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MINI REVIEW

Placental Exosomes Trigger Maternal Inflammation and Vascular Dysfunction in Preeclampsia

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ABSTRACT

Preeclampsia is a pregnancy-specific disease associated with inadequate placental formation, chronic inflammation, and maternal vascular dysfunction. Preeclampsia affects about 5-8% of pregnant women and it is a prevalent cause of maternal mortality. The level and composition of exosomes in the maternal circulation are altered in preeclampsia, and studies have shown that the major source of this greater level of exosomes is the placenta. We propose that exosomal contents from the placenta trigger maternal inflammation and vascular dysfunction, thereby exacerbating the disease progression. This mini-review will focus on the content of placental exosomes and how they could contribute to the development of preeclampsia.

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PREECLAMPSIA

Preeclampsia, previously known as toxemia, is a pregnancy condition that usually begins after 20 weeks of pregnancy, during labor, or early postpartum [1]. This condition is characterized by hypertension, proteinuria, and organ dysfunction and in more severe cases, restrictions in fetal growth in an otherwise healthy woman [2]. It could also be characterized by swelling of the hands, legs, and feet and has been known to lead to blood clotting impairment [3]. It affects 5-8% of all pregnancies and about 1 in 25 pregnancies in the United States [4]. Preeclampsia is a major contributor to fetal and maternal morbidity and mortality in pregnancy [5,6]. Some severe cases of preeclampsia lead to eclampsia, which is characterized by seizures and coma. Currently, the only effective treatment is the delivery of the fetus and the placenta. In addition to the cardiovascular risks to the mother and fetus during pregnancy, preeclampsia is independently associated with a higher risk of cardiovascular disease later in maternal life [7-9].

PATHOPHYSIOLOGY OF PREECLAMPSIA

The exact cause of preeclampsia is not known, and as preeclampsia is a complex clinical syndrome, several pathogenetically important events in the development of preeclampsia have been described in the etiology of the disease [10]. These events include aberrant vascular remodeling and poor cytotrophoblast invasion of the spiral arteries. This shallow remodeling leads to decreased uteroplacental perfusion and consequently preeclampsia [10]. Studies of basal plates of placentas of abnormal pregnancies demonstrated that the spiral arteries remain as small resistance vessels and do not transform into large, dilated vessels with the increased flow at reduced pressure as in unaffected pregnancies. It was observed that the remodeling

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of the spiral arteries that occurs in normal pregnancy was inadequate or completely absent in preeclampsia [11]. Furthermore, the defective uteroplacental blood flow leading to preeclampsia has been studied in animal models. Findings suggest that although, the initiating event is thought to be decreased uteroplacental perfusion as a result of aberrant vascular remodeling, the main cause of this aberrant remodeling is currently unknown, and several maternal factors have been proposed to contribute to clinically overt preeclampsia, including environmental, genetic and immunologic factors [12,13].

Another potentially important contributor to the pathophysiology of this condition is the increased levels of circulating soluble fms-like tyrosine kinase-1 (sFlt-1). sFlt-1 is an antiangiogenic factor expressed as an alternatively spliced variant of Vascular Endothelial Growth Factor Receptor 1 (VEGFR-1) that lacks both the transmembrane and cytoplasmic domains. sFlt-1 binds VEGF and Placental Growth Factor (PlGF) and blocks their angiogenic effects of VEGFR. sFlt-1 may also form a heterodimer with the surface membrane VEGFR-1 and inhibit its post-receptor signaling actions [14]. An imbalance between sFlt-1, VEGF, and PlGF that favors anti angiogenesis has been reported in preeclampsia [15-17]. Endoglin (Eng) is another antiangiogenic soluble factor that is highly expressed in vascular endothelial cells and, along with sFlt-1, has been related to cardiac dysfunction during pregnancy in human mothers with preeclampsia [18]. Eng interacts with sFlt-1 to increase its effects on angiogenesis [19].

Innate and adaptive immunity in preeclampsia

It has been suggested that preeclampsia is an immune disease and is initiated by the generation of Damage-Associated Molecular Patterns (DAMPs) in response to aberrant placentation, oxidative stress [20], and endothelial dysfunction. DAMPS activate the innate immune system through recognition by Toll-like Receptors (TLRs) [21]. DAMPs are usually contained within the cells, but during some disease conditions where the cell is stressed or damaged, these molecules are expressed on the cell surface and also diffuse out of the cell into the extracellular space where they are transported to other cells and are sensed by the TLRs as danger and the immune system is activated [22]. Studies have shown that TLRs are expressed in the human placenta and contribute to the establishment of pregnancy [23]. Furthermore, excessive activation of TLRs during pregnancy triggers preeclamptic-like symptoms in rodents [24,25]. Double-Stranded RNA (dsRNA) is believed to be the most potent viral trigger of the innate immune signaling [26]. Viral dsRNA is sensed by TLR3 which also recognizes endogenous dsRNA [27]. Activation of TLR3 using the exogenous ligand, poly I:C led to the development of preeclamptic-like symptoms in both pregnant rats and mice [28]. However, the molecular mechanism underlying the development of hypertension was not elucidated and warrant further investigation.

Exosomes exert effects in distant tissues

Exosomes are extracellular vesicles released by all cells, they are composed of a lipid bilayer containing transmembrane protein and they carry nucleic acids, proteins, lipids, and metabolites into the extracellular environment (Figure 1). They are mediators of near and long-distance intercellular communication in health and disease and affect various aspects of cell biology [29]. They were first described in 1981 by Trams et al. in cultures of normal or neoplastic cells [30]. These cells were able to exfoliate micro-vesicles of 500-1000 nm diameter and contained a second population of vesicles of about 40nm diameter, with the ecto-enzyme activity of 5'-nucleotidase. The micro-vesicles (of about 40 nm diameter) released from the plasma membrane were then referred to as exosomes [30]. Exosomes are generally classified as extracellular vesicles measuring between 30-150nm diameter, that are formed by late endosomes [31]. Exosome formation occurs from endosomes. First, the lumen of the endosomes becomes full of intraluminal vesicles, this leads to an inward budding and forming small vesicles containing endosome-derived molecules known as the multivesicular bodies or MVB [32]. Secondly, the small vesicles then fuse to the plasma membrane and are then secreted into the extracellular space through exocytosis [33]. Exosomes are taken into target cells by different mechanisms including endocytosis, micropinocytosis, phagocytosis, and internalization [34]. Exosomes mediate selective intercellular communication, and the effect of the exosome on a target tissue is determined by the composition of the proteins/glycoproteins present on the surface of the exosomes and the target cells [35].

Apart from mediating intercellular communication, exosomes carry out other physiological and pathophysiological functions. These functions include the progression of cancer [36-39]. Identification of key proteins and microRNA (miRNAs), circular RNAs (circRNA), or long non-coding RNA (lncRNA) associated with different diseases including type 2 diabetes, nephropathy, aldosteronism, atherosclerosis, and several types of cancer (bladder, gastric, prostate cancers) [40-44]. The studies in cancer convincingly demonstrated that exosomes could have significant effects in distant tissues.

Studies have shown that injected exosomes are efficient at entering other cells and can deliver a functional cargo with minimal immune clearance upon exogenous administration. Importantly, the cargos within an exosome reflect the pathophysiological state of the originating cell [45]. The cargos can activate cell surface receptors or/and be taken up by or incorporated into recipient cells, leading to changes in the cellular phenotypes. Lee, et al. [46] recently demonstrated that the mitochondria dsRNA generated by alcohol-associated stress in hepatocytes is delivered by exosomes to activate TLR3 in Kupffer cells. Activation of TLR3 by the exosomal dsRNA stimulates the production of

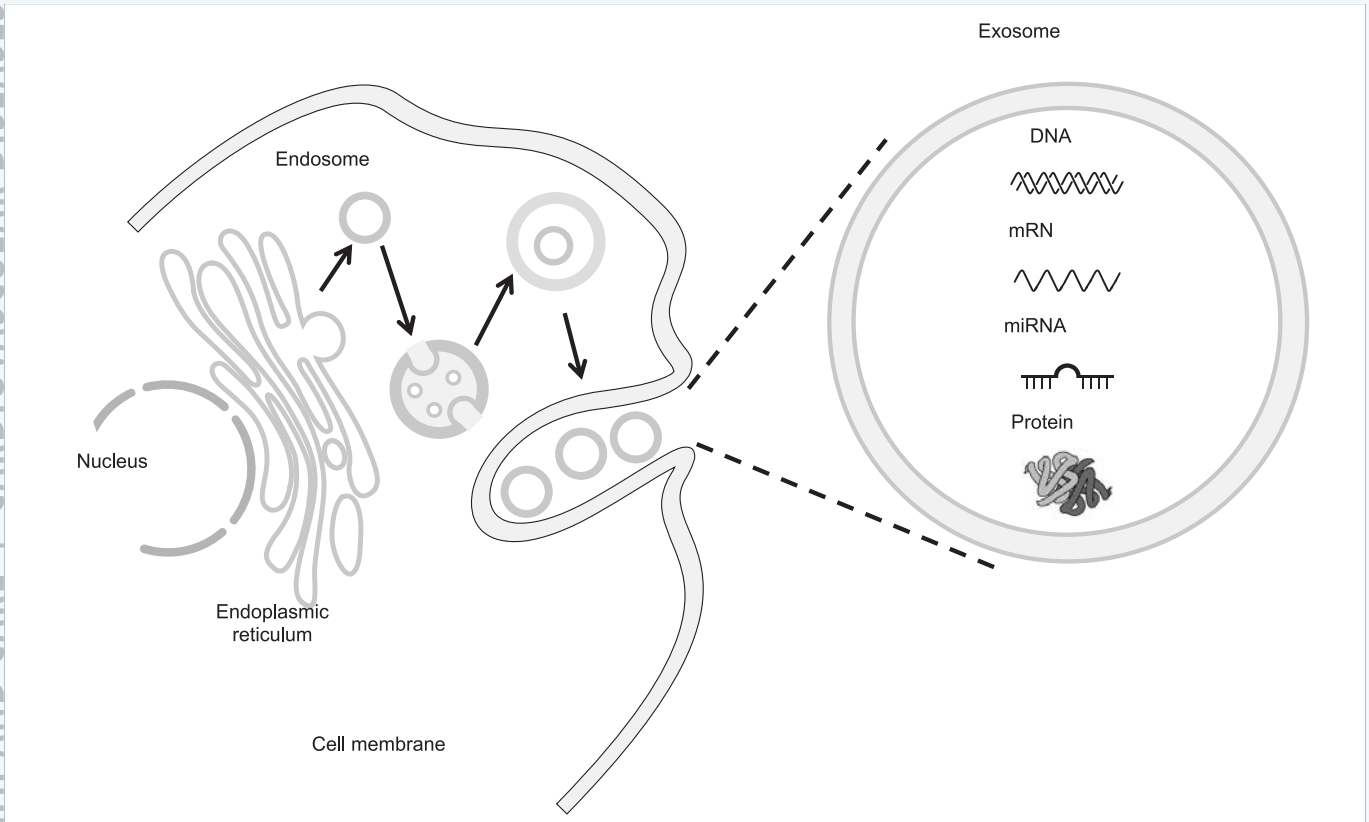

Figure 1 Biogenesis, secretion, and constituents of exosomes.

IL-1β. A study also demonstrated that plasma exosomes regulate systemic blood pressure in rats [47], but the mechanism was not elucidated.

Exosomes are released in pregnancy - what happens in preeclampsia and what do they do?

The concentration of circulating exosomes during normal pregnancy is increased, and it has been reported that the increase in circulating exosomes is greater in preeclampsia [48,49]. Furthermore, the concentration of circulating exosomes in hypertensive pregnant women directly correlates with the disease severity [48,50]. Apart from this increase, the exosomal contents are also altered in preeclampsia. Evidence for this was provided by groups who studied exosomes from normotensive and preeclamptic women and observed that exosomes-released sEng and sFlt-1 were increased in the maternal circulation of preeclamptic women [51,52]. Furthermore, the altered exosomal contents in preeclampsia are biologically active and stimulate adverse effects including attenuating the proliferation, migration, and tube formation of human umbilical vein endothelial cells in vitro, and in a mouse model, exosomes from preeclamptic women caused vascular dysfunction, elevated their blood pressure, and these mice also had a decreased body weight compared to their controls [52]. The placenta secretes exosomes into the maternal circulation [53]. However, other sources of the maternal circulating exosomes include B cells, T cells neutrophils, and endothelial cells [49]. The concentration of exosomes originating from the placenta increases in a time-dependent manner throughout pregnancy [53]. The exosomes are taken up into the target maternal cells by endocytosis.

These changes in the release, concentration, composition, and bioactivity of exosomes in preeclampsia versus normotensive pregnancy have led to exosomes being currently evaluated as potential biomarkers for preeclampsia. Also, exosomes can be isolated from the blood of women in early pregnancy; they can be targeted in the intervention of preeclampsia and also in the early prediction of the development of the disease. Taken together, these data suggest that exosomes could mediate or facilitate the maternal vascular dysfunction observed downstream of placental ischemia.

CONCLUSION AND FUTURE DIRECTIONS

The exact role of exosomes in the pathophysiology of preeclampsia is not yet completely understood, but the current knowledge indicates that exosomes play a role in the pathophysiology of the disease. Apart from aberrant placenta formation and vascular remodeling and maternal vascular dysfunction, chronic inflammation is one of the major hallmarks of preeclampsia [54]. In preeclampsia, it has been reported that placental ischemia results in the

release of pro-inflammatory cytokines [55], these cytokines interact with the maternal vascular wall to induce maternal vascular dysfunction [10]. The contents of the placenta-derived exosomes are also altered induces adverse effects on maternal function and pregnancy outcomes [56]. The role of exosomes from non-placental cells in mothers affected by preeclampsia has also not been well-defined.

Exosomes derived from preeclamptic women must be studied to reveal the state of the parents' cells, reveal the specific alterations in the exosomal contents associated with preeclampsia, and pave the way in developing therapeutic targets for this disease.

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