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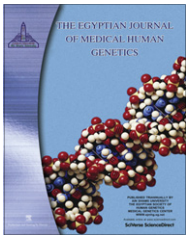

REVIEW

Micro RNA: New aspect in pathobiology of preeclampsia?

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Abstract The discovery of miRNA in 1993, by Ambros et al. has had a huge influence in pathogenesis theory; diagnosis and treatment approach to some diseases. Some scientifically proven theories have been proposed to seek the association of alterations of miRNA expression to incidences and severity of preeclampsia (PE). In this review we explore the result of such investigations that discuss the association of miRNA and PE along with the role of various mRNAs in PE pathogenesis.

Contents

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1. Introduction

Preeclampsia (PE) is a disease of pregnancy characterized by hypertension (defined as systolic blood pressure $\geqslant$140 mm Hg or diastolic blood pressure $\geqslant$90 mm Hg) and proteinuria (300 mg or greater in a 24-h urine specimen and/or protein to creatinine ratio of $>$0.30), developing after 20 weeks of gestation [1–3]. It has been estimated that PE affects 3–5% of pregnancies worldwide [4], recently, it has been reported that PE complicates 3–8% of pregnancies [5]. There is much evidence shown that PE originates in the placenta [6,7] and thus the placenta is believed as the central basis to the pathogenesis of PE [8]. But the molecular basis for placental dysregulation of these pathogenic factors remains unknown. Many hypotheses have emerged that attempt together a causal framework for the disease, causing PE to be named the 'disease of theories' [9].

MicroRNAs (miRNAs) are small, noncoding RNAs ~22 nucleotides (nt) in length that regulate gene expression, with important functions in the regulation of a variety of biologic processes involved in development, cell differentiation, regulation of cell cycle, metabolism and apoptosis [10–12]. Albeit only 1% of the genomic transcripts in mammalian cells encode miRNA [13], miRNAs are predicted to control the activity of more than 60% of all protein-coding genes [14]. It has been estimated that miRNAs regulate ~30% of human genes [10,15].

MicroRNAs regulate mRNA, which encodes proteins that modulate cellular functions, therefore, miRNAs play important roles in physiological homeostasis in health and pathophysiological derangement in disease [13]. MicroRNAs are known to have function in pathological process and prognosis of diseases such as diabetes [16], neurodegenerative disorder [17], gastrointestinal diseases [18] and cancer and its resistance toward chemotherapy [19]. It has been also proposed 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 patient prognosis [20]. Certain miRNAs are tissue-specific and the temporal expression of the tissue-specific miRNAs correlates closely with the specific physiological or pathological status of the corresponding organs [13].

Research conducted by Pineles et al. [21] shows that PE is associated with alterations in placental miRNA expression. This research reported that miR-210 and -182 are expressed differentially in the human placentas of patients with PE compared with control subjects [21]. In this review we will discuss the role of miRNA as a new aspect in pathophysiology of PE.

2. Discussion

2.1. Biogenesis and mechanism action of miRNA

The first report on miRNA was presented in 1993 by Ambros et al. who described a 22-nucleotide RNA in *Caenorhabditis elegans* encoded by the *lin-4* gene, which can bind to the lin-14 transcript and interfere with its expression [13]. Functional studies indicate that miRNAs participate in the regulation of almost every cellular process investigated so far and that changes in their expression are associated with many human pathologies [22].

MicroRNAs are processed from RNA polymerase II (RNA-PII)-specific transcripts of independent genes or from introns of protein-coding genes [23]. These initial miRNA precursors, known as pri-miRNAs, are processed into ~70 nt hairpin structures known as pre-miRNAs – in the nucleus – by a nuclear enzyme complex known as the microprocessor that contains an endoribonuclease – Drosha – and a double-stranded RNA binding protein – DiGeorge syndrome critical region 8 (DGCR8). This process called as Drosha–DGCR8 step [22,24]. Drosha is an RNase III enzyme which contains two RNase domains which cleave the 5′ and 3′ ends, releasing the pre-miRNA [25]. Some pre-miRNAs are produced from very short introns (mirtrons) that bypass the Drosha–DGCR8 step [22].

The pre-miRNA is exported from the nucleus to the cytoplasm by Exportin-5 (XPO5) [26]. In the cytoplasm, the pre-miRNA is further cleaved by another RNase III enzyme – Dicer, which removes the loop to yield the ~22 nucleotide miRNA duplex [13]. After being unwound by a helicase, one strand of miRNA is destined to be the mature miRNA called as guide strand and the complementary strand – called as passenger strand or miRNA*– is rapidly degraded [13]. The thermodynamic stability of the miRNA duplex termini and the identity of the nucleotides in the 3′ overhang determine which strands act as the guide strand [20]. Then the guide strand is incorporated into a miRNA-induced silencing complex (miRISC) [15,22].

Guided by the sequence complementarity between the small RNA and the target mRNA, miRNA–RISC-mediated gene inhibition is commonly divided into three processes: (a) site-specific cleavage, (b) enhanced mRNA degradation and (c) translational inhibition [27].

The miRISC–mRNA interaction can lead to several modes of direct and indirect on translational repression [13]. Direct on translational repression involved: (a). Initiation block: The miRISC inhibits translation initiation by interfering with eIF4F-cap recognition and 40S small ribosomal subunit recruitment or by antagonizing 60S subunit joining and preventing 80S ribosomal complex formation. (b) Postinitiation block: premature ribosomal drop-off, the 40S/60S ribosomes are dissociated from mRNA, stalled or slowed elongation, the 40S/60S ribosomes are prohibited from joining during the elongation process or facilitating proteolysis of nascent polypeptides [13,25,28]. The indirect on translational repression occurs via mRNA deadenylation and degradation [13,28]. Deadenylation of mRNAs is mediated by glycine–tryptophan protein of 182 kDa (GW182) proteins – the components of miRISC, poly(A)-binding protein (PABP), and Argonaute (AGO) pro-

tein [22,25,27]. Argonaute (AGO) proteins are core components of the miRISC which are directly associated with miRNAs [22]. Then this molecule will interacts with the CCR4/CAF1 deadenylase complex to facilitate deadenylation of the poly(A) tail [22,25]. Following deadenylation, the 5′-terminal cap is removed by the decapping enzyme – decapping DCP1-DCP2 complex [25]. Endonucleolytic cleavage and mRNA degradation that miRNA-mediated by AGO2 [22,29].

2.2. Molecular mechanisms of preeclampsia

Angiogenic factors such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) and their receptors Flt1 [also known as vascular endothelial growth factor receptor 1 (VEGFR-1)], VEGFR-2, Tie-1, and Tie-2, are essential for normal placental vascular development [8]. Alterations in the regulation and signaling of angiogenic pathways in early gestation contribute to the inadequate cytotrophoblast invasion seen in PE [8]. Additionally, perturbation of the renin–aldosterone–angiotensin II axis, excessive oxidative stress, inflammation, immune maladaptation, and genetic susceptibility may all contribute to the pathogenesis of PE [8].

Several placentally derived "toxins" were suggested, including cytokines, anti-angiogenic factors, syncytiotrophoblast microparticles (STBM), and formed blood products activated in the intervillus space [30].

The role of these anti-angiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng) in early placental vascular development and in trophoblast invasion is just the beginning to be explored in placental dysregulation. Hypoxia is likely to be an important regulator [8]. Oxidative stress was an attractive component as part of the linkage [31]. Reactive oxygen species could be generated by the reduced perfusion of the placenta with the consequent activation of monocytes and neutrophils passing through the intervillus space. Oxidative stress would also stimulate the release of cytokines, antiangiogenic factors, microparticles and other potential linkers [30].

Some factors such as genetic factors, oxidative stress, catechol-*O*-methyltransferase (COMT) deficiency, hemoxygenase deficiency and immunologic/inflammatory factors cause placental dysfunction which leads to angiogenic imbalance, increase sFlt1 and sEng, decrease PlGF and VEGF [8,32,33].

sFlt1 and sEng levels have been shown to be elevated in the serum of preeclamptic women, as compared to those of normal pregnant women, weeks before the appearance of overt clinical manifestations of the disease [34,35]. Compared to normo-tensive controls, in patients with severe PE, free PlGF and VEGF levels are significantly declined [34,35] and sFlt1 levels are significantly elevated [36].

It is clear that the increase of sFlt1 expression associated with decreased PlGF and VEGF signaling causes inadequate placental vascular development [34,37,38]. These alterations cause widespread endothelial dysfunction that results in hypertension, proteinuria, and other systemic manifestations of preeclampsia [32,38].

2.3. The role of miRNA in preeclampsia pathogenesis

The first research that linked miRNA and PE was conducted by Pineles et al. [21] The study was performed to determine whether PE and small-for-gestational age (SGA) are associated with alterations in placental miRNA expression. Thus they evaluated placental miRNAs' expression from patients with PE, SGA, PE + SGA along with a control group. They found that seven miRNAs (miR-210, miR-155, miR-181b, miR-182*, miR-200b, miR-154*, and miR-183) were significantly higher expressed 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. Based on Gene Ontology (GO) analysis, miR-182 has a role to down-regulate anti-apoptosis genes. They speculated that high expression of miR-182 in PE may contribute to the increased apoptosis in the placentas of patients with PE. The targets of both miR-182 and miR-210 are enriched in immune processes, which support the association between abnormal immune responses and PE as descripted previously by Kim et al. [39]. Beside that, angiogenin and VEGF-β are potential targets of miR-182 and miR-182*, respectively [21]. These molecules have a role in angiogenesis. A study by Yang et al. [40] elucidates miRNA essentiality, that in mice with deficient miRNA, defective angiogenesis is caused that leads to embryonic lethality.

A study with small sample in China found the expression of miR-130a, miR-181a, miR-222, miR-16, miR-26b, miR-29b and miR-195 in the placenta of severe PE women [41]. The other research reported that miR-16, miR-29b, miR-195, miR-26b, miR-181a, miR-335 and miR-222 were significantly increased in placenta from women with severe PE [42]. This research revealed that some angiogenic growth factors were potential targets of the altered miRNA, such as cysteine-rich 61 (CYR61), PlGF, VEGF-A which were targets of miR-222, miR-335 and miR-195, respectively [42]. It describes the role of this angiogenics factors for the development of PE. It is well known that the expressions of VEGF-A and VEGF receptor-1 are down-regulated in the cytotrophoblasts of PE placenta [32,43]. Several articles reviewed by Lam et al. [44] provide sufficient evidence that PlGF is also dysregulated in serum or the placental tissue of women with PE.

The research by Mo et al. [45] found that CYR61 is essential for placental development and vascular integrity. Gellhaus et al. [46] found that CYR61 is significantly decreased in PE placenta. CYR61 is a secreted matrix protein expressed by nearly all types of vascular cells and trophoblasts and implicated in diverse cellular processes such as proliferation, migration, differentiation, and adhesion. It was found that the expression of CYR61 in human placenta was significantly lower than that of the normal control [46]. Recently, a study reported that overexpression of miR-155 contributes to PE development by targeting and down-regulating angiogenic regulating factor CYR61 [47]. It was also reported that CYR61 has been demonstrated to be one of the important early angiogenic factors during pregnancy, this role is probably because CYR61 can induce the expression of VEGF [47].

Poliseno et al. [48] found that overexpression of miR-221/222 inhibits tube formation, migration, and wound healing in response to stem cell factor in human umbilical endothelial cells (HUVEC). This effect, arises because c-kit is a target of miR-221/222. c-kit is a tyrosine kinase receptor for stem cell factor and has been shown to promote survival, migration, and capillary tube formation HUVEC [49].

The other study by Zhu et al. [50] was conducted in China population. They investigated that 34 miRNAs were expressed differentially in PE placentas, compared to normal placentas.

Of these, 11 microRNAs were over-expressed, and 23 miRNAs were under-expressed in PE placentas. miR-518b showed significant overexpression in severe PE vs control; miR-18a, -363, and -542-3p were significantly underexpressed in severe PE vs control. miR-152 showed significant overexpression in mild PE vs control specimens and in severe PE vs control specimens. miR-411 and miR-377 were under-expressed in mild PE vs control specimens and in severe PE vs control. Zhu et al. [50] also found that miR-210 was significantly underexpressed in mild PE vs the other two groups; while significant overexpression was found in severe PE vs all other groups. In their comments, they mention that the increase in miR-210 expression in sPE induced by the focal regions of ischemia/hypoxia in placentas is the cause of poor placentation in PE pregnancies, as a previous study showed that the expression of miR-210 was increased on exposure to hypoxia [51]. They speculated the decrease of miR-210 in mPE to be a compensatory mechanism in the pregnancies with mPE, but there is no sufficient explanation.

Recently, Enquobahrie et al. [52] found that eight miRNAs were differentially expressed (miR-210 up-regulated and 7 – miR-328, miR-584, miR-139-5p, miR-500, miR-1247, miR-34C-5p and miR-1-down-regulated) among PE cases compared with controls. These miRNAs target genes that participate in organ/system development (cardiovascular and reproductive systems), immunologic dysfunction, cell adhesion, cell cycle, and signaling. In their comment consistent with the other scientist, they stated that miR-210 plays roles in endothelial cell response to hypoxia, formation of capillary-like structures, vascular endothelial growth factor – driven cell migration, cell differentiation, and survival, events that are integral to PE pathogenesis. Enquobahrie et al. [52] utilizing the results of previous study conducted by Ikeda et al. [53] speculated that miR-1 influences risk of PE through its effect on calcium signaling. They demonstrated that miR-1 influences calcium signaling through negative regulations of the calmodulin-coding mRNAs, Mef2a and Gata4, mainly in smooth muscle cells. It is believed that PE has associated with abnormal calcium metabolism and related consequences [54].

The association between PE and altered miRNA expression suggests the possibility of a functional role for miRNA in this disease. These different miRNAs may play an important role in the pathogenesis of PE and may become diagnostic markers and therapeutic target for PE.

3. Conclusion

In summary, we have shown that there are many scientific evidences that have proven the fact that the differential placental and plasma miRNA expression is associated with PE. Some researches also identify novel candidate miRNAs (and pathways they regulate) that may be of etiologic relevance in the pathogenesis of PE. It provides novel targets for further investigation of the pathogenesis of PE and these differential miRNAs may be potential markers for the diagnosis and provide a potential therapeutic target for PE. Further investigations on posttranscriptional regulation in PE to evaluate biologic effects of identified miRNAs (including the confirmations of miRNA and target gene interactions) are needed.

4. Disclosure statement

There is no conflict of interest in writing of this manuscript.

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