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# The acroframosome-acroplaxome-manchette axis may function in sperm head shaping and male fertility

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ABSTRACT

Sperm malformation is one of the main reasons for male infertility, but the precise mechanisms of this process remain undiscovered. The major process of spermiogenesis is sperm head shaping. Cytoskeleton is a crucial unit in this process, as the acroplaxome and manchette are two kinds of momentous structures cooperated with various functional proteins to insure the formation of acrosome and nucleus. One is primarily formed by filamentous actin (F-actin) and responsible for transverse acrosome extension and concentration, another plays as the mainstay of nuclear deformation through circular arrangement of microtubules (MTs). We suspect that the acroplaxome alone cannot maintain such a spatial framework of the acrosome. Previous studies have also revealed that a nucleus without acrosome could not induce the formation of ectoplasmic specialization. In this review, we integrated most of the key proteins that have been proven to participate in the essential developmental steps of post-meiosis. We also propose that the ambient MTs of the acrosome might be emanated from the Golgi apparatus. They form a novel cytoskeleton termed acroframosome (AFS) to transport vesicles and proteins during acrosome biogenesis. The hypothesis of the acroframosome-acroplaxome-manchette (AAM) cytoskeletal system is likely to be the axis of head-to-tail spermiogenesis.

## 1. Introduction

There is no doubt that in contemporary society, it has become a common puzzle for a huge number of male adults with teratozoospermia, including asthenozoospermia, globozoospermia, oligoasthenozoospermia, and other symptoms (Coutton et al., 2015). The lengthy process of spermatogenesis is up to 21.6 days in humans, 22.7 days in rats, which is necessary for attaining plenty of mature spermatozoa with specialized morphology and improving the efficiency of fertilization (Hermo et al., 2010). Actually, the pre-existing study has stated that the post-meiotic procedure is much more complex with 19 steps in 14 epithelial cycle stages focusing on sperm head shaping, which could be divided into two parts: the acrosome region and the manchette covered region (Leblond and Clermont, 1952a). Cytoskeletons are regarded as the crucial units for supporting the celluar development and transformation (Fouquet and Kann, 1994), as the acroplaxome and manchette are two kinds of momentous structures cooperating with various functional proteins to insure the formation of acrosome and nucleus during spermiogenesis (Kierszenbaum et al., 2003a; Mochida et al., 1998). However, the precise mechanism of each cytoskeleton remains undetermined, and a recent spermiogenesis proteomic analysis has revealed that a cluster of proteins are involved in this process with elusive characteristics (Guo et al., 2010). We suspect that it is difficult to develop a complex spatial framework like the acrosome with only an acroplaxome. Previous research has also revealed that an acrosome without nucleus cannot induce the formation of ectoplasmic specialization (Russell et al., 1983). A novel cytoskeleton termed acroframosome (AFS), the microtubule (MT)-based frame of the acrosome, was observed in Decapod crustaceans previously (Hou and Yang, 2013). The acroframosome represents that the peripheral MTs around the Golgi functions as a framework for acrosome biogenesis, and the Golgi apparatus works as the noncentrosomal MT organizing center (MTOC) in spermatids. Herein, such an acroframosome-acroplaxome-manchette (AAM) cytoskeletal system is likely the trunk of head-to-tail spermiogenesis. Besides, it is difficult to culture the spermatids alone in vitro, because of the intricate and rigorous microenvironment of the seminiferous tubule. Meanwhile, the blood-testis barrier, hormone-like testosterone and follicle-stimulating hormone (FSH) could provide a proper condition for mitosis, meiosis and spermiogenesis, are also required for the culture of the spermatocytic cells

*Abbreviations:* AAM, acroframosome-acroplaxome-manchette; AFS, acroframosome; F-actin, filamentous actin; FSH, follicle-stimulating hormone; G-actin, globular actin subunits; IFT, intraflagellar transport; IMT, intramanchette transport; LCx, lamellar complex; LINC, linker of nucleoskeleton and cytoskeleton; MAPs, microtubule-associated proteins; MT, microtubule; MTOC, microtubule organizing center; PRM, protamine; TGN, trans-Golgi network; TP, transition protein; UBP, ubiquitin-proteasome pathway

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**Table 1**
Characteristics and major functions of AAM axis components.

| Structure | Cytoskeleton | Related protein | Major function | Species | Contributors |
|---|---|---|---|---|---|
| AFS | MT | KIFC1 | Traffic materials; acrosomal development | *Exopalaemon modestus*; *Macrobrachium nipponensis* | Hou and Yang (2013); Li et al. (2010); Wang et al. (2012) |
| Acroplaxome | Microfilament | Keratin5; Dpy19l2; CLIP-170; Centrobin; Myosin Va | Limit the spreading area of acrosome; link acrosome with nucleus; modulate the compression force from Sertoli cells; chromatin removement; ubiquitylation | *Homo sapiens*; *Mus musculus*; *Rattus norvegicus* | Akhmanova et al. (2005); Bryant et al. (2015); De Vries et al. (2012); Göb et al. (2010); Langford (2002); Liska et al. (2009); Pierre et al. (2012); Kierszenbaum et al. (2003a), (2004); Zhao et al. (2013) |
| Membrane complex (acroplaxome-like) | Microfilament | Myosin Va | Form proacrosomal granule; link acrosome with nucleus | *Eriocheir sinensis* | Sun et al. (2010) |
| Manchette | MT; microfilament | GBA2; KDM3A; MEIG1; Katanin p80; *E*-MAP-115; KIF3A; Fu; RAN; BSCL2; PARP11; LIST1; KIF17B; SPEM1 | Nucleocytoplasmic transportation; nuclear condensation and elongation | *Homo sapiens*; *Mus musculus*; *Rattus norvegicus* | Bao et al. (2010, 2011); El Zowalaty et al. (2015); Kasioulis et al. (2014); Kierszenbaum et al. (2002); Komada et al. (2000); Lehti et al. 2013, (2015); Matsuoka et al. (2008); Meyerfica et al. (2015); Nozawa et al. (2014); O'Donnell et al. (2012); Penttilä et al. (2003); Raju et al. (2015); Saade et al. (2007); Wang et al. (2013); Yamaguchi et al. (2004); Zhang et al. (2009); Zou et al. (2002) |

(Minaee et al., 2013). Therefore, exploring the detail mechanism of such a complex process is essential for further study of male infertility.

## 2. Dynamic transformation of cytoskeletons during spermiogenesis

Both in vitro (aquatic invertebrates) and in vivo fertilization (terrestrial animals) cases, spermatozoa have undergone a sophisticated biogenesis to gain enough energy for fertilization. Thus, three inextricable parts surmise to execute synergistic functions in post-meiotic stages: the AFS, a novel MT structure substantiated by Li et al. (2010), seemed to be a framework supporting the initiation of the acrosome and guiding vesicles towards the nucleus (Li et al., 2010). The AFS was speculated to interact with the acroplaxome or subacrosomal chamber and stabilize the linkages between them. Due to the condensation and reconstruction of nuclei, spermatids form a temporary configuration, manchette, at the late stage of spermiogenesis (Rivkin et al., 1997). In order to further condense the organelles, these cytoskeletons cooperate in the recruitment of related proteins and undergo a series of deformation (Table 1). Eventually, the spermatozoa cast away the residual cytoplasm and stretch out with spikes or flagella.

### 2.1. The development and functions of the acrosome

Collectively, the acrosome, an irreplaceable component locating at the apex of mature spermatozoa, presents to be the vital part when penetrating into the egg. The course of such a systematical formation is mainly composed of four parts (Clermont et al., 1959; Leblond and Clermont, 1952b), coinciding various protein interaction with vesicle trafficking: (1) Golgi phase (step 1–3). The Golgi apparatus, as the primary organelle of spermiogenesis, can secrete proacrosomal vesicles and recruit several key factors, such as Smap2 (Funaki et al., 2013) and PICK1 (Xiao et al., 2009), which need accurate positioning followed by cytoskeletal guidance. Afterwards, proteins such as Dpy19l2 (Yassine et al., 2015) and SPAG4L (Frohnert et al., 2011) assist these proacrosomal granules attaching to the nucleus. To some extent, a retrograde vesicle ferrying pathway occurs at this phase as well, by which the tethering complex could retrograde cargos to the trans-Golgi network (TGN) directly and maintain the polarized Golgi stacks. This may be an essential mechanism in *Drosophila* to establish an intact acroblast for acrosome shaping (Fári et al., 2016). (2) Cap phase (step 4–7). Proteins take part in proacrosomal vesicles collection and integration, then under the interplay of some elements like ACRBP-V5 and Hrb, the acrosome increasingly covers up to one-third of the nucleus and forms a marginal fossa (Kanemori et al., 2016; Kang-Decker et al., 2001). (3) Acrosome phase (step 8–14). With the reconstruction of the nucleus, the acrosome contacts to the surface of the cell and bents into a hook-like structure. At the same time, the Golgi complex transfers to the distal side of the cell with cytoplasm. (4) Maturation phase (step 15–19). The swelling acrosome and subacrosomal region protrudes towards the nucleus accompanied by the elimination of residual materials.

The processes mentioned above may be affected by the dynamic changes of the whole conformation, rather than a single structure of the spermatid, suggesting for pivotal roles of the cytoskeleton in managing the acrosome development. In spite of this, researchers only acknowledged the acroplaxome in the acrosome area in mammalian animals so far, which not only jointed the acrosome and the nucleus together, but took part in anchoring proacrosomal sacs to restrict its proportion (Kierszenbaum et al., 2003b). Here, Myosin Va, a predominant motor, attend to transfer cargos as well as persist the marginal ring (Langford, 2002). The similar function of myosin Va has been discovered in *Eriocheir sinensis* that it may transport the Golgi-derived vesicles to form the proacrosomal granule. Besides, they could largely aggregate to the membrane complex, an acroplaxome-like structure in crab with F-actin and some degenerated materials, when the nuclear membrane starting to concave downward and wrap the proacrosomal vesicles (Sun et al.,