Placental Specific MicroRNAs in Pregnancy and Preeclampsia
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ABSTRACT
MicroRNAs could play a fundamental role in a variety of physiological and pathological events in pregnancy. Many miRNAs are expressed in human placenta and some of them are specifically expressed in the placenta and also in serum where they have the potential to become novel biomarkers of pregnancy disorders and could be provided as prognostic and diagnostic tools for compromised pregnancies such as preeclampsia.

Key words: MicroRNA, Placenta Specific, Preeclampsia

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Introduction:

Preeclampsia (PE) is a common pregnancy complication and important cause of maternal and infant morbidity and mortality in the world. It is characterized by hypertension and proteinuria after 20 weeks of gestation. Pre-eclampsia is a multi-system disease that is unique to human pregnancy, affecting 5–7% of pregnancies (1). Although estimated incidence of preeclampsia is 6–10% of all pregnancies in the United States; the incidence is believed to be even more in underdeveloped countries (2). Approximately 75000 mothers and 500000 babies die every year because of preeclampsia complications (3). In fact, pre-eclampsia has a polymorphic nature, and every organ system could be affected, thus predisposing women to serious complications, including disseminated intravascular coagulation, abruptio-placenta, cerebral hemorrhage, acute renal failure, circulating collapse, HELLP syndrome (hemolysis, elevated liver enzymes and thrombocytopenia), liver failure, cerebral edema with seizures and rarely death (4). Potential fetal complications include fetal growth restriction (FGR), prematurity and death (5).

PE is associated with abnormal placentation following to alterations in the vascular remodeling of uteroplacental arteries mainly due to abnormal invasion of trophoblasts and unconverted narrow spiral arteries (6). These processes are the cause of underperfusion and persistent hypoxia in the placenta (7).

Thus, the placenta is thought to release various mediators into the maternal circulation, which causes local endothelial dysfunction and vasoconstriction of uterine arteries and lead to systemic blood pressure elevation (8).

Because of the important role of the placenta in pre-eclampsia, there has been much investigation on how early abnormalities in placental vascular remodeling may play a role in the disease.

As a member of nonprotein coding short RNAs family miRNAs through binding to the 3’ untranslated region of specific target genes regulate their expression through translational regulation. MicroRNAs (miRNAs) are less than 22 nucleotides in length that control gene expression, with major functions in the regulation of a variety of biologic processes involved in development, cell differentiation, regulation of cell cycle, metabolism and apoptosis (9).

Recent studies have reported the expression aberration of a number of miRNAs in placentas and fetal membranes affected by preeclampsia (10,11). MiRNAs have roles in physiological and pathological processes such as cell differentiation, proliferation, growth, apoptosis, angiogenesis, inflammation and other endothelial cell functions. Since these processes are frustrated in preeclampsia, miRNAs can potentially play important roles in preeclampsia pathogenesis (12).

The association between PE and altered miRNA expression suggests the possibility of a functional role for miRNA in this disease (13). Here, we reviewed the current state of miRNA research in human placenta, focusing primarily on placental specific miRNA expression in pregnancy and PE.

MiRNAs and cancer

Owing to the critical role of miRNAs in various biological processes, it is therefore not surprising that altered miRNA expression contributes to development and progression of cancers. The first evidence of link between miRNAs and cancer derived from studies on chronic lymphocytic leukemia (CLL), particularly in an attempt to identify tumor suppress at chromosome 13q14 that frequently deleted in CLL [15]. Thanks to high-throughput profiling techniques, the aberrant miRNA expression profiles have subsequently been documented in various types of malignancies [16-19]. Although, miRNAs have been revealed to be both down- as well as up-regulated in cancerous cells as compared with non-neoplastic tissues, it is widely believed that the miRNAome globally downregulated during cell transformation and tumorogenesis [13]. The aberrant expression of miRNAome may be stems from chromosomal instability, epigenetic alterations, genomic mutations, polymorphisms and altered expression or function of the miRNA biogenesis machinery components in tumor cells [20,21]. The predicted targets for the differently expressed miRNAs suggest that miRNAs could serve functionally as “oncogenes” or “tumour suppressor” genes [13,20].

MiRNA Role in Preeclampsia

MicroRNAs (miRNAs), small non-coding RNAs, are highly conserved post-transcription regulators of gene expression through inhibition of protein translation or promotion of mRNA
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MicroRNAs play key roles in physiological homeostasis in health and pathophysiological states in disease. MicroRNAs are known to have function in pathological process and prognosis of diseases such as diabetes (19), neurodegenerative diseases (20), preeclampsia (21), cancer and its resistance against chemotherapy (22). It has been also believed that the presence of single nucleotide polymorphism (SNP) in the processing machinery and target binding sites genes of miRNA affects cancer risk, treatment efficacy and prognosis of some diseases.

The first study that linked miRNA and PE was done by Pineles et al (23). The study was conducted to determine whether PE and small-for-gestational age (SGA) are associated with aberrations in placental miRNA expression. Thus they evaluated placental miRNAs’ expression from patients with PE, SGA, PE + SGA along with a control group (Table 1).

They found that seven miRNAs (miR-210, miR-155, miR-181b, miR-182+, miR-200b, miR-154+, and miR-183) had higher expression between PE + SGA and the control group. The expression of miR-182 and miR-210 was significantly higher in PE than in the control group.

Some studies have reported the expression of a number of miRNAs in placentas and fetal membranes with altered expression in these tissues affected by preeclampsia (10,11). The association between PE and altered miRNA expression indicates the possibility of a functional role for miRNA in this disease (13). MicroRNAs produced by human trophoblast cells could be secreted into maternal plasma or serum via an exosome-mediated pathway and have the potential to be used as biomarkers (24). Detection of miRNAs in the maternal circulation consider the possibility of using miRNAs as biomarkers to monitor the progression of normal pregnancy and gestational diseases such as preeclampsia. Aberrant expression of miRNAs in placenta from compromised pregnancies also discuss the potential of using miRNAs as therapeutic targets.

**Placental Specific miRNAs**

Many miRNAs are expressed in human placenta and some of them, such as the C19MC and C14MC clusters, are specifically or preferentially expressed in the placenta (25). The three most famous clusters are the chromosome 19 miRNA cluster (C19MC), C14MC and miR-371-3 cluster, which is also localized on chromosome 19. MiRNA members of these clusters are not only detected in the placenta, but also in other compartments, e.g. in serum where they have the potential to become novel biomarkers of pregnancy disorders. Antagonism of some of these miRNAs or their targets may lead to novel therapeutic points for the development of new drug classes in pregnancy disorders (26). The C19MC, located in chromosome 19q13.41, is the largest miRNA cluster identified to date and is encoded by paternally imprinted genes. This cluster 46 pre-miRNAs transcribed from a non protein coding host gene and expressed only in the placenta (27).

The C19MC is primate specific and expressed from the paternal harbors allele (28). On the other hand, the C14MC cluster, containing 46 miRNAs in 14q32, is also highly expressed in the human placenta but is encoded by maternally imprinted genes (29). MicroRNAs 518b belongs to C19MC.

MiR-154* is located on 14q32.31 and has predominant expression pattern from placenta tissue. It is one of the pregnancy-associated
miRNAs and showed major decreased concentrations in maternal plasma after pregnancy (30).

Luo et al. 2008 found that miRNAs are exported from the human placental syncytiotrophoblast into maternal circulation, where they could target maternal tissues (24). Miura et al. (2010) showed that as the pregnancy progressed into the third trimester, the plasma concentrations of cell-free chromosome 19–derived miRNAs (has-miR-515-3p, has-miR-517a, has-miR-517c, has-miR-518b, and has-miR-526b) enhanced significantly, whereas that of cell-free has-miR-323-3p on chromosome 14q32.31 showed no change (31).

Hromadnikova et al. (2012) showed that both quantification approaches revealed significant upregulation in extracellular placenta–specific miRNA levels over time in women with normally progressing pregnancies; however, they did not have the capacity to differentiate between normally progressing and complicated pregnancies at the time of preeclampsia and/or IUGR onset. Also, significant elevation of extracellular miRNA levels was observed during early gestation (ie, within the 12th to 16th weeks) in women who later developed preeclampsia and/or IUGR (32). In Kotlabova et al. study (2011) seven microRNAs (miR-516-5p, miR-517*, miR-518b, miR-520a*, miR-520h, miR-525 and miR-526a) were identified as new pregnancy associated microRNAs with diagnostic potential but they mentioned only miR-518b had all criteria for selection as microRNA marker with diagnostic and or prognostic potential because of: 1) detection rate of 100% in full-term placentas, (2) detection rate of ≥67% in maternal plasma throughout gestation (at least four positive wells out of six tested wells) and (3) not detectable in blood and plasma samples of nonpregnant women(33). A quantitative real-time RT-PCR analysis of the expression of eight placenta-specific miRNAs in trophoblast cells with different proliferative activities by WANG et al. (2012) indicated that the expression levels of two miRNAs (miR-517b and miR-1283) were increased and miR-519a was decreased in trophoblast cells with lower proliferative activities (34).

Table 1. Expression of some microRNAs in placenta

<table>
<thead>
<tr>
<th>miR name</th>
<th>Sample</th>
<th>Expression</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>16, 29b, 195, 26b, 181a, 335, 222, 181a, 584, 30a-3p, 210, 152, 517, 518b, 519e, 638, 296, 362, 512-3p</td>
<td>severe PE placenta</td>
<td>High Expression</td>
<td>Hu et al. 2009, Zhu et al. 2009, Mayor et al. 2011</td>
</tr>
<tr>
<td>101, 10b, 218, 590, 204, 32, 126, 18a, 19a, 411, 377, 154, 625, 144, 195, 150, 1, 18b, 363, 342-3p, 450, 223, 374</td>
<td>severe PE placenta</td>
<td>Low Expression</td>
<td>Zhu et al. 2009</td>
</tr>
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</table>
Conclusion:

MicroRNAs (miRNAs) are expressed in the human placenta and could be detected in maternal plasma. Specific miRNA profiles have been explained for the placenta, maternal plasma and pregnancy disorders such as PE. It has been observed that numerous miRNAs, which are predominantly or exclusively expressed during pregnancy in placenta, are clustered in chromosomal regions, may be controlled by the same promoters, may have similar seed regions and targets, and work synergistically. MiRNA members of these clusters are not only detected in the placenta, but also in serum where they have the potential to become novel biomarkers for early detection of pregnancy disorders. Antagonism of selected miRNAs or their targets may lead to novel targets for the development of new drug classes in pregnancy disorders such as PE.

References:


17. Donker RB, Mouillet J-F, Nelson DM, Sadovsky Y. The expression of Argonaute2...