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Review

Myosin superfamily: The multi-functional and irreplaceable factors in spermatogenesis and testicular tumors

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ABSTRACT

Spermatogenesis is a fundamental process in sexual development and reproduction, in which the diploid spermatogonia transform into haploid mature spermatozoa. This process is under the regulation of multiple factors and pathway. Myosin has been implicated in various aspects during spermatogenesis. Myosins constitute a diverse superfamily of actin-based molecular motors that translocate along microfilament in an ATP-dependent manner, and six kinds of myosins have been proved that function during spermatogenesis. In mitosis and meiosis, myosins play an important role in spindle assembly and positioning, karyokinesis and cytokinesis. During spermiogenesis, myosins participate in acrosomal formation, nuclear morphogenesis, mitochondrial translocation and spermatid individualization. In this review, we summarize current understanding of the functions of myosin in spermatogenesis and some reproductive system diseases such as testicular tumors and prostate cancer, and discuss the roles of possible upstream molecules which regulate myosin in these processes.

Contents

Abbreviations: AMPK, AMP-activated protein kinase; AR, androgen receptors; AT, acrosomal tubule; EV, endoplasmic reticulum vesicle; IC, individualization complex; MAP, mitogen-activated protein; MLCK, myosin light chain kinase; MYPT1, myosin phosphatase targeting subunit 1; NM, nuclear matrix; Mo25, mouse protein 25; PAKs, p21-activated kinases; PG, proacrosomal granule; PLX1, Polo-like kinase 1; PP1C, protein phosphatase 1; RMLC, regulatory light chain of myosin II; ROCK, Rho-associated coiled-coil domain-containing protein kinase; STRAD, ste-related adaptor protein; TLK1, tousled-like kinase1; TNF, tumor necrosis factor-α.

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1. Introduction

Spermatogenesis is a process in which haploid mature spermatozoa are generated from male primordial diploid germ cells called spermatogonia. It takes place in the seminiferous tubules and includes three phases: mitosis, meiosis and spermiogenesis. The spermatogonia develops into primary spermatocytes through mitosis; after meiosis, primary spermatocytes transform into spermatids; during spermiogenesis, the round spermatids differentiate into well shaped spermatozoa involving cellular remodeling and pronounced nuclear morphogenesis (Clermont, 1972; Pudney, 1995). Spermatogenesis involves dramatic asymmetric partitioning of cellular contents including specific organelles, cytoplasmic components, cytoskeletal structures and vesicles. Some cellular contents are selectively sorted into growing sperm while others are selectively eliminated.

The process of spermatogenesis is under the complex and specific regulation of various factors, and myosin is found to play an essential role in recent years' researches. Myosins constitute a diverse superfamily of actin-based molecular motors that translocate along microfilaments in an ATP-dependent manner. Myosins are typically comprised of three functional subdomains: the head domain is motor domain, which is highly conserved. It interacts with ATP and actin, containing the primary force production machinery (Mooseker and Cheney, 1995); the neck domain binds calmodulin or light chains which have a variable number from one to six (Mooseker and Cheney, 1995); the tail domain are highly divergent which is responsible for cargo binding and position the motor domain so that it can interact with actin (Mooseker and Cheney, 1995; Baker and Margaret, 1998; Sellers, 1999). In addition, many myosin tails contain coiled-coil α-helix forming regions, which allow dimmer assembly and produce bipolar filaments. There are also some much smaller tails of the monomeric myosin which lack obvious self-association but contain a highly basic domain binding to membranes (Mooseker and Cheney, 1995; Mooseker and Cheney, 1995).

By phylogenetic analyses of the motor domains, people have found that there are at least 15 distinct classes of myosins. Each of them was named by a roman numeral according to their order of discovery (Mooseker and Cheney, 1995; Cope et al., 1996). Each kind of myosins plays different but necessary roles during spermatogenesis. Myosin I has been demonstrated to contribute to intracellular transport, especially post-Golgi transportation (Fath et al., 1994), and the budding and fusion of Golgi vesicles are related to the acrosomal formation (Abou-Haila and Tulsiani, 2000). It is reasonable to think of the possibility that Myosin I associates with the acrosomal formation (Sun et al., 2011). Myosin II and myosin X are motors responsible for cytokinesis, which regulate the spindle assembly and chromosome separation in mitosis and meiosis during spermatogenesis (Yang et al., 2012; Rosenblatt and Cramer, 2004; Woolner et al., 2008). Myosin V has been shown to participate in vesicle trafficking, mitochondrial motility, acrosome formation, intramanchette transport and nuclear shaping during the spermatogenesis (Altmann et al., 2008; Kierszenbaum et al., 2003; Kierszenbaum et al., 2004; Sun et al., 2010). It was found that Myosin V might function in sperm individualization in *Drosophila* (Mermalla et al., 2005). Myosin VI is involved in maintaining actin cone organization (Isaji et al., 2011) and stabilizing actin network (Noguchi et al., 2006). Kelleher et al. (2000) examined the myosin VI deletion mutant of *Caenorhabditis elegans*, and they concluded that myosin VI was responsible for the unequal partitioning of both organelles and cytoskeletal components. Myosin VII is an unconventional myosin which mainly associates with the development and function of the ear and eye (Hasson, 1999), and it also exists in testis, where it is involved in the formation of specialized adhesion plaques named ectoplasmic specializations which may function in the development of Sertoli cells and germ cells (Velichkova et al., 2002). The information of various myosins related to spermatogenesis is demonstrated in Table 1.

In addition to spermatogenesis, myosin superfamily also has multifunctional and irreplaceable functions in some reproductive system diseases, such as testicular tumors and prostate cancer. Myosin IIa and related cytoskeleton tension are implicated in inhibition role in tumor cell aggregation (Saias et al., 2015). Myosin V plays an essential role in cancer differentiation levels, cancer cell migration and nodal metastasis (Lan et al., 2010; Dong et al., 2013). Myosin VI is an early marker of prostate cancer development and myosin VI overexpression occurs before cells become obviously malignant. Other experiments show that some genetic alterations in tumor cells will connect with myosin VI and myosin VI plays an essential role during the development of prostatic intraepithelial neoplasia and the progression to invasive cancer (Knudsen, 2006). Myosin X is a motor protein whose role is best known for filopodia formation. Some latest researches implicate myosin X as responsible for a number of diseases, such as cancer metastasis and pathogen infection by participating in formation of three actin-based protrusions: filopodia, invadopodia, and filopodium-like protrusions (Coursona and Cheney, 2015). Various kinds of myosins are involved in the formation and development of cancer cells, hence researching the relationship and mechanisms between myosin and testicular tumors or prostate cancer will be necessary for normal spermatogenesis and male fertility.

Currently, spermatogenesis and reproductive system diseases have become urgent issues, and thus related regulatory molecules and mechanisms underlying different developmental phases have drawn great attention. Recently, an increasing number of studies have taken a close look at myosins' functions in spermatogenesis and reproductive system diseases. However, some upstream signaling molecules and detailed mechanisms remain controversial. More candidate myosins participating in spermatogenesis need to be indentified and their function and mechanism need to be clarified. In order to illustrate the association between myosins and spermatogenesis, and to provide a further vision for more mechanism studies and possible medical treatments of reproductive system-related diseases, in this review, we will summarize the existing knowledge about the functions and roles of various myosins during spermatogenesis, and clarify the relationship between myosins and some reproductive diseases, such as testicular tumors and prostate cancer.

1.1. Myosins function in mitosis and meiosis

Mitosis and meiosis are respectively the first and second phases of spermatogenesis. The spermatogonia transform into spermatids after mitosis and meiosis. At these two phases, cells show the most drastic alterations in morphology and cytoskeletal organization including cell rounding, spindle assembly, chromosome segregation and cytokinesis (Matsumura et al., 2011). Recent reports have indicated that various myosins are relevant to spindle assembly and karyokinesis (Matsumura et al., 2011). We summarize current knowledge of the functions of myosins in mitosis and meiosis of higher eukaryotes, and discuss the roles of possible upstream signal molecules that regulate myosins in these events.

1.1.1. Spindle assembly and positioning

Mitotic and meiotic spindles are microtubule-based structures responsible for chromosome partitioning during cell division. Previous works have proved and established the roles of microtubules and microtubule-based motors in mitotic and meiotic spindles, however, the specific functions and mechanism of actin filaments (F-actin) and F-actin-based motors (myosins) are still controversial (Woolner et al., 2008).

The role of myosin II in mitosis and meiosis is usually thought to be restricted to cytokinesis. A new evidence shows that cortical myosin II contributes to spindle assembly. Drug- or RNAi-mediated inhibition of myosin II in cells interferes with spindle assembly, orientation and positioning (Rosenblatt and Cramer, 2004; Kunda and Baum, 2009;