The role of some microRNAs in the pathogenesis of intrauterine growth restriction

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Abstract. MicroRNAs (miRNAs) are small RNA sequences, on average 22 nucleotides in length, with the ability to regulate gene expression in different organisms. Their action is mediated through the inhibition of translation or the promotion of mRNA degradation . Their genes are encoded within the genome, suggesting that their transcription might be coordinated with the transcription of other genes. In summary, generation of the mature miRNA molecule involves the processing of a primary miRNA transcript in the nucleus to obtain the final product in the cell cytosol, a small single RNA strand which participates in a variety of cellular processes (development, proliferation, function, and differentiation) and in the pathogenesis of many human diseases . miRNAs can target genes with relative specificity [1] .

Interestingly, recent studies have shown that miRNAs are also expressed in the placenta, suggesting a potential regulatory role in its development. In addition, some miRNAs have been described to be hypoxia-regulated and associated with intrauterine growth restriction [2].

Keywords: intrauterine growth restriction, microRNA, hypoxia, placenta

There are about 2,500 miRNA sequences which are known in humans (miRbase v21) , and it was predicted that 30–80% of the human genes may be influenced by at least one miRNA .

Human placental dysfunction has been associated with common complications of pregnancy, primarily preeclampsia and fetal growth restriction (IUGR) [3].

IUGR comprises two varieties: early-onset IUGR (<34 weeks) is less frequent and is characterized by the existence of placental disease, deceleration of fetal growth, and progressive hemodynamic dysfunction, typically affecting in its onset the uterine and umbilical Doppler examination, while late-onset IUGR (>34 weeks) is more frequent and is defined by the unbalance between fetal demands and placental supply, resulting in the detection of a characteristic low cerebroplacental ratio (CPR) regardless of the estimated fetal weight (EFW) Late-onset IUGR tends to be subtle. However, despite what might be thought, it is especially harmful, as it leads to frequently undiagnosed suboptimal arborization and brain underdevelopment [4].

IUGR entails significant fetal and maternal morbidity and mortality. Newborns surviving these pregnancies are at a higher risk of short- and long-term diseases during infancy, childhood, and adulthood [5].

Attempts to achieve a better understanding of placental dysfunction leading to intrauterine growth restriction have been hampered by insufficient in vivo models, inaccurate diagnostic tests, and limited therapeutic and preventive approaches.

Diagnostic imaging by sonography or magnetic resonance imaging has markedly improved in the last decade, yet their impact on elucidating disease pathobiology or on diagnostics in the context of these conditions has been limited [6].

The search for blood tests that can be harnessed for understanding diseases of human pregnancy has been bolstered by the identification of circulating placental proteins that may aid in disease diagnosis even before full clinical manifestation.

Intrauterine growth restriction is a syndrome with multiple causative pathways that often reflect earlier placental maldevelopment , and generally become symptomatic in the third trimester.

Maternal–fetal microRNAs uptake could modulate key pathways in pregnancy establishment and maintenance, from implantation to immune modulation. MiRNAs are sensitive to small changes in the cellular environment, making them potentially powerful biomarkers but difficult to delineate without proper patient stratification [7].

Partly owing to these challenges, investigations of the same pregnancy pathology have identified different altered miRNAs in the maternal circulation.

To date, most studies have focused on profiling maternal circulating miRNAs in intrauterine growth restriction diagnosed in the second trimester. This information could give some indication of markers or mediators of disease progression; however, any miRNA with value as a biomarker or plausibility as a mediator of pathogenesis must be measurably altered at the gestational week at which pathology arises, or at least before the current point of diagnosis. As such, miRNAs altered in early pregnancy are of most interest [8].

One of the most well characterized miRNAs in pregnancy complications is miR-210 . Under hypoxic conditions, miR-210 is upregulated by the transcription factor HIF-1α . The intrauterine environment in pregnancies complicated by IUGR or preeclampsia has been suggested to be hypoxic due to decreased perfusion of maternal blood to the feto-placental unit. miR-210-3p is common to all patient groups [9].

In many research works about IUGR the majority of miRNAs remained unique. There are some clusters: C19MC (520a-3p, 520f-5p, 515-5p, 519-5p), C14MC (299-3p, 494-3p, 376a-5p, 382-3p, 154-3p, 369-3p), the two miRNA clusters known to be specific to the placenta. Enrichment of gene targets in GO categories such as cell migration and proliferation is not a surprising finding since recent literature evidence has shown the role of miRNAs in these functions, in addition to cell invasion and differentiation [10].

Its interesting that intrauterine growth restriction pathogenesis includes the disorder of neuronal plasticity and cellular growth.

miR-148b seems to have special relevance in diverse molecular mechanisms related to neuronal hypoxia, neurogenesis, and neuronal metabolism and development. Particularly, miR-148b-3p upregulation promoted Schwann cell (SC) migration, whereas silencing of miR148b-3p inhibited SC migration in vitro . The molecular background of miR-148b-3p is in fact very interesting. It belongs to the miR-148/152 family , which includes miR-148a, miR-148b, and miR-152 and is considered a placenta-associated miRNA, which means it is expressed ubiquitously , not only in the placenta butalso in other tissues. Overexpression of miR-148-3p enhanced the migratory ability of SCs, while inhibition attenuated SC migration in vitro . These effects occur in unison with other miRNAs such as miR-132, miR-210, miRNA sc-3, miR-221, and miR-222, which also increase the migratory ability of SCs, and miRNA sc-8, miR-9, miR-98, miR-1, and miR-182, which diminish this ability [11].

A parallel may therefore be drawn between peripheral nerve repair and axonal development (arborization) in the central nervous system. A good example of this is miR-132, which apart from promoting peripheral nerve repair mediated by SCs, as indicated, has been

found to protect the central nervous system: miR-132 controls dendritic plasticity and is required for normal dendrite maturation in newborn neurons [12] .

Therefore, in an analogous way, miR-148b-3p might also play a role in the protection of the central nervous system.In theory, as brain tissue depends on myelination, miR148b-3p might contribute to the protection of brain tissue under different circumstances, such as in chronic hypoxia [13].

Regarding carbohydrates, miR-148b inhibits hypoxia-induced elevation of lactate production and hypoxia-induced increase in glucose consumption, thereby reducing cellular growth . Regarding amino acids and proteins, miR-148b-3p and miR-25-3p behave as key regulators of biosynthesis of valine, leucine, and isoleucine and also regulate protein processing at the endoplasmic reticulum, both pathways of special relevance to fetal growth during the last trimester of pregnancy and during periods of nutritional deprivation. Finally, regarding fatty acid metabolism, both miR-25-3p and miR148b-3p control biosynthesis of fatty acids and sphingolipids , essential molecules for stem cell differentiation morphogenesis and embryo development that are also related to preeclampsia and IUGR [14].

Since the pathological processes precede the clinical signs and symptoms of IUGR, it is possible that the miRNAs identified in different studies may be altered in the maternal circulation early in pregnancy and may serve as potential biomarkers that may predict the disorder.

Future studies may include analysis of maternal plasma samples completed retrospectively by measuring miRNA levels in plasma samples obtained early in pregnancy as a part of routine clinical care to more accurately assess diagnostic value across gestation.

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