks [60]. Cargoes transported by cytoplasmic dynein include endosomes [61], lysosomes [62], phagosomes [63], melanosomes [64], peroxisomes [65], lipid droplets [66], mitochondria [67] and vesicles from the endoplasmic reticulum (ER) destined for the Golgi [68]. These cargo transports hence regulate the intracellular function of cells and tissues through different cell signaling pathways.

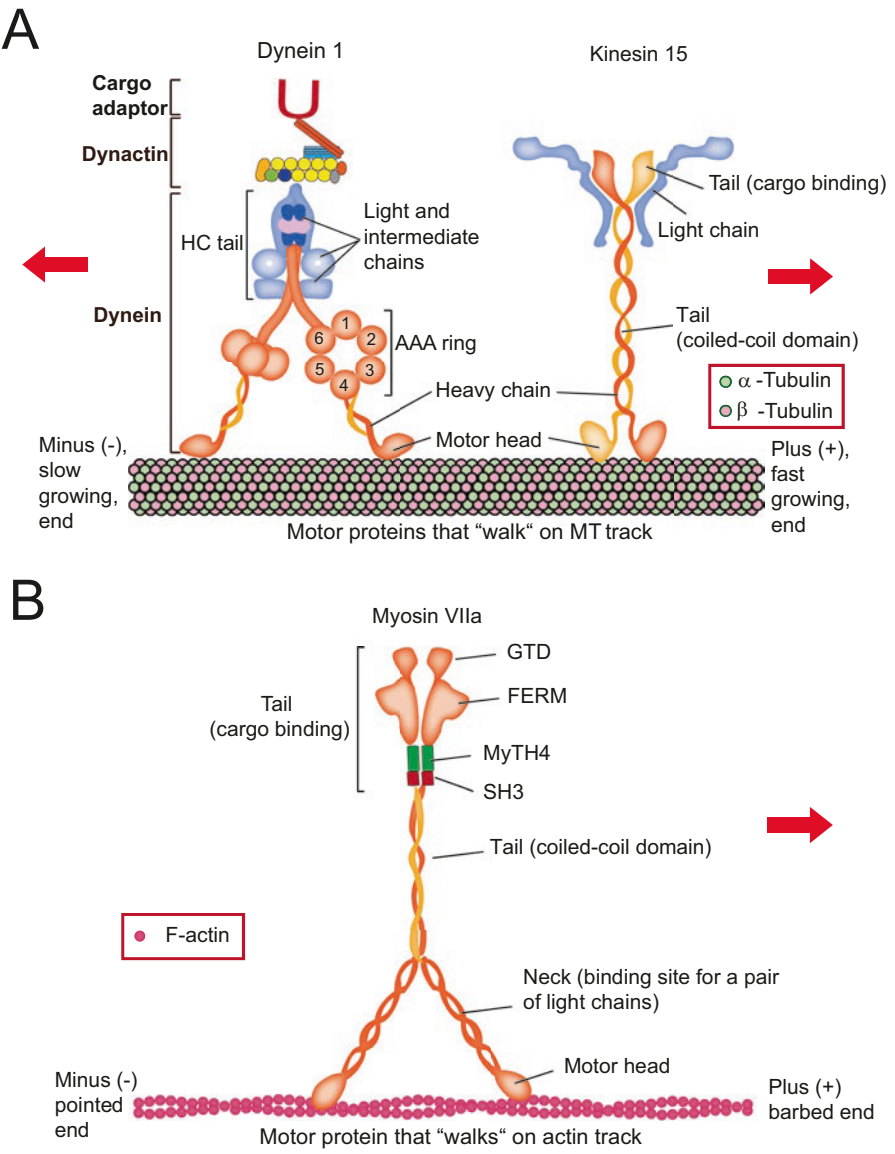

Fig. 3 Schematic illustrations on the structural components of the functional motor proteins dynein 1, kinesin 15 and myosin VIIa. (**A**) A functional dynein motor protein (e.g., dynein 1) complex is composed of the dynein, dynactin and the cargo adaptor (*left* panel). The dynein motor protein consists of two monomers. Each monomer is composed of a heavy chain (HC) motor and several other subunits: an intermediate chain, a light intermediate chain, and three light chains called LC7 (light chain 7) LC8 and Tctex. Each HC has the N-terminus at the tail and the C-terminal motor unit contains six AAA (ATPase Associated with Cellular Activities) domains, AAA1 to AAA6, and organized into a ring-like structure, which in turn connects to the microtubule binding domain (MTBD) in the motor head at the C-terminus which also binds onto the microtubule. AAA1

In the rat testis, dynein 1 is necessary to confer Sertoli cell TJ-permeability barrier function since its knockdown by RNAi perturbs the TJ-barrier function due to gross defects of F-actin and microtubules (MTs) across the Sertoli cell cytosol wherein both cytoskeletons become extensively truncated [69]. These defects, in turn, perturb the distribution of BTB-associated proteins at the site, including the cell adhesion complexes CAR/ZO-1 and N-cadherin/β-catenin [69]. Furthermore, dynein 1 knockdown also perturbs the polymerization activities of F-actin and MTs [69], possibly due to defects in transporting machineries (e.g., actin or MT polymerization proteins) necessary to support cytoskeletal nucleation. More important, the loss of dynein 1 function by RNAi also perturbs the BTB function in vivo since the barrier no longer restricts the diffusion of small molecular biotin across the immunological barrier [69]. Multiple defective sperms are also noted in the epididymis including extensive defects in spermatid heads, tail, and sperm morphology due to defects of intracellular trafficking to support the assembly of essential cellular components during spermiogenesis [69]. The importance of dynein-based motor proteins is also noted in Table 1 since its KO in mice led to embryonic lethality.

Kinesin

Kinesin is a group of related motor proteins that use MT track in anterograde movement, to transport cargoes towards the plus (+) ends of MTs [96–98] (Fig. 2). In brief, a kinesin motor protein transports cargoes away from the center of the cell, usually to cell peripheries to support cell homeostasis, or to the base of the seminiferous epithelium in the testis (Fig. 1). Kinesin superfamily members in humans and

Fig. 3 (continued) is the major site of ATP hydrolysis with other AAA sites play the regulatory roles. AAA1 converts the chemical energy (from ATP hydrolysis via ATPase) to mechanical force which is transmitted to the HC tail at the N-terminal region. Dynein 1 interacts with its cofactor called dynactin (which also composed of multiple subunits as earlier reviewed [47]) to form the functional dynein-dynactin complex. This complex in turn interacts with the cargo adaptor to form a functional motor protein to support cargo transport. On the *right* panel is the kinesin motor protein (e.g., kinesin 15) which is also a dimeric protein, composed of two monomers. Each monomer has a heavy chain (HC) with its N-terminal region contains the motor head which is the site for ATP hydrolysis to generate the chemical energy to be transmitted to the mechanical energy via the tail to propel cargo transport at the C-terminal region. The motor head at the N-terminal region also contains the microtubule binding domain. This is followed by the α-helical coiled-coil domain that constitutes the stalk and ends with the C-terminal tail of cargo binding. (**B**) A functional actin-based plus (+) end directed motor protein myosin (e.g., myosin VIIa) is also a dimeric protein comprised of two monomers. Each monomer has a heavy chain (HC) that begins with the motor head at its N-terminal region which contains the ATP hydrolysis motor domain and the actin-binding domain. This is followed by the neck region that transmits the chemical energy derived from ATP hydrolysis at the motor head to the tail cargo binding site through the coiled-coil domain in the tail. The neck region has a pair of light chains which facilitates the transmission of chemical energy to the cargo propelling mechanical force at the tail cargo binding site. The C-terminal tail region contains the FERM (F, 4.1 protein; E, ezrin; R, radixin; M, moesin), MyTH4 Myosin tail homology 4) and SH3 (SRC homolog 3) domains, and the globular tail domain (GTD) at the C-terminus to support cargo binding

rodents are organized into 14 families [99, 100]. A functional kinesin motor protein is a tetrameric protein, comprised of two heavy chains and two light chains (Fig. 3A). Each heavy chain has a globular motor head where microtubule binding and ATP hydrolysis take place at its N-terminal region, which in turn generate the energy via ATPase that converts chemical energy into mechanical force to elicit cargo transport. The head region is connected by a short neck linker to a long intertwined coiled-coil stalk, to be followed by the tail at its C-terminal region (Fig. 3A). A light chain associates with a tail which serve as the adapter for binding to a cargo while moving along the MT track towards the MT plus (+) end to facilitate cargo (e.g., spermatid, residual body, phagosome) transport [49, 97, 101] (Table 1). Kinesins typically move cargoes in the direction of MT plus (+) end on MT tracks, such that cargo is transported from the center of the cell to its periphery (i.e., anterograde movement). However, some kinesins (members of the kinesin-5 family), such as kinesin-14, move cargoes to the MT minus (−) end along the MT tracks wherein the motor region is located at the C-terminal region of the heavy chain [102]. On the other hand, kinesin-5 Cin8 (members of the kinesin-5 family) is a bidirectional kinesin which can move a cargo towards the microtubule minus (−) end when works alone but to the plus (+) end in an ensemble with a team of motors [103]. Emerging evidence has shown that kinesins are crucial to support tumorigenesis. For instance, KIF18A promotes invasion and metastasis by activating Akt and MMP-7/MMP-9-related signaling pathways [104] whereas kinesins also support proliferation, cell differentiation, aggressiveness and epithelial-mesenchymal transition of tumor cells [105–109]. A recent report has demonstrated the importance of kinesin-9 in conferring progressive motility in mouse spermatozoa since a deletion of 16 bp nucleotides of the *Kif9* gene in mice ($Kif9^{-16/-16}$) using CRISPR/Cas9 led to defects in flagellar movement of sperm tails [110]. Studies have also shown that kinesin-7 CENP-E is crucial to support chromosome alignment and genome stability of spermatogenic cells (e.g., spermatogonia and spermatocytes) during mitosis and meiosis [111], whereas kinesin-5 Eg5 supports spindle assembly and chromosome alignment of mouse spermatocytes [112]. Nonetheless, much work is needed to better understand the role of kinesins in supporting spermatogenesis in the testis. However, as noted in Table 1, deletion of one of the several kinesins in mice led to embryonic lethality, illustrating the physiological significance of kinesin-based motor proteins in supporting cellular function.

F-actin-Based Motor Proteins: Myosins

Myosins

Myosins are the only known actin-based motor proteins in mammalian cells and tissues including the testis [47, 113]. There are 18 classes of myosin superfamily members known to date based on phylogenetic analysis of their motor domain, and at least 40 myosin genes have been identified [57, 114]. By converting chemical energy via hydrolysis of ATP at the myosin motor head to mechanical energy, which

Table 1 Phenotypes in mice following specific knockout (KO) of different motor protein genes

Gene name	KO type	Phenotype(s)	References
Mdhc7$^{-/-}$ [Mouse dynein heavy chain-7 KO]	Global	Asthenozoospermia	Neesen et al. [70]
Dync2h1$^{-/-}$ [Dynein cytoplasmic 2 heavy chain 1 KO]	Global	Preweaning lethality	Adams et al. [71]
Dnal1$^{-/-}$ [Dynein, axonemal, light chain 1 KO]	Global	Preweaning lethality	Adams et al. [71]
Dnah2$^{-/-}$ [Dynein, axonemal, heavy chain 2 KO]	Global	Male infertility; abnormal locomotor activation and impaired glucose tolerance	Adams et al. [71]
Mdnah5$^{-/-}$ [DNAH5 KO]	Global	Primary ciliary dyskinesia and hydrocephalus	Ibanez-Tallon et al. [72]
Dnah6$^{-/-}$ [Dynein, axonemal, heavy chain 6 KO]	Global	Enlarged heart and abnormal kidney morphology	Adams et al. [71]
Dnah17$^{-/-}$ [Dynein, axonemal, heavy chain 17 KO]	Global	Male infertility and sparse hair in female mice	Adams et al. [71]
Drc7$^{-/-}$ [Dynein regulatory complex subunit 7 KO]	Global	Male infertility and abnormal behavior; cardiovascular system phenotype	Adams et al. [71]
Dynlrb1$^{-/-}$ [DYNLRB1 KO]	Global	Embryonic lethality at E8.5	Harada et al. [73]
Kif1b$^{-/-}$ [KIF1B KO]	Global	Preweaning lethality	Adams et al. [71]
Kif2c$^{-/-}$ [KIF2C KO]	Global	Preweaning lethality	Adams et al. [71]
Kif3a$^{-/-}$ [KIF3A KO]	Global	Embryonic lethality at E10.5	Takeda et al. [74]
Kif3b$^{-/-}$ [KIF3B KO]	Global	Embryonic lethality at E12.5	Nonaka et al. [75]
Kif3c$^{-/-}$ [KIF3C KO]	Global	Embryonic lethality at E15.5	Adams et al. [71]
Kif5a$^{-/-}$ [KIF5A KO]	Global	Preweaning lethality	Adams et al. [71]
Kif5b$^{-/-}$ [KIF5B KO]	Global	Embryonic lethality at E9.5–11.5	Tanaka et al. [76]
Eg5$^{-/-}$(*Kif11*$^{-/-}$) [KIF11 KO]	Global	Embryonic lethality at E2.5–3.5	Castillo and Justice [77], Chauviere et al. [78]
Kif16b$^{-/-}$ [KIF16B KO]	Global	Embryonic lethality at E4.5	Ueno et al. [79]

(continued)

Table 1 (continued)

Gene name	KO type	Phenotype(s)	References
Kif18a$^{-/-}$ [KIF18A KO]	Global	Testis atrophy and germinal cell aplasia	Liu et al. [80]
Kif18b$^{-/-}$ [KIF18B KO]	Global	Preweaning lethality	Adams et al. [71]
Kif20a$^{-/-}$ [KIF20A KO]	Global	Preweaning lethality	Adams et al. [71]
Kif21a$^{-/-}$ [KIF21A KO]	Global	Embryonic lethality at E12.5	Adams et al. [71]
Kif21b$^{-/-}$ [KIF21B KO]	Global	Abnormal neuroanatomy such as microcephaly; brain dysfunction such as negative effect on neuron and synaptic transmission; social, learning and memory deficits.	Kannan et al. [81], Muhia et al. [82], Gromova et al. [83], Morikawa et al. [84]
Kif26a$^{-/-}$ [KIF26A KO]	Global	Megacolon and dysfunction of nociceptive responses; preweaning lethality	Wang et al. [85], Zhou et al. [86]
Kif26b$^{-/-}$ [KIF26B KO]	Global	Preweaning lethality	Adams et al. [71]
Kif28$^{-/-}$ [KIF28 KO]	Global	Preweaning lethality	Adams et al. [71]
Myo1e$^{-/-}$ [Myosin IE KO]	Global	Impaired renal function	Krendel et al. [87]
Myo1h$^{-/-}$ [Myosin IH KO]	Global	Preweaning lethality	Adams et al. [71]
Myo2a$^{-/-}$ [NMHC IIA KO]	Global	Embryonic lethality at E7.5	Conti et al. [88]
Myo2b$^{-/-}$ [NMHC IIIB KO]	Global	Embryonic lethality at E14.5	Tullio et al. [89], Ma et al. [90]
Myo3a$^{-/-}$ [Myosin XVIIIA KO]	Global	Abnormal behavioral response to light and increased urine magnesium level	Adams et al. [71]
Myo3b$^{-/-}$ [Myosin XVIIIB KO]	Global	Convulsive seizures and decreased leukocyte cell number	Adams et al. [71]
Myo7a$^{-/-}$ [Myosin VIIA KO]	Global	Abnormal neuroanatomy; decreased body weight; metabolic disorder; abnormal bone morphology and structure and persistence of hyaloid vascular system	Adams et al. [71]
Myo9a$^{-/-}$ [Myosin IXA KO]		Hydrocephalus and abnormal development of ventricular system	Abouhamed et al. [91]

(continued)

Table 1 (continued)

Gene name	KO type	Phenotype(s)	References
Myo10$^{-/-}$ [Myosin X KO]	Global	Embryonic semi-lethality. Abnormal coat/hair pigmentation, curly tail, abnormal eye development, and webbed digits	Heimsath et al. [92]
Myo15$^{-/-}$ [Myosin XV KO]	Global	Absent pinna reflex; increased total body fat amount and decreased red blood cell distribution width	Adams et al. [71]
Myo18a$^{-/-}$ [Myosin XVIIIA KO]	Global	Embryonic lethality at E13.5	Horsthemke et al. [93]
Myo18b$^{-/-}$ [Myosin XVIIIB KO]	Global	Embryonic lethality at E10.5	Ajima et al. [94]
Myo3a^{-}*Myo3b*$^{-}$ [Myosin IIIA KO and Myosin IIIB KO]	Global	Deafness	Lelli et al. [95]

in turn is used to propel cargo to be transported along the actin-based tracks, which are most notable in late Stage VIII tubules across the seminiferous epithelium in the testis [38]. Besides the regular myosins noted in mammalian cells, there is an emerging long-tailed unconventional class of myosins, namely myosin 1E and myosin 1F [115]. In general, each myosin has a Mr of 520 kDa, consisting of six subunits: two 220 kDa heavy chains, and two pairs of light chains (20 kDa for each light chain) (Fig. 3) [116]. Thus, there are two monomers in a functional myosin motor protein, with each monomer consists of a heavy chain and a pair of light chains to a total of three subunits. Each heavy chain, in turn, can be divided into distinctive head, neck and tail domains (Fig. 3B). The globular head domain interacts with actin filaments (i.e., actin-based track) though its actin binding site at the N-terminal region which also contains the ATPase site, capable of hydrolyzing ATP to convert the chemical energy to mechanical energy to propel cargo transport. The neck region of each heavy chain serves as a linker, which also transduces force generated by the catalytic motor domain at the head region. The neck region also provides the binding site for a pair of light chains, which are distinct protein subunits that interact with the neck region (Fig. 3B). The C-terminal tail contains a relatively long α-helical coiled-coil domain and at its C-terminal region, it contains the sequential SH3 (SRC homology 3), MyTH4 (myosin tail homology 4), FERM (F, 4.1 protein; E, ezrin; R, radixin; M, moesin) domains and the globular tail domain (GTD) at its C-terminus. GTD domain is supported by the FERM, MyTH4 and SH3 domains, and GTD also recognizes different cargoes through direct interactions or mediated through adaptor proteins, such as vezatin in the testis [117] (Fig. 3B). Most myosins (e.g., myosin VIIa) walk along actin filaments to the actin plus (+) end, but Myosin VI moves cargoes to the minus (−) end of actin tracks [113]. Myosin VIIa is a member of the

myosin superfamily found in testis and other tissues [118] In testes, actin filament bundles constitute the ectoplasmic specialization, which also serve as the attachment site for cell adhesion protein complexes (e.g., N-cadherin-β-catenin, occludin-ZO-1, nectin-afadin). It also supports the transport of spermatids or organelles (i.e., cargoes) by serving as the track [12, 18]. Studies of myosin VIIa in the testis have shown that the knockdown of myosin VIIa in the testis in vivo by RNAi perturbs the organization of F-actin, but also MT tracks, across the seminiferous epithelium wherein these cytoskeletal tracks are extensively truncated [119]. These disruptive changes are likely the results of a considerably reduction in actin and MT polymerization activity in Sertoli cells [119] due to defects in intracellular protein trafficking. These defects also lead to formation of multiple defective sperms with gross changes in their morphology including round-shaped epididymal sperm heads, consistent presence of cytoplasmic droplets in the head region, and structural defects of sperm necks [119]. These findings are also consistent with earlier reports which have shown that KO of myosin motor proteins lead to embryonic fatality in mice (Table 1), and its mutation or genetic variations in humans also lead to defects in brain and heart development due to defects in intracellular protein trafficking.

Concluding Remarks and Future Perspectives

Herein, we summarize findings regarding the role of MT- and actin-based motor proteins in supporting mammalian spermatogenesis. As seen in studies using genetic models through gene deletion in mice (Table 1), and genetic mutations or gene variants in humans (Table 2), embryonic lethality (in mice) and serious pathological conditions (in humans) are noted in Tables 1 and 2, illustrating the significance of these motor proteins in cells and tissues, besides the testis. However, there are main questions remain. For instance, what are the biomolecules that trigger the use of specific plus (+) end or minus (−) directed motor proteins to initiate cargo transport of germ cells or other organelles to support spermatogenesis through different epithelial cycles? What is the mechanism(s) in place that selects the use of actin- or MT-based tracks or both? How does actin- and MT-based cytoskeletons coordinate with each other to streamline the transport of cargoes using their tracks to support spermatogenesis? It is now known that the several locally produced biomolecules, namely the F5-, NC1- and LG3/4/5-peptide, that regulate spermatogenesis exert their regulatory effects through their corresponding downstream signaling molecules on cytoskeletal organization. What is the mechanism(s) by which these biomolecules select the appropriate cytoskeleton, namely the F-actin or MT cytoskeleton, to execute their function? The answers to many of these questions will be helpful to understand and better manage unexplained male infertility. In brief, an intensive race is on to search for answers to some of these questions in the years to come, such as the role of many genes known to regulaste spermatogenesis to support motor protein function [191]. It is likely that the use of scRNA-seq and scATAC-seq coupled with transcriptome profiling and bioinformatics analyses will provide

Table 2 Pathological conditions in humans with mutation(s) and/or genetic variations of motor genes

Mutation(s) or genetic variations	Human diseases/pathological conditions	References
DYNC1H1 (Dynein Cytoplasmic 1 Heavy Chain 1)	Malformations of brain, Charcot-Marie-Tooth disease (CMT) and spinal muscular atrophy	Poirier et al. [120], Weedon et al. [121], Harms et al. [122], Vissers et al. [123], Willemsen et al. [124], Chen et al. [125]
DYNC2H1 (Dynein Cytoplasmic 2 Heavy Chain 1)	Asphyxiating thoracic dystrophy (ATD) and short rib polydactyly syndrome (SRP) Type III	Dagoneau et al. [126], El Hokayem et al. [127], Schmidts et al. [128], [129]
DNAI1 (Dynein intermediate chain 1)	Asthenozoospermia (AZS) and primary ciliary dyskinesia (PCD)	Zuccarello et al. [130], Zariwala et al. [131]
DNAH5 (Dynein Axonemal Heavy Chain 5)	Asthenozoospermia (AZS)	Zuccarello et al. [130]
DNAH11 (Dynein Axonemal Heavy Chain 11)	Asthenozoospermia (AZS)	Zuccarello et al. [130]
KIF1A (Kinesin Family Member 1A)	Hereditary spastic paraplegia (HSP), cognitive Impairment, spastic Paraparesis, axonal neuropathy, and cerebellar atrophy	Blackstone [132], Lee et al. [133]
KIF1B (Kinesin Family Member 1B)	Charcot–Marie–Tooth type 2 (CMT2)	Hirokawa and Tanaka [134]
KIF1C (Kinesin Family Member 1C)	Hereditary spastic paraplegia (HSP)	Caballero Oteyza et al. [135]
KIF3B (Kinesin Family Member 3B)	Autosomal-Dominant Ciliopathy	Cogne et al. [136]
KIF3C (Kinesin Family Member 3C)	Infantile spasms syndrome (ISs)	Dimassi et al. [137]
KIF4A (Kinesin Family Member 4A)	Hydrocephalus internus	Meier et al. [138]
KIF5A (Kinesin Family Member 5A)	Hereditary spastic paraplegia (HSP), Charcot–Marie–Tooth type 2 (CMT2), amyotrophic lateral sclerosis (ALS), myoclonus and neonatal onset progressive leukoencephalopathy, slowly progressive atypical motor syndrome	Reid et al. [139], Goizet et al. [140], Crimella et al. [141], Liu et al. [142], Brenner et al. [143], Duis et al. [144], Rydzanicz et al. [145], Filosto et al. [146]
KIF6 (Kinesin Family Member 6)	Neurodevelopmental defects and intellectual disability	Konjikusic et al. [147]
KIF12 (Kinesin Family Member 12)	Congenital anomalies of the kidney and urinary tract (CAKUT)	Westland et al. [148]

(continued)

Table 2 (continued)

Mutation(s) or genetic variations	Human diseases/pathological conditions	References
KIF14 (Kinesin Family Member 14)	Abnormal development in brain, kidney, ureter and female genital organs	Meier et al. [138]
KIF15 (Kinesin Family Member 15)	Braddock–Carey Syndrome (BCS)	Sleiman et al. [149]
KIF16B (Kinesin Family Member 16B)	Novel autosomal-recessive intellectual disability syndrome	Alsahli et al. [150]
KIF21A (Kinesin Family Member 21A)	Congenital fibrosis of the extraocular muscle type 1 (CFEOM1)	Yamada et al. [151]
KIF21B (Kinesin Family Member 21B)	Brain malformations, including corpus callosum agenesis (ACC) and microcephaly	Asselin et al. [152]
KIF26B (Kinesin Family Member 26B)	Autosomal dominant spinocerebellar ataxia and pontocerebellar hypoplasia	Nibbeling et al. [153], Wojcik et al. [154]
MYH2 (Myosin-2)	Myopathy, proximal, and ophthalmoplegia (MYPOP)	Martinsson et al. [155]
MYH3 (Myosin-3)	Arthrogryposis and contractures, pterygia, and variable skeletal fusions syndrome	Chong et al. [156], Carapito et al. [157], Scala et al. [158], Cameron-Christie et al. [159], Toydemir et al. [160], Tajsharghi et al. [161]
MYL3 (Myosin light chain 3)	Cardiomyopathy, familial hypertrophic 8 (CMH8)	Poetter et al. [162], Olson et al. [163], Richard et al. [164], Jay et al. [165]
MYH6 (Myosin-6)	Atrial septal defect 3 (ASD3), cardiomyopathy, sick sinus syndrome 3 (SSS3)	Ching et al. [166], Carniel et al. [167], Holm et al. [168]
MYH7 (Myosin-7)	Cardiomyopathy, familial hypertrophic 1 (CMH1)	Fananapazir et al. [169], Rayment et al. [170], Bundgaard et al. [171], Blair et al. [172], Richard et al. [164], Erdmann et al. [173], Van Driest et al. [174], Hougs et al. [175]
MYH8 (Myosin-8)	Carney complex variant (CACOV)	Veugelers et al. [176]
MYH9 (Myosin-9)	Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss (MATINS), deafness, Alport syndrome and cataract	Seri et al. [177], Heath et al. [178], Kunishima et al. [179], Seri et al. [180], Arrondel et al. [181], Deutsch et al. [182], Seri et al. [183], Mhatre et al. [184], Lalwani et al. [185]

(continued)

Table 2 (continued)

Mutation(s) or genetic variations	Human diseases/pathological conditions	References
MYH10 (Myosin-10)	Intellectual disability (ID), brain malformations and/or congenital diaphragmatic hernia (CDH).	Tuzovic et al. [186], Hamdan et al. [187]
MYH11 (Myosin-11)	thoracic aortic aneurysm/aortic dissection (TAAD) and patent ductus arteriosus (PDA)	Zhu et al. [188]
MYH14 (Myosin-14)	Peripheral neuropathy, myopathy, hoarseness, and deafness	Donaudy et al. [189], Choi et al. [190]

many of the missing information in this race to tackle male infertility (or fertility) in the years to come.Declaration of Conflicts of InterestThe authors have nothing to declare,

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