

THERAPEUTIC POTENTIAL OF MicroRNAs IN PREGNANCY-RELATED DISORDERS

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Introduction

Pregnancy-related complications, such as gestational diabetes mellitus (GDM), preeclampsia (PE), and preterm delivery (PTD), affect approximately 15% of pregnant women worldwide (Wallis et al., 2008). They have very serious adverse effects on maternal and fetal morbidity and mortality. Especially in the long term, it has severe negative effects on the health of mother and baby dyads. Early identification of pregnant women at risk can enhance the effectiveness of interventions and thus decrease the effect of these diseases that negatively affect life and the cost of neonatal care (Wallis et al., 2008).

MikroRNA (miRNA) is included in non-coding RNAs that can be classified in accordance with their length as small (<200 nucleotides) and long (>200 nucleotides) RNAs as well as cleaning and regulatory RNAs according to their functions. (Bartel, 2004; Lycoudi et al., 2015).

Research on miRNA is a relatively new subject, with research going back 25 years in bacteria in 1993 and its detection in humans in 2000 (Lee et al., 1993; Verduci et al., 2021; Wightman et al., 1993).

Normal development and optimal performance of the placenta is regulated by miRNAs expressed specifically in the placental tissue. Deregulation of miRNAs expressed in the placenta is associated with placentation disorders and ultimately complications of pregnancy. miRNAs expressed from the placenta can be used as biomarkers. Placental miRNAs can also be found in maternal plasma. Placental development, including cell differentiation, adhesion, migration, apoptosis, and angiogenesis, during pregnancy are regulated by placental miRNAs. Defects in the expression of these miRNAs have been associated with the occurrence of complications during pregnancy (Lycoudi et al., 2015). miRNAs in the placenta are thought to be effective in the development of pregnancy complications such as PE, intrauterine growth restriction, GDM, PTD, obesity, and miscarriage (Kotlabova et al., 2011). In addition, placental miRNAs have been used to determine normal pregnancies and diseases related to pregnancies and the importance of their effects on the pathogenesis is highlighted (Kotlabova et al., 2011). Further, miRNAs in the placenta, as well as placental-specific miRNAs in maternal circulation, are prone to alters in the maternal environment, including and exposure to toxicants (Kotlabova et al., 2011).

Hence, miRNAs may be benefited as biomarkers to xenobiotic exposures as well as related clinical syndromes (Addo et al., 2020).

In last studies on miRNA made from placenta and maternal blood, pregnancy follow-up showed a difference in expression between pregnant women with normal and increased pregnancy risk requiring close follow-up. Valuable information about the effects of these miRNAs in pathophysiology has been obtained and they have been identified as biomarkers that can be useful for clinical follow-up of complications that can be seen in high-risk pregnancies (Bhatti et al., 2021; Lycoudi et al., 2015).

Epigenetic regulation

Epigenetics is defined as inherited changes in gene expression that occur without changes in the DNA sequence (Bhatti et al., 2021). Epigenetic mechanisms are inherited changes in gene expression that appears without any changes in the DNA sequence in the cell, indicating alter in phenotype without any change in genotype (Bird, 2007; Goldberg et al., 2007; Seborova et al., 2021). miRNAs behave as epigenetic regulators by changing the expression of the protein levels of target mRNAs without affecting the gene sequences. In miRNAs, some of the cytosine in DNA is methylated and histone modifications constitute important epigenetic mechanisms that affect gene regulation, development, and carcinogenesis. Some studies have shown that changes in epigenetic mechanisms such as DNA methylation and histone modification can affect it. This information clearly reveals a relationship between epigenetic mechanisms and miRNA. The irregularity of the miRNA-epigenetic feedback loop interferes with physiological and pathological processes and contributes to a diversity of diseases (Lycoudi et al., 2015; Sarkar & Kumar, 2021; Yao et al., 2019).

To date, approximately 2000 miRNA have been reported in humans and their numbers continue to increase. The miRNA biogenesis pathway includes numerous transcriptions, primary conversion of miRNA to precursor miRNA, and transcription targeting steps. miRNAs normally bind complementary sequences of target mRNAs and lead to translational suppression and / or target degradation and act as negative regulators of mRNA expression. (Catalanotto et al., 2016). Consequently, a miRNA may modulate the expression of multiple target genes and a gene may be regulated by multiple miRNAs. More than 30% of human genes are estimated to be coordinated by miRNA. These small molecules can activate many cellular functions

including cellular differentiation, proliferation, growth, stress response, apoptosis, metabolism, and angiogenesis. Recent studies have shown that irregularities in miRNA expression cause cancer, neurological and cardiovascular disorders, diabetes mellitus, immune disorders and complications during pregnancy, and other major health problems (Braoudaki & Lambrou, 2015; Verduci et al., 2021).

miRNAs have also been determined in extracellular fluids, including serum and plasma, enabling long-range connections between cells. This novel category of miRNAs, known as circulating miRNAs, is very consistent, due to their resistance to endogenous ribonuclease activity and function as vesicles forming exosomes with lipoprotein membranous complexes or clusters with specific proteins such as Argonaute2 (Valadi et al., 2007). This feature makes circulating miRNAs important and useful as non-invasive biomarkers for diagnosing and tracking diseases (Verduci et al., 2021).

Pregnancy and miRNAs

Pregnancy-related miRNAs perform important and absolutely essential functions at many stages from the onset of pregnancy, including preparation of the endometrium for implantation of the gestational sac, regulation of genes associated with immune development, placental development and angiogenesis (Fu et al., 2013; Pan & Chegini, 2008). The impaired expression of these molecules has long been linked to impaired placental development and pregnancy complications. Currently, these complications are treated symptomatically. Determining the predisposition of pregnant women to high-risk pregnancy complications can facilitate pregnancy follow-up and management. In addition, it is important to understand the physiopathological mechanisms of pregnancy-related complications, for accurate diagnosis, better follow-up and treatment (Bogdanet et al., 2021; Memtsa et al., 2019).

The miRNAome of the normal human placenta

The placenta ensures the bi-directional linkage between mother and fetus and simplifies the exchange of nourishment, waste, and respiratory gases during pregnancy. It is also an endocrine organ that produces hormones and growth factors essential to embryonal growth. Adequate placement is essential for the development of the fetus and to maintain a healthy pregnancy. The information obtained from research activities shows that miRNAs play an important role in inducing change from epithelium to mesenchyme, which is

a fundamental process during the implantation of conceptus (Huangyang & Shang, 2013; Verduci et al., 2021). During implantation in the uterine cavity after fertilization, trophoblast cells differentiate and migrate and form placental villi. Regarding vascularization, the formation of spiral arteries is one of the important stages of placental development. A disarrangement occurring in this process causes some complications during pregnancy. It is known that miRNAs that regulate the development and function of the placenta play a very important role at this step. miRNAs found in the placenta may be specific to their functions or tissue. (Kotlabova et al., 2011; Liang et al., 2007). Studies in human placental tissues have revealed that miRNA has a transient expression pattern at different stages of placental development (Liang et al., 2007; Mayor-Lynn et al., 2011). The role of miRNA in the expression of placental miRNA and its potential effect on pregnancy and fetal development are discussed (Fu et al., 2013; Gao et al., 2012; Yu et al., 2012).

Conclusions

miRNAs reveal irregular expressions in women with pregnancy complications (Bogdanet et al., 2021; Memtsa et al., 2019; Rana et al., 2020). Further research is required to further define an individual miRNA as a biomarker in placental disorders. Checking for disorganized placental and circulatory miRNAs is necessary in large-scale preclinical studies. According to the literature, generally, large-scale clinical trials should be planned to evaluate the clinical significance of circulating miRNAs in pregnancy-related conditions. This is important, since it will help determine their sensitivity and specificity for inclusion in clinical diagnostics and follow-up tests. Considering the multiple factors influencing the growth of pregnancy, it appears likely that a panel of various biomarkers, including genomic, transcriptomic, proteomics, and biophysical ones, combined with maternal characteristics, can be utilized to make better the health care for pregnant women in the future.

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