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Review article

Perspectives on mammalian chromatoid body research☆

Rita Luiza Peruquetti*

Health Science Center, University Sagrado Coração (USC), Bauru, São Paulo, Brazil

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ABSTRACT

Several genetic and epigenetic events that take place in the nucleus (i.e. meiotic recombination, meiotic silencing, chromatin reorganization and histone replacement) are crucial for the spermatogenesis process, as well as, is the assembling of cytoplasmic bodies (or chromatoid bodies). In this minireview, we give special attention to the most recent research approaches involved in the molecular structure and physiology of the chromatoid body (CB). Though it was described several decades ago, the CB is still a very intriguing cytoplasmic structure of male germ cells. It plays roles in the most important steps of the spermatozoon formation, such as mRNA regulation, smallRNA-mediated gene control, and cell communication among round spermatids. Studies that have been done on the CB largely focus on two main topics: (1) CB proteome, in this minireview focused on '*Evidences linking the nucleolar cycle and the CB assembling; and Circadian proteins found in the CB*'; and (2) CB transcriptome, in this minireview focused on '*miRNAs and piRNAs pathways; and X but not Y chromosome transcripts enriching the CB*'. Herein, we described the most relevant results produced in each of these subjects in order to clarify the main physiological role played by this intriguing cytoplasmic structure in the germ cells of male mammals, which though long since described, still fascinates researchers in the field.

Contents

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* Correspondence to: Health Science Center, University Sagrado Coração, Bauru, São Paulo, Zip Code: 17011-160, Brazil. Tel.: +55 14 3204 7112.
E-mail address: rita.peruquetti@usc.br

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1. Important features of germ cells

Meiotic cell cycle is an essential and fascinating event important for the survival and evolution of sexually reproductive species because it assures the completion of gametogenesis (Handel and Schimenti, 2010). Development of both male and female germ cells is controlled by unique gene expression programs. These programs involve genetic events and epigenetic reprogramming, such as histone modifications and DNA methylation (reviewed by Kota and Feil, 2010; Meikar et al., 2013). One of the most important genetic events that take place during gametogenesis is meiotic recombination provided by the crossover between paired regions of homologous chromosomes. The unpaired regions of these homologous chromosomes do not undergo crossover, and they are inactivated by a mechanism known as meiotic silencing (Hess, 1999). Thus, mammals meiotic division will make the generation of new diploid organisms possible. These new organisms are genetically different from their parents due to meiotic recombination cluster into narrow segments of the genome, defined as hotspots (Baudat et al., 2010). In addition to these genetic events, there are several epigenetic programs that determine the success of the meiotic cell cycle. The most well described epigenetic event during spermatogenesis is the intense chromatin reorganization, which involves DNA methylation and other covalent chromatin modifications. These epigenetic modifications allow early germ cells to suppress somatic cell differentiation in order to prepare for entrance into the meiotic cell cycle (Kota and Feil, 2010; Meikar et al., 2013). These chromatin reprogramming events ensure the appropriate expression of germline-specific genes, a process which contributes to the maintenance of chromosome integrity and meiosis, and they also prepare the genome for gene expression in the embryo (Kimmins and Sassone-Corsi, 2005). In addition to these common events that occur in both male and female germ cells, there are some specific events for each germ cell line. After meiosis II, male germ cells, which are called round spermatids at that stage, differentiate into mature spermatozoon. During this remarkable remodeling process in mammalian male germ cells, there is an incorporation of histones by H1, H2A, H2B, and H3 histone variants, as well as an acquisition of acetylation on the N-terminal lysines of histone H4. All of these alterations seem to make the chromatin more accessible. Subsequently, histone proteins are replaced by small basic proteins known as transition nuclear proteins (TNPs), and they are replaced by protamine proteins during later stages (Kota and Feil, 2010; Meikar et al., 2013; Hess, 1999; Kimmins and Sassone-Corsi, 2005). The replacement of histones by protamines is essential for postmeiotic male germ differentiation, and it also seems to help in the protection of the sperm genome against damages induced by mutagens (Rathke et al., 2010). However, some fragments of the sperm genome do not incorporate the histone variants, which in turn make the histone replacement in these fragments impossible. This phenomenon may play a role in conferring paternal epigenetic information to the zygote (Govin et al., 2007). Thus, these epigenetic modifications can be transmitted to the embryo and may contribute to their appropriate developmental gene expression (Kota and Feil, 2010). Underscored by these epigenetic alterations in the sperm nucleus is the relationship between the sperm development and male fertility, since sperm samples from subfertile individuals with sperm abnormalities and unusually high histone contents are frequently detected in humans. This may have a direct effect on the transmission of epigenetic information (Ramos et al., 2008).

Germ cell differentiation takes place during the entire life cycle of mammals. Differentiating germ cells drastically change their morphology, their expression profiles, and also the number and morphology of their cellular bodies. In addition to the relevant genetic and epigenetic reprogramming that occurs during germ cell differentiation, there is also a variety of cellular organelles present in the nucleus and in the cytoplasm during the different phases of germ cell development that are critical for germ cell differentiation. These organelles include the female Barr body, polar bodies, and Balbiani body, as well as the male chromatoid body (CB) (Lopes and Roelen, 2010). The CB was described 130 years ago as one of the six types of 'nuage' specific for germ cells. 'Nuages' are enriched by several proteic and non proteic components including RNA helicases, and the CB accumulates both 'nuage' and non 'nuage' components (Yokota, 2012). The CB is an irregularly-shaped cytoplasmic granule that is visible in pachytene spermatocytes and round spermatids. Its number in spermatocytes varies, but it is a single granule in mouse and rat spermatids. In round spermatids, the CB is a dynamic granule that moves actively within the vicinity of the nuclear pores. During spermiogenesis, however, the CB moves caudally to the base of the flagellum at the opposite site of the acrosome region, where it disperses or it is degraded. The CB does not have an encircling membrane, but it is surrounded by several small vesicles. To date, all the evidence available has supported the idea of a role for this intriguing structure in mRNA regulation and smallRNA-mediated gene control (Kotaja and Sassone-Corsi, 2007; Nagamori and Sassone-Corsi, 2008; Meikar et al., 2011). In addition, recent findings indicate that microRNA (miRNA) and RNA decay pathways that play a crucial role in the completion of spermatogenesis (Meikar et al., 2013; Yadav and Kotaja, 2014) converge to the CB (Kotaja and Sassone-Corsi, 2007; Nagamori and Sassone-Corsi, 2008; Meikar et al., 2011). Although most evidences point for the role that CB could play for mRNA regulation during the spermatogenesis a review by Kleene and Cullinane (2011) put this question at a glance. The authors state that they have found no convincing evidence that silenced mRNAs are localized exclusively in the CB. This discrepancy could be due to experimental artifacts or to CB working more as a center for mRNP remodeling and export to other cytoplasmic sites than as storage for repressed mRNA (Kleene and Cullinane, 2011).

Addressing the question regarding the functions that CB could play during the spermatogenesis process researchers in the field produced some mice models showing ablation of some proteins that are indispensable for CB assembly, such as the ATP-dependent DEAD-box RNA helicase VASA (or MVH–mouse VASA homologue) (Toyooka et al., 2000), and the mouse Argonaute/PIWI family RNA-binding proteins (MIWI) (Deng and Lin, 2002). Those ablations