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The Role of Exosomes in the Pathogenesis of Intrauterine Growth Restriction (IUGR): Future Perspective

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Abstract

Background: Exosomes are among the factors whose importance has been shown in many diseases today. Recently, it has been shown that exosomes play an important role in the pathogenesis of Intrauterine Growth Restriction (IUGR); however, few studies have been conducted in this regard.

Methods: The articles in this review study were retrieved from some databases including PubMed, Google scholar, and Scopus. All the included articles were in English, and those in other languages were excluded. Search keywords included IUGR, exosome, pathogenesis, Mechanism, Cell Signaling, Oxidative Stress, Inflammation, and Endothelial Dysfunction.

Results and conclusion: Studies have shown that exosomes contain factors, molecules and gene activators that affect molecular pathways regulation. These molecules play an important role in regulating inflammatory reactions, oxidative stress, and production of Reactive Oxygen Species (ROS). The activation of these pathways can aggravate the clinical symptoms of IUGR. In addition, exosomes can impress induction or inhibition of endothelial dysfunction, which leads to the development of IUGR. Hence, identifying upstream and downstream pathways helps design therapeutic strategies to treat patients.

Key Words: Exosome, Intrauterine Growth Restriction, Mechanism, Pathogenesis.

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1- INTRODUCTION

Intrauterine Growth Restriction (IUGR) is a condition in which the growth rate of the fetus decreases due to pathological factors (1, 2). The prevalence of this disease is different in different parts of the world, but on average, it happens in 5-20% of pregnancies (3). The clinical symptoms are organ failure, extreme thinness, paleness, and dry skin (4). Pathological factors that cause these conditions include maternal causes (blood pressure, diabetes, anemia, and malnutrition), fetal causes (genetic disorders such as aneuploidy, fetal infections, and congenital anomalies), and placental insufficiency (5).

On the other hand, exosomes are one of the causes of IUGR. Exosomes are a collection of extracellular vesicles with an average diameter of 100 nm. They originate from different organs and could transfer different molecules (6). Exosomes that originate from the placenta carry products, which affect various reproductive processes such as fetus and placenta development and also the adaptation of the mother and fetus during pregnancy; it is possible that if this system is affected, the IUGR phenomenon will occur (7, 8). In this study, we intend to investigate the role and function of exosomes in the pathogenesis of IUGR.

1-1. Search strategy

The articles in this review study were retrieved from some databases including PubMed, Google scholar, and Scopus. All the included articles were in English, and those in other languages were excluded. Search keywords included IUGR, exosome, pathogenesis, Mechanism, Cell Signaling, Oxidative Stress, Inflammation, and Endothelial Dysfunction.

1-2. Exosome and inflammation

Inflammation is one of the events that contributes to IUGR (9). CD81 increases the expression of IL-6 by activating the JAK/STAT pathway. IL-6 increases the differentiation of naïve T cells to TH17, and suppresses Treg cells followed by increased inflammation. Increased expression of CD81 is seen in IUGR. Therefore, CD81 targeting can be considered as a therapeutic pathway (10). By inhibiting the JAK1/STAT3 pathway, CD63 reduces the expression of IL-6 and IL-27 followed by reduced inflammation. Decreased expression of CD63 has been observed in IUGR. Therefore, increasing the expression of CD63 can reduce inflammation and prevent the progression of IUGR (11).

The mir-1-3p suppresses the ETS1 gene by activating the TLR/MYD88 pathway. ETS1 prevents the interaction between NF-kB and CREB molecules; NF-kB and CREB binding increases the expression of MUC5AC, and subsequently promotes inflammation. On the other hand, by suppressing the ETS1 gene, mir1-3p facilitates the differentiation of naïve T cells into TH17 and finally causes inflammation. Increased expression of mir-1-3p is seen in IUGR. Therefore, targeting mir-1-3p can help in the treatment process of patients (12, 13). FASL, mir-520a, mir-16-5p, and mir-26-5p molecules reduce the NF-kB level by suppressing TLR/MYD88 pathway. FASL and mir-520a cause degradation of the P65 subunit of NF-kB and subsequently suppress inflammation (14, 15).

Mir-16-5P decreases PDCD4 expression by inhibiting the TLR/MYD88 pathway. PDCD4 activates the NF-kB and increases inflammation. Decreased expression of mir-16-5P has been reported in IUGR (16). Mir-26-5P reduces CTGF expression by inhibiting the TLR/MYD88 pathway. This gene is also one of the NF-kB activators (17). Mir-100-5P inhibits the mTOR pathway and reduces its expression. mTOR is one of the molecules that increases the process of protein synthesis

and energy production, and increasing the expression of this molecule causes the inflammation process to intensify. Therefore, reducing the expression of mTOR molecules, which occurs due to being targeted by mir-100-5P can be used as a therapeutic strategy for IUGR (18).

Mir-145-5p reduces the expression of TLR4 and MUC1 genes by inhibiting the TLR/MYD88 pathway. Decreased expression of Mir-145-5p has been observed in IUGR (19). Mir-125-5p, mir-146a-5P and mir-548e-5p molecules decrease TRAF6 gene expression by inhibiting the RAS/MAPK and TLR/MYD88 pathways. TRAF6 is one of the activators of NF-kB and MAPK molecules. The expression of mir-125-5p, mir-146a, and mir-548e-5p decreases in IUGR; it can create a new way to treat IUGR by targeting the target molecules of these miRs (20, 21).

Mir-126-5p reduces HIF1 gene expression by inhibiting the PI3K/AKT pathway. On one hand, HIF1 activates NF-kB and on the other hand, it increases the proliferation of immune system cells (22). Mir-195-5p reduces ATF6 gene expression by inhibiting the TLR/MYD88 pathway. ATF6 increases its expression in response to endoplasmic reticulum stress and subsequently increases TNFα expression and causes inflammation (23). Mir-199-5p reduces the expression by inhibiting the mTOR pathway. Rheb, directly, activates mTOR and increases the inflammation. Mir-199-5p expression is observed in IUGR (24).

Mir-210 decreases DR6 expression by inhibiting the TLR/MYD88 pathway. DR6 is an NF-kB activator that increases inflammation (25, 26). Mir-221-3p reduces apoptosis and inflammation by inhibiting the CDKN1B (27). Mir-342-3p decreases AEG-1 expression by inhibiting the TLR/MYD88 pathway. AEG-1 is also a NF-kB activator that can increase inflammation (28). Mir-518b decreases RAP1B expression by inhibiting the RAS/MAPK pathway. RAP1B increases the migration of neutrophils and also the expression of IL-6. Decreased expression of mir-518b has been observed in IUGR (29, 30). In general, it can be concluded that inflammation has an important role in various diseases, including IUGR. Thus, we can take an important step in the diagnosis and treatment of IUGR by identifying molecules that can cause or increase inflammation.

1-3. Exosome and oxidative stress

One of the important factors in the IUGR occurrence is the increase of molecules resulting from the oxidative stress process during pregnancy. In addition to IUGR, ROS increment can affect the occurrence of other diseases such as preeclampsia and gestational diabetes. Therefore, we can identify the effective molecules and use them in the diagnosis, treatment, and prognosis determination (31). By inhibiting the RAS-MAPK pathway, mir-1-3p decreases IGF1 expression, and then increases ROS in the cells. Inhibiting mir-1-3p is one of the appropriate therapeutic tools, for example, a drug called propofol has been designed to inhibit this molecule and reduce the amount of ROS in cells to treat colorectal cancer (32, 33).

Mir-26-5p reduces ADAM17 gene expression by suppressing the notch-delta signaling pathway. This gene, under the influence of ROS molecules, causes further inflammation and cell damage. In this way, the observation of a decrease in the expression of mir-26-5p in IUGR can be understood and explained (34). Nox4 or NADPH OXIDASE 4 is one of the molecules increasing the amount of ROS in the cell under the influence of JAK-STAT and PI3K-AKT pathway. On the other hand, mir-100-5p by targeting the nox4 reduces ROS production. Mir-100-5p down expression can be seen both in the process of inflammation and production of oxidative substances (35).

Mir-195-5p, mir-145-5p, and mir-125-5p suppress VEGF and TGFB by inhibiting the PI3K pathway, which finally prevents the production of oxidant substances. TGF-β can control ROS production directly or by reducing the antioxidant systems. Meanwhile, ROS elevation can also lead to TGFB up regulation. ROS elevation is also associated with VEGF increment; moreover, the VEGF molecule itself increases the amount of ROS in the cells by inducing the angiogenesis process (36, 37).

One of the important mechanisms of the cell to deal with oxidative substances is to activate the NRF2/SIRT1 signaling pathway. The activation of NRF2 increases the production of effective proteins on oxidant inhibition. Mir-126-3p reduces oxidants by activating the SIRT1/Nrf2 signaling pathway. Decreased expression of this molecule is observed in IUGR (38). Mir-199-5p decreases CAV1 expression through activating the NRF2 pathway. The CAV1 induces cell autophagy under the oxidative stress conditions, while mir-199-5p activates NRF2 by inhibiting the CAV1; as mentioned in the previous section, NRF2 activation increases the production of antioxidant proteins.

One of the weapons of war and bioterrorism is chemical substance (Sulfur mustard). This molecule can cause fatal damage to the body by increasing the oxidants in the lungs. Increasing the expression of mir-199-5p can significantly reduce this mortal damage, which proves the therapeutic role of this molecule (39). Mir-103-3p and mir-210 decrease the expression of BNIP3 through inhibiting the autophagy pathway. In line with ROS elevation, BMIP3 is activated as a sensor and moves the cell towards autophagy. Therefore, ROS increment is associated with BNIP3 up-regulation and mir-103-3p and mir-210 downregulation. Mir-210, mir-103-3p, and BNIP3 can be used as determining factors in detecting the progress in the oxidative stress process. Decreased expression of mir-210 and mir-103-3p has been observed in IUGR (40-42).

Mir-221-3p down regulates the HIF1α expression through inhibiting the PI3K/AKT pathway. The HIF1α gene can cause angiogenesis by activating the VEGF, and inflammation in different tissues by activating the NF-kB. In this way, increasing the expression of mir-221-3p can play a therapeutic role in IUGR (43). Mir-517a downregulates CDKN1C expression through inhibiting the JNK pathway. Silencing the mir-517a molecule increases the expression of CDKN1C, increases cell proliferation, and consequently increases the amount of ROS in the cells. The expression of HIF1α increases under hypoxia conditions (44). On the other hand, it can act as a transcription factor for many other molecules, including HLA-G. Researchers have observed a link between hydrogen peroxide increment and HLA-G; so, it can be concluded that the increased level of HLA-G can be used as a diagnostic or therapeutic strategy (45, 46).

1-4. LncRNAs and endothelial dysfunction

One of the important causes of IUGR is endothelial cell (EC) dysfunction. It is also effective in preeclampsia and other complications caused by placental syndrome. Therefore, it is important to identify the molecular pathways involved in EC dysfunction in the process of timely diagnosis, prevention, or treatment of the disease (47).

The exosome derived from platelet-rich plasma (PRP-exosome) leads to dysfunction of retinal vascular endothelium through activation of TLR4 signaling pathway. TLR4 signaling in EC may be stimulated by LPS and oxidized phospholipids and can lead to endothelial activation and inflammation. LPS leads to

the activation of TLR4 through the signaling pathways of NADPH oxidase, ROS, Endothelial nitric oxide synthase (eNOS), MAPK, and NFκB, which lead to inflammation and EC dysfunction. This mechanism is also effective in placental vascular endothelium disorder and IUGR (48-50).

Increased expression of miR-143/145 by activating the TGFb1 signaling pathway causes disruption in the differentiation and function of pulmonary artery smooth muscle cells (PASMC); it is also a possible mechanism for increasing the pulmonary artery pressure in patients. TGFb1 exerts strong effects on EC and SMCs. The release of large amounts of TSP1 (thrombospondin 1) and TGEB1 from activated platelets through an increased response to collagen may lead to increased proliferation of EC. Inhibitors of TSP1 or its receptor CD47 may stop aberrant cell proliferation in the vascular endothelium. In general, the role of TSP1 and galectin-3 in inducing EC dysfunction through TGFB1 signaling pathway can be used in the treatment of patients. TGFb1 reduces the production of NOS and instead increases the production of endothelial NOS. Increased expression of mir-143 is seen in the vascular smooth muscle layer of the patients with increased pulmonary artery pressure. The same mechanism can lead to placental vascular EC dysfunction and cause IUGR (51, 52).

Trimethylamine-N-oxidase (TMAO) is a new factor causing inflammation and EC dysfunction. By stimulating the cell, it triggers exosome production; it also leads to the induction of cell inflammation and apoptosis through NF-kB signaling pathway activation. This signaling pathway is activated by the advanced glycation end product (AGE) receptor and is a key regulator of inflammation and oxidative stress. By stimulating the oxidative stress, it leads to the dysfunction of placental vascular EC and lays the foundation of IUGR creation. On the other hand, inhibiting this signaling pathway limits the vicious cycle of inflammation and oxidative stress; this mechanism can be used for therapeutic purposes.

Various studies have shown the impressive role of AGE receptors in cellular processes, such as inflammation, degradation, and oxidative stress (53-55). The death of ECs leads to the release of apoptotic-exosome like vesicles (APOExo). APOExo regulates the survival of EC and affects migration, angiogenesis, and cell differentiation. ECs that are exposed to APOExo through the activation of NF-kB signaling pathway show reduced levels of apoptosis and angiogenesis activity; it also leads to dedifferentiation and gradual loss of ECs related markers as well as acquirement of Mesenchymal cell (S100A4, αSMA) markers. Finally, vascular dysfunction occurs. NF-κB silencing reverses the anti-apoptotic and pro-migratory effects and prevents the angiostatic properties and CD31 downregulation in ECs exposed to ApoExo. ApoExo has been identified as a novel inducer of NF-κB activation in ECs; it shows the pivotal role of this signaling pathway in coordination with the ApoExo-induced functional changes in ECs. Hence, targeting the ApoExo-mediated NF-κB activation in ECs provides novel avenues to prevent EC dysfunction (56). Activation of this signaling pathway in pregnant women leads to IUGR and other disorders related to placental vessels (56, 57).

miR-34a leads to dysfunction of vascular endothelium and acceleration of end organ damage through the oxidant-sensitive mechanism and reducing the activity of Sirt 1 signaling pathway. Activation of SIRT1 by 1720SRT ameliorates EC dysfunction with aging through increasing the COX-2 signaling and reducing the oxidative stress and inflammation. Specific activation of SIRT1 is a promising therapeutic strategy for age-related EC

dysfunction in humans. Oxidative stress is the main mechanism of this signaling pathway in placental vascular endothelial dysfunction (58).

Microtubulin inhibitor MT189 suppresses angiogenesis by reducing the EC proliferation, migration, and differentiation through the JNK-VEGF/VEGFR-2 signaling axis. miR-210 also leads to EC protection against oxidative stress through the activation of the VEGF/VEGFR2 signaling pathway. Neural Progenitor Cells (NPCs) protect ECs against oxidative stress caused by AngII, which leads to apoptosis and EC dysfunction. As a therapeutic target, this mechanism can be used in the IUGR treatment and reduce the effect of oxidative stress caused by AngII in the placental vascular endothelium (59).

Exosomal miR424-5p induced by the endoplasmic reticulum-stressed head and neck squamous cell carcinoma leads to the inhibition of angiogenesis and migration of ECs through the inactivation of the Wnt/B catenin signaling pathway. IL-8, a known angiogenesis factor, is also a transcriptional target of the Wnt/B catenin signaling pathway in ECs. Expression of Wnt-1 or B-cateninS37A induces IL-8 expression. Therefore, it could be concluded that the cited signaling pathway probably induces angiogenesis through the induction of known angiogenesis regulators such as IL-8. A similar mechanism can play a role in placental EC dysfunction and IUGR (**Table 1**) (60, 61). IL-1- associated Kinase-1 (IRAK-1) and TNF receptor-associated factor 6 (TRAF6) have been identified as the direct targets of mir-155. It can directly bind to the NF-kB P65.

All these target genes are important mediators of inflammation and EC dysfunction. In fact, Exosomal mir-155 also leads to endothelial and mitochondrial cell dysfunction by activating the NF-kB signaling pathway; it could be also useful as a therapeutic target for pregnancies complicated by IUGR and other disorders related to placental vessels (62).

Table-1: Potential therapeutic mechanisms of exosome from different sources

Source	Mechanism	Ref.
umbilical cord blood	Increased expression of mir-150 causing angiogenesis	(63)
pulmonary vascular endothelial cells and pulmonary arterial smooth muscle cells	mir-214-3p, mir-326-3p, and mir-125b-2-3p inhibition FoxM1 expression and decreased pulmonary hypertension in IUGU	(64)
fibroblast	mir-200 expression causing angiogenesis	(65, 66)
Mesenchymal cell	mir-20 expression causing angiogenesis	(67, 68)

2- CONCLUSION

In general, exosomes contain many molecules, factors, and regulators of gene expression, each of which regulates different molecular pathways. However, most of them are involved in inflammation induction and ROS production as well as endothelial dysfunction. These factors can contribute to the exacerbation of IUGR. Hence, the identification of upstream and downstream pathways can play an important role in designing therapeutic strategies.

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