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Testicular miRNAs in relation to spermatogenesis, spermatogonial stem cells and cancer/testis genes

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ABSTRACT

The process of spermatogenesis in human involves three organized biological processes, through which spermatogonia cells undergo mitosis, meiosis and finally differentiation into mature spermatozoa. Spermatogenesis requires a specifically regulated gene expression patterns. The microRNAs are a novel class of post-transcriptional regulators that have been reported to be involved in so many cellular processes including spermatogenesis, in which microRNAs are expressed in a stage-specific manner. Specific microRNAs are involved in the process of spermatogenesis and they have been identified to regulate and renew spermatogonia stem cell as well as been implicated in cancer biology regarding their effect in regulation of some of the cancer/testis genes.

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Introduction

Spermatogenesis is the process by which spermatozoa, are produced within the epithelium of highly convoluted seminiferous tubules inside the testis [1]. It begins during post-natal life same time when spermatogonial stem cells enter the differentiation pathway [2]. Colony expansion of the differentiating germ cells occurs when differentiating spermatogonia undergo successive mitotic divisions [3]. After colonial expansion phase, germ cells enter the five sub stages of long-lasting meiotic prophase I as spermatocytes during which homologous chromosomes pair to form synaptonemal complex and homologous recombination occurs [4]. Subsequently, spermatocytes undergo a second meiotic division called reduction division to separate the sister chromosomes into two cells to generate secondary spermatocytes, however secondary cells are short lived as they divide again very quickly to generate four haploid round spermatids that initiates the spermiogenesis phase. Spermiogenesis phase entails the formation of sperm-specific structures, nucleus reshaping and compaction of the chromatin via the replacement of histone with sperm-specific protamines [5]. Finally the mature spermatozoa are released into the seminiferous tubular lumen through the process of spermiation [6]. Anatomically the seminiferous epithelium is structured into cyclic stages at a specific phase of spermatogenesis that are identifiable by groups of germ cell types through the

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cross-sectional area of the tubule. There are 12 cyclic stages usually labeled I–XII that have been identified in mice, 6 stages in man and 12 stages also in monkeys, all arranged in a coherent order of developmental progression [7].

Finally, the complex process of spermatogenesis is also under the control of the secretion of hypothalamic-pituitary-gonadal secretions like gonadotropin-releasing hormone regulates the release of two important hormones, Follicle stimulating hormone and Luteinizing hormone from the anterior pituitary gland, which are both responsible for the stimulation of interstitial Leydig cells to produce T-cells or to regulate Sertoli cells [8].

Spermatogenesis requires a high level of meticulous and temporally regulated gene expression patterns governed by transcriptional, post-transcriptional and epigenetic processes [9]. Numerous protein coding genes have been reported to be involved in the process of spermatogenesis [10,11]. However, the underlying mechanisms are yet to be fully understood.

MicroRNAs (miRNAs) are evolutionary conserved, short single-stranded non-coding RNA sequences ranging from 19 to 24 nucleotides that post-transcriptionally regulate up to 60% of protein encoding genes by binding to complementary sequences in the 3′ untranslated region of messenger RNA transcripts, to prevent translation [12]. They are responsible for endogenously regulating gene expression at the post transcriptional level via translation repression or mRNA degradation. MicroRNAs are critical controllers of cell differentiation and functions, mediating a several cellular processes including those integral to spermatogenesis. In addition, they have also been implicated in the pathogenesis of several diseases like Alzheimer [13], cerebral malaria [14], malaria [15] prostate cancer [16]. Research studies have demonstrated that small RNAs including miRNAs are extensively involved in male germ cell differentiation and development [17,18] and as well are transcribed during spermatogenesis. The miRNAs are differentially expressed in a cell-specific and step-specific manner [19,20]. In this mini-review, we will give a comprehensive report on the role of miRNAs in the regulation of spermatogenesis and the related consequences.

Biogenesis of miRNA

Normal progression of the process of spermatogenesis depends on precise regulated gene expression. According to miRNA database (http://www.mirbase.org), there are 1881 miRNA loci that have been identified in the human genome making up of 1% of the total human genomes [21]. miRNAs are considered by several researchers as important regulatory factors that are responsible for the control and regulation of the expression of a wide range of protein-coding genes and regulatory mechanisms of these miRNAs occur at epigenetic and transcriptional levels. It should be noted that meiotic cells are synthesizing sites for numerous spermiogenic proteins mRNAs and are translationally regulated and momentarily stored until further stages of spermatogenesis when they are needed. The mechanism of regulation of the miRNAs function is largely post-transcriptionally via the modification of the stability of their target mRNAs [22,23]. Castellano and co-workers reported that the miRNA genes are located in the intergenic regions of the mammalian genome [24]. In addition, recent and previous research works have demonstrated that small fraction of the transcribed human genome encodes for proteins [25] as such large fraction of the RNA transcripts are non-coding, however these non-coding RNAs have been implicated in several important cellular functions. In 2012, Rinn and Chang demonstrated that these non-coding RNAs have an important role in the regulation and control of gene expression, both functioning at transcriptional and post-transcriptional levels [25].

The transcribing process of most miRNAs are done by the enzyme RNAPol II [26] which serves as hairpin loop precursors and are acted upon by a nuclear microprocessor complex, that is made up of RNase III enzyme (Drosha) and the double-stranded RNA-binding protein DGCR8 (DiGeorge syndrome critical region 8 gene). DGCR8 is responsible for identifying the RNA substrate and Drosha performs the function of an endonuclease enzyme [27]

Yadav and colleagues reported that the male germ cells have shown to express different classes of small RNAs, that include Dicer- independent PIWI-interacting RNAs, Dicer-dependent miRNAs and endogenous small interfering RNA (siRNA) (endo-siRNAs) [28].

Several researchers have reported the miRNA profiling of an immature sertoli cells via techniques like sequencing, microarray, reverse transcriptase-PCR [29,30,31] and the expression of these miRNA are regulated by male sex hormone called androgen [32,33]. However these miRNA are differently expressed in the testis but are also responsible for regulating the various genes expressed within the Sertoli cells as such the male sex hormone plays a vital role in regulating and controlling the process of spermatogenesis via miRNA-dependent process [32].

Functions of miRNAs as a spermatogonial stem cell regulators

The Y-chromosome has been identified as the trigger behind the development of the testis through its gene Y-chromosomal testis-determining gene, SRY [34]. Expression of this gene within the precursors of the supporting cell or Sertoli cells of the genital ridge initiates series of events that leads to the differentiation of testis-specific cell types [35]. The testicular cords are formed by Sertoli cells located and surrounded by primordial germ cells, that later differentiates into gonocytes and peritubular cells [36]. Furthermore gonocytes cells are earlier undergo a rapid mitotic division but are later arrested in the G_0 phase of cell cycle, where they remain inactive and differentiate into spermatogonia after birth [37]. The seminiferous tubules are basically made up of two compartments namely: basal compartment and adluminal compartment, the basal compartment houses the spermatogonial stem cells (SSCs) and are responsible for the maintenance of the stem cell pool by undergoing self-renewal divisions. The regulation of spermatogonial stem cells status is among the functions of the

miRNAs and as a matter of fact some specific miRNA has been identified to be preferentially expressed in spermatogonial stem cells namely: miR-2, miR-34c, miR-182, miR-183, and miR-146a via a high-throughput sequencing technique.

Niu and co-worker reported that the inhibition of miR-21 in SSC-enriched germ cell cultures resulted in apoptosis of germ cells [38], suggesting that miR-21 plays a vital role in sustaining spermatogonial stem cell population. miR-20 and miR-106a though preferentially expressed in spermatogonial stem cells have also been identified to be responsible for the targeting Stat3 and Ccnd1 [39]. In addition, Huszar and colleague also reported that miR-146 which is highly expressed in undifferentiated spermatogonia cell can be down-regulated by retinoic acid-induced differentiation of spermatogonia and they suggested that miR-146 may be involved in the regulation and control of retinoid acid-induced spermatogonial differentiation in the mouse [40]. There are other groups of miRNAs that have been identified to specifically on X-chromosomes involved in the maintenance of an undifferentiated status of spermatogonia called the X-chromosomes clustered miR-221 and miR-222 [41].

Furthermore, Yang and co-worker reported cases of loss of stem cell differentiation abilities after impaired functions of miR-221/miR-222 [41]. The deletion of Mir-17-92 cluster led to reports of small testes, oligospermial within the epididymis in mice by Tong and colleagues [42]. However, the authors also reported that deletion of Mir-17-92 cluster also resulted in high expression of another miRNA named miR-106b-25, suggesting an inversely proportional expression relationship between these two clusters [42]. However not all miRNA increases the differentiation of spermatogonia stem cells, few of them like the let-7 family miR- NAs, have been demonstrated to have a contrasting and opposite expression effects, that can be triggered by retinoic acid stimulation and differentiation followed by down-regulation of Mycn, Ccnd1, and Colla2 which are all let-7 family targets [43].

Expression profiling of testicular miRNAs

Several studies have demonstrated that multiple miRNAs are expressed exclusively in both human and mice testis or germ cells through the use of profiling techniques like miRNA microarrays, RT-PCR, or small RNA sequencing [44,45,46]. Yang and colleagues reported 770 known and five novel miRNAs in normal human testes via Solexa sequencing technology [41]. Through microarray analysis, it was reported that most miRNAs are differently expressed in meiotic germ cells [47]. The expression of miRNAs arrays varies between mature and immature testes in human which was corroborated by Yan and colleague when they reported the detection of 14 expressed and 5 less-expressed miRNAs in immature testes when compared with adult testes [48]. Table 1 shows summarized expression profile of miRNAs in testis.

miRNA and spermatogonial stem cell renewal

The process of spermatogenesis is initiated from spermatogonial stem cells (SSCs), which can either continue to replicate to ensure a constant supply of spermatogonia to initiate spermatogenesis as spermatogonial A dark or as spermatogonial A pale to undergo differentiation into a spermatogonial progenitor and mitotically divides into Type B cells [49,50,51,52,53]. van den Driesche and co-workers reported that constant supply of spermatozoa depends on striking a balance between the process of self- renewal and differentiation of spermatogonial stem cells by sustaining and conserving a populace of undifferentiated spermatogonial stem cells [52]. miRNAs, serves as an important endogenous regulator in mammalian cells and as such regulates the fate of SSCs during spermatogenesis. Several researchers have reported the expression of numerous miRNAs in THY1-enriched undifferentiated spermatogonia and they include miR17–92 cluster [42], miR290–295 cluster [54,55], miR146 [40], miR20 [39], miR106a [39], miR221, and miR222 [41]. Kotaja reported the under expression of these miRNAs during retinoic acid-induced spermatogonial differentiation suggesting their critical role in regulating the process of proliferation and differentiation of SSCs during spermatogenesis [56]. Table 2 shows summary of miRNAs linked to the maintenance of pluripotency in germ cells.

The role of miRNAs in spermatocytogenesis and spermiogenesis

Spermatocytogenesis and spermiogenesis are important and crucial cellular processes to germ cells in the male. High transcriptional activity but reduced translational activities are the properties of the phases of Spermatocytogenesis. According to Kotaja, control of gene expression after transcription process is an important feature of spermatogenesis in mammals [56]. He also reported that numerous miRNAs are differently expressed by spermatocytes and spermatids and are important in regulating meiotic and post-meiotic gene expression [56]. See Table 3 summarizes some important miRNAs that play a regulatory role in spermatocyte meiosis and spermiogenesis.

Testicular miRNAs and Cancer/ Testis genes

Cancer/Testis genes (CT genes) are a group of testis specific genes which are tumor-associated and immunogenic antigens and are abnormally expressed in human tumors. Based on their in vivo immunogenicity and tumor-restricted expression pattern, CT genes are known as potential targets for tumor-specific immunotherapeutic targets and developing cancer vaccines [57]. Most of CT genes express both during spermatogenesis and tumor growth, so the testicular miRNAs may influence the target genes in cancer cells as well.

Table 1
Expression profile of miRNAs in testis. Culled and modified from Wang and Xu [18].

Location	Expression	References
Mouse testis	29 miRNAs were identified as novel out of 141 detected miRNAs from the mouse testis	[44]
Human testis	Through Solexa sequencing technology, 770 known and 5 novel human miRNAs were detected.	[74]
Saanen dairy goat testis Immature and mature testes (mouse)	91 novel paired miRNAs were detected and 14 were expressed and 5 non-expressed miRNAs were found in the immature testis compared with the adult testis	[75,48]
Immature and mature testes (pig)	51 miRNAs were significantly expressed and 78 miRNAs were less expressed in mature testes	[76]
Testis tissue from the immature rhesus monkey, mature rhesus monkey, and mature human	26 miRNAs were shared by the IR and MR, and the IR and MH.	[77]
Mouse spermatogonia	In the neonatal mice spermatogonia cells, both miR17–92 and miR290–295 clusters were found to be enriched	[78]
Human spermatozoa	68 small RNAs have been identified.	[79]
Spermatozoa of patients with varicocele	In patients with varicocele compared with the control group, miR15a was significantly down regulated.	[80]
Testes of patients with non-obstructive azoospermia and normal human testes	In patients with non-obstructive azoospermia, 154 differentially down-regulated and 19 up-regulated miRNAs were found.	[81]
Human spermatozoa in patients with different spermatogenic impairments	50 expressed and 27 less expressed miRNAs were found in asthenozoospermic males while 42 expressed and 44 less expressed miRNAs were found in oligoasthenozoospermic males compared with normozoospermic males	[82]
Cryptorchid and normal testes	In a mouse with cryptorchid testes, miR135a was expressed at a reduced level.	[83]
Human testicular tissues of infertile men with different histopathological patterns	Samples from Sertoli cell only, mixed atrophy, and germ cell arrest groups, contains a total of 197, 68, and 46 miRNAs respectively when compared with normal spermatogenesis	[84]

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Table 2
miRNAs implicated in maintenance of pluripotency in germ cells. Culled from Wang and Xu [18].

miRNA	Expression	Targets gene	References
miR17–92 cluster	THY1^{+}-enriched undifferentiated spermatogonia	Bcl2l11, Kit, Socs3, and Stat3	[42]
miR106b-25	THY1^{+}-enriched undifferentiated spermatogonia	Bcl2l11, Kit, Socs3, and Stat3	[42]
miR290–295 cluster	Highly enriched in the germ cell population of the 6-day-old testis, multipotent adult germ cells, and embryonic stem cell	Stat3 and Ccnd1	[54]
miR146	Highly expressed in undifferentiated spermatogonia	Med1	[40]
miR221 and miR222	THY1^{+}-enriched undifferentiated spermatogonia		[41]
miR20 and miR106a miR21	Spermatogonial stem cells.	P12	[39,38]
miR135a	Spermatogonial stem cells.	Foxo1	[83]
miR302-367 cluster	Primordial germ cells, ES cells	NR2F2	[85]
miR376a	Less expressed in mature mouse testes	CDK2 and AGO2	[86]
miR302 cluster	Overexpressed in adult (undifferentiated) and pediatric germ cell tumors	NR2F2	[85]
miR335 and miR367	Less expressed in mature mouse testes and Embryonal carcinoma, ES cells	CCNT2, CCD2, RSBN1, RUNX2, LATS2, KLF4, RUNX1, SYNJ1, and SMAD6	[87,88]

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Synaptonemal complex proteins (SYCP) help homologous chromosome pairs to join in the process of homologous recombination in meiosis. SYCP3 is known as a cancer testis gene as well, with over expression in different cancers such as breast cancer [58,59]. There are reports on the effects of miRNAs to control their expression in some spermatogenic stages [60].

Opa interacting protein 5 (OIP5) which show testicular expression is upregulated in some types of human cancers such as acute myeloid leukemia [61] and breast cancer [62]. Li H et al. reported that OIP5 is a target for miR-15b-5p which

Table 3
miRNAs that play a regulatory role in spermatocyte meiosis and spermiogenesis. Culled from Wang and Xu [18]

miRNAs	Expression	Targets	Functions	References
miR449	Expressed in mature rhesus monkey and mouse testis, differently expressed in mouse testes and limited to spermatocytes and spermatids	MECP2, ASB1, BCL2, NOTCH1, CASP2, KITLG, VCL, FOXJ2, INHBB, SOX11, CCNE2, GMFB, and DLL1	Suppresses the proliferation of a germ cell line, GC-1spg	[89]
miR34a	Expressed in mature mouse testis, up-regulated from day 7 to day 14 in mouse testis	CCND2, BLC2, GMFB, and SIRT1	Suppresses proliferation, promotes apoptosis	[45,90]
miR34b	Expressed in mature rhesus monkey testis, up-regulated from day 7 to day 14 in mouse testis	NOTCH1, LGR4, VEZT, MAN2A2, and FOXJ2	Regulates the germ cell proliferation and survival	[91]
miR34c	Highly expressed in isolated pachytene spermatocytes and round spermatids	CCND3, CCNG1, CCNB1, CCNC, CCNE1, CDK4, CDK6, E2F5, FOS, CDC2, TGIF2, NOTCH2, STRBP LGR4 KLF4, NOTCH1 PPP1CC, GALT, KITLG, SPAG4, CCNL, ZFP148, and GMFB	Cycle regulator, promoted mGSC apoptosis, SSC differentiation, enhances the germinal phenotype of cells already committed to this lineage	[92,93]
miR184	Localized to the germ cells of mouse testis	Ncor2	Promotes the proliferation of a germ cell line, GC-1spg	[75]
miR24	Pachytene spermatocytes	MBD6 and H2AX	Potential role in meiosis	[47]
miR214	Mainly expressed in pachytene spermatocytes	WDTC1, heat shock proteins	Potential role in meiosis	[47]
miR320	Expressed in all germ cells	Protocadherins	Cell adhesions	[47]
miR18	Highly expressed in spermatocytes	HSF2	Male germ cell maturation	[94]
miR122a	Enriched in late-stage male germ cells	TNP2	Regulates the chromatin	[95]
miR355	Up-regulated in adult testis	Rsbn1	Transcriptional regulation in haploid germ cells	[48]
miR181b	Up-regulated in adult testis	Rsbn1	Transcriptional regulation in haploid germ cells	[54,48]
miR181c	Up-regulated in adult testis	Sox5, Sox6, and Rsbn1	Transcriptional regulation in haploid germ cells	[54,48]
miR185	Preferentially expressed in pachytene spermatocytes	RHOA and CDC42	Cell cycle regulator	[47]
miR191	Highly expressed in testis, preferentially expressed in beta pachytene spermatocytes, down- regulated in teratozoospermia	BNC2	Required for normal sperm morphology	[47]

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regulates hepatocellular carcinoma growth and metastasis, through the AKT/mTORC1 and β-catenin signaling pathways [63]. Zeng H et al. reported that breast cancer progression inhibits by targeting SOX2 via upregulation of miRNA-129-5p, when downregulation of lncRNA OIP5-AS1 occurs [64].

The Testis Specific Gene A10 (TSGA10) is localized in sperm tail as a fibrous sheath protein. The expression pattern suggests that TSGA10 may be involved in active cell division, differentiation, and migration [65]. Expression of Tsga10, as a gene with critical function in spermatogenesis, increases in 6.6 folds during transition from meiotic to post-meiotic phase [66]. TSGA10 has close interaction with hypoxia inducible factor (HIF-1α) and increased expression of TSGA10 correlated with decreased HIF-1α transcriptional activity which ends to inhibition of angiogenesis as well as invasion characteristics in HeLa cells [67]. Aberrantly expression of TSGA10 is reported in several cancers such as acute lymphoblastic leukemia [68], breast cancer [69] and bladder carcinoma [70]. Bao L et al. reported that angiogenesis mediates by repressing TSGA10 as a novel target gene, by metastasis-associated miR-23a, from nasopharyngeal carcinoma-derived exosomes [71]. Yuan X et al. suggested two binding sites for miR-577 at the 3′UTR of the TSGA10 and in interactions of MiR-577 and TSGA10 regulates esophageal squamous cell carcinoma [72].

Tumor suppressor function of miRNA-874 via targeting Cancer/Testis gene HCA587/MAGE-C2 is reported by J Cancer et al. HCA587/MAGE-C2 plays an active role in tumorigenesis by promoting the growth and survival of tumor cells. Overexpression of miR-874, as well as HCA587/MAGE-C2 silencing, resulted in suppression of tumor cell proliferation and invasion [73]

Conclusion

Several studies have successfully demonstrated the clinical and biological importance of miRNAs in the regulation of spermatogenesis; however, their expression still remains phase and cell specific which plays a significant feature in regulating the process of spermatogenesis. Future in-depth studies about the phase and cell specific expression of miRNAs during spermatogenesis are still required in either human or rat testes as it would unravel the missing links of etiology of male infertility and thereby leading to possible potential diagnosis and treatment of male infertility and the wide aspects of spermatogonial stem cells as well as their application in cancer/testis gens biology. Application of single-cell small RNA sequencing could accurately profile the miRNAs for specific type of germ cells. Furthermore, the use of CRISPR/cas9 system to knock out specific spermatogenesis related gene would help unravel the mechanism underlying the role of miRNA in spermatogenesis.

CRediT authorship contribution statement

Maryam Beigom Mobasheri: Writing - original draft, Validation. **Kehinde Adebayo Babatunde:** Writing - original draft, Validation.

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Conflict of interest

All authors declared no conflict of interest.

Supplementary materials

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