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Chapter

Spermatogenesis in *Drosophila melanogaster*: Key Features and the Role of the NXF1 (Nuclear Export Factor) Protein

Elena Golubkova, Anna Atsapkina, Anna K'ergaard and Ludmila Mamon

Abstract

Now there is interest in finding factors that, once in the ovum, can affect the development of offspring. The *sbr* (*Dm nxf1*) gene in *D. melanogaster* belongs to the evolutionarily conserved family of nxf (nuclear export factor). It is involved in controlling of male fertility and forming the factor that affects the segregation of maternal and paternal chromosomes after fertilization. The Dm NXF1 (SBR) protein seems to play a role in forming this mysterious factor during the meiotic period of spermatogenesis. Male germ cells develop as a syncytium, and success of spermatid individualization depends, to a great degree, on gene expression in primary spermatocytes. Most transcripts formed in primary spermatocytes are long-lived. The presence of the Dm NXF1 protein in the nucleus as well as in the cytoplasm suggests that it plays a role in the biogenesis of long-lived RNA and in cytoskeletal reorganization.

Keywords: spermatogenesis, meiosis, *Drosophila*, NXF, cytokinesis, RNA-binding protein

1. Introduction

Spermatogenesis is an evolutionary conservative process. In testes, the developing germline cells divide synchronously and with incomplete cytokinesis remaining interconnected by cytoplasmic bridges. Therefore, the germline cells develop as a syncytium and only become separated from each other at the end of spermatogenesis during spermatid individualization. In *Drosophila melanogaster*, the stem cell daughter, the gonialblast, undergoes four rounds of synchronous mitotic divisions to produce 16 precursor cells, called spermatogonia [1–3]. The spermatogonia then become spermatocytes and grow 25 times in size [1, 4]. During the growth phase, the majority of the transcripts for sperm differentiation are expressed and potentially stored until their protein activity is required [5–7]. Many of the transcribed genes are important for meiosis and post meiotic stages [6] or as are suggested to be reserved up to sperm maturing and delivered into the egg at fertilization [8, 9]. After the growth phase, the spermatocytes divide twice by meiosis and then differentiate into 64 haploid spermatid interconnected in a syncytium. At sperm individualization, most unneeded products are pushed to the end of the spermatozoon and an

actin structure, termed the investment cone, forms a new membrane [10, 11]. Each cell becomes independent and turns into a mobile spermatozoon. Development of a mature spermatozoon with the change of histones on protamines in nucleus, the building of an acrosome and a tail, the forming of cellular membrane, occurs without transcription owing to translation of the long-lived mRNAs. Such mRNAs are keeping as a part of the RNP-complexes localized in the different cellular compartments. The testis-specific isoform of the Dm NXF1 (SBR) protein can be an important component of these RNP-complexes.

2. Long-lived transcripts and interacting proteins: role in the sperm maturation during spermiogenesis

Most transcripts formed in primary spermatocytes are not translated immediately after exiting from the nucleus. These RNAs are reserved in the ribonucleoprotein protein (RNP) complexes for a long time up to the elongation stage during spermatid individualization [6]. In *D. melanogaster*, 529 of the 553 mRNAs detected in spermatid were transcribed in primary spermatocytes [12].

The existence of the NXF (Nuclear eXport Factor) specialized transport receptors, which are the products of paralogous genes of the NXF family and are expressed predominantly in the testes or the brain of humans and mice, has been associated with the presence of long-lived, temporary non-translatable transcripts [13–17]. The most evolutionary conservative member of this family (NXF1) provides transport of the majority of the mRNAs from the nucleus to the cytoplasm [18–21]. The paralogous members of the NXF family differ from the NXF1 protein by divergent sequences enabling interaction with nucleoporins—proteins of nuclear pore complexes and the domain of LRR (leucine-rich repeats). These sequences are responsible for interaction with the partner proteins forming RNP complexes at different steps of mRNA biogenesis [13–15]. The primary localization of testis-specific NXFs in the cytoplasm suggests their participation in the biogenesis of long-lived mRNAs, which are temporarily untranslated [16, 17].

In *D. melanogaster*, the testis-specific *Nxf* paralogous genes are unknown. Unlike its orthologous in humans and mice, the *Dm nxf1* (*sbr*) gene does have testis-specific products [22, 23]. The short testis-specific *sbr* transcripts use the alternative promoters in intron 3 and do not include exons 1–3. As a result, the testis-specific truncated SBR protein excludes nuclear localization signals (NLS) present in the canonical SBR protein and in the part of the RNA binding domain (RBD)

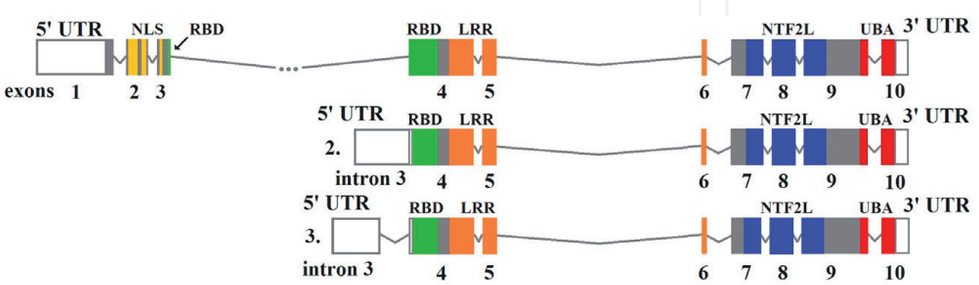


Figure 1.
The testis-specific sbr *mRNAs are detected by 5′ and 3′ RACE-PCR. Boxes indicate exons included in the sbr mRNAs. Exon numbers are signed under each box. RBD – RNA-binding domain; LRR – leucine-rich domain; NTF2L – nuclear transport factor 2 like; UBA – ubiquitin associated domain; NLS – nuclear localization signal. In testes, all* sbr *mRNAs have the shortened 3′ UTR. In all transcripts, length of the 3′ UTR varies from 44 to 124 nucleotides. Two* sbr *mRNAs, using the alternative promoters in intron 3, give rise the shortened protein isoform without NLS and the part of RBD, which are present in the canonical full-length SBR (published in Mamon et al. [24]).*

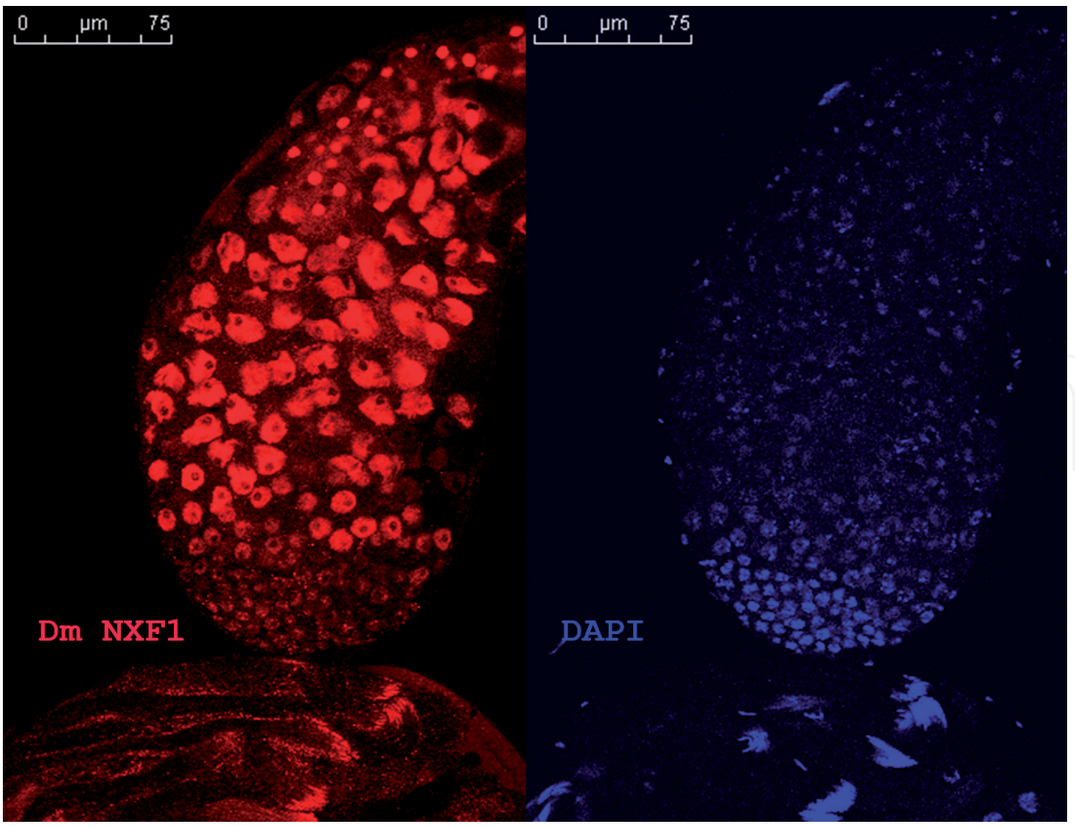


Figure 2.
Adult testis immunofluorescence using anti-SBR (Alexa 546 goat anti-mouse). In the prophase of meiosis (arrowhead) and at the round spermatid stage (arrow)—The SBR proteins are primarily localized in the nucleus. Asterisk denotes the stem cells zone. Scale bar, 75 μm.

(**Figure 1**) [24]. Such truncated SBR form can have other functions in addition to the nuclear RNA export, which are important for spermatogenesis.

During transcriptional activities—the prophase of meiosis and the round spermatid phase—the SBR protein is primarily found in the nucleus (**Figures 2, 3**). This is coordinated with the known universal function of NXF1 proteins in various organisms [18–21]. Unfortunately, antibodies to C-terminal part of the SBR protein cannot contradistinguish full-sized and truncated SBR isoforms.

Nuclei of spermatids in onion stage are brightly painted fluorochromes conjugated with anti-SBR (**Figure 2**). Nebenkern is near each of nucleus and is free from SBR. Only 24 genes are transcribed in *Drosophila* spermatids [12], but spermatid nuclei show the brightest coloring by anti-SBR. Why at onion stage such high concentration of transport receptors for mRNA is necessary. It is possible that spermatid nuclei may be one of the docking place for some long-lived mRNAs because the most dramatic events depending from translation of these mRNAs are related to nucleus and/or structures connected with nucleus during the sperm maturation. In elongated spermatids, the SBR protein is localized on a nuclear surface asymmetrically, only along one of its sides (**Figure 4**). Spermatid elongation is period of intensive nuclear morphogenesis [1]. The nuclear envelope becomes asymmetrical, with nuclear pores being disposed along one side of elongated nucleus. In this region, the dense body consisting from a microtubule (MT) and actin-rich structure is formed and also localized along one side of the nucleus [25]. Nucleoporin binding domains (NTF2L and UBA) in the SBR proteins (**Figure 1**) allow them to participate in the storing of the RNP complexes with the long-lived RNAs connected with the nucleoporins on the nuclear envelope. After the RNP complexes dissociate, the translation of their mRNAs begins close to the nucleus, where there is a need for appropriate proteins. Then the components of the RNP complexes, including the SBR proteins,

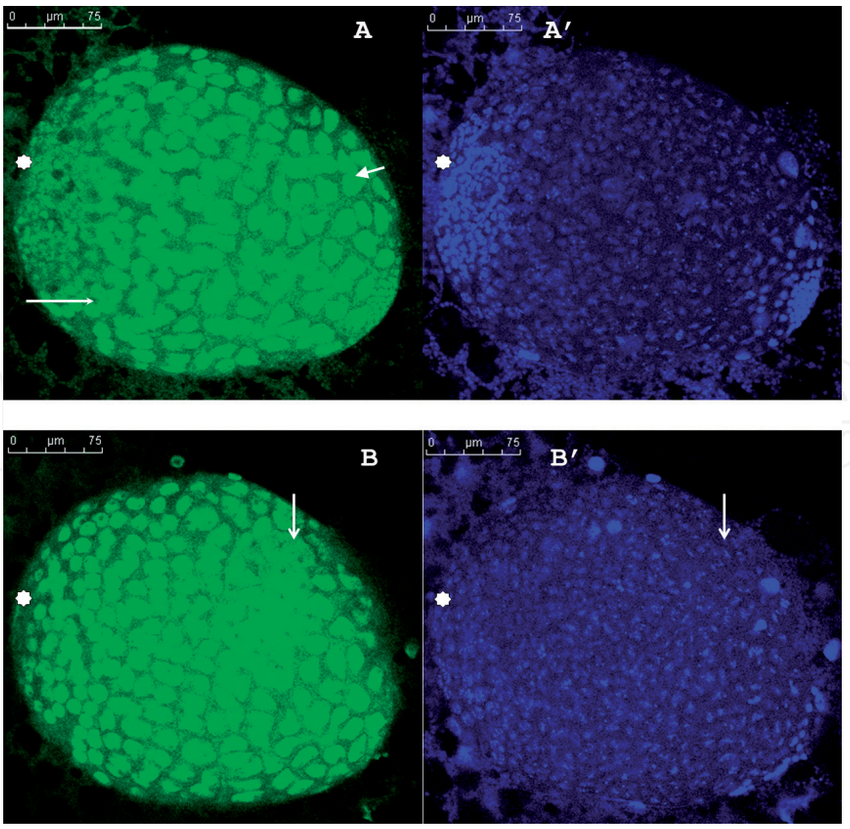


Figure 3.
Prepupal testis immunofluorescence using anti-SBR (Alexa 488 goat anti-mouse – A, B) and DAPI (A', B'). A. Most part of the future gonad is represented of growing spermatocytes, primary spermatocytes, and meiocytes. Initially, the shape of the nucleus is round (A, thin arrow); then the shape becomes irregular (A, short arrow). B. Cyst of 16 meiocytes with the cytoplasmic localization of the SBR protein. Bivalents partially condensed (arrows). Asterisk denotes the stem cells zone. Scale bar, 75 µm.

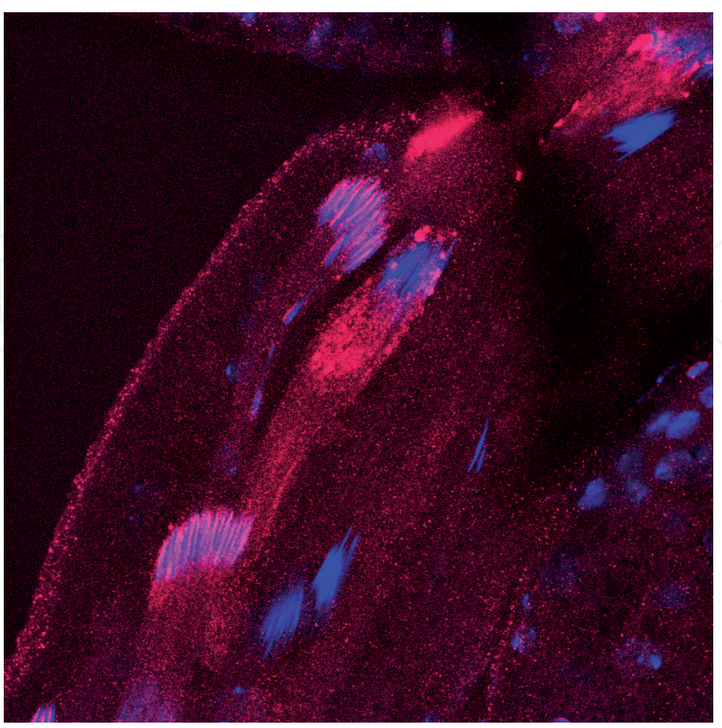


Figure 4.
Spermatids at the elongation or individualization stages in D. melanogaster *males (Alexa Fluor 546). Spermatids at the elongation stage: the SBR protein moves onto one side of the spermatid nuclear. The SBR protein leaves the condensed nuclei and is translocated in large granules into the formed spermatozoon tails at the final stage of spermatid elongation before individualization. 63× magnification.*

relocate in a spermatozoon tail as the granules and are degradate (**Figure 4**) [26, 27]. Proteasome degradation of the proteins is necessary for the formation of mature sperm [28]. SBR (Dm NXF1) protein has UBA-like domain (**Figure 1**), which are involved in a variety of cellular functions and many are connected to the ubiquitin proteasome system, an essential pathway for protein degradation in eukaryotic cells [29, 30]. Proteasome degradation is important for cell cycle progression [31]. Testis-specific proteasome degradation in *D. melanogaster* probably provides effective elimination of SBR during spermatid individualization (**Figure 4**).

It is important that mRNAs encoded by all of the post-meiotically transcribed genes are localized to the extreme distal ends of elongated spermatids. These mRNAs are subdivided into two classes named by comet and cup transcripts [12]. There is not a concentration of SBR to the distal ends of elongated spermatids.

A feature of spermatogenesis is that many genes produce shortened transcripts that encode shortened proteins. These proteins cannot function as the full-sized proteins encoded by the same genes [32]. This is due to the presence of testis-specific promoters or alternative splicing variants [33]. In addition, testis-specific transcripts often use an alternative polyadenylation site located upstream, compared to those in the transcripts of the same gene in other organs [33, 34]. This may be important for the regulation of translation and degradation of transcripts during spermatogenesis. All the transcripts of the *Dm nxf1* (*sbr*) gene have the shortened 3′UTR in testes [22, 23].

3. Allele-specific effects of the *sbr* gene including the male infertility

Mutations of the house-keeping genes are characterized by a broad range of pleiotropic effects. It is no surprise that mutations of the *Dm nxf1* gene lead to both male and female sterility and increase the frequency of the development malformations (FlyBase [35]). That may be the result of disruption of the NXF1 general functions. Allele-specific effects of mutations in the *Dm nxf1* gene suggest that its products may have specialized functions. The organ-specific products of *sbr* can provide such specialization [22–24]. In addition, the source of specialized functions may be the presence of functionally significant sequences in the SBR protein, responsible for interaction with the certain partners. As a result, SBR may be involved in other processes than the nuclear-cytoplasmic export of mRNAs [36, 37]. A mutant product that disrupts the system of macromolecular interactions can have a dominant negative effect, in this case heterozygosity at the null allele will be better than the presence of a mutant protein along with the normal product [38]. Among the mutant alleles of the *sbr (Dm nxf1)* gene with the dominant effects are the formation of three-pole spindles during the first meiotic division in sbr^{5}/+ females [36] and sterility of sbr^{12}/*Dp (1;Y)y* + *v* + males. *Dp (1;Y)y* + *v* + is the duplication of the segment of the X chromosome with the *sbr*+, y + and v + alleles, translocated on the Y chromosome. The duplication compensates a lethal effect of the different alleles of the *sbr* gene localized on X-chromosome [39]. sbr^{10} is the thermosensitive allele with a block of the heat shock protein synthesis under heat shock (HS) [40]. It is a recessive feature of the sbr^{10} allele [38]. Adult males carrying the sbr^{10} allele are thermosensitive and die from 37°C, 1 h [8]. HS increased the number of abnormalities, of not only paternal but also maternal sex chromosome sets, in the offspring of the sbr^{10} males. Meiocytes were the thermosensitive stage for this unexpected effect [8].

It was interesting to know what feature is characterized the SBR protein distribution in the future gonads of *D. melanogaster* males on the pupal stage. On a pre-pupa stage of development, the future gonad in *D. melanogaster* males is spherical with two poles with dividing cells (**Figure 3**). One pole produces germ-line cells and

another—somatic cells of a future gonad. Both poles are quite poor SBR protein. It is as a rule characteristic for SBR in a zone of dividing cells in different tissues. Most part of a future gonad is represented by cysts with 16 spermatocytes. Cysts from 16 meiocytes are outstanding by the highest content of the cytoplasmic SBR protein (**Figure 3B**).

As the growing spermatocytes are characterized by the high level of transcriptional activity, the long-lived RNAs seem to be the most appropriate candidate for the role of factors that, along with the spermatozoon, enter an ovum during fertilization and can participate in chromosome disjunction. Due to the process of translation, a small number of these molecules are sufficient for the regulation of chromosome segregation. This is particularly important during the first hours of embryonal development of *D. melanogaster*, as it takes place in the absence of transcriptional activity of the zygotic genome [41]. It has been demonstrated that along with the spermatozoon, paternal RNAs that may also play a role in fertilization, as well as zygotic and embryonic development, also enter the oocyte [42, 43]. High level of the SBR protein in cytoplasm shows that this protein may play a crucial role in biogenesis of the long-lived RNAs in *D. melanogaster*. The significance of SBR in forming the meiotic spindle in female *D. melanogaster* [36] and for the mitotic divisions in early embryos [44] leave unknown the molecular partners of the SBR protein involved in these processes.

One more target of sbr^{12} mutant alleles is the sperm flagellum [26, 45, 46]. The sperm axoneme as a main component of a flagellum defining mobility of a spermatozoon enters the ovum during fertilization [47, 48]. Axoneme is a derivative of a spermatid centroiole, which becomes the basis for the paternal centrosome formation, providing fusion of pronuclei and division of embryonic nuclei [49].

4. The centrosome for male meiosis and building of the axoneme

The centrosome plays a special role in spermatogenesis. It determines the polarity of the stem cells, maintaining contact with the hub and enabling the asymmetric division of stem cells [50]. Male spermatocytes of the wild type contain two centrosomes each. Each centrosome has two orthogonal centrioles that are 10 times larger than those in other cells [51]. Thus, during meiosis I, each of two centrosomes contains a pair of duplicated centrioles.

No centriole duplication occurs before meiosis II. Before chromatid segregation in secondary spermatocytes, each pair of centrioles divides into two single centrioles. Prior to chromatid segregation during meiosis II, one of the centrioles migrates to the opposite pole of a cell. As a result, each spermatozoon inherits only one centriole, which becomes the basal body forming the axoneme [1, 52]. Paternal centrosome participates in the formation of astral microtubules for moving male and female pronuclei toward each other [49]. The role of centrosome RNAs in the asymmetry distribution of cytoplasmic determinants among daughter cells [53] makes plausible the hypothesis that centrosome may be a carrier of the paternal factors, affecting the embryo development.

The axoneme growth during sperm maturation needs translation of the long-lived mRNAs coding the components of axonemal complex. Morphological defects of axoneme are a characteristic dominant manifestation of sbr^{12} mutant allele (**Figure 5**) [26, 27].

Translational control is crucial for morphogenical events that take place in the absence of transcription during spermiogenesis [26, 54]. The transcripts encoding proteins required for post-meiotic processes including spermiogenesis are almost all

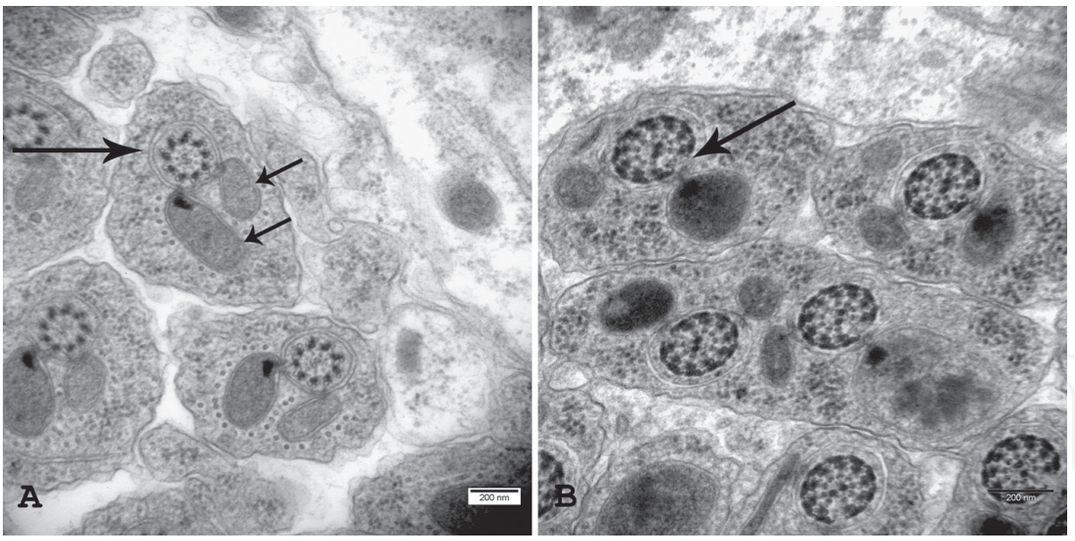


Figure 5.
Electron microscopy images of a cross section of 64 cell cysts. (A) Control (males of Oregon R*). (B) Morphological defects at the spermatid elongation stage in* D. melanogaster sbr12/Dp (1; Y) y + v + *males. Spermatids are often not subdivided into individual cells, and there are anomalies in axoneme structure (long arrow) and in mitochondrial derivatives (short arrow) (published in Mamon et al. [27]). Scale bar, 200 nm.*

abundantly transcribed in spermatocytes [5]. In *D. melanogaster*, elongation of the flagellar axoneme does not require the ubiquitous process of intraflagellar transport [55, 56]. The axoneme growth and spermatid elongation can be carried out at the expense of translation of mRNAs encoding tubulin subunits and other axonemal proteins within the ciliary pocket [25]. The genetic analysis of male fertility has identified numerous genes involved in spermiogenesis control [25, 57]. Spermatid individualization process depends on genes involved in RNAs metabolism [58].

In *sbr**12**/Dp (1;Y)y + v +* males, the morphology of mitochondrial derivatives and cytokinesis are defective in the elongated spermatids (**Figure 5**). Mitochondria morphogenesis depends on translation efficiency [54], also as a creation of new cellular membrane.

5. Incomplete cytokinesis providing a cellular communication as a feature of male generative cells

Syncytial development during the formation of male generative cells is conservative and is characteristic for different animals [59, 60]. It is assumed that the link between the cells in the syncytium is important primarily for synchronizing differentiation processes [59]. The cytoskeleton and the molecules providing a cellular communication are the main components supporting of equality of each cell in the syncytium.

The cytokinesis of spermatogenic cells is characterized by the formation of ring canals linking the cells that have undergone meiosis or mitosis [61]. During cell division, a contractile ring, made of actin and myosin II filaments, assembles as a result of the interaction between the plus ends of the microtubules and the cell cortex [62]. The contractile ring is double-sided. The microtubules whose minus ends directed toward centrosome on one pole of the dividing cell bind to one side of the contractile ring by their plus ends. The microtubules that have their minus ends turned toward centrosome on the other pole of the dividing cell bind to the opposite side of the contractile ring. Thus, the ring attached equatorially to the membrane of the dividing cell forms an actin-myosin cleavage furrow [60]. The ingression of the cleavage furrow is accompanied by the growth of the daughter cell membranes.

+TIPs—complexes linked to the plus-ends of the microtubules—play a special role in the interaction of the plus-ends of the microtubules with the cell cortex [63]. +TIPs also play an important role in finding and capturing microtubule targets—the cortex and the chromosomes [64, 65]. Localized mRNAs are anchored at the plus ends of microtubules especially in polarized cells [66]. SBR also may be one of the factors that interact with the plus-ends of microtubules.

It is worth noting that the Hs NXF1 (TAP) factor in humans was initially identified *not* as a protein enabling transport of mRNA from the nucleus into the cytoplasm, but as a factor important for cellular adhesion and involved in cell signaling [67]. For this reason, the protein Hs NXF1 was called TAP—Tip-associated protein, where Tip stands for tyrosine kinase-interacting protein.

Tyrosine phosphorylation is important for regulating the assembly and disassembly of the actin cytoskeleton at cell-cell junctions. In many cases, tyrosine phosphorylation in proteins of the junction complex—plakoglobin and β-catenin in adherens junctions—disrupts interactions between cytoskeleton and membrane [68]. It is believed [61] that tyrosine phosphorylation in targets leads to the disassociation of phosphorylated actin from the contractile ring that forms during the cytokinesis of the cells comprising the syncytium during spermatogenesis. This stabilizes the interaction between the walls of the ring and the cell membrane, ends cell division, and forms the ring canal [61]. Building a new cell wall at the cleavage site during cytokinesis requires the involvement of components of the cell membrane and the signaling molecules [69]. A system of transport molecules ensures the delivery of the necessary elements to the region where the cell membrane is being formed [70].

Interactions of NXF1 with cytoskeleton [27] and the cellular membrane [67] may help finding partners of NXF1 in the cytoplasm. Not surprisingly, the closest evolutionary relative of NXF1 is dynein. Dynein plays a significant role in cytokinesis, chromosome segregation, and in enabling the movement of the flagellum of the sperm [70, 71].

6. Homology of proteins of the NXF family and axonemal dyneins as a source of evolutionary relationship

Searching for related proteins and aligning sequences using the multiple sequence alignment tool base has demonstrated that among the proteins that are homologous to the factor NXF1, axonemal dynein of various organisms—especially its light chain—is most frequent. Aligning sequences that exhibit homology demonstrates that the N-terminus of the Dm NXF1 protein, which includes RBD domains and the LRR (leucine-rich repeats), corresponds to the axonemal light chain of dynein in vertebrates (**Figure 6**). At the LRR site, there is a sequence that exhibits a high degree of homology (marked by bold typeface in **Figure 6**), both when comparing different NXF factors (orthologous and paralogous), and comparing the SBR protein with sequences of light chains of dynein (**Figure 6**). The functions of this sequence are yet to be determined.

The dynein complex is a multicomponent system consisting of light, light intermediate, intermediate, and heavy chains of dynein [72]. Interacting with a multitude of protein and ribonucleic partners, the LC8 and TcTex1 light chains of dynein enable a link between different forms of the transported cargo and heavy chains of dynein that function as molecular motors [73, 74]. By interacting with its partner dynacin complex, the dynein complex enables cytoplasmic transport of macromolecular complexes, vesicles, and organelles [75], including particles containing RNAs [74, 76].



Figure 6.
Results of the alignment of the amino acid sequences of LRR domains of different NXF factors, including SBR, and dynein light chain fragment of D. melanogaster *(DNAL1 Dm) (A). The alignment of the amino acid sequences of dynein light chain fragments (DNAL1) of different organisms (*Danio rerio *– DANRE;* Xenopus laevis *– XENLA) and the LRR domain of SBR (NXF1 DROME) (B). Red letters denote identical amino acids; blue – identical amino acids in the dynein light chain and in the SBR. The bold type notes most often meeting amino acids in corresponding position in protein. Gray color notes interchangeable amino acids. Green color notes sequence of the LRR (leucine rich repeats) domain in SBR protein (http://www.uniprot.org/align/20 1202072EGVYDYGWG).*

In the fruit fly, the null mutants of the genes that encode the light or heavy chain of dynein have anomalies of wings and bristles, exhibit male and female sterility, and are characterized by disrupted sensory axon trajectories [71], thus demonstrating a similarity to the mutants of the *sbr* gene.

During spermatid individualization, the dynein light chains 1 (DLC1) participate in the assembly of the F-actin [77]. Dynein is necessary for centrosome separation, for forming the division spindle, and for aligning chromosomes equatorially during metaphase [78, 79]. During the interaction with the surface of microtubules, dynein also interacts with MAP proteins [80]. During prometaphase, the DYNLT3 light chain can be observed in kinetochores. During metaphase, dynein moves toward the spindle pole [81, 82]. The dynein complex leaves the kinetochores along with checkpoint proteins. This could be related to the transport of checkpoint proteins (for example, Bub3) from kinetochores to spindle poles [83]. If we recall the homology of the proteins Bub3 and Rae1 [84] and the fact that the protein Rae1, found in RNP complexes that are important for forming the spindle, is capable of direct interaction with NXF1 [85], it is possible to consider these factors as polyfunctional. They are taking part both in nuclear-cytoplasmic transport of macromolecules and in the formation of the mitotic apparatus of the cell.

Because it is the light chain of dynein in the dynein complex that is responsible for interaction with the cargo [72], this resemblance to the N-terminus of the SBR protein suggests that SBR may have the same partners as a dynein complex (that these proteins can have the general partners or the general functions, and they are evolutionary conservative).

7. Conclusion

In *D. melanogaster*, the evolutionarily conservative *sbr (Dm nxf1)* gene is characterized by the testis-specific gene products. The cytoplasmic localization of the SBR protein in meiotic cysts is quite impressive. Some *sbr* mutant alleles cause male sterility and the specific morphological defects of the spermatids at the individualization stage. Transcriptional activity during pre-meiotic and meiotic stages of spermatogenesis is crucial for the sperm motility in *D. melanogaster*. During these stages, the factors are formed that are able to affect the frequency of aneuploidy arising in the offspring after fertilization. The *sbr* gene is an attractive model for investigation of male sterility and the paternal effect on the embryonic development due to the RNA-binding protein SBR involvement in formation and fate of the long-lived RNAs.

Acknowledgements

We are grateful to the staff of KHROMAS (the Center of study of ultrastructure and molecular composition of biological objects at Biological Faculty of St. Petersburg State University) and to its head Elena R. Gaginskaya for their most important assistance in performance of this work.

Funding

The Russian Foundation for Basic Research supported the work (project 19-04-01255).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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