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The role of microRNAs in mammalian oocytes and embryos☆

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ABSTRACT

Advanced genomic analysis has revealed an enormous inventory of non-coding RNAs (ncRNAs), which are functionally important at transcriptional and post-transcriptional level for different cellular processes. Among the ncRNAs, microRNAs (miRNAs) have recently been highlighted extensively for their pivotal role in disease, fertility and development through post-transcriptional regulation of gene expression. The presence and spatio-temporal expression of miRNAs and miRNA processing machinery genes in oocytes and preimplantation embryos has evidenced the involvement of miRNAs for growth and maturation of mammalian oocytes, early embryonic development, stem cell lineage differentiation and implantation. Therefore, this article aims to highlight primary evidences on the importance of miRNAs and their mediated translational reprogramming in the physiology and development of mammalian oocytes and embryos.

1. Introduction

Advances in the analysis of human and other higher eukaryotic genomes have disclosed a large fraction of the genetic material (ca 98%) which does not code for proteins (Adams et al., 2000). Major portion of this non-coding genome is in fact transcribed into an enormous repertoire of functional non coding RNA molecules (ncRNAs) rather than encoding any proteins. Recent fascinating and fast progress in bioinformatic, high-throughput sequencing and other biochemical approaches have fuelled rapid growth in our appreciation of the tremendous number, diversity and biological importance of these ncRNAs in gene regulation both at transcriptional and post-transcriptional level. Based on their size, ncRNAs could be broadly categorized into three classes namely, microRNAs (miRNAs, ~20 nucleotides), small RNAs (25–200 nucleotides) and macro ncRNAs (≥200 nucleotides). Among the ncRNAs, microRNAs (miRNAs) have revolutionized our understanding of eukaryotic gene expression as an integral part of gene regulatory networks. MiRNAs are estimated to comprise 1–5% of animal genes (Bartel, 2004; Bentwich et al., 2005; Berezikov et al., 2005) or a given genome could encode nearly thousands of miRNAs (Bentwich et al., 2005). Moreover, a typical miRNA could be involved in regulation of hundreds of target genes (Brennecke et al., 2005; Krek et al., 2005; Lewis et al., 2005; Xie et al., 2005) and altogether they could target up to 30% of the human genome (Lim et al., 2005). Changes in the expression of even a single miRNA found to have a significant impact on the outcome of diverse cellular activities.

MiRNAs have shown to play a pivotal role in disease, fertility and development (Lau et al., 2001; Lai, 2003; Ambros, 2004; Bartel, 2004; Alvarez-Garcia and Miska, 2005; Plasterk, 2006; Chen and Rajewsky, 2007). Inhibition of miRNA biogenesis has been found to result in developmental arrest in mouse and fish (Bernstein et al., 2003; Wienholds et al., 2003; Giraldez et al., 2005) and female infertility in mouse (Otsuka et al., 2007, 2008). They are found to be potentially involved in the physiological regulation of reproductive tissues and cells, including embryonic development. The precise translational

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regulation of mRNAs in oocyte and embryonic development are dictated and controlled by the combination of key elements on the untranslated regions and other post-transcriptional regulatory factors (Brevini et al., 2007). By the nature of binding to 3′ untranslated region and silencing mRNAs at post-transcriptional level, miRNAs could be involved in translational programming. Thus, differential expression of miRNAs might be temporally associated with oocyte maturation in early embryonic development (Biemar et al., 2005; Watanabe et al., 2005; Tang et al., 2007). However, this is just beginning to elucidate the role of miRNAs in the cellular mechanisms that influence subsequent oocyte and embryonic growth and development. Here, we review the recent works regarding miRNAs focusing on their diverse roles in the physiology and development of mammalian oocyte and early embryos.

2. miRNA biogenesis and mechanism of miRNA mediated gene regulation

Most miRNA are transcribed by RNA polymerase II (Pol II) as a primary transcript called 'primary miRNA' (pri-miRNA). These pri-miRNAs can range from several hundred nucleotides to tens of kilobases (Cai et al., 2004; Lee et al., 2004). Like mRNAs, the pri-miRNAs contain 5′ cap polyadenylated structures,and may also be spliced (Bracht et al., 2004; Cai et al., 2004). Moreover, the transcript of pri-miRNAs are found to have a hairpin structure of 60–120 nt long with a mature miRNA in one of the two strands (Fig. 1). The pri-miRNA is further processed and cleaved by the microprocessor, a multi-core protein complex composed of RNAse III enzyme Drosha and the double-stranded RNA binding domain (dsRBD) protein DGCR8/Pasha (Lee et al., 2003; Denli et al., 2004; Gregory et al., 2004; Han et al., 2004; Landthaler et al., 2004). The resulting precursor miRNA (pre-miRNA) is transported to the cytoplasm via Exportin-5. This pre-miRNA further cleaved by RNAse III enzyme, Dicer, which interacts with the dsRBD proteins TRBP to generate the mature ~22 nt miRNA:miRNA* duplex (Hutvagner et al., 2001; Ketting et al., 2001; Lee et al., 2003; Chendrimada et al., 2005; Forstemann et al., 2005; Jiang et al., 2005; Saito et al., 2005; Lee et al., 2006). Subsequently, TRBP/Loquacious recruits the argonaute (Ago) proteins and together with Dicer they form a complex that initiates the assembly of the RNA-induced silencing complex (RISC), a ribonucleoprotein (RNP) complex (Gregory et al., 2005; Maniataki and Mourelatos, 2005).

In addition to Dicer, an alternative pathway mediated by argonaute 2 (Ago2) has been proposed to be involved in microRNA biogenesis from the pre-miRNA hairpin to the mature functional miRNA (Diederichs and Haber, 2007). Here, Ago2 has been found to have an essential nonredundant slicer-independent function within the mammalian miRNA pathway (O'Carroll et al., 2007). Ago2-mediated pre-miRNA cleavage has been observed in the processing of miRNAs derived from the 5′-arm of the pre-miRNA hairpin having no mismatches at the immediate cleavage site (Han et al., 2006; Diederichs and Haber, 2007). So, Ago2-mediated cleavage of pre-miRNAs, followed by uridylation and trimming, generates functional miRNAs independent of Dicer (Cifuentes et al., 2010).

Following cleavage by Dicer, one of the strands of the miRNA duplex incorporated into RISC guides to complementary 3′ untranslated region of mRNA to seed sequence resulting in inhibition of mRNA translation (Pillai et al., 2005) (Fig. 1). Blocking the translation of mRNAs occurs through either interaction of RISC with eukaryotic translation initiation factor 6, which prevents assembly of 18s ribosomes (Chendrimada et al., 2007), or through inhibition of translation after initiation (Jackson and Standart, 2007). Depending on the degree of complementarity between the miRNA and the target sequence, mRNAs are either cleaved or degraded (perfect or near perfect complementarity) or their translation is repressed (imprecise complementarity) (Hutvagner and Zamore, 2002; Martinez and Tuschl, 2004). In addition, miRNPs can have other effects on targeted mRNAs, including promoting deadenylation, which might result in degradation (increased turnover) (Nilsen, 2007). Those mRNAs, which are repressed by miRNAs, are further stored in the cytoplasmic foci called P-bodies (Liu et al., 2005a,b; Rehwinkel et al., 2005). However, apart from the mRNA degradation or translational inhibition, a forward action of miRNA on mRNA and protein synthesis has been documented. For instance the involvement of miRNAs are reported to be involved in translational enhancement (Vasudevan et al., 2007; Orom et al., 2008) or post-transcriptional activation of gene expression (Mortensen et al., 2011).

3. miRNA in germ cell proliferation and differentiation for oogenesis

Primordial germ cells (PGCs) give rise to germ line stem cells (GSCs) and which upon differentiation undergo oogenesis. Functionality of GSCs for oogenesis requires intrinsic signaling mechanisms and extrinsic signals from neighboring cells. Processing and functioning of PGCs are found to be affected by many factors including miRNAs mediated regulation and miRNA machinery genes (Harris and Macdonald, 2001; Tang et al., 2007; Hayashi et al., 2008; Kaneda et al., 2009). For instance, several conserved miRNA clusters (miR-17–92 cluster and miR-290–295 cluster) which are associated with promoting cell cycle were found to be enriched in PGCs. However, the expression pattern of miR-141, miR-200a, miR-200c and miR-323 were found to be progressively decreased as the PGCs development proceeds (Hayashi et al., 2008). In addition to the miRNAs, the involvement of Dicer during PGCs development has been evidenced. Germ line specific knockouts of Dicer causes the oocytes to be arrested in meiosis I stage, displayed defective and misaligned chromosomal segregation and disorganized spindle formation attachments, decondensed chromatin and anaphase bridges (Murchison et al., 2007). It has been assumed that the defects could be either due to the loss of centromeric repeat derived siRNAs which could prevent the establishment of appropriate centromeric chromatin structure for assembly of the Kinetochore or the loss of miRNAs leading to deregulation of essential gene products. Furthermore, analysis of the transcripts found in developing oocytes lacking Dicer were found to be enriched with genes implicated in microtubule related processes including the predicted miRNA

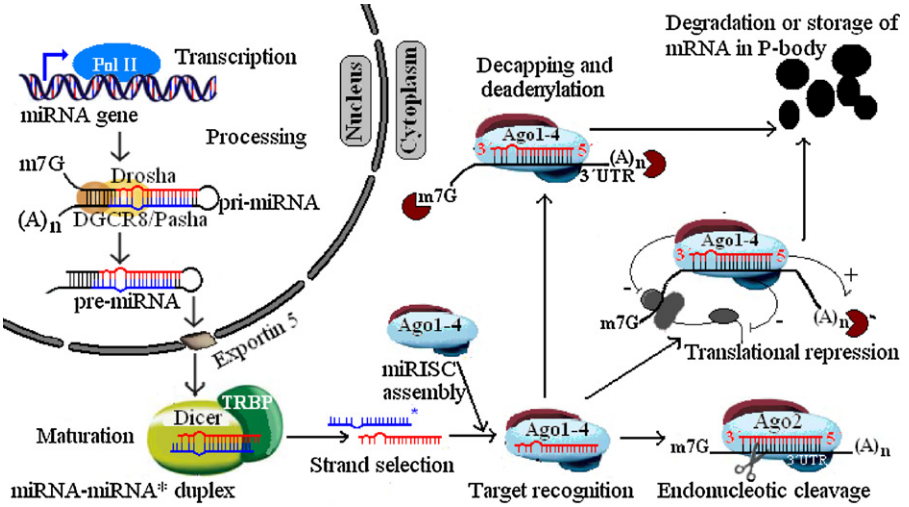

Fig. 1. Biogenesis of miRNAs and their mechanism of gene regulation Figure shows the basic steps in miRNAs biogenetic pathways, which involve transcription of pri-miRNA RNA polymerase II, generation of pre-miRNAs by processing of Drosha in the nucleus, transportation of pre-miRNA into the cytoplasm via exportin and mechanism to process pre-miRNAs into mature functional state of miRNAs. Argonaute proteins 1–4 (Ago1-4), inhibition of initiation of translation (−), Promoting deadenylation (+), 7-methyl-G cap (m7G).

target gene whose activity is known to be directly regulated by the chromosomal condensation (Murchison et al., 2007).

In addition to Dicer, conditional deletion of Ago2 in the developing mouse oocytes revealed abnormal spindles and misaligned chromosomes with ability to develop mature oocyte similar to the phenotype of Dicer-deficient oocytes (Kaneda et al., 2009). This study has suggested that Ago2 plays a key role in global regulation of miRNA stability which have a positive or negative consequence on the gene expression during oocyte development. However, it is apparent that all the miRNAs or genes are not causal to these defects but detail functional analysis of candidate miRNA is still missing for their specific role. Moreover, the mechanism of miRNA mediated meiotic spindle assembly and the establishment of proper meiotic spindle–chromosome interactions during the various stages of meiotic process requires further investigation.

4. miRNAs in relation to oocyte growth, maturation and developmental competence

Development of mammalian oocyte begins during fetal life through proliferation of primordial germ cells by mitosis, Oocytes then progress into the first meiotic prophase that consists of several transient stages. Once an oocyte in the primordial follicle is triggered to grow, it embarks on an intricate effect on numerous molecular and morphological changes on the follicular cells during the process of follicular developmental. In fact these processes are controlled by closely coordinated endocrine and paracrine factors contributed by oocyte and surrounding somatic cells. In turn this process is controlled by multiple genes whose expression and interaction is tightly regulated in oocyte, granulosa and theca cells (Bonnet et al., 2008). Apart from the gene action, oocyte growth and development is also hypothesized to be regulated by miRNAs. For instance, higher expression and functional importance of Dicer1 has been identified in the oocyte during folliculogenesis and in the mature oocytes (Su et al., 2002; Choi et al., 2007; Murchison et al., 2007). Similarly, the role of Dicer1 in mouse ovarian follicle development was explored in another study by using Dicer1 conditional knockout (cKO) mouse ovarian tissue, where follicular development and its related gene expression were comparatively assessed between wild type and Dicer1 cKO mouse ovaries (Lei et al., 2010). The study revealed an important role of Dicer1-regulated miRNA signaling pathway in mouse follicular development through the regulation of follicular cell proliferation, differentiation and apoptosis.

Competency for successful fertilization is usually acquired by the oocyte during the process of meiosis and at the final stage of development during maturation. During the initiation of maturation, large germinal vesicle (GV) breaks down, the decondensed, dispersed and transcriptionally active chromosomes condense (Smith and Richter, 1985) and the, chromosomes loose their transcriptional activity (Masui and Clarke, 1979). Advances in molecular analysis revealed that miRNA could be involved in different processes of oocyte maturation. Importance of miRNA in the maturation of oocyte has initially been evidenced from Dicer knockout or knockdown studies and it has become clear that Dicer is required for meiotic spindle integrity and completion of meiosis I (Murchison et al., 2007). Oocytes lacking Dicer (an enzyme important for biogenesis of miRNAs) were unable to complete meiosis and arrested with multiple defects on meiotic spindle organization and chromosome congression. Depleting Dicer1 in oocytes resulted in the meiotic failure phenotype and revealed that Dicer1-conditioned ooplasm of primary oocytes contains Dicer1-dependent factors that are crucial for chromosome segregation and for the

progression of metaphase to anaphase during meiotic maturation (Mattiske et al., 2009). Another Dicer knockdown study in mouse oocytes identified significant reduction in oocyte maturation with increasing abnormal spindle and chromosomal organization (Liu et al., 2010). In addition, miRNAs, spindle formation proteins (plk1 and AURKA) and spindle check points (Bub1, Bublb) were found to be reduced remarkably. Thus, Dicer and miRNA appeared to play an important role during oogenesis and are essential for completion of meiotic division. However, further study on miRNAs themselves rather than on Dicer alone is needed to elucidate such miRNA mediated regulation of oocyte maturation.

Investigation on the expression of miRNAs in immature and in vitro matured bovine oocytes using heterologous approach revealed a differential expression of 59 miRNAs (Tesfaye et al., 2009). Among them, 31 and 28 miRNAs were found to be preferentially expressed in immature and matured oocytes, respectively. The expression of seven microRNAs (miR-496, miR-297, miR-292-3P, miR-99a, miR-410, miR-145 and miR-515-5p) in matured and two microRNAs (miR-512-5p and miR-214) in immature oocyte showed higher abundance by at least 2-fold difference (Tesfaye et al., 2009). Where, miR-496 (5.2-fold change) and miR-512-5p (2.3-fold change) revealed the higher fold changes up regulation in matured and immature oocytes, respectively. In addition, the expression of miRNAs in fully grown and growing oocytes (selected through BCB staining) by qRT-PCR analysis revealed higher expression of miRNAs in growing (BCB−) oocytes as compared to the fully grown (BCB+) ones (Tesfaye et al., 2009). In addition to bovine, differential expression of miRNAs has also been observed in human oocytes (Xu et al., 2011). Although, all these efforts provide initial evidence for the role of miRNAs in the oocyte development, in depth functional analysis and mechanism of action of individual miRNAs during oocyte growth, development and maturation needs to be further elucidated.

5. miRNAs as paracrine and maternal mRNA translation regulators

Dynamically regulated, complex and coordinated ovarian functions with ultimate goal to produce a competent oocyte include sequential recruitment, selection and growth of the follicles, atresia, ovulation and luteolysis are under control of closely coordinated endocrine and paracrine factors. All these factors are controlled by tightly regulated expression and interaction of a multitude of genes in different compartments of the ovary (Bonnet et al., 2008). Several studies on identification and expression profiling of miRNAs in the ovary have been carried out in different animal species through small RNA library construction and sequencing (Ro et al., 2007; Mishima et al., 2008; Hossain et al., 2009; Ahn et al., 2010). Regardless of species, these studies showed that let-7 family, miR-21, miR-99a, miR-125b, miR-126, miR-143, miR-145 and miR-199b to be most commonly abundant miRNAs in the ovary. Further, bioinformatic prediction and analysis of ovary specific mRNAs targets revealed the presence of several molecular pathways that are believed to be required for ovarian follicular development (Hossain et al., 2009).

Transport of nutrients and paracrine factors between oocytes and cumulus cells through gap junction is essential both for oocyte maturation and somatic cell proliferation (Eppig, 1991; Grazul-Bilska et al., 1997; Tanghe et al., 2002; Gilchrist et al., 2004). Oocyte secreted factors are evident to regulate key cumulus cell functions which in turn enhance subsequent development of the oocytes (Sugiura et al., 2005). Similar to such factors, miRNAs have been shown to be regulated and function in a paracrine manner. Dynamic changes in expression of miRNAs are observed between the oocytes matured with cumulus cells and oocyte matured without cumulus cells. Remarkably, the changes of miRNAs expression were observed in the cumulus cells matured with or without the oocyte cytoplasm (Abd El Naby et al., 2011). Dependency of the two cell types to each other for changing the miRNA expression may be involved in the regulation of genes associated to impaired or normal nuclear maturation of oocytes due to absence or presence of cumulus cell factors, respectively. This implies that the level of miRNAs transcription or mode of transcriptional regulation by the miRNAs in the oocyte or cumulus granulosa cells is dependent on their secreted factors in a paracrine manner. The presence of miRNAs, their differential expression and bioinformatics analysis can give the primary clue for their potential role in ovarian cellular function. However, further functional characterization of these miRNAs in different cell types of ovary (oocyte, granulosa, theca cells and ovarian stroma) for their paracrine regulation at different follicular stage remains to be elucidated.

Translational reprogramming during oogenesis, oocyte growth and maturation involves synthesis and storage of large quantities of dormant mRNAs, spatially restricted protein synthesis, repression of localized mRNAs and finally activation in time for embryonic axis formation. Restraining all the mRNAs by oocyte to establish a new life involves many changes, where miRNAs could be one of the reasons to turnover many maternal transcripts essential for meiotic maturation by promoting deadenylation or degrading mRNA through binding to its 3′ UTR. Several studies provide initial clue for the role of miRNAs in the oocyte and thereby suggested that a large proportion of the maternal genes are directly or indirectly under the control of miRNAs (Murchison et al., 2007; Tang et al., 2007). However, study on the effect of deletion of another miRNAs processing molecules called Dgcr8 and revealed contrasting conclusion that the effects on the phenotypes in Dicer deficient oocytes are rather due to endogenous siRNAs (Suh et al., 2010). Moreover, the expression level of miRNAs in Dgcr8 deficient oocyte found to be reduced as similar to the Dicer deficient oocyte. In addition, there was no effect due to deletion of Dgcr8 allele even from maternal and zygotic genome on the phenotype as well as mRNA profile which were very unlikely for Dicer deficient oocytes. These findings show that miRNA function is globally suppressed during oocyte maturation and preimplantation development (Suh et al., 2010). So, miRNA function is considerably low in translational repression and mRNA degradation than previously thought (Ma et al., 2010).

6. miRNAs in epigenetic and endocrine control of oocyte development

Progression of meiosis in mammalian oocytes entails a complex and dynamic epigenetic mechanism (De La Fuente et al., 2010). Differentiation of chromatin structure and function during postnatal oocyte growth is also critical for the acquisition of meiotic and developmental competence (De La Fuente, 2006). Remarkably, different non-coding RNAs including miRNAs have recently become one of the key regulators of chromatin and other epigenetic processes (De La Fuente et al., 2010). The relationship between miRNA and epigenetics is presently being elucidated through Dicer knock out studies. Conditional loss-of-function for Dicer in mammalian cells demonstrates a critical role in the epigenetic regulation of heterochromatin function through the induction of specific histone modifications (Fukagawa et al., 2004; Kanellopoulou et al., 2005). Dicer has been found to induce histone methylation in somatic and embryonic stem cells (reviewed in (De La Fuente et al., 2010)). This post-translational modification may directly or indirectly affect the patterns of DNA methylation by affecting the binding of DNA methyltransferase enzymes (Goldberg et al., 2007). However, less is known about epigenetic regulation of specific miRNAs that are required for development of oocytes although research on the field of epigenetics is rapidly moving forward.

The growth and differentiation of oocyte during the follicular development are regulated by the activity of granulosa cells whose functions are regulated by various hormones and other secreted factors. Steroid hormones have been found to induce oocyte maturation in a number of vertebrate species. In mammals, hormones targeting oocyte development exert their action on somatic cells of the follicle, which then relay the signal to the oocyte. The pituitary gland releases the gonadotropins FSH and LH. FSH causes the follicular cells to proliferate and differentiate and LH initiates the oocyte's progression through meiosis and ovulation (Voronina and Wessel, 2003). Several studies revealed interesting relationship between ovarian steroids and miRNAs. It has been also shown that LH/hCG regulates the expression of selected miRNAs, which affect posttranscriptional gene regulation in mouse within ovarian granulosa cells (Fiedler et al., 2008). Estrogen was found to suppress the levels of a set of miRNAs in mice and human cultured cells through estrogen receptor α (ERα) by associating with the Drosha complex and preventing the conversion of pri-miRNAs into pre-miRNAs (Yamagata et al., 2009). Several miRNAs are found to play important roles in the ovarian steroidogenesis (Sirotkin et al., 2009). Genome-wide screening of miRNAs revealed the involvement of miRNAs in control of releasing of ovarian steroid hormones progesterone, androgen and estrogen in human ovarian cells (Sirotkin et al., 2009). However, the complex regulatory mechanisms for interrelationship between miRNAs and the steroids are still unclear. The involvement of miRNAs for ovarian endocrine regulation to mediate oocyte growth and maturation could be much interesting in the future studies.

7. miRNAs are essential for pre-implantation embryo development

The well-orchestrated expression of genes that are derived from the maternal and/or embryonic genome is required for the onset and maintenance of distinct morphological changes during the embryonic development. Optimum regulation of genes or critical gene regulatory event in favor of early embryonic development has been shown to be directly (individual miRNAs study) or indirectly (disrupting miRNAs biogenesis) under the control of miRNAs. A significant number of miRNAs has been identified at specific stages of mouse embryonic development through massively parallel signature sequencing technology (Mineno et al., 2006) and in bovine embryo through small RNAs library construction (Coutinho et al., 2007). MiRNAs are found to be maternally deposited and essential for the early stages of mouse embryonic development. It has been shown that the maternal mRNA degradation in mouse embryos is dependent on the 3′ untranslated region of the mRNA transcript and miRNAs (Alizadeh et al., 2005; Bagga et al., 2005; Jing et al., 2005). For instance, miR-430 has been proved to promote deadenylation and clearance of maternal mRNAs in zebra fish oocytes (Giraldez et al., 2006). These initial facts indicate that miRNA could be involved or indirectly important in controling zygotic genome activation (Li et al., 2006; Yang et al., 2008). However, findings on loss of P-bodies and GW182-AGO2 interaction in the oocytes reveal that miRNAs are not required for translational repression during oocyte-to-zygote transition (Flemr et al., 2010). Hence, it is speculated that the relief of miRNA repression may contributes to oocyte-to-zygote transition by facilitating the switch between maternal miRNAs (especially the Let-7 family) and zygotic miRNAs (particularly the miR-290 family) (Svoboda, 2010).

Zygotes resulted from miRNA-depleted oocytes were found to fail to complete the first cell division, lethality in early development and depleted of stem cells in mouse and zebrafish (Bernstein et al., 2003; Wienholds et al., 2003). Interestingly, co-existence of dynamic synthesis and degradation of miRNAs has been shown with overall quantity and embryonic stage-dependent miRNAs increases as the embryos develop in mouse (Yang et al., 2008). On the other way, the proportions of the embryonic non-stage dependent miRNAs were found to be decreased during the mouse preimplantation embryo development. For example, higher expression of miR-503, miR-182, miR-34b, and miR-140*/miR-211 were observed in 2-cell, 4-cell, morula and blastocyst stage, respectively. Whereas, miR-503, miR-182, and miR-103 showed down-regulation in 4-cell compared to 2-cell, 8-cell and zygote, respectively (McCallie et al., 2009). Authors suggested an exquisite temporal specificity to miRNA expression signature in the preimplatation embryo development which could be involved in regulation of temporal switch for modulating embryonic developmental transition. Aberrant profiles of miRNA expression were evidenced in morphologically similar blastocysts derived from patients with infertility compared to donor fertile control blastocysts (McCallie et al., 2009). Even, miRNAs were found to play an

important role in differentiation/maintenance of tissue identity during early embryonic development through directing the spatiotemporally expressed genetic network (Wienholds et al., 2005).

Importance of miRNAs has been shown in vertebrate development through inactivation of the Dicer1 gene in zebrafish and subsequently observed in the early developmental arrest (Wienholds et al., 2003). While defective generation of miRNAs was observed in Dicer-null mouse embryonic stem cells with severe defects in differentiation both in vitro and in vivo, the re-expression of Dicer in the knockout cells has been found to rescue these defective phenotypes (Kanellopoulou et al., 2005). Additionally, maternal miRNAs have been shown to be essential for the earliest stages of mouse embryonic development through the loss of maternal inheritance of miRNAs following deletion of Dicer from growing oocytes (Tang et al., 2007). So, these initial reports suggested that miRNAs are essential for embryonic development as the effect of loss of Dicer1 could primarily arise from an inability to process endogenous miRNAs which later on functioning in gene regulation. Through target prediction, validation and functional study, it has been shown that Newborn ovary homeobox gene (NOBOX) – a transcription factor which is stage-specifically expressed during oocyte maturation, early embryonic development and critical to expression of pluripotency genes (Tripurani et al., 2011a) is post-transcriptionally regulated by miR-196a (Tripurani et al., 2011b). Through injection of miR-196a mimic to the bovine zygote shows that miR-196a is a bona fide negative regulator of NOBOX during bovine early embryogenesis. Recently, a zygotic specific miRNA miR-135a found to modulates the first cell cleavage in mouse through regulating the expression of E3 Ubiquitin Ligase Seven In Absentia Homolog 1A (Siah1a) (Pang et al., 2011). While critical roles for miRNAs biogenesis in the early embryonic development are well established, roles for individual miRNAs have only recently been investigated mostly in the mouse.

8. miRNAs in lineage differentiation and implantation of embryos

The first cell-fate decision of mammalian development involves segregation of the trophectoderm from the inner cell mass of the embryo. Expression of miRNAs has been found to be changed during this lineage process. Several miRNAs have been shown to be involved in the trophoblast specification in murine embryos namely miR-297, miR-96, miR-214, miR-125a, miR-424, miR-21, miR-29c, miR-7 and miR-376a (Viswanathan et al., 2009). In vitro gain- and loss-of-function experiments showed that the expression of cyclooxygenase-2, a gene critical for implantation, is post-transcriptionally regulated by two miRNAs namely: mmu-miR-101a and mmu-miR-199a* (Chakrabarty et al., 2007). Another study has identified higher expression of miR-21 in the subluminal stromal cells at implantation sites on day 5 of pregnancy but not detected during pseudopregnancy or even under delayed implantation (Hu et al., 2008). This revealed that the expression of mmu-miR-21 in the implantation sites regulated by the active blastocysts. Moreover, in the same study, the role of miR-21 in embryo implantation has been suggested due to targeted regulation of the Reck gene (Hu et al., 2008). Recent microarray based miRNAs expression profiling in elongated cloned and in vitro-fertilized bovine embryos has suggested that the reprogramming of miRNAs occurred in cloned bovine elongated embryos (Castro et al., 2010). However, status of reprogramming error in the extra embryonic tissues (or placenta) has not yet been separated which could be the main reason for the cloned pregnancy loss during the first trimester.

9. miRNAs in embryonic stem cell

A number of studies identified a unique set of miRNAs expression and its functional importance in embryonic stem cells (ES cells). Initial effort has identified that miR-290 through miR-295 (miR-290 cluster) are ES cell-specific and thereafter suggested that they could potentially participate in early embryonic processes such as the maintenance of pluripotency in mouse (Houbaviy et al., 2003). Similar study in human has also identified some clustered miRNAs (miR-296, miR-301 and miR-302: homologous to the miRNAs reported by Houbaviy et al. in mouse) specifically expressed in human ES cells and not in differentiated embryonic cells or adult tissues (Suh et al., 2004). These clustered miRNA organization is presumably effective for coordinated regulation of their expression and regulation of common targets because a common seed is shared between some miR-290 cluster miRNAs, miR-302a–d and miR-93 (Houbaviy et al., 2003, 2005). The role of miR-290 cluster in embryogenesis has been evidenced in a study, in which the generation of a mouse mutant with a homozygous deletion of the miR-290 cluster resulted in the death of embryos (Ambros and Chen, 2007). By the loss- or gain-of-function studies of Dicer, DGCR8 and ES-related miRNA genes such as miR-290–295 cluster have strongly suggested that miRNAs play an important role in ES cell maintenance, differentiation (Benetti et al., 2008; Sinkkonen et al., 2008) and lineage determination (Kanellopoulou et al., 2005; Wang et al., 2007; Ivey et al., 2008; Tay et al., 2008). Despite the fact that knowledge on the role of miRNAs in the embryonic development and stem cell maintenance, differentiation and lineage in mouse and human is increasingly building, it is yet to be elucidated for ruminants.

10. Conclusion

Molecular and cellular processes required for the gradual oocyte growth throughout the folliculogenesis and embryo development dependent on temporal expression and interaction of multiple regulatory gene products. To date, much of the work on miRNAs has focused on expression profiling rather than their regulation and functional characterization. However, this area of research is rapidly moving forward and it is expected that lot of information regarding miRNA-mediated post-transcriptional gene regulation in oocytes and embryos will be known in the future. Once relevant miRNAs and functional targets are identified, possible clinical use for these molecules will represent the

next front line and may lead to novel strategies for better enhancing or manipulating reproductive efficiency.

Conflict of Interest

The authors declare that they have no conflict of interest.

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