Endometrial regulation by miRNA

Subjects: Reproductive Biology

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The human endometrium is the only tissue that undergoes cyclic monthly structural modifications including proliferation, differentiation and shedding of the superficial layer during the so-called menstrual phase. During the proliferative phase, from day 1 of menses to ovulation day, the superficial layer regenerates from the basal layer under the action of estradiol. In the secretory phase, progesterone induces decidualization in the estradiol-primed endometrium, a crucial step for embryo implantation. These structural and functional modifications at the cellular and intercellular levels are finely orchestrated by numerous extrinsic and intrinsic factors. The molecular responses to hormonal stimuli are modulated at the transcriptional and post-transcriptional stages. Imbalance in cellular and molecular endometrial homeostasis may lead to gynecological disorders such as endometriosis, implantation failure, and endometrial cancer.

miRNA endometrium recurrent implantation failure endometriosis endometrial cancer

1. Overview

The molecular responses to hormonal stimuli in the endometrium are modulated at the transcriptional and post-transcriptional stages. Any imbalance in cellular and molecular endometrial homeostasis may lead to gynecological disorders. MicroRNAs (miRNAs) are involved in a wide variety of physiological mechanisms and their expression patterns in the endometrium are currently attracting a lot of interest. miRNA regulation could be hormone dependent. Conversely, miRNAs could regulate the action of sexual hormones. Modifications to miRNA expression in pathological situations could either be a cause or a result of the existing pathology. The complexity of miRNA actions and the diversity of signaling pathways controlled by numerous miRNAs require rigorous analysis and findings need to be interpreted with caution. Alteration of miRNA expression in women with endometriosis has been reported. Thus, a potential diagnostic test supported by a specific miRNA signature could contribute to early diagnosis and a change in the therapeutic paradigm. Similarly, specific miRNA profile signatures are expected for RIF and endometrial cancer, with direct implications for associated therapies for RIF and adjuvant therapies for endometrial cancer. Advances in targeted therapies based on the regulation of miRNA expression are under evaluation.

2. Human Endometrium

The human endometrium is the only tissue that undergoes cyclic monthly structural modifications including proliferation, differentiation and shedding of the superficial layer during the so-called menstrual phase [1]. During the proliferative phase, from day 1 of menses to ovulation day, the superficial layer regenerates from the basal

layer under the action of estradiol. In the secretory phase, progesterone induces decidualization in the estradiol-primed endometrium, a crucial step for embryo implantation [2][3]. These structural and functional modifications at the cellular and intercellular levels are finely orchestrated by numerous extrinsic and intrinsic factors. The molecular responses to hormonal stimuli are modulated at the transcriptional and post-transcriptional stages. Imbalance in cellular and molecular endometrial homeostasis may lead to gynecological disorders such as endometriosis, implantation failure, and endometrial cancer [4][5][6][7][8].

MicroRNAs (miRNAs) are non-coding small RNAs composed of about 21–25 nucleotides. They modify the expression of around 60% of proteins at a post-transcriptional level. To date, 3000 miRNAs have been identified. A single miRNA can control the expression of several messenger RNAs (mRNAs) and a single mRNA may be targeted by more than one miRNA, thus creating a complex network of cooperative regulation [9].

miRNAs are involved in a broad variety of physiological mechanisms such as morphogenesis, differentiation, apoptosis, and cellular metabolism [10]. Expression levels of some miRNAs are associated with endometrial receptivity [11] and fluctuate according to progesterone blood levels during controlled ovarian hyperstimulation [12]. Their implication in the pathogenesis of endometriosis and endometrial cancer has been described [13][14]. Recently, we have shown that some miRNA expression profiles are associated with the prognosis of endometrial cancer [15].

3. miRNAs

miRNAs are non-coding RNAs composed of about 22 nucleotides. In animals, they are involved in the post-transcriptional regulation of protein expression. While they can be encoded by solitary genes controlled by their own promoters and regulatory sequences, most of the animal miRNAs are organized in tandem and arranged in clusters. Thus, they are frequently co-regulated together with other members of the cluster [16].

miRNAs are transcribed from introns of protein-coding genes or from the intergenic regions mainly by RNA polymerase II and, less frequently, by RNA polymerase III [17][18]. The primary miRNAs are then cleaved into stem-loop pre-miRNAs about 60–70-nt-long either by Drosha RNase III endonuclease or by an alternative Drosha-independent mirtron pathway. Pre-miRNAs are actively exported to the cell cytoplasm and cleaved by the Dicer enzyme, which removes the loop structure to form mature miRNA duplexes with an overhang at the newly formed 3′ end. Dicer guides the so-formed miRNA duplexes to the Argonaute (AGO) protein—part of the RNA-induced silencing complex (RISC)—which unwinds the duplexes to form single-stranded miRNA-5p and miRNA-3p products. The mature miRNA is integrated into RISC. Target mRNAs are bound to the miRNA–RISC complex and are thus deactivated as the ribosomal assembly is repressed. Bound mRNAs are stored in cytoplasmic structures called P-bodies, from which they are released upon a cellular signal or destroyed [19][20].

The endometrial expression of miRNAs is cell-dependent and their biogenesis is finely regulated by the physiopathological profile of the cell, the microenvironment, and environmental factors. Expression is dependent on

a single nucleotide polymorphism, and epigenetic modifications regulate transcription (methylation or acetylation of DNA, histone modifications) and interactions with RNA-binding proteins, and edit miRNA maturation [20].

miRNAs are characterized by an imprecise complementarity to their target mRNA [16]. According to the degree of complementarity, the target mRNA can either be degraded or its translation blocked. The action of miRNAs also varies according to the target mRNA binding site and can even, in some conditions, activate gene expression [20].

In addition to this complexity of miRNA action, a single miRNA can target numerous mRNAs, thus regulating hundreds of proteins and various networks [21]. On the other hand, one mRNA can also be targeted by different miRNAs [20].

4. Conclusions

miRNA are non-coding small RNAs responsible for the post-transcriptional regulation of gene expression. A single miRNA can control the expression of several mRNAs and a single mRNA may be targeted by more than one miRNA, thus creating a complex network of cooperative regulation. The action of each miRNA is tissue-specific and cannot be generalized to other organs.

miRNA expression patterns in the physiological and pathological endometrium are currently a hot topic of research. miRNA expression profile in the human endometrium varies according to the menstrual cycle and is regulated by sex steroids. On the other hand, miRNA can impact the action of sex steroids, so that modifications in miRNA expression profile in pathological endometrium could either be a cause or a result of the pathology.

Deregulated miRNA identified in RIF patients are frequently involved in adhesion, proliferation, and angiogenesis processes. In endometriosis the identified miRNA are frequently associated to proliferation, apoptosis and cell adhesion. Finally, miRNA involved in EMT are frequently found in endometrial cancer.

Recent progress allowing global analysis of known miRNA in the human endometrium may allow further understanding of their actions and hopefully lead to the development of diagnostic and/or theragnostic signatures.

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