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REVIEW

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Mesenchymal Stem/Stromal Cells and Their Role in Oxidative Stress Associated with Preeclampsia

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Preeclampsia (PE) is a serious medically important disorder of human pregnancy, which features *de novo* pregnancy-induced hypertension and proteinuria. The severe form of PE can progress to eclampsia, a convulsive, life-threatening condition. When placental growth and perfusion are abnormal, the placenta experiences oxidative stress and subsequently secretes abnormal amounts of certain pro-angiogenic factors (eg, PlGF) as well as anti-angiogenic factors (eg, sFlt-1) that enter the maternal circulation. The net effect is damage to the maternal vascular endothelium, which subsequently manifests as the clinical features of PE. Other than delivery of the fetus and placenta, curative treatments for PE have not yet been forthcoming, which reflects the complexity of the clinical syndrome. A major source of reactive oxygen species that contributes to the widespread maternal vascular endothelium damage is the PE-affected decidua. The role of decidua-derived mesenchymal stem/stromal cells (MSC) in normotensive and pathological placenta development is poorly understood. The ability to respond to an environment of oxidative damage is a "universal property" of MSC but the biological mechanisms that MSC employ in response to oxidative stress are compromised in PE. In this review, we discuss how MSC respond to oxidative stress in normotensive and pathological conditions. We also consider the possibility of manipulating the oxidative stress response of abnormal MSC as a therapeutic strategy to treat preeclampsia.

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Abbreviations: ALDH, aldehyde dehydrogenases; MSC, mesenchymal stem/stromal cells; DMSC, decidua MSC; EVT, extravillous cytotrophoblast; PE, preeclampsia; HUVEC, human umbilical vein endothelial cells; MDA, malondialdehyde; miR, microRNAs; NO, nitric oxide; eoPE, Early onset PE; loPE, late onset PE; PlGF, placental growth factor; PDGF, platelet-derived growth factor; PDGF-Rβ, platelet-derived growth factor receptor-β; sFlt-1, soluble fms-like tyrosine kinase-1; RONS, reactive oxygen and nitrogen species; TH1, T helper-1; UC-MSC, umbilical cord human MSC; vWF, von Willebrand Factor.

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DEFINITION AND CLINICAL FEATURES OF PREECLAMPSIA

The birth of a healthy infant at term depends on normotensive placental development, whereas abnormal placentation is associated with a variety of pregnancy complications [1]. Among these complications, preeclampsia (PE) is the most important in the clinic. PE is a major cause of maternal, fetal, and neonatal morbidity and mortality [2]. The ISSHP and ACOG Committees define PE as new-onset hypertension and proteinuria after gestational week 20, or new onset of PE-associated signs in the absence of proteinuria [3].

PE can be divided into two major subtypes based on the time of delivery. Early onset PE (eoPE) cases deliver before 34 weeks and are associated with significant deleterious short- and long-term health consequences for both mother and baby, whereas late onset PE (loPE) cases deliver after 37 weeks with health consequences primarily affecting the mother. An important difference between these subtypes is poor placentation and fetal growth restriction, which is associated with eoPE. On the other hand, maternal factors are suggested to cause loPE, without significant placental involvement [4]. However, the etiology of PE, particularly of loPE is not completely understood and an alternate model posits that eoPE and loPE both feature placental dysfunction before the onset of clinical features, but the causes and timing of the placenta dysfunction differ [5].

PE left untreated, increases the risk that the patient will progress to eclampsia with accompanying convulsions, stroke, and death [6]. Clinical experience shows that the mother and the fetus benefit from early detection, careful monitoring of the pregnancy and timing of delivery, and supportive care [7]. Despite decades of intensive research, the incidence of PE remains unchanged. Delivery of the baby and removal of the placenta remain the only effective cure, regardless of gestational age. Here, we review the role of a novel cell type called mesenchymal stem/stromal cells in oxidative stress associated with PE and highlight the potential of these cells as therapeutic agents in treating PE and potentially other oxidative stress-related syndromes and diseases.

THE MATERNAL-FETAL INTERFACE IN NORMOTENSIVE PREGNANCIES AND IN PE

Normal Placental Development and Oxidative Stress

The human placenta is a complex, vascular organ that facilitates gas and nutrient exchange between the fetal and maternal circulations. Throughout gestation, the placenta develops an intimate association between the fetal tissues and the maternal decidua vasculature, and in doing so, forms a maternal-fetal interface that is essential for meeting the increasing metabolic requirements of the rapidly growing fetus [8]. Proper development of the maternal-fetal interface is essential for a successful pregnancy. Two units comprise the maternal-fetal interface; the chorionic plate (ie, the amnion, the extra-embryonic mesenchyma, and placental villi that are enveloped by an inner layer of villous cytotrophoblasts and an outer syncytiotrophoblast layer) and the basal plate (ie, extravillous trophoblast, maternal decidua, and the inner myometrium). The intervillous space comprises the intervening maternal-blood filled region (Figure 1). Placental villi are the functional units of the placenta that contain fetal blood vessels. The fetal blood circulation in the human term placenta is separated from the maternal blood circulation by the outer syncytiotrophoblast layer of the placental villi, which acts as a barrier preventing exposure of the fetal blood vessels to maternal blood circulating in the intervillous space [9].

A hallmark of normotensive pregnancies is the differentiation of villous cytotrophoblast cells into extravillous cytotrophoblast (EVT) at the tips of some placental villi. EVT proliferate and form columns of cells that undergo further differentiation, allowing EVT to migrate and invade into the maternal decidua and underlying inner myometrium (Figure 1). This process facilitates the anchoring of the placenta into the uterus. Most important is that migratory and invasive EVT encounter the maternal spiral arteries that supply blood to the intervillous space. EVT replace the resident vascular endothelial cells and other components of the vascular niche, including smooth muscle cells and the elastic lamina. This process transforms spiral arteries and they become distended, thin-walled flaccid vessels that allow increased low velocity blood flow into the intervillous space. The increased blood flow allows the placenta to cope with the ever-increasing demands for nutrient and waste products exchange by the rapidly growing fetus (Figure 1).

Oxidative stress plays a key role in normotensive placental development and features an imbalance between the production of reactive oxygen and nitrogen species (RONS), and the capacity of antioxidant defenses to scavenge the RONS. The onset of the maternal blood circulation into the placenta coincides with a burst of oxidative stress that triggers placental villous differentiation, EVT invasion, and the production of angiogenic factors [10,11].

The placenta is a major contributor to increased oxidative stress that is common among pregnant women. Elevated lipid peroxidation is a common feature of normotensive pregnancy [12,13]. Lipid peroxidation products, including malondialdehyde (MDA), lipid hydroperoxides and thiobarbituric acid reactive substances, are elevated

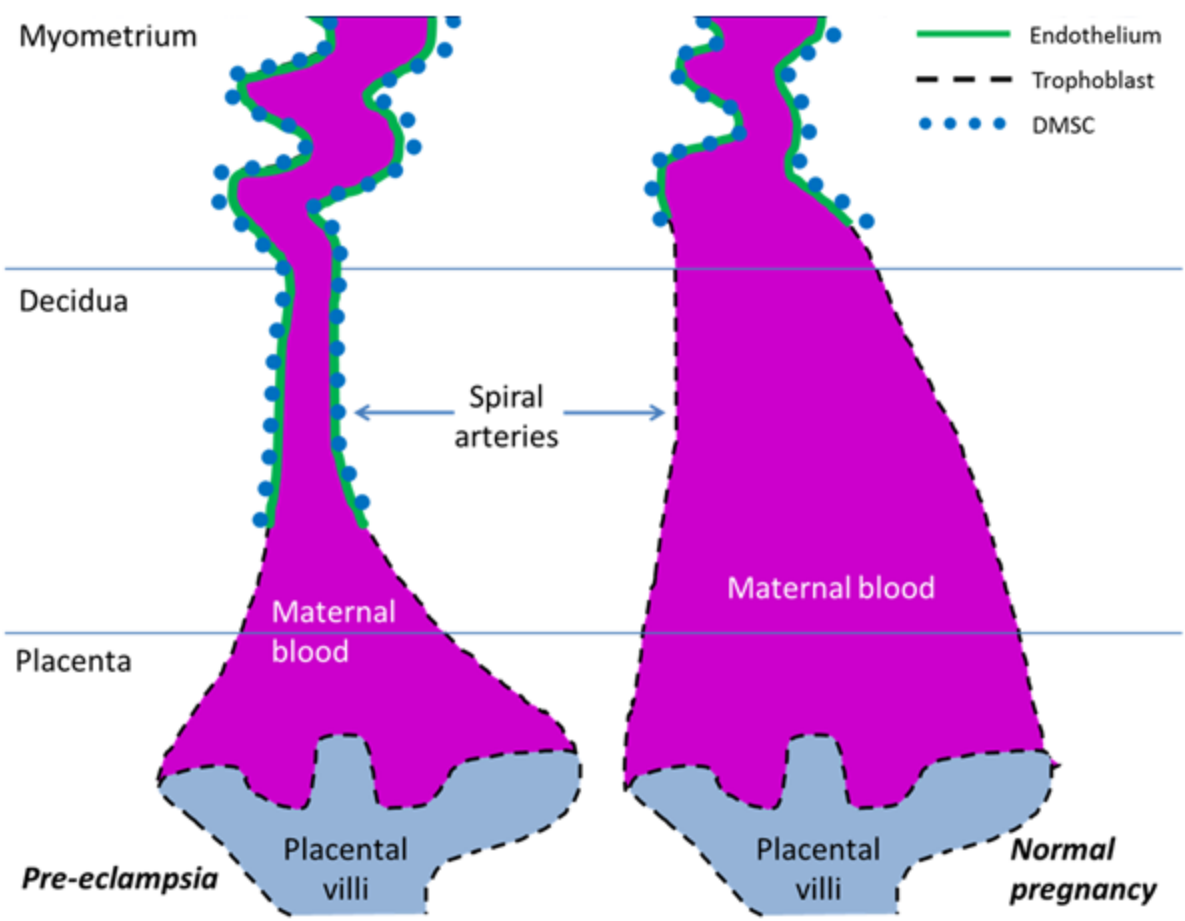

Figure 1. **Proposed model of endothelium and DMSC replacement by EVT cells in spiral artery remodeling**. The model is based on Kusuma et al. 2015 [46]. Right panel illustrates normotensive pregnancy where there is deep extravillous trophoblast invasion of the spiral artery into the inner third of the myometrium and replacement of the vascular niche comprising endothelial cells and underlying decidual mesenchymal stem/stromal cells (DMSC). Left panel shows that in PE, extravillous trophoblast invasion is shallow with much of the vascular niche remaining intact.

in pregnant women compared with non-pregnant women [10,12]. Therefore, placental detoxification systems exist to prevent deleterious changes in oxygen tension in early pregnancy and to protect against abnormal changes in oxidative stress [12]. Overall, the physiological changes associated with pregnancy, particularly decidualization, spiral artery remodeling, and the development of placental antioxidant systems, are necessary for a successful pregnancy. While elevated levels of oxidative stress are normal in pregnancy, highly elevated levels of oxidative stress are associated with the clinical syndrome of PE.

Placental Development in PE Pregnancies

A hallmark of eoPE is placental tissue hypoxia, which triggers the overexpression of hypoxia–inducible transcription factor (HIF) and inadequate angiogenesis. These events ultimately give rise to the clinical PE symptoms of hypertension, proteinuria and, sometimes, fetal growth restriction. An important consequence of placental hypoxia is incomplete, shallow transformation of the spiral arteries in maternal decidua and inner myometrial segments by invading and migrating placental EVT (Figure 1). The placental beds in patients with eoPE frequently contain fewer fully transformed spiral arteries [14]. The spiral arteries in eoPE are narrower, contain thick walls because they retain their smooth muscle and elastic lamina, and are more tortuous [15]. Vessel dilatation at the end of the spiral arteries, which open into the intervillous space is reduced (Figure 1) resulting in reduced but high velocity blood flow into the intervillous space, which damages the placental villi and causes increased release of oxidative stress factors into the maternal circulation. Thus, poor transformation of the spiral arteries causes placental hypoperfusion, which increases oxidative stress in placental tissues, and subsequent ischemia

and reperfusion damage exposes the placenta to oxidative stress factors from the utero-placental circulation [16].

Placental Oxidative Stress in PE

In patients with PE, oxidative stress and endothelial dysfunction in the placenta associate with altered release of factors into the maternal circulation [16]. Circulating markers of endothelial dysfunction in PE include soluble vascular endothelial growth factor receptor-1 or sFlt-1, thrombomodulin, von Willebrand Factor (vWF), soluble endoglin, plasminogen activator inhibitor-1, fibronectin, endothelin, E-selectin, platelet-derived growth factor (PDGF), placental protein 13 (PP-13), placental growth factor (PlGF), a disintegrin and metalloproteinase domain 12 (ADAM 12), and pregnancy-associated plasma protein A [7,12,17,18].

One of the most sensitive markers of oxidative stress is the level of 8-isoprostane. This vasoconstrictor is likely to contribute to hypertension in PE [19,20]. Accumulating evidence suggests that women with PE have increased lipid peroxidation and a deficiency in several important antioxidants [21]. Levels of RONS including superoxide anions, nitric oxide (NO), and hydroxyl radicals are higher in the PE placenta, whereas the activity of the antioxidant enzymes (ie, superoxide dismutase, glutathione peroxidase) and scavengers (ie, Glutathione, amino thiols, and vitamin E) are lower [21-23].

Oxidative stress induces tissue necrosis and damages endothelial cells, but it can also compromise maternal-placental blood flow caused by luminal thrombosis and luminal obstruction due to swelling of endothelial cells, and by impairment of endothelial-dependent vasoregulation [24]. Lipid peroxides also interact with, and modify, vascular endothelial cell function and they cause contraction of the vasculature because of elevated levels of oxidized low-density lipoproteins, which inhibit endothelial-dependent relaxation [12]. Increased oxidative stress in the maternal circulation also changes the balance between thromboxane and prostacyclin to support increased vasoconstriction, and thrombocyte aggregation [12,25]. An additional source of oxidative stress in women affected by PE is the activation of circulating leukocytes. In PE cases, maternal circulating neutrophils and monocytes become activated, which subsequently generates superoxide, cytokines such as IL-6, TNF-α and vascular adhesion molecule-1 [21,26].

Overall, the deleterious consequences of oxidative stress on DNA, protein synthesis, and protein function(s) lead to the loss of cell structural integrity and consequently to placental abnormalities. Trophoblasts and placental villi exhibit increased apoptosis in patients with PE. MDA is a primary breakdown product of lipid peroxides and was among the first factors associated with increased lipid peroxidation in PE-affected women [22,27-29]. Elevated levels of phospholipids, cholesterol, lipid peroxides, and 8-isoprostane are a feature of the PE-affected decidua [19,30]. Sufficient evidence shows RONS promote vascular endothelial cell dysfunction leading to PE. In summary, PE patients display imbalances in RONS production, increased lipid peroxidation, and abnormal levels of antioxidant defenses.

Many decades of PE research focused primarily on well-known fetal and maternal cell types (ie, trophoblast cell types, and maternal vascular endothelial cells, and stromal cells) described above. However, recently a novel cell type, the mesenchymal stem/stromal cell, resides in both fetal and maternal components of the maternal-fetal interface and accumulating evidence suggests a potentially important role for this cell type in modulating oxidative stress in the normotensive and PE-affected placenta.

MESENCHYMAL STEM/STROMAL CELLS IN THE HUMAN PLACENTA

Hematologists searching for alternative sources of mesenchymal stem/stromal cells (MSC) to bone marrow MSC, discovered placental MSC. Bone marrow MSC self-renew and differentiate into multiple tissues, including bone, fat, cartilage, and other tissues of mesenchymal origin, making them attractive candidates for clinical applications. However, bone marrow MSC require an invasive surgical procedure for extraction, are difficult to isolate, are present in low numbers in bone marrow and therefore require extensive expansion in cell culture.

The human term placenta is an ethically acceptable and plentiful source of MSC that does not require invasive procedures for their isolation. MSC are harvested from the umbilical cord, fetal membranes (ie, amnion and chorion), amniotic fluid, chorionic villous stroma, and the maternal decidua and myometrium [31]. Placenta-derived MSC differentiate into cells of the mesenchymal lineage, express common MSC markers, but lack hematopoietic markers. These MSC display anti-inflammatory and immunosuppressive properties [32-35].

Various studies describe the isolation and characterization of MSC derived from the basal layer of the endometrium and decidua [36-40]. Endometrial MSC are present during the cyclical regeneration of human endometrium [36,41]. Evidence suggests endometrial MSC are perivascular cells and are isolated using CD146 and platelet-derived growth factor receptor-β (PDGF-Rβ) markers [42]. These cells were thought to be derived from endogenous stem cells, but there is evidence suggestive of a bone marrow contribution [43]. Endometrial MSC show clonogenic activity, the ability to differentiate into mesenchymal lineages and expression of typical MSC surface markers (CD29, CD73, and CD90), while lacking common hematopoietic cell markers (CD3, CD14, CD19,

CD34, CD45, and HLA-DR) [41,42,44].

An abundant source of MSC is the maternal decidua (DMSC, from the basal plate) [37,45-50]. Dimitrov et al. [51] isolated first trimester decidual MSC that express common MSC markers that differentiate into mesenchymal lineages, and that decidualize *in vitro* after stimulation with progesterone and cAMP. Most studies however, isolate DMSC from the decidua that remains attached to the term placenta following delivery. Lu et al. [52] showed that DMSC maintain a normal karyotype, are highly proliferative in long-term *in vitro* culture, and display immunoevasive effects. The above studies provide evidence that the decidua is a readily available and plentiful source of DMSC [52,53].

The Role of MSC in Normal Placental Development

While many studies focus on placental MSCs and their potential use as therapeutic agents, our understanding of their role in normal placental development remains limited [54]. We provided evidence that MSC were present in a vascular niche within the placental villi of the term human placenta (CMSC), the maternal *decidua parietalis* component of the fetal membranes (DPMSC), and the maternal *decidua basalis* component of the placenta (DMSC) [46,55,56].

The ability of MSC to differentiate into multiple cell types of the mesenchymal lineage and MSC in vascular niches in both the fetal and maternal components of the placenta provided important clues as to their potential role in normal placental development. Kusuma et al. [47] showed that subcutaneous implantation of CMSC and DMSC into immunodeficient SCID mice resulted in ectopic *de novo* formation of cells and tissues of the mesenchymal lineage including bone, stromal cells smooth muscle, and blood vessels. Thus, a possible role for MSC in the normal placenta is to act as a reservoir of cells for new tissue formation, or for the repair of damaged tissue.

The MSC vascular niche is conserved in many human organs and tissues [57]. The presence of CMSC and DMSC around placental blood vessels suggests potential involvement in the formation or maintenance of the complex vascular network that accompanies placentation. Genetic evidence for this idea comes from the murine knockout model of PDGF-Rβ; a well-known MSC/pericyte marker. The PDGF-Rβ knockout placenta shows defective vessel morphology and function, suggesting that MSC have a role in maintaining the placental vasculature [58].

MSC and Oxidative Stress

Another role for MSC in normal placental development is to up-regulate stress responses and repair pathways, which facilitate the removal of toxic products [59]. Thus, human placental MSC are potentially useful for the treatment of pathologies where oxidative stress damages tissues. Human umbilical cord MSC, in combination with the free radical scavenger drug edaravone, increased cell survival and promoted host liver regeneration by reducing RONS production in a murine acute liver failure model [60]. A limb ischemia mouse model provided evidence that human placental MSC reduced oxidative stress and ischemic damage [61]. Similarly, in a murine model of myocardial infarction, treatment with human placental MSC showed beneficial effects on contractile function, increasing left ventricular wall thickness and smaller infarct size [62]. Human placental MSC had a neuroprotective effect on hypoxic-ischemic brain damage in rats, which was due to reduced oxidative stress [63]. In a pilot study, Wang et al. [64] showed that human placental MSC were safe and efficacious in treating the diabetic foot with ischemia limb arterial disease. Together, these examples show the effectiveness of MSC response to oxidative stress and their potential as an intervention in oxidative stress-related diseases.

Placental MSC and Immune Regulation

Placental MSC reduce the effects of oxidative stress in ischemic environments, often in the presence of a strong inflammatory response. MSC from placenta, umbilical cord tissue, or other adult tissues such as bone marrow have an immunomodulatory effect on T, B lymphocytes, macrophages, and dendritic cells [32,65-67]. In addition, several studies have demonstrated the potential of MSC to treat immune-mediated diseases [32,67]. In a pilot study, patients with severe acute graft-versus-host disease, which features an exacerbated inflammatory response, were treated with DMSC and showed partial or complete responses [68]. More recently, Sadeghi et al. [69] showed in a pilot study that the immunosuppressive effects of DMSC resulted in decreased inflammatory cytokine levels in patients with COVID-19.

The immunosuppressive properties of MSC were also shown in disorders of pregnancy, including PE, which is considered to be a pregnancy-induced immune syndrome [70]. In a Th-1 (T helper-1) cell-induced PE mouse model, DMSC reduced blood pressure and proteinuria, suppressed glomerulonephritis, and reverse the expression of the proinflammatory cytokine TNF-α in uterine and splenic lymphocytes of PE-affected animals [70]. MSC immunosuppressive properties in pregnancy were also demonstrated in a rat PE model. Intravenous injection of MSC derived from the Wharton's jelly component of the human umbilical cord (WJMSC) into pregnant hypertensive rats, reduced blood pressure and this was associated with improved remodeling of spiral arteries [71]. In addition, WJMSC decreased serum TNF-α levels and increased levels of the anti-inflamma-

tory cytokine IL-10 in pregnant hypertensive rats [71]. In other studies, umbilical cord-derived MSC (WJMSC and UCMSC) were used in a lipopolysaccharide-induced rat PE model where they reduced blood pressure as well as the levels of pro-inflammatory cytokines including TNF-α [72,73] (Table 1).

MSC IN PE

As described above, defective placentation and a hypoxic placenta are generally accepted as the underlying causes of PE, particularly of eoPE. Determining the role(s) of various MSC populations in normotensive and PE-affected placentation is clearly important. Recent investigations into the functional properties of placental-derived MSC (eg, their roles in immunomodulation, angiogenesis, coagulation, inflammation) provide some new insights into our understanding of placenta-related disorders, including PE [66,74-80].

Rolfo et al. [81] reported an aberrant release of pro-inflammatory cytokines (sFlt-1 and macrophage migration inhibitory factor) by chorionic villous MSC (CMSC) isolated from PE-affected placental tissue (PE-CMSC). They also reported a slow proliferative rate together with increased senescence in PE-CMSC, suggesting reduced self-renewal capacity of PE-CMSC in the villous stroma [81]. Analysis of cytokine expression in conditioned medium collected from normotensive and PE-affected DMSC (PE-DMSC), found levels of soluble intercellular adhesion molecule-1 (sICAM-1) and stromal cell-derived factor-1 (SDF-1) were significantly higher in normotensive DMSC compared with PE-DMSC [82]. High level expression of sICAM-1 and SDF-1 in normotensive DMSC was also reported elsewhere [83]. Hwang et al. [82] suggested that decreased sICAM1 expression in PE-DMSC compared to normotensive DMSC was a consequence of altered immune responses in PE, however, elucidating the exact nature of these immune responses requires further studies. SDF-1 plays an important role in the maintenance and survival of bone marrow MSC and may play a similar role in normotensive DMSC. Reduced levels of SDF-1 in PE-DMSC would therefore have a deleterious effect. Secreted SDF-1 also promotes angiogenesis in *in vivo* and *in vitro* models [84]. In the PE-affected vascular niche where PE-DMSC are adjacent to endothelial cells, reduced SDF-1 production and signaling by PE-DMSC to endothelial cells may impair angiogenesis and hinder the repair of oxidative stress damage.

Further support for abnormal placental stem cell function in PE come from studies of stem cell markers in PE that report higher levels of CD34, CD44, and leukemia inhibitory factor in PE decidua samples compared with those from normotensive patients [85]. Furthermore, there are reports of differences in characteristic MSC surface marker expression (ie, CD105, CD90, CD73, and CD44) between PE- affected amnion MSC (PE-AMSC) and PE-CMSC, compared with normotensive controls [86].

Microarray analyses identified several microRNAs (miR) (ie, miR-16, miR-29b, miR-30a, miR-100, miR-136, miR-140-5p, miR-221, miR-495, and miR-49) that showed increased levels in PE-DMSC, suggesting that differential miR levels may be involved in the development of PE [87,88]. Overexpression of miR-16 inhibited the migration and proliferation of normotensive DMSC, reduced the ability of human umbilical vein endothelial cells (HUVEC) to create blood vessels and reduced trophoblast cell migration [87]. miR-136 and miR-494 are highly expressed in PE-DMSC, and both miRs are responsible for increased cell apoptosis and suppression of the angiogenic activity of HUVEC [89,90]. miR-181a expression is increased in PE-DMSC and umbilical cord MSC from PE patients, and miR-181a-transfected MSC show decreased proliferation and immunosuppression ability [91].

Together, the data suggest PE-DMSC populations are abnormal both in terms of their autocrine and paracrine functions, and this is likely to exacerbate PE. However, with human *in vitro* studies, it is difficult to prove these effects of PE-DMSC are a cause or consequence of PE. Resolving this important issue warrants further investigations using *in vivo* animal models.

DMSC AND OXIDATIVE STRESS

Our particular interest was in the effect of oxidative stress on DMSC in the normotensive and PE-affected placenta. As described above, DMSC reside in a vascular niche in close proximity to the endothelium and they surround the spiral arteries (Figure 1). Furthermore, DMSC in the vascular niche are replaced by invading extravillous trophoblasts in fully transformed spiral arteries [46]. We postulated that in the PE-affected placenta, PE-DMSC are subjected to an environment of high oxidative stress, with potentially deleterious consequences. MDA, a highly reactive aldehyde, is elevated in placenta tissues collected from PE patients compared to normotensive patients [21]. Lipid peroxidation products, such as MDA, acrolein, and 4-hydroxy-2E-nonenal, are implicated in the etiology of many oxidative stress-related diseases including atherosclerosis, diabetes, alcoholic liver disease, metabolic syndrome, neurodegenerative diseases [92], and more recently in pregnancy related disorders [15,21,25,93]. Therefore, it was important to determine whether DMSC are resistant to elevated levels of oxidative stress in a normotensive pregnancy, and resistant to the even higher levels of oxidative stress that PE-DMSC

Table 1. Studies Showing a Potential Therapeutic Effect of Placenta-derived MSC

Model/ Setting	Mode of PE	Human Source of MSC	Treatment mode	PE Outcome	
Mouse	Heme oxygenase (HO-1) null mutant	WJMSC_EV	Intravenous injection	WJMSC_EV modified markers of inflammation within the pregnant uterus. Decreased PE-associated fetal growth restriction by improving fetal lung branching and expression of developmental genes.	[107]
Mouse	Th-1 null mutant	DMSC	Intravenous injection	DMSCs reduced blood pressure and proteinuria. Abnormal TNF-a expression in uterine and splenic lymphocytes was reduced.	[70]
Mouse	Heme oxygenase Hmox1−/− null mutant	WJMSC_EV	Intravenous injection	WJMSC_EV reduced fetal loss and fetal growth restriction, improved spiral artery remodeling, and ameliorated maternal PE symptoms. Cytokine profiles suggested numerous altered immune populations within the pregnant uterus.	[108]
Rat	LPS treatment	WJMSC	Intravenous injection	WJMSC lowered blood pressure and increased fetal weight. Altered levels of proinflammatory and anti-inflammatory cytokines. Altered expression of vascular endothelial cell function markers TNF-α and ICAM-1.	[72]
Rat	LPS treatment	UCMSC	Intravenous injection	UCMSC reduced blood pressure, urinary protein, and white blood cell count. Anti-inflammatory IL-10 levels increase whereas pro-inflammatory IL-1β and TNF-α levels decreased.	[73]
Rat	Angiotensin receptor agonistic autoantibody (AT1-AA)	WJMSC	Intravenous injection	WJMSC reduced blood pressure, increased fetal eight and improved kidney function as well as spiral artery remodeling. TNF-α levels were decreased. Heme oxygenase (HO-1) and IL-10 levels increased.	[71]
Rat	N^G-nitro-l-arginine methyl ester (L-NAME)	UCMSC_EV	Abdominal injection	UCMSC_EV reduced blood pressure and urinary protein production. Improved fetal and placental development and increase in fetus number. Cell apoptosis decreased and sFLT1 levels decreased. Increased expression of angiogenesis markers.	[109]
Human cell culture	MSC isolated from human PE placenta	PE-DMSC	Aspirin treatment	Aspirin increased PE-DMSC attachment. Levels of pro-inflammatory cytokines IFN-γ and IL-8 were reduced. PE-DMSC antioxidant capacity increased.	[110]
Human cell culture	ALDH1A1 siRNA knockdown followed by H_2O_2 treatment	DMSC	ALDH agonist treatment	ALDH agonist compound 2 increased resistance to oxidative stress by increasing protein and mRNA of ALDH1A1.	[96]

Human cell culture	LPS treatment and PE serum treatment of HUVEC	DMSC_EV	DMSC_EV addition to PE cell culture model	DMSC_EV increased attachment and proliferation, and reduced levels of pro-inflammatory cytokine IL-6 in LPS and PE serum-treated HUVEC. Addition of DMSC_EV to PE serum-treated HUVEC reduced levels of lipid peroxidation.	[111]
Human cell culture	H_2O_2 treated HUVEC	CMSC	CMSC and H_2O_2 conditioned CMSC addition to PE cell culture model	CMSC and H_2O_2 conditioned CMSC prevented oxidative stress-related damage in H_2O_2 treated HUVEC endothelial cells by increasing their proliferation and migration.	[103]
Human cell culture	Trophoblast cell lines JEG and HTR-8, and placental explant cultures growing in hypoxic conditions (2% O_2)	AMSC_EV	AMSC_EV treatment of hypoxic trophoblast cells	AMSC_EV increase trophoblast proliferation and autophagy in hypoxic conditions. Autophagy is partially inhibited by AMSC_EV through inactivation of the mTOR signaling pathway.	[101]

are exposed to.

One of the most important enzyme families responsible for imparting resistance to oxidative stress in MSC are the aldehyde dehydrogenases (ALDH). The detoxification capacity of ALDH enzymes protects stem cells from oxidative damage and this may be an important factor in controlling their longevity [94,95]. The ability to respond to oxidative stress is a "universal" property of stem cells, but in PE we speculated that these protective stem cell mechanisms are overwhelmed and fail to function properly. In DMSC, increased stem cell survival in environments of high oxidative stress is primarily achieved through high intracellular expression level of the ALDH enzymes [53]. We provided evidence that ALDH enzyme activity is significantly reduced in PE-DMSC and this correlates with their reduced capacity to respond to oxidative stress [96]. Using short interfering RNA (siRNA) we showed that inactivating a specific ALDH gene (ALDH1A1) in DMSC resulted in reduced resistance to oxidative stress like that in PE-DMSC. We also showed reduced ALDH1A1 levels in siRNA-treated DMSC were restored by treating DMSC with an ALDH agonist. Thus, in a human cell culture, we provided evidence that reduced ALDH1A1 levels were a cause rather than a consequence of reduced resistance to oxidative stress in PE-DMSC. Whether this is the case in the *in vivo* situation requires further investigation using animal models of PE.

REGENERATIVE MEDICINE STRATEGIES TO TREAT PE

Treating placental disorders using MSC-based stem cell therapies to reduce the effects of oxidative stress and inflammation remains are at the basic research or pre-clinical research stage. For example, from our research, we proposed to reduce oxidative stress in PE by targeting ALDH using ALDH enzyme agonists and thus allowing PE-affected MSC to resume their essential functions [96].

As described above, DMSC-based therapy was tested in a murine model of Th1-induced PE, where delivery of DMSC resulted in amelioration of several PE clinical features such as hypertension, proteinuria, and glomerulonephritis [70]. Studies that employ animal or human cell culture models of PE reported potential beneficial therapeutic effects of various types of placenta-derived MSC on oxidative stress and inflammation (Table 1).

Recently, preclinical studies involving MSC of various types have pivoted to the use of MSC-derived extracellular vesicles (MSC_EV) [97]. MSC_EV used in therapeutics are nanoparticles (~30-1,000nm) that are secreted by MSC yet retain many of the reparative and restorative properties of the parent MSC [98]. MSC_EV have many practical advantages over MSC as therapeutic agents, the most important being the very low risk of long-term pathological transformation compared with the use of whole MSC. Examples of the potential for MSC_EV as therapeutic agents for treating PE are given in Table 1.

Therapeutic applications of MSC also focus on engineering their therapeutic effect by manipulating the growth environment of MSC [99] and enhancing the delivery modes for cell-based therapies, as outlined in Figure 2. For example, Gala et al. [100] reviewed the beneficial therapeutic effect of low oxygen conditions on bone marrow MSC and bone marrow MSC_EV. Similarly, hypoxia preconditioning of amnion-derived MSC_EV

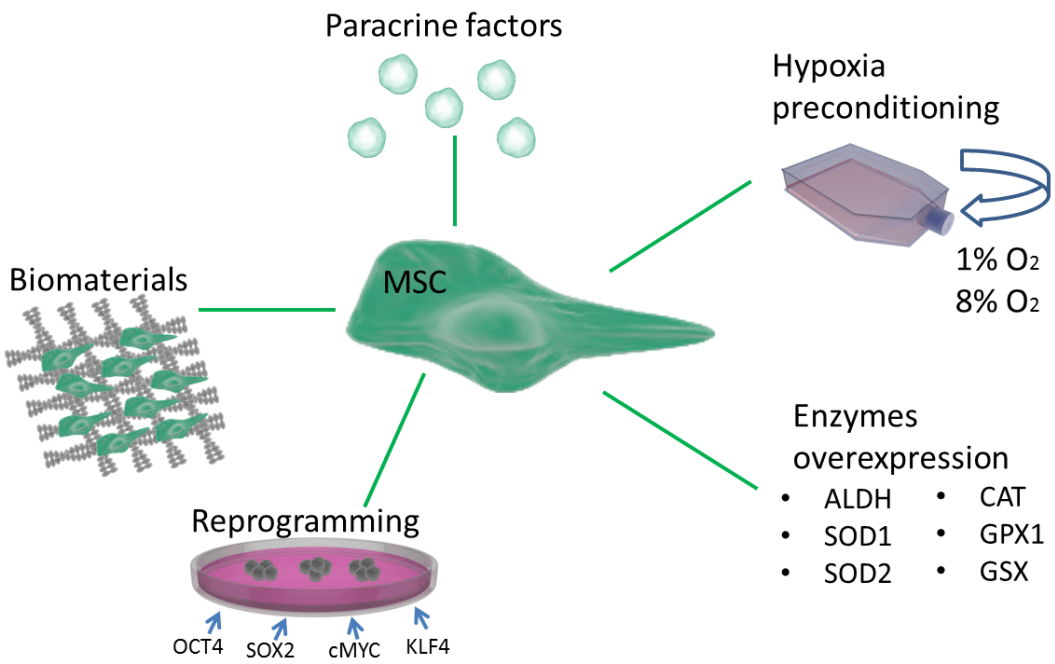

Figure 2. Regenerative medicine approaches and modes of delivery to exploit MSC resistance to oxidative stress. MSC release biologically active substances which exert paracrine actions on different cell types leading to tissue repair and regeneration. Insight into microenvironmental cues that could affect MSC functions *in vivo* are essential for successful therapeutic outcomes, and this can be achieved by hypoxia preconditioning, enzyme overexpression, and cellular reprogramming. Tailored functional biomaterials play an important role in the tissue engineering field and hold significant promise in influencing MSC signaling and specific functions.

[101], LPS-mediated preconditioning of DMSC [102], and H_2O_2 conditioning of CMSC [103] are of potential therapeutic benefit. Other strategies such as enzyme overexpression [104] and cellular reprogramming [105] could facilitate the application of MSC in oxidative stress-related pathologies. Another possibility is that engineered biomaterials/matrices can modulate MSC functions and guide specific responses of MSC [106].

CONCLUSION

The cause of oxidative stress in PE is thought to be of vascular origin because it is associated with abnormal remodeling of the maternal spiral arteries and a hypoxic placenta. Antioxidant therapies and vitamin supplementation to target oxidative stress (eg, vitamin E, vitamin C, carotenoids, coenzyme Q10, and selenium) in women at risk of PE, show marginal or no benefit in preventing PE. It is now evident that the placenta contains a reservoir of MSC, and these cells could be of major clinical importance. Given the rapid development of allogeneic and autologous MSC-based cell therapies to combat various chronic diseases, including oxidative-stress related pathologies, we envision the use of placenta-derived MSC as a much-needed source for therapeutic interventions for pregnancy disorders. Future research needs to unravel the precise biological functions and mechanisms of action, of MSC in normotensive and PE-affected placentation. This information will lay the groundwork to identify diagnostic markers for the early detection of PE, and to devise rational therapies to treat not only PE, but also other pregnancy complications associated with increased levels of oxidative stress, such as fetal growth restriction and preterm birth.

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