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Open Access Journal of Veterinary Science & Research
ISSN: 2474-9222

Putative Role of Micro-RNAs in Female Reproductive Tract

Hitit M[1]* and Kurar E[2]

[1]Deparment of Animal Genetics, Selcuk University, Turkey

[2]Department of Medical Biology, Necmettin Erbakan University, Turkey

Review Article

Volume 2 Issue 2

Received Date: March 01, 2017

Published Date: April 04, 2017

***Corresponding author:** Mustafa Hitit, Deparment of Animal Genetics, Faculty of Veterinary Medicine, Selcuk University, Konya, Turkey, Email: hititmustafa@selcuk.edu.tr

Abstract

Female reproductive tract is composed of ovarium, oviduct, cervix and uterus. Development and function of reproductive tract is dispensable for maintenance and achievement of reproduction. Reproductive tract responses to cyclic changes and ovarium hormones which provide optimum conditions for gamete movement and development. While the potential influence of pituitary and gonadal hormones on reproductive function is clearly understood, the molecular mechanism regulating reproductive tract remains elusive. Although, post-transcriptional gene regulation has critical role in cell differentiation and proliferation, little information is available in post-transcriptional gene regulation in reproductive tract. Post-transcriptional gene regulation includes splicing, processing, transport and translation of mRNA. In addition, role of RNA binding proteins and recently discovered miRNAs were also implicated in reproductive tract.

Keywords: miRNAs; Reproductive Tract; Gene Expression

miRNA Biogenesis

miRNAs are short non-coding RNA molecules which regulates gene expression post-transcriptionally. While they are involved in normal biological process, aberrant expression of miRNAs is associated with different disease conditions [1,2]. The genes of miRNAs not only reside in genes and introns, but also present in exons [3,4]. The transcription of miRNAs is mediated by RNA polymerase II and III [5]. miRNAs transcription occurs primarily in nucleus through binding of pri-miRNA to Di-George critical syndrome region 8 (DGCR8). Then, Drosha cleaves complex of pri-miRNA-DGCR8 to 70nt of stem loop precursor miRNA (pre-miRNA). Pre-miRNA is transported to cytoplasm by exportin-5 and RAN-GTP. Once in cytoplasm, it is cleaved to 21nt RNA duplex by Dicer (RNase III). While, one of strand from complex is subject to degradation, the other one is loaded to RNA induced silencing complex (RISC), composed of argounate and TRBP (TAR RNA binding protein) [6]. miRNA, in RISC complex binds to 3' untranslated region (3'-UTR) of mRNA. If complementarity of mature miRNA to 3'-UTR is accurate, mRNA transcript undergoes degradation. On the other hand, protein translation is suppressed if perfect homology is missing.

Functional Role of miRNAs in Development of Reproduction Tract

miRNAs and siRNAs were shown to be relevant for accurate development and function of female reproductive tract as well as other organs. One study using hypomorhpic Dicer1 allele showed that deficiency of Dicer1 resulted in infertility. In this study, decline of Dicer1 expression lead to luteal insufficiency and abort. These disorders were suggested to be caused by lack of miR-17-5p andlet7b [7]. However, another study also reported infertility and disorders of reproductive tract by inactivation of Dicer1 [8]. Likewise, Dicer1-defficient mice were shown to have less glandular texture [9].

In a recent study, specifically the role of miRNAs in the development of mouse ovaries as a result of deletion of Dicer1 in mouse follicular granulosa cells

has been discovered. More degenerated follicles were observed due to accelerated early follicle development resulting from inactivation of Dicer1 in follicular granulosa cells [10]. Sixty-seven miRNAs found to be differentially expressed in fetal ovine ovaries and testes in early and mid-gestational days, found to regulate some gonadal genes [11].

Expression Profiles of miRNA in Reproductive Tract

Understanding of expressions, regulation, and function of miRNAs in reproductive tract has been recently advanced. Global profile and expression of 345 unique miRNAs was investigated in forty different human tissues [12]. While miR-26b was highly expressed in oviduct, uterus, and cervix, it was not detected in ovarium [13]. The study investigating expression profiles of miRNA in newborn mice ovarium revealed miR-26a and let7c as the most abundantly expressed miRNAs. On the one hand, miR-709 was determined to be a novel mouse miRNA which has no human homolog [14]. Choi et al. (2007) identified 122 different miRNAs in two weeks' adult mouse ovarium, 15 of which previously were not reported to be novel.

miRNA expression profiles were also investigated in some animal species other than human and mouse ovary. In cattle ovarium, 50 previously known and 24 novel miRNAs were identified and characterized. Of these miRNAs, 38 were identified in bovine for the first time at 43 different loci. While, precursor of twenty-two miRNAs was conserved in more than one species, sixteen of them were reported to be bovine specific [15]. Likewise, 679 miRNAs were identified in cattle fetal ovarium by sequencing. As a result of this study, 58 miRNAs were identified expressing in the fetal ovary and 15 miRNAs were cloned for the first time in the cattle [16]. In goats, 617 conserved and 7 novel miRNAs were identified. Of these, 407 were simultaneously expressed in both pregnant and non-pregnant libraries. Furthermore, while, 90 miRNAs were pregnancy-specific, 56 were non-pregnancy-specific. miRNA prediction also showed that Frizzled-6 and -3 receptor genes were to be the target miR-143 in Wnt/beta-catenin signaling pathway [17]. In another study, miRNA profiles were examined in ovine during anestrus and the breeding season, and 483 miRNAs were expressed in ovine ovary. Of these, 25 miRNAs were determined to be differentially expressed in ovine anestrus other than three stages [18]. Recent study by Miao et al. revealed genome wide-analysis of miRNAs in ovaries of goat using RNA-Seq technology, and 603 novel miRNAs out of 5254 were conserved. Also, fertility related 30 miRNAs determined by pathway analysis were present in Jining Grey and Laiwu Black goats [19].

miRNAs in Ovarium

Functional role of miRNAs has been also implicated in ovarium development. In Dicer-1 knockout mice, miR-503 expression was shown to be significantly suppressed. While, expression of miR-503 was reported to be suppressed during early follicle development, expression was increased before ovulation in late stages [10].

miRNA mediated post-transcriptional regulation is also required for development of mice embryonic germ cells. However, it is not known which miRNA is individually involved [20]. MiR-290-295 cluster were abundantly found in embryonic cells [21], and first embryonic miRNAs were regulated [22]. In mouse granulosa cells, miR-181a inhibited expression of ACVR2A, thus prevented granulosa cell proliferation [23].

Role of miRNAs which control steroidogenesis were identified in ovarium. In cultured granulosa cells, 32 miRNAs were found to suppress progesterone release, while 10 miRNAs promoted progesterone release. Furthermore, transfection of cells with anti-sense miR-15a and miR-188 improved progesterone [24]. Components of steroidogenic pathway were also affected by miRNAs. miR-133b was shown to inhibit expression of FOXL2 by binding to mRNA sequence and thereby regulate FOXL2-mediated transcription of StAR and CYP19A suggesting elevation of estradiol production by miR-133b [25]. In an effort to elicit the role miRNAs in cell function of ovarium including proliferation, apoptosis and release of steroid hormones. Antisense miRNA miR15a (anti-miR15a) was transfected to granulosa cells and ended up elevation in proliferation and apoptosis while decrease in progesterone and testosterone and an increment in estradiol release. However, precursor miR-15a (pre-Mir15a) transfection to cell culture with and without FSH caused decrease in proliferation and apoptosis while improved release of progesterone and testosterone [26]. Moreover, in granulosa cells, induction of miR-136-3p by HCG resulted in destabilization of luteinized hormone receptor (LHR) mRNA, and transient suppression of LHR mRNA after transfection [27].

miRNAs in Oviduct

Function and regulation of miRNAs were also identified in oviduct in the context of reproductive tract. In this regard, expression of miRNAs was examined in

wild-type and Dicer1 conditional knockout mice oviduct by deep sequencing. Twenty-eight miRNAs were reported to be down-regulated in Dicer1 conditional knockout mice oviduct. Moreover, 23 miRNAs out of 28 were shown to target genes, and also involved in mesenchyme-derived structures and Müllerian duct differentiation [8]. miRNAs were also implicated in carcinogenesis of oviduct. In conditionally inactivated Dicer1 mice, primer epithelial cancers were suggested to drive from fallopian stromas and, resulted from mesenchyme-derived cells [28].

The study using *in vitro* bovine oviductal cells assessed the reaction of miRNAs regarding inflammatory mediators. Bovine oviductal cells treated with lipopolysaccharide (LPS) for consecutive hours then, miRNAs expression was examined. Interestingly, while miR-21 expression was increased at 6 hour after treatment, miR-155, miR-146a, miR-223, miR-21, miR-16 and miR-215 were found to be inhibited [29].

miRNAs in Uterus

I nvolvement of miRNAs was evaluated in endometrium with respect to expression profiles, embryo implantation, pathologies. In order to discover miRNA biogenesis which regulates transcription of miRNAs, We evaluated expression patterns of miRNA biogenesis (DICER1, DROSHA, EIF2C1-4 and TARBP2) at different stages of oestrus cycle days including days 4–8), days 12–15, and (17–21 in bovine endometrium. We reported upregulation of DROSHA and EIF2C3, and while decrease of TARBP2 in days 12–15 and days 17–21 suggesting that miRNA biogenesis might be influenced by cyclic changes [30].

In pre-implantation mouse uterus, expression profiles of 380 miRNAs were identified, and these were also common to human. While, expressions of 32 miRNAs were increased in receptive phase comparing to prereceptive phase, expressions of 5 miRNAs were suppressed. On the other hand, miR-101a and miR-199a were approved to regulate expression of cyclooxygenase-2 (COX-2) which is relevant for embryo implantation post-transcriptionally [31].

miRNA expression profiles were examined in normal, eutopic and ectopic endometrium by microarray. Of these miRNAs, miR-183 was the most suppressed miRNAs in ectopic and eutopic endometrium tissues. Suppression of miR-183 expression was shown to increase the invasion potential of endometrial stromal cells and to suppress apoptosis. In addition, it was reported that miR-183 expression may be inhibited by ovarian steroids and inflammatory factors. These findings indicate that abnormal expression of miR-183 may be an epigenetic mechanism in the development and prognosis of endometriosis [32]. In addition to this study, Altmäe et al. also detected eight differentially expressed miRNAs in receptive phase compared to perceptive phase. Of these eight miRNAs, it was reported that miR-30b, miR-30d and miR-494 regulate human endometrial receptivity [33].

In recent studies, we have also revealed miRNAs profiles concerning embryo implantation in ovine endometrium, we identified 22 ovine, 102 bovine, 101 mouse, and 371 human miRNA sequences at 13th day of pregnancy (P13) and comparable days in ovine endometrial tissue in at least one ewe. Interestingly, six miRNAs were found to be differentially expressed between cyclic and pregnant endometrium on day 13 [34]. Lastly, we determined miRNAs profiles during peri-attachment period of pregnancy (P12, P16, and P22) in the ovine endometrium. In this respect, 64 miRNAs between P12 and P16, 1040 miRNAs between P12 and P22, and 1135 miRNAs between P16 and P22 were reported to be significantly expressed [35].

miRNAs in Cervix

It is observed that the important knowledge in our understanding of the role of miRNAs in the cervix is the work carried out on cancer samples and cell lines. Understanding cervical biology is also necessary to understand abnormalities as necessary to understand the normal pregnancy process.

In a study of human papilloma virus (HPV) genotype, histologic and clinical grading, expression of eight different miRNAs from formalin-fixed paraffin-embedded (FFPE) primary human cervical cancer samples were examined. Over expression of miR-21, miR-27a, miR-34a, miR-196a and miR-221 was shown to be associated with HPV-positive squamous cell carcinoma [36]. Likewise, expression of miR-196 was found to be decreased in HPV16-infected cervical tissues. In addition to this, miR-196a expression was reduced by HPVE5 gene [37].

Also, to evaluate apoptosis in cervical cancer, the pluripotent transcription factor OCT4 activated miR-125b-1, suppressing the translation of BAK1. However, decreased expression of BAK1 has been shown to arrest apoptosis and trigger tumor progression. In general, it was shown that the OCT4/miR-125b/BAK1 pathway plays a role in human cervical carcinogenesis [38].

In another study conducted in patients with squamous carcinoma and Si Ha cell lines, miR-20a and miR-203 expression, which are abnormally expressed, have been associated with malignant process of cervical

cancer, particularly invasion and metastasis [39]. Recently, a systematic study investigating dysregulated miRNAs in cervical cancer has identified 63 differentially expressed miRNAs, suggested that their possible usage as biomarker in cancer process by revealing their interaction in related pathway [40].

Conclusion

It has been determined that miRNAs play important roles in the function and development of reproductive tissues. Studies conducted up to now evaluated miRNA profiles, expressions, and function in reproductive tissues. In future, pathways associated with miRNA-mediated post-transcriptional gene regulation will be elucidated in the female reproductive system. However, further studies will enlighten the functions of circulating miRNAs regarded as potential biomarkers, transcriptional factors, and functions in cellular events of reproduction system.

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