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Review

Nucleocytoplasmic transport as a driver of mammalian gametogenesis

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ABSTRACT

Adult fertility requires appropriate and coordinated instruction of somatic and germ cell activity during lineage specification, development and maturation. Driven by alterations in the complement of nuclear proteins such as transcription factors and chromatin remodelling components, these events proceed by sequential changes in gene expression in response to a myriad of signalling cues. Controlled access of proteins to the nucleus is a key driver of developmental switches. This review discusses key examples of regulated nucleocytoplasmic transport during mammalian gametogenesis and the mechanisms underpinning these transport events, focusing on examples critical for the establishment of fertility.

Contents

Abbreviations: ACT, activator of CREM in the testis; AR, androgen receptor; CREB, cyclic AMP response element binding protein; CREM, cyclic AMP response element modulator; dpc, days post coitum; dpp, days post partum; Hh, hedgehog; IMP, importin; NES, nuclear export signal; NLS, nuclear localizing signal; NPC, nuclear pore complex; NUP, nucleoporin; PGC, primordial germ cell; PKA, protein kinase A; TGFβ, transforming growth factor beta.

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1. Introduction—regulated nuclear transport in gametogenesis

Developmental switches that drive undifferentiated cells into specific lineages and enable their subsequent maturation require changes in gene expression and nuclear architecture. These are accomplished by a shift in nuclear protein composition, including those which package DNA (such as histones), proteins which modify transcriptional activity through alterations in chromatin structure (e.g. histone deacetylases, acetyl transferases and methyltransferases) and transcription factors. Nuclear protein composition is influenced by the capacity of nuclear transport machinery to traffic such proteins into and out of the nucleus. Pioneering studies in the nematode and fruitfly revealed the importance of controlled production and activation of both transport components and their cargo during invertebrate gametogenesis [1–4]. This review updates and expands upon our previous examination of unique aspects of nuclear transport activity that feature in mammalian gametogenesis [5]. Building on a model in which the coordinated production of nuclear transport factors and nuclear-acting proteins drives spermatogenesis, we present examples of key developmental switches that orchestrate gamete specification, differentiation and maturation, to enable a new generation to be formed (Fig. 1A).

2. Gametogenesis

2.1. The bipotential germ cell—the first specification event

The primordial germ cell lineage, from which sperm and eggs are ultimately produced, is first specified within the mouse embryo in cells of the proximal epiblast at around 6.25 days post coitum (dpc; Fig. 1B), marked by the expression of *Blimp1* (*Prdm1*) and *Prdm14* [6–11]. Irrevocable commitment to the germ cell lineage occurs by 7.5 dpc, coincident with the onset of Stella expression [12]. Arising outside of the gonad, primordial germ cells continuously proliferate as they migrate to the urogenital ridge where, between 10.5 and 11.5 dpc, they colonize the developing gonad in a bipotential state (reviewed in [13]). Their further commitment into the gender-specific processes of spermatogenesis and oogenesis occurs in response to signals from the somatic environment (reviewed in [14,15]). Much of our knowledge of germ cell specification and differentiation has been gained from studies of rodents, hence the events described below are related to the timing of mouse development (Fig. 1B).

2.2. Spermatogenesis: preparation of the paternal genome for delivery

In a male embryo, testis development starts around 10.5 dpc due to expression within somatic pre-Sertoli cells of *Sry* from the sex-determining region of the Y chromosome [15–17]. A cascade of transcriptional activation events involving increased levels of the Sox9 chromatin remodelling factor programs gonadal somatic cells towards the male phenotype. Testicular cords are formed by these somatic cells, and factors they secrete also direct the germ cells they surround, now termed gonocytes, into the male differentiation pathway (Fig. 1B). Gonocytes proliferate until approximately 14.5 dpc, then rapidly enter mitotic arrest for around 6 days [13,18]. Within 1 day after birth, the gonocytes migrate from the seminiferous cord centre to the periphery and resume proliferation, forming the spermatogonial cell population [19,20]. Some spermatogonia will differentiate to produce mature spermatozoa, while others self-renew and thereby sustain spermatogenesis throughout adulthood [19,21].

The first spermatogenic wave begins around 5 days post partum (dpp). Spermatogonia undergo nuclear division with incomplete cytokinesis, yielding two daughter spermatogonia linked by a cytoplasmic bridge. A precise number of synchronous mitoses generates clones of up to 256 linked spermatogonia [19,22]. These undergo a final DNA synthesis round without an associated nuclear division and thus differentiate into spermatocytes which first appear around 10 dpp. Spermatocytes proceed through the protracted stages of prophase (leptonema, zygonema, pachynema and diplonema) and then complete the two reductive divisions that yield haploid spermatids, first appearing around 20 dpp. As they mature, spermatocytes and spermatids reposition within the seminiferous epithelium, detaching from the basement membrane and moving towards the tubule lumen. These post-mitotic germ cells are entirely dependent upon Sertoli cells for nutritional and developmental cues, as they are no longer in direct contact with vasculature or lymphatics [23].

Spermiogenesis constitutes the morphogenesis of haploid male germ cells into spermatozoa. Each initially round spermatid develops a flagellum, an acrosome (a Golgi-derived organelle) and unique head morphology which are characteristic for each species. Transcription ceases in elongating spermatids as the nucleus and genomic DNA condense and residual cytoplasm is eliminated. Extensive nuclear changes during this period involve removal and replacement of the majority of histones, first with transition proteins and then protamines, creating the unique arrangement of DNA in sperm [24]. Nascent spermatozoa separate from clonal siblings only upon release into the seminiferous tubule lumen, moving to the excurrent ducts [23,25] for subsequent transfer into the female tract at ejaculation.

The first wave of spermatogenesis in juveniles coincides with the final maturation stages of the somatic Sertoli cells which surround and nurture all germ cells. Although the general progression of germ cell differentiation is consistent between the first wave and ongoing adult spermatogenesis, some features are unique (reviewed in [26]), owing partially to the distinct growth factor and hormone signalling milieu at each developmental age.

2.3. Oogenesis

The absence of *Sry* synthesis in the fetal female gonad enables resident primordial germ cells to differentiate into oogonia which proliferate until 13.5 dpc. Stimulated by retinoic acid produced in the adjacent mesonephros, they enter meiosis I and arrest at diplotene, enveloped by the somatic pre-granulosa cells in follicles. Now termed oocytes, they remain quiescent for an extended period and then undergo a dramatic growth phase in which a vast pool of maternal mRNAs and proteins is made and stored. From puberty,