Emerging roles for nucleoporins in reproductive cellular physiology[1]

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Abstract

Nucleoporins are a specialized subset of nuclear proteins that comprise the nuclear pore complex and regulate nucleocytoplasmic transport. Recent demonstrations of roles for individual nucleoporins in multiple paradigms of differentiation via mechanisms independent of nuclear trafficking represent conceptual advances in understanding the contributions of nucleoporins to cellular development. Among these, a functional role for nucleoporins in reproductive fitness and gametogenesis has been identified, supported by robust models and clinical studies that leverage the power of next generation sequencing technology to identify reproductive-disease-associated mutations in specific nucleoporins. Proper nucleoporin function manifests in different ways during oogenesis and spermatogenesis. However, nonhuman models of gametogenesis may not recapitulate human mechanisms, which may confound translational interpretation and relevance. To circumvent these limitations, identification of reproductive pathologies in patients, combined with next generation sequencing approaches and advanced in silico tools, offers a powerful approach to investigate the potential function of nucleoporins in human reproduction. Ultimately, elucidating the role of nucleoporins in reproductive biology will provide opportunities for predictive, diagnostic, and therapeutic strategies to address reproductive disorders.

Résumé :

Les nucléoporines constituent un sous-ensemble spécialisé de protéines nucléaires, qui comprennent le complexe des pores nucléaires et participent à la régulation du transport nucléo-

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cytoplasmique. De récentes démonstrations des rôles de nucléoporines données dans de multiples paradigmes de différentiation par l'intermédiaire de modes d'action indépendants des échanges nucléaires correspondent à des avancées conceptuelles dans la compréhension des contributions de nucléoporines au développement de la cellule. Parmi celles-là, on a établi que les nucléoporines jouent un rôle fonctionnel dans la santé de la reproduction et la gamétogenèse, observations appuyées par des modèles et des études cliniques robustes qui tirent profit de la puissance de nouvelles générations de technologies de séquençage en vue de déceler des mutations de nucléoporines spécifiques associées à des maladies de la reproduction. Le bon fonctionnement des nucléoporines se manifeste de différentes manières au cours de l'ovogenèse et de la spermatogenèse. Cependant, les modèles de gamétogenèse non humains pourraient ne pas reprendre les modes d'action chez l'humain, ce qui pourrait contrecarrer l'interprétation et la pertinence translationnelles. En vue de contourner ces limites, relever des pathologies reproductives chez les patients, en association avec de nouvelles générations d'approches de séquençage et des outils informatiques évolués, offre une approche puissante pour l'étude d'éventuelles fonctions des nucléoporines dans la reproduction humaine. Ultimement, élucider le rôle des nucléoporines dans la biologie de la reproduction fournira l'occasion d'établir des stratégies prédictives, diagnostiques et thérapeutiques en vue de s'attaquer aux troubles de la reproduction.

Keywords

nucleoporins; oogenesis; spermatogenesis; nuclear pore complex; reproduction

Mots-clés:

nucléoporines; ovogenèse; spermatogenèse; complexe des pores nucléaires; reproduction

Introduction

Mounting evidence supports the paradigm of specific nucleoporins as noncanonical epigenomic regulators of differentiation and disease (Capelson and Hetzer 2009; Ibarra et al. 2016). Alternative to their role as facilitators of nucleocytoplasmic traffic, nucleoporins exert direct and indirect effects at genomic and transcriptomic levels to secure diverse cell fates (Gomez-Cavazos and Hetzer 2015; Jacinto et al. 2015; Raices and D'Angelo 2012). Genetic and biochemical studies have identified germline and gametogenic robustness dependent on nucleoporin stability (Akiyama et al. 2013; Park et al. 2016), underscored by gonadal expression and cellular localization dynamics during reproduc tive development (Popken et al. 2016). These observations reinforce the hypothesis that nucleoporin (dys)functions underlie metazoan reproductive biology (Weinberg-Shukron et al. 2015), and the precise mechanisms of how nucleoporins accomplish this is a rich area of investigation.

Nucleoporins

Nucleoporins are a class of specialized proteins that form the nuclear pore complex (NPC), a macromolecular structure that is highly conserved from yeast to higher eukaryotes (Beck and Hurt 2017). The NPC mediates a GTP-facilitated molecular transport mechanism that

shuttles cargoes >40 kDa in size between the nuclear and cytosolic compartments (Gomez-Cavazos and Hetzer 2015). These cargoes include different classes of RNA molecules and proteins that utilize distinct receptor-mediated mechanisms of transport. The variety of nuclear transport receptors, i.e., karyopherins, that control trafficking participates in an intricate process that integrates soluble transport machinery, e.g., karyopherins, RanGTPase, RanGEF, with the nuclear envelope-localized NPC to regulate gene expression (Ritterhoff et al. 2016; Yaseen and Blobel 1999).

The NPC has been shown to be evolutionarily conserved and although the general mechanism of how molecules move through the pore is well understood, precise details of molecular transit are still uncharacterized (von Appen and Beck 2016). Structurally, the NPC is composed of approximately 30 discrete nucleoporins constitutively organized to create well-defined cytoplasmic, inner, and nuclear regions within the NPC (Fig. 1) (Beck and Hurt 2017; von Appen and Beck 2016). Within these regions, multiple copies of nucleoporins are stacked and linked together to form subcomplexes to establish NPC domains critical for nuclear transport. Molecular cargo then interacts with sites at the cytoplasmic face or with the nuclear basket structure of the NPC prior to transiting through the central channel (Fig. 1).

Role of nucleoporins in development

Individual nucleoporins have demonstrated gene regulation of pluripotency independent of their canonical role in architectural support and facilitated transport functions of the NPC (Gomez-Cavazos and Hetzer 2015). For example, analysis of an embryonic stem (ES) cell line deficient in the NPC inner ring subcomplex nucleoporin, Nup155, revealed global dysregulation of gene expression in *Nup155* compromised ES cells (Preston et al. 2018). Abnormal gene over- and under-expression in the *Nup155*-insufficient ES cell line led to reprioritized functional gene ontologies that included membrane biology and RNA metabolism. Furthermore, the splicing factor *Srsf2* was identified as essential to the overall architecture of a cardiogenic gene subnetwork (Preston et al. 2018). Previous work in which conditional knockout of *Srsf2* in ventricular tissue leads to poor calcium handling upon increased pacing has been reported (Ding et al. 2004), in line with the effects observed on contractile embryoid bodies derived from *Nup155*-deficient ES cells (Preston et al. 2018). This is supported by earlier observations of a clinical mutation for *NUP155* associated with incidences of sudden cardiac death in a consanguineous pediatric cohort (Zhang et al. 2008).

Independent work examining direct regulatory interactions of nucleoporins with chromatin support the observed effects of nucleoporin deficiency on transcriptome remodeling. In a study that looked at the nuclear basket nucleoporin Nup153 and its potential to regulate gene expression by interacting directly with chromatin, discrete sites of Nup153 enrichment were found throughout the genome at specific intergenic super enhancer regions (Ibarra et al. 2016). Furthermore, these interactions with these super enhancer regions occurred at the nuclear periphery, supported by previous evidence indicating gene regulatory functions of NPC at the nuclear envelope (Popken et al. 2016). These NPC proximal and distal regulatory modalities suggest that discrete nucleoporins can facilitate gene regulation, and that

regulation in the context of cell fate specification is more dynamic and intricate than first anticipated.

In addition to direct interactions with chromatin, nucleoporins may exert regulatory effects on developmental programming through indirect mechanisms. In a study conducted on mouse ES cells, it was observed that pluripotency was maintained by polycomb-repressive complex 1 (Prc1) recruitment to multiple and specific transcriptional start sites via Nup153 (Jacinto et al. 2015). Furthermore, *Nup153* was downregulated during constitutive neural differentiation, whereas *Nup153* knockout mice maintained high levels of multiple ectodermal markers that prevented neurogenesis, precluding cellular ability to acquire terminal identity (Jacinto et al. 2015).

A dramatic example of nonstandard roles for nucleoporins in differentiation was observed for gp210 in skeletal muscle differentiation (Gomez-Cavazos and Hetzer 2015). In these experiments, gp210 depletion led to endoplasmic reticulum stress suggested to be the primary catalyst for C2C12 myogenesis. It was hypothesized that components within the endoplasmic reticulum lumen, contiguous with the periplasmic space of the nuclear envelope, mediated cell fate commitment in response to physiological stress detected by the endoplasmic reticulum.

Overall, these studies demonstrate multiple modalities by which nucleoporins may contribute to development. Within this emerging area of research, studies of nucleoporins and their roles in reproductive development are a resurgent and exciting field. The new state of knowledge regarding noncanonical functions of nucleoporins in regulatory development provides unprecedented opportunities to study the role of nucleoporins in reproductive biology and physiology. Here, we highlight current knowledge regarding nucleoporin function in reproductive development in female and male animal models.

Roles of nucleoporins in gametogenesis

Gametogenesis is the main biological process in reproductive development, where diploid precursor cells differentiate and develop into mature haploid gametes with either an X or Y chromo-some (Spiller and Bowles 2015). In eukaryotes, gametogenesis is completed through meiosis, and proceeds into 2 different forms dependent on sex. In females, the production of ova is called oogenesis (Fig. 2), while the corresponding production of spermatozoa in males is known as spermatogenesis (Fig. 3) (Saitou and Miyauchi 2016; Spiller and Bowles 2015). The molecular mechanisms behind these processes and related meiotic disorders have been studied for several decades (Martin 2008), and the emergence of new technologies and conceptual advances facilitates characterization of novel aspects of gametogenic development.

Nucleoporins and their association with reproductive development was first implicated by reports in various *Drosophila* and *Xenopus* models. Feldherr and colleagues suggested that NPC size determines macromolecular transport efficiency during oogenesis (Feldherr et al. 1998), while mutations in *Nup154*, the homo-logue of *Nup155* in *Drosophila*, was reported to have negative impacts on *Drosophila* gametogenesis (Colozza et al. 2011; Gigliotti et al.

1998). Most recently, Nup50 was identified as a necessary factor for survival of primordial germ cells critical for both sexes (Park et al. 2016). Importantly, select nucleoporins have been observed to regulate gametogenesis and gonadal differentiation in a sex-specific manner, with a variety of molecular mechanisms underlying phenotype.

Nucleoporins in oogenesis

In most eukaryotes, oogenesis comprises 3 distinct sequential sub-processes: oocytogenesis, ootidogenesis, and maturation into an ovum (Fig. 2). Despite the overarching stepwise process in eukaryotes, mechanisms behind oogenesis vary among species, i.e., human and *Drosophila* oogenesis (Figs. 2A and 2B) (Avilés-Pagán and Orr-Weaver 2018; Nakamura et al. 2011). It is known that lifetime production of ova in most mammals is significantly smaller than in genera like *Xenopus* and *Drosophila*, where hundreds to thousands of eggs can be produced and released simultaneously.

Studies of *Drosophila* oogenesis (Fig. 2B) provided some of the first evidence of a role for nucleoporins in female gametogenesis. For example, Gigliotti and colleagues studied 2 mutant *Nup154* alleles of lesser or greater severity, *tlp1* and *tlp2*, respectively, and their roles in oogenesis and spermatogenesis (Gigliotti et al. 1998). Both mutations caused several abnormalities during gametogenesis, resulting in alterations of egg chambers, abnormal cell body morphology, and lack of chorionic dorsal appendages, all of which contributed to reproductive disorders that included incomplete sterility, diminished oocyte production, and decreased rates of fertilization (Gigliotti et al. 1998). Another study demonstrated that *Nup154* mutation in oogenesis exhibited abnormal sub-cortical F-actin organization in mutated egg chambers during early stages of *Drosophila* oogenesis, along with alterations in late stage initiation of apoptosis (Riparbelli et al. 2007). This is in line with the understanding of actin as an essential factor for maturing oocytes (Clarke 2017; Mogessie and Schuh 2017).

Changes in NPC size as well as rate and quality of macromolecular nuclear transport occurs in oocytes during various stages of development (Feldherr et al. 1998). These alterations were linked to a key nuclear transport factor, p10, that exhibited elevated concentrations in early stage oocytes compared with mature oocytes, which were suggested to account for NPC size dependent differences in transport (Feldherr et al. 1998). It is important to note that p10 serves as a translocating factor that binds discretely to p62 nucleoporin (Nup62) as well as to the central channel complex containing p62, Nup58, and Nup54 on the cytoplasmic region of the NPC (Lane et al. 2000).

The nucleoporin Seh1, and its interactions with missing oocyte (Mio), was identified as critical to securing and maintaining normal meiosis and oocyte fate during *Drosophila* oogenesis (Senger et al. 2011). It was demonstrated that Mio and Seh1, a component of the Nup107-containing Y complex that is an essential subcomponent of the NPC (Hayashi et al. 2016), were crucial in the development of mature ovum, but were expendable for somatic development.

Nucleoporins in spermatogenesis

Spermatogenesis produces mature spermatozoa from spermatogenic germ cells by mitotic and meiotic divisions, and can be divided into distinct subprocesses: spermatocytogenesis, spermatidogenesis, and spermiogenesis (Fig. 3). However, in comparison with oogenesis, the interspecies differences in spermatogenesis are less apparent, as depicted in a comparison between human and *Drosophila* spermatogenesis (Figs. 3A and 3B).

Dynamics of the NPC are believed to play a role in later stages of sperm maturation and (or) fertilization, based on the observation of a global redistribution of NPCs to the redundant nuclear envelope compartment in developing spermatids in a mouse model (Ho 2010). At the level of the individual nucleoporins, a subset have been associated with spermatogenic disorders, with strong testis-specific mRNA and (or) protein enrichment (Cho et al. 2009; Whiley et al. 2012). The results from a study by Gigliotti and colleagues on *Nup154* mutation in *Drosophila* identified severe spermatogenic defects compared with effects on oogenesis (Gigliotti et al. 1998), where complete sterility, greatly diminished testis size, and developmental arrest of spermatocytes was observed. In another *Drosophila* model of male meiosis, the Y subcomplex, composed of Nup37, Nup43, Nup85, Nup96, Nup107, Nup133, Nup160, Sec13, Seh1, and Elys, regulated nuclear lamin integrity essential for meiotic cytokinesis (Hayashi et al. 2016). Disruptions of other nucleoporins have also been reported to have consequences on sperm development. Tmem48/Ndc1 is a major nucleoporin that mediates interaction of the NPC with the nuclear membrane (Akiyama et al. 2013). Recently, the interaction between Tmem48/ Ndc1 and Sept12 was observed to be essential for mammalian spermiogenesis (Lai et al. 2016). In this work, Ndc1 demonstrates a capacity to regulate distribution of Sept12 that regulates sperm head and tail development.

The essential contribution of proper nucleoporin function to gametogenesis thus manifests in sex-specific manners. Understanding the diverse roles of nucleoporin function at the molecular level is critical for translational interpretation, as nonhuman models of gametogenesis may not precisely recapitulate human mechanisms. In spite of these limitations, the combination of patient cohorts exhibiting reproductive disorders paired with advanced high throughput sequencing technology and bioinformatic tools for deep data mining provides a powerful alternative to investigate the potential function of nucleoporins in human reproduction.

Translational relevance

As described earlier in this review, the Y subcomplex is a key feature of the NPC scaffold whose individual components have been associated with reproductive disorders in the clinic as well as in models at the bench. For example, independent work identified a missense D447N mutation in Nup107 in 4 female patients diagnosed with XX-gonadal dysgenesis who were members of an extended consanguineous family (Weinberg-Shukron et al. 2015). XX-ovarian dysgenesis is an uncommon disorder in humans characterized by nonfunctional streak ovaries and, when modeled in *Drosophila*, the authors observed outcomes that included abnormal oogenesis with structurally abnormal egg shells and egg chambers that resulted in almost complete infertility (Weinberg-Shukron et al. 2015).

Beyond gametogenesis, nucleoporins may be associated with human implantation. In one study, complete colocalization of Nup153 and Nup62, and partial colocalization of Tpr with nucleolar channel systems were observed (Guffanti et al. 2008). The nucleolar channel system is a well-characterized and transient feature of postovulation endometrium (Kittur et al. 2007), and the study by Guffanti et al. was the first demonstration of nucleoporin localization to the nucleolar channel system. The notion that nucleoporin-containing nucleolar channel systemss are key markers and possible contributors to proper implantation and uterine receptivity is supported by the results of a prospective study that discovered enrichment of FG nucleoporins following controlled ovarian hyperstimulation (Zapantis et al. 2013).

These examples of essential and constitutive roles for nucleoporins in gametogenesis (Table 1) establish a precedence for other regulatory functions for nucleoporins in reproductive development. With the increased recognition of individual nucleoporins able to regulate gene expression via differential genome binding and transcriptome remodeling (Pascual-Garcia et al. 2017), the use of advanced next generation sequencing tools can achieve greater depths of analysis and investigation into the systems-level role that nucleoporins may play in reproductive health.

Leveraging high throughput technologies to address reproductive disorders

Next generation sequencing accelerates current understanding of global molecular dynamics underlying development (Faustino et al. 2008; Preston et al. 2018), and has emerged as an invaluable and versatile tool with the ability to identify rare genetic changes (Smith et al. 2007). Application of this technology is valuable for basic and clinical research and provides unique insights into system wide epigenomic and (or) transcriptome remodeling that occurs under normal and diseased conditions (Ernst et al. 2017; Wyles et al. 2015; Zhang et al. 2017).

These techniques have provided the foundation to design novel, robust, and sensitive cost-effective tools for clinical diagnosis. For example, preimplantation genetic screening leverages the advantage of next generation sequencing and bioinformatic analysis to enhance precision at reduced overhead (Fiorentino et al. 2014). Another important clinical use has been screening patients for novel sources of infertility (Bramble et al. 2016). In this study, whole exome sequencing was applied to interrogate the genome of a patient with primary ovarian failure and infertility. A loss-of-function N408Y mutation in the follicle stimulating hormone (FSH) receptor that rendered the patient insensitive to FSH stimulation was identified by this approach. Another application of whole exome sequencing helped identify gene candidate variants and potential underlying mechanisms afflicting an otherwise healthy 34-year-old woman who experienced 18 consecutive miscarriages (Filges et al. 2015). Comprehensive whole genome se quencing was used to interrogate the prevalence of de novo gametogenic mutations in 816 parent–offspring trios that defined parent-of-origin specific molecular signatures, as well as identified differing mutational mechanisms for spermatogenesis versus oogenesis (Goldmann et al. 2016). In an impressive demonstration

of next generation sequencing at high resolution, single cell transcriptomes were analyzed to map developmental trajectories of individual human fetal germ cells and their gonadal niche cells (Li et al. 2017). These powerful sequencing approaches generate deep multi-dimensional data sets in basic and clinical research that must be parsed using bioinformatics (Hawkins et al. 2010). The availability of a variety of open source in silico tools makes such investigation accessible to researchers, which can be used to identify trends in genome dynamics and transcriptome remodeling underlying normal and dysfunctional reproductive development.

Indeed, methodologies that characterize global epigenomic or transcriptomic remodeling have identified noncanonical epigenomic regulatory functions for various nucleoporins in multiple model systems. Pioneering high throughput and chromatin immunoprecipitation studies in *Drosophila* established the precedence for regulatory chromatin binding and gene expression roles for Sec13 and Nup98, both of which activate specific gene subsets in a developmentally regulated manner, independent of the NPC and the nuclear envelope (Capelson et al. 2010). In support of this functional capacity for Nup98, genomic, transcriptomic, and proteomic work investigating epigenomic regulation of hematopoiesis identified Nup98 as critical for hematopoietic histone recruitment (Franks et al. 2017). In another example, high throughput gene expression profiling studies from Raices et al. complemented and corroborated earlier proteomic work by Hansson et al. showing that Nup210 was critical for pluripotency and myogenesis (Hansson et al. 2012; Raices et al. 2017). Epigenomic roles for nucleoporins have been implicated for cardio-genesis, through RNA-seq and network biology analyses applied to a *Nup155*-compromised stem cell line that gives rise to rhythmically impaired cardiomyocytes (Preston et al. 2018). In this study, the authors demonstrated that dysregulated gene expression with reprioritization of multiple functional ontologies occurred downstream of *Nup155* disruption, with impairment of proper calcium handling and potential impacts on elements of the cardiac conduction system. Thus, these high throughput investigations are essential in defining the global impact of nucleoporins, and are relevant when consideration is given to the recognized systems-level functions of nucleoporins on development and disease (Capelson and Hetzer 2009).

Extant chromatin occupancy work has linked nucleoporin biology to chromatin wide-silencing and super enhancer access in the context of stem cell fate and identity (Ibarra et al. 2016; Ruben et al. 2011). Insights into this functional modality for nucleoporins in the context of reproductive physiology was first provided by early studies that observed specific interactions of Nup153 with the *Drosophila* genome (Vaquerizas et al. 2010). These nucleoporin-DNA areas were termed "Nucleoporin-Associated Regions", or NARs, that regulated X-chromosome dosage compensation. Most recently, clinical studies linking mutant *Nup107* to ovarian development demonstrates that other nucleoporins may be involved in reproductive development (Ren et al. 2018; Weinberg-Shukron et al. 2015), and are clear examples of exciting and emerging data in the nascent field of nucleoporin-regulated reproductive development.

Summary and future directions

The precedence for human reproduction to be regulated by discrete nucleoporins independent of their role in nucleocytoplasmic transport is supported by recent clinical evidence of nucleoporin mutations as the underlying cause for dysfunctional gonadogenesis. It is possible that nucleoporins possess sexually dimorphic phenotypes in this regard, with specific nucleoporins preferentially or exclusively contributing to proper oogenesis or spermatogenesis. Furthermore, the capacity to capture the underlying molecular etiology of reproductive disorders that arise from nucleoporin mutation is possible with a depth and precision facilitated by advanced next generation sequencing technologies. In the future, applications of these technologies in the clinical setting, with nucleoporins as an alternative marker/target to guide diagnosis, treatment, and resolution of abnormal gametogenesis and (or) gonadogenesis, may offer refined and personalized approaches to address reproductive disorders and infertility.

Acknowledgements

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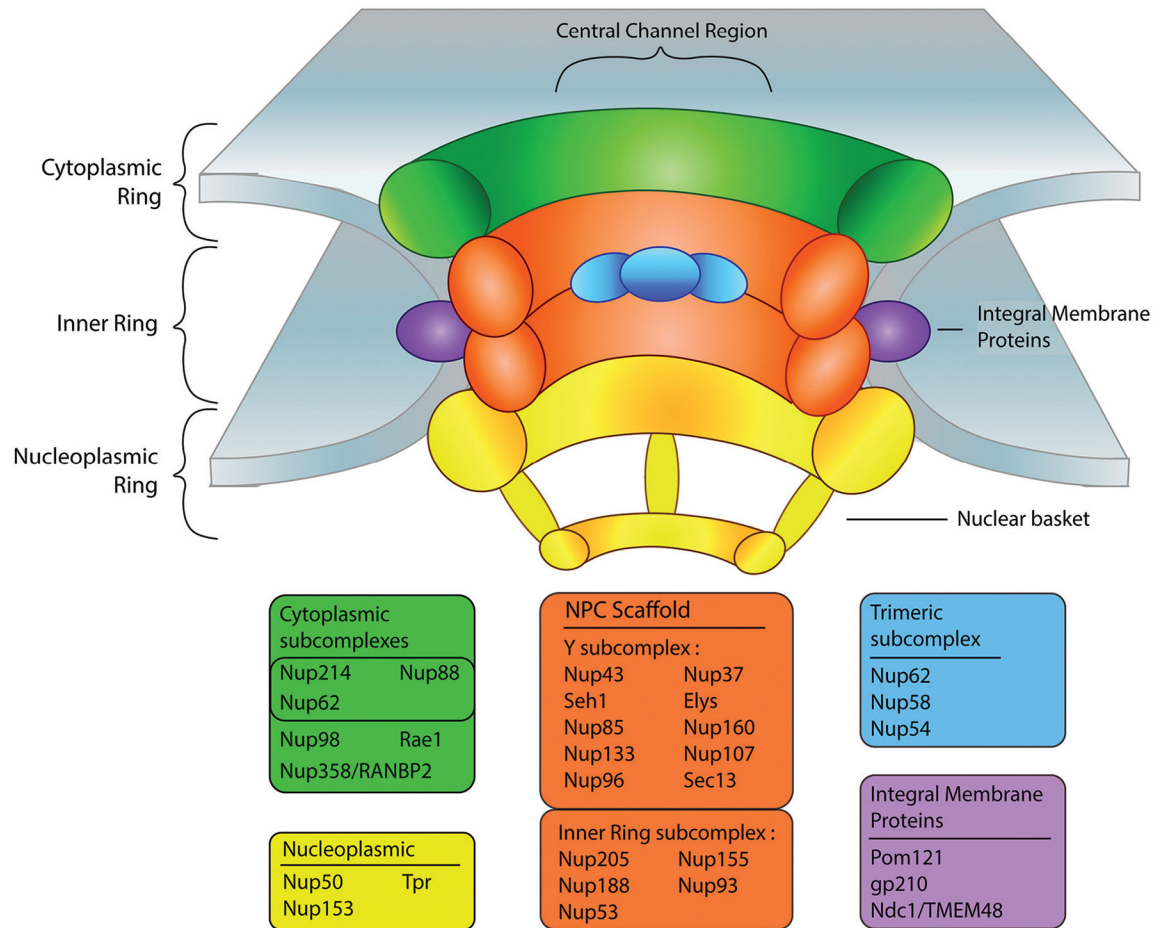
Nuclear Pore Complex

Fig. 1.

Nuclear pore complex (NPC) structural components. Illustration of the different regions that comprise the NPC: cytoplasmic, nucleoplasmic, and inner rings. Multiple copies of nucleoporins assemble within these regions in a stack-like manner forming subcomplexes. The nucleoporins are separated into corresponding color-coded boxes that signify each subcomplex and their localization within the NPC. Elys, embryonic large molecule derived from yolk sac; gp210, nuclear pore membrane glycoprotein 210; Nup, nucleoporin; Rae1, ribonucleic acid export 1; RANBP2, Ran binding protein 2; Pom121, nuclear envelope pore membrane protein of 121 kDa; TMEM48, transmembrane protein 48; Tpr, translocated promoter region.
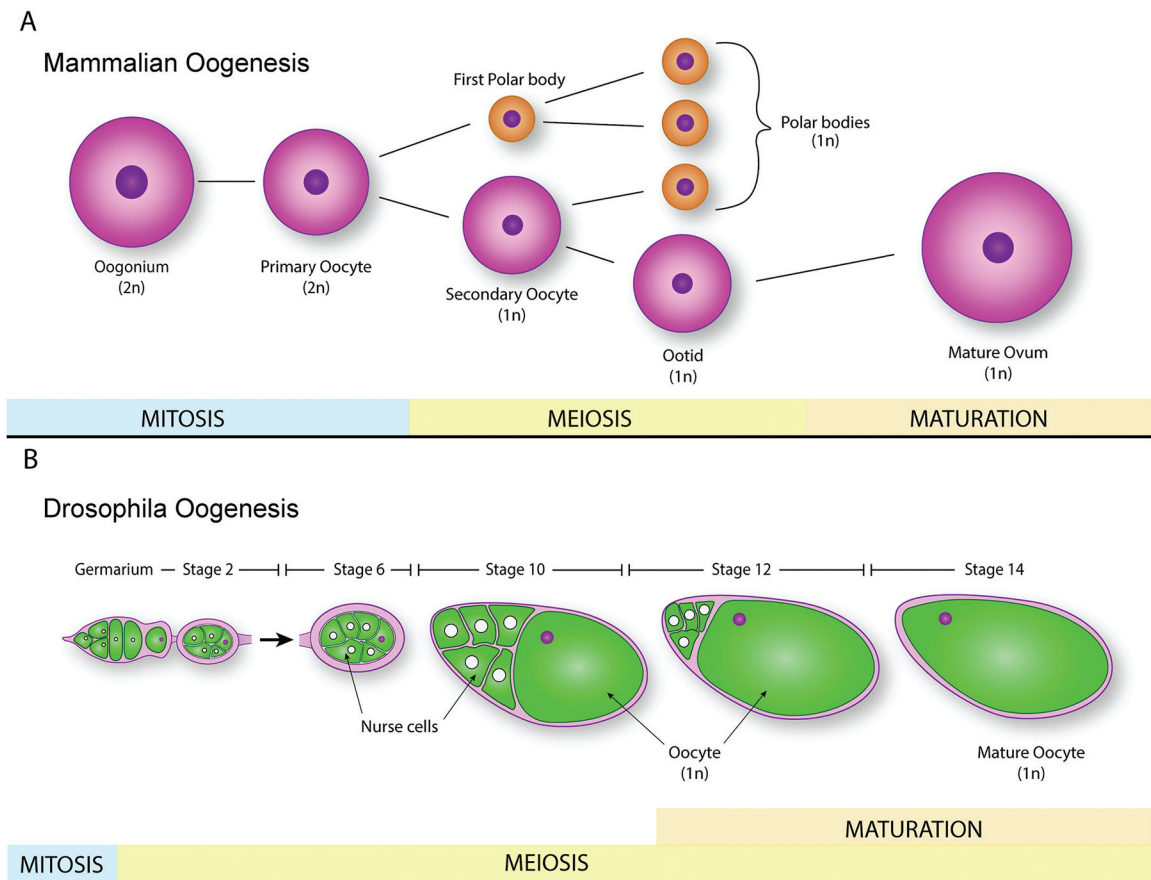
Fig. 2.
Mammalian and *Drosophila* oogenesis. (A) Schematic representation of mammalian oogenesis from oogonium to mature ovum, depicting mitosis, meiosis, and maturation stages. (B) *Drosophila* oogenesis schematic representation, where initiation of the oocyte maturation occurs during meiosis (depicted here as overlapping of maturation and meiotic stages). 2n, diploid cells; 1n, haploid cells.
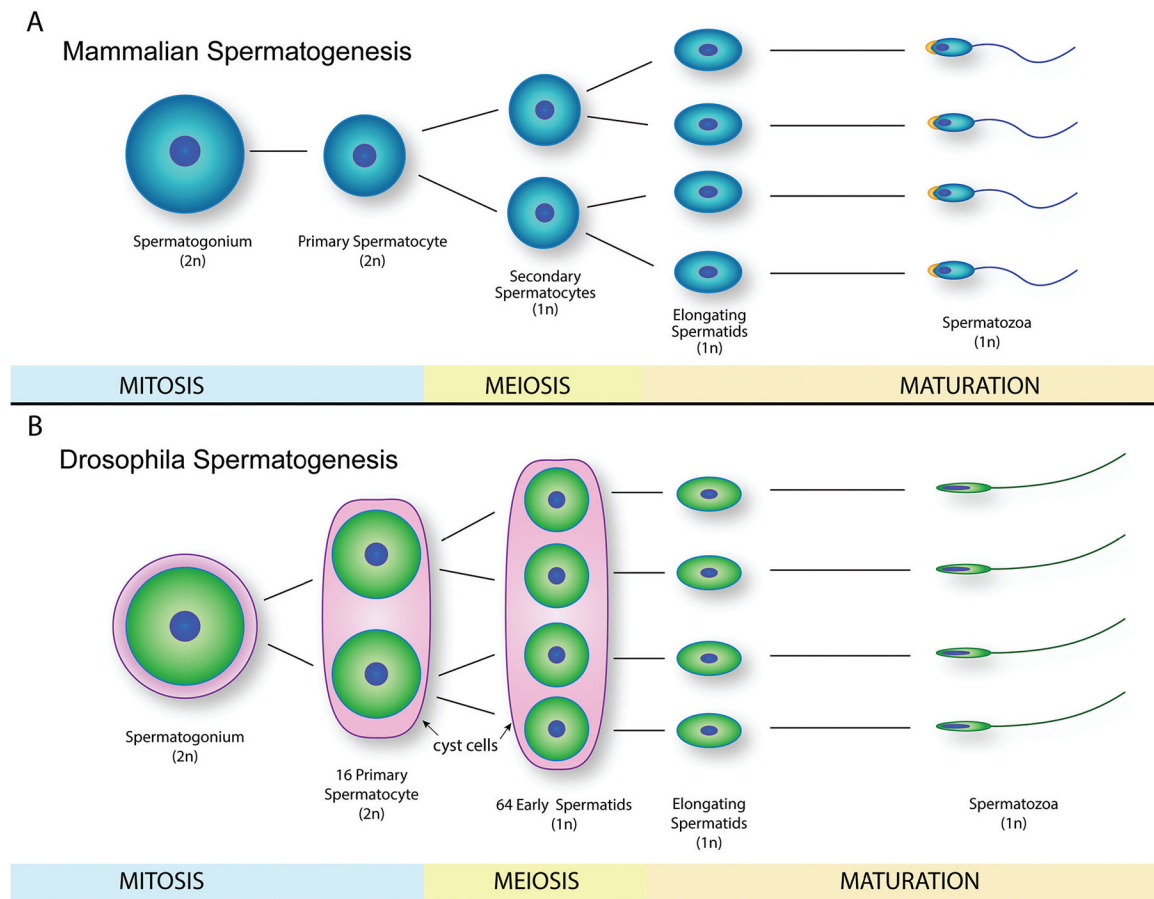
Fig. 3.
Mammalian and *Drosophila* spermatogenesis. (A) Schematic representation of mammalian spermatogenesis from spermatogonium to spermatozoa, depicting mitosis, meiosis, and maturation stages. (B) *Drosophila* spermatogenesis schematic representation, where spermatozoa have a more elongated nucleus and lack of acrosome region when compared with mammalian spermatozoa. 2n, diploid cells; 1n, haploid cells.

Table 1.

Nucleoporin-associated alterations and disorders in male and female reproduction.

Nucleoporin	Alteration	Model	Associated alterations in reproduction	Reference
AAAS	$Aaas^{-/-}$	Mice	Female sterility with alterations in meiosis, diminished quality of mature oocytes, low fertility rates, and halted development after fertilization.	Carvalhal et al. 2017
Elys	X-linked CG14215, Elys mutant strains	*Drosophila*	Female sterility, alterations in zygote viability with disruption of mitotic progression.	Hirai et al. 2018
Nup50	$Nup50^{-/-}$	Mice	Impaired development of primordial germ cells in both males and females.	Park et al. 2016
Nup107	Missense D447N mutation	Human and *Drosophila*	Human XX-gonadal dysgenesis; in *Drosophila* model, females had abnormalities in egg shells, egg chambers, nurse cells, accompanied by cell death and sterility.	Weinberg-Shukron et al. 2015
Nup107-Nup160 complex	*UAS-Nup107 RNAi*	*Drosophila*	Abnormality in nuclear lamina in male spermatocytes with impaired meiosis and cytokinesis.	Hayashi et al. 2016
Nup154	P-element induced mutation l(2)01501: *tlp1* and *tlp2*	*Drosophila*	Females had alterations in egg chamber development, low oocyte production, and decreased rates of fertilization. In males, alterations in cyst formation, spermatocyte proliferation, and meiotic progression with developmental arrest of spermatocytes.	Gigliotti et al. 1998
Nup154	*tlp1* mutant	*Drosophila*	Females had abnormal organization of actin filaments egg chambers with defective nurse cell dumping and delayed apoptosis.	Riparbelli et al. 2007
Nup154	*tlp1* mutant	*Drosophila*	Males exhibited increased apoptosis and reduced proliferation of germ cells, as well as alteration in meiosis and differentiation during spermatogenesis.	Colozza et al. 2011
Ndc1/TMEM48	Exon-trapped *Tmem48*	Mice	TMEM48-associated spermatogenesis arrest at prophase of meiosis I.	Akiyama et al. 2013
Ndc1	SEPT12D197N mutation	Mice	Ndc1 modulates SEPT12 localization in male germ cell line. SEPT12-Ndc1-complex associated alterations during sperm head and tail formation.	Lai et al. 2016
Seh1	$Seh1^{A15}$, $Seh1^{A86}$ deletions	*Drosophila*	*Drosophila* females had diminished egg chambers, oocyte production, and lower hatching rate. Interaction of Seh1 with Mio is crucial for the development of mature ovum.	Senger et al. 2011

Note: AAAS, aladin WD repeat nucleoporin; Elys, embryonic large molecule derived from yolk sac; Mio, missing oocyte; Ndc1, Ndc1 transmembrane protein; Nup, nucleoporin; TMEM48, transmembrane protein 48; tlp, tulipano mutation; SEPT12, septin 12.