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Mesenchymal stem cells as potential regenerative treatment for pre-eclampsia: a review

Abstract

Research in regenerative medicine and tissue engineering has continued to show advancement towards being a potential cure for autoimmune disorders. Specifically, mesenchymal stem cells show great potential in tissue regeneration and repair. Pre-eclampsia is a systematic endothelial dysfunction disorder that leads to hypertension and proteinuria. This occurs when syncytiotrophoblast are under stress and can't properly remodel the spiral arteries of the placental bed. Mesenchymal stem cells are being used to reverse the damage already done by pre-eclampsia and restore equilibrium. Current research shows promising outcomes when tested on animals. Experiments are being ran to test all aspects of the disorder from regeneration and reconstruction to genetic foundations.

Keywords: pre-eclampsia, Mesenchymal Stem Cells, Hypertension, T-Helper Cell 1/T-helper Cell 2 (Th1/Th2), Cytokines

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Sarah Tanner, Vincent Gallicchio
Department of Biological Sciences, College of Science, Clemson University, USA
Clemson, SC 29636

Correspondence: Dr. Vincent S Gallicchio, Department of Biological Sciences, College of Science, 122 Long Hall Clemson University, Clemson, SC 29636, USA, Email vsgal@clemson.edu

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Abbreviations: PE, Pre-eclampsia; MSC, Mesenchymal Stem Cells; DC, Dendritic Cell; Th (#), T-helper Cell #; IL-1β, Inflammatory Cytokines; TNF-α, Tumor Necrosis Factor α; IL-10, anti-inflammatory cytokine (IL-10)

Introduction

Pre-eclampsia is a systematic endothelial dysfunction disorder of the placenta effecting particularly first pregnancies. Hypertension and proteinuria are commonly seen due to vasoconstriction of arteries, interfering with proper endothelial development.[1] These symptoms are triggered by the soluble particles released from syncytiotrophoblast when they are under stress. Syncytiotrophoblast are the primary outer layer of trophoblast that enter through the uterine wall to form the outer layer of the placenta. They form a branching structure that allows them to remain in contact with maternal circulation in order to receive essential nutrients and create a foundation for gas exchange.[2] Syncytiotrophoblasts with exposed anionic phospholipids on their outer membrane create a hypercoagulable state (increased risk of blood clotting) and are unable to invade properly causing malfunction in the formation of the placental bed; as shown in Figure 1. Over production of these cells and inability of trophoblast to remodel the spiral arteries cause an amplification in maternal response to inflammation, coagulation disorders, and endothelial dysfunction that differs from the normal maternal response.[2] Due to the amplification, the pregnancy conditions become abnormal and put the placenta into oxidative stress and an antiangiogenic state; entering into a pathological state of pre-eclampsia.

There are two sub-types of pre-eclampsia: early onset and late onset.[3] The divide between the two is before or after 34 weeks' gestation. There is small variation between the two in terms of increased risk factors. Risk factors include maternal age, primiparity, stroke, diabetes mellitus, chronic hypertension, and hyperthyroidism. The risk most commonly associated with late-onset pre-eclampsia is primiparity, when a woman is bearing a child for the first time;[3] while chronic hypertension and older age are strongly correlated with early-onset.[5] Mothers with early-onset pre-eclampsia run a bigger risk of acquiring fetal growth restriction, hemolysis, and neurological complications. The higher rates of severe fetoplacental complication in early-onset pre-eclampsia can be contributed to impaired placentation. Placentation is the failure of normal spiral arteries to form causing an angiogenic/anti-angiogenic imbalance. This imbalance can be used as a biomarker to predetermine the risk of developing early-onset pre-eclampsia. Late-onset is more common than early-onset and accounts for 90% of cases.[4]

This hypertensive disorder is the leading cause of maternal and perinatal morbidity and mortality worldwide. It affects 2-8% of all pregnancies and has the ability to affect various organ systems.[6] It is responsible for 16% of all maternal deaths in developed countries by causing renal failure, stroke, cardiac dysfunction, respiratory compromise, and liver failure.[7] Pre-eclampsia also allots for 15-20% of preterm births and 12-25% of fetal growth restrictions.[6] Unfortunately, the only current known cure for pre-eclampsia is early or immediate delivery of the fetus and placenta. Following, there is still a 7-20% chance of pre-eclampsia recurrence in succeeding pregnancies.[8]

Stem cells

Due to the lack of a cure for pre-eclampsia, multiple stem-cell therapies are being tested and considered.[10] Stem cells have become extremely popular and show great promise in current research of tissue regeneration and repair. Due to their diversity, there is still much to learn about their therapeutic potential. Stem cells are unique cells with extensive renewal capacity and the ability to generate daughter cells that undergo further differentiation.[10] There are two major classes of stem cells: pluripotent stem cells (PSC) and multipotent stem cells (MSC). PSCs are derived from the inner cell mass of preimplantation embryos and eventually form into aggregations known as the germ layers.[10] They start out with a lot of potency, meaning they have the ability to specialize into any cell in the adult body. In human development, they are only present for a small period of time in the embryo until they begin to differentiate into multipotent stem cells.[11] MSCs have much less potency. They tend to specialize into specific lineages for particular tissues.

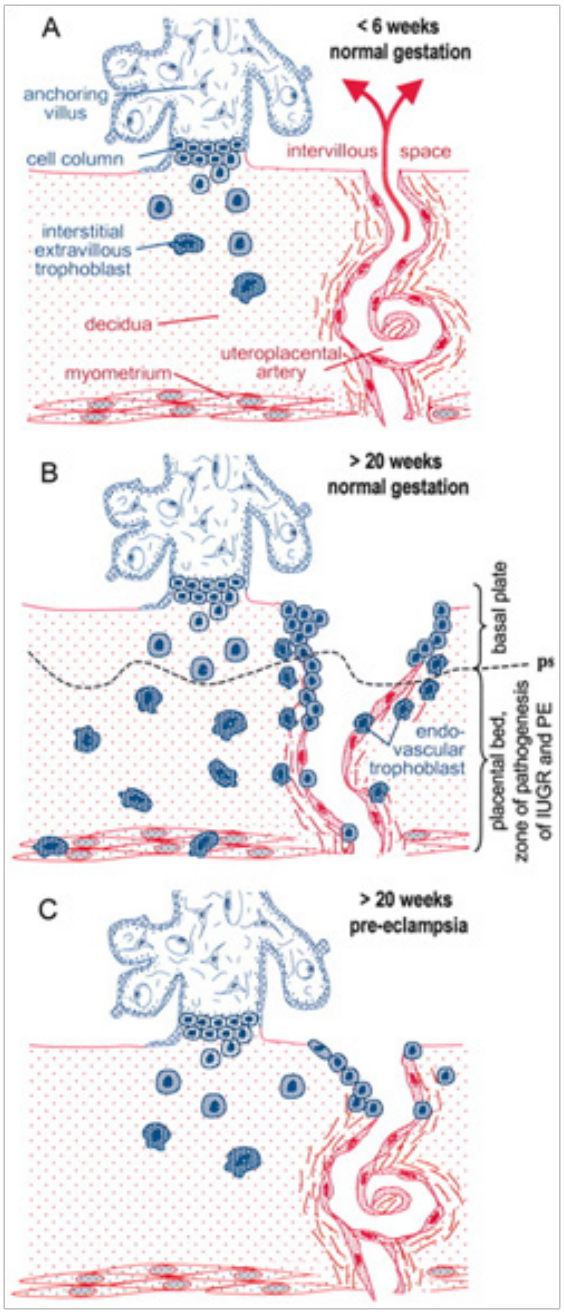

Figure 1 Representation of both interstitial and endovascular trophoblast invading the uterine wall and forming the placental bed in (A) female pregnancy before 6 weeks, (B) after 20 weeks of normal gestation, and (C) after 20 weeks of pre-eclamptic gestation.

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Stem cell formation begins with the blastocyst, formed by fertilization of the ovum by sperm.[10] Short-lived embryonic stem cells (pluripotent stem cells) form the walls of the blastocyst. The walls are composed of two different cell types: the inner cell mass and trophectoderms. The inner cell mass forms the epiblast (outer wall of the embryo) and induces fetus development while trophectoderms develop into specialized extraembryonic support structures, like the placenta. The inner cell mass continues to stay differentiated and dividing. Embryogenesis begins when the pluripotent embryonic cells of the inner cell mass start to aggregate and form the three germ layers: endoderm, mesoderm, and ectoderm. This is what starts the development of the fetus and eventually formation of the adult human. Following this aggregation, the cells begin to give rise to multipotent stem cells through different physiological conditions that differentiate and specialize for the appropriate tissues.[10] A representation of the series of differentiation can be seen in Figure 2.

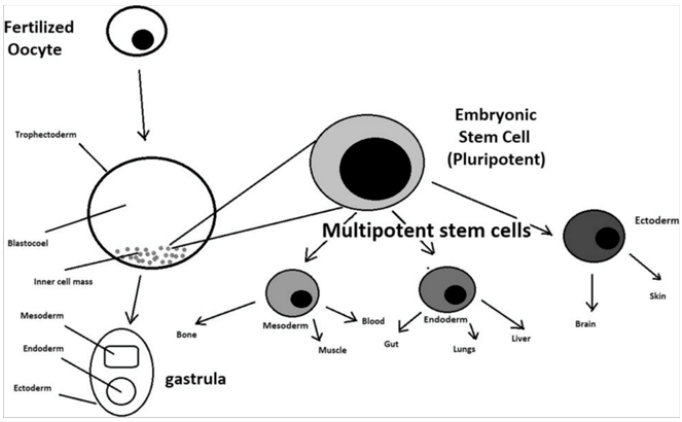

Figure 2 Blastocyst development of pluripotent embryonic stem cells that eventually aggregate into the germ layers: mesoderm, endoderm, and ectoderm. Giving rise to more specialized, multipotent stem cells.

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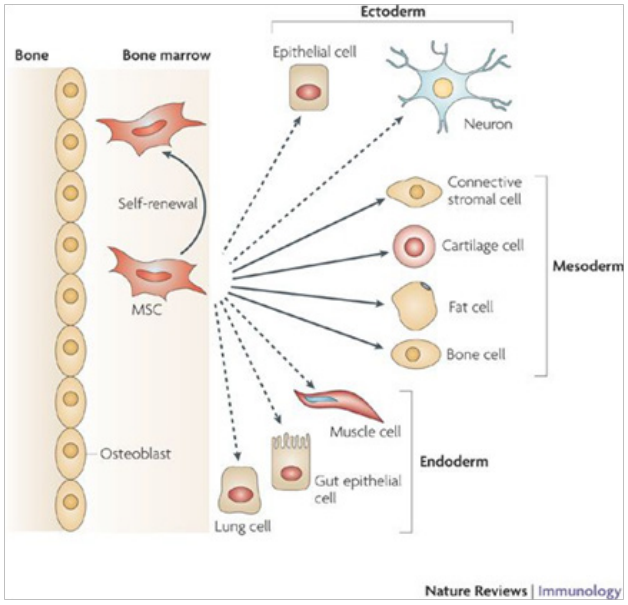

Figure 3 Representation of mesenchymal stem cells ability to self-renew in the bone-marrow cavity (curved arrow) and to differentiate (straight, solid arrows) down the mesodermal lineages.

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Discussion

Mesenchymal stem cells and their involvement with pre-eclampsia

Mesenchymal stem cells (MSCs) are a diverse subset of stromal - connective tissue - stem cells that can be derived from embryonic or adult tissue and used to interact with cells of both the intrinsic and adaptive immune system.[12] They divide and commit to a specific phenotypic lineage where they become a part of a unique tissue type. These cells have the ability to differentiate into osteoblasts, chondrocytes, adipocytes, tenocytes, neural cells, and hematopoietic-supporting connective tissue.[13] MSCs have a high degree of plasticity and can be utilized as embryonic mesenchymal stem cells and adult mesenchymal stem cells. Embryonic MSC's are pluripotent progenitor cells that give rise to the mesoderm germ layer that is responsible for the bodies skeletal elements, such as: cartilage, bone, tendon, ligament, marrow stroma, and connective tissue. The ability of these embryonic MSCs to fill space and migrate into this layer is what makes them ideal for injury repair in adult organisms.[14] Eventually these embryonic MSCs become multipotent adult cells.

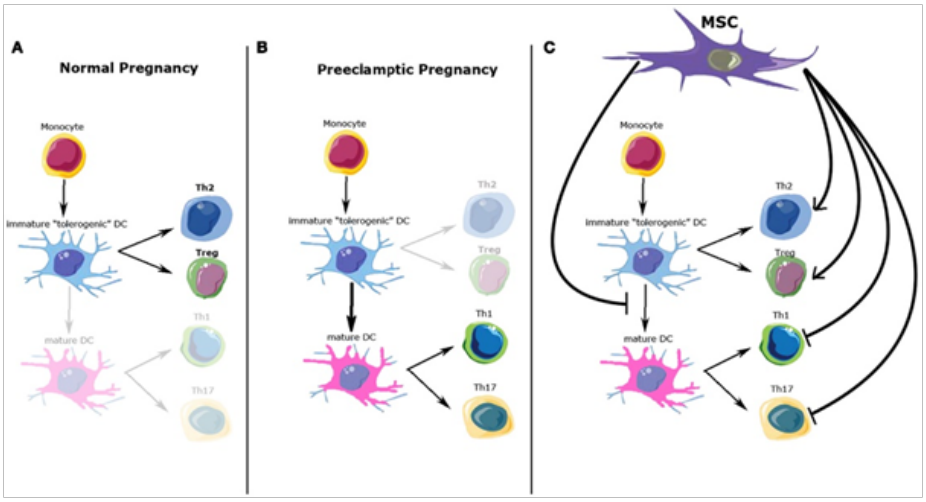

Figure 4 Immunomodulatory role of mesenchymal stem cells over the immune cells involved in normal and preeclamptic pregnancy. (A) Normal pregnancy is in a Th2 immunological state. Th2 ($CD4^+$ T-cells) and TREG cells control and regulate cytokine concentration predominantly. (B) Pre-eclamptic pregnancy is classified as a maternal pro-inflammatory state where Th1/Th17 predominate. (C) The MSCs have an effect on the immune cell types. MSCs inhibit dendritic cells maturation allowing immature DCs to be maintained. This promotes and controls TREG and Th2 proliferation and cytokine secretion while inhibiting Th1/Th17 proliferation.

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Mesenchymal stem cells serve many purposes. One is to form the HSC niches in bone marrow. These niches are used to support the growth and development of hematopoietic stem cells that eventually become mature blood cells. More importantly, MSCs have the ability to work as anti-inflammatories and immunoregulators. As seen *in vitro*, myeloid dendritic cells (DCs) present antigens to naïve T-cells in the immune system, causing pro-inflammatory cytokines and/or pathogen-associated molecules. MSCs decrease the DC expression and impair its ability to present antigens triggering an anti-inflammatory response.[12]

Normal pregnancies are considered to be in a Th2 (T- helper type 2 cell) immunological state that prevents fetal rejection through its immune-tolerant environment.[15] Patients with pre-eclampsia are generally classified with a Th1/Th2/Th17 imbalance. This imbalance includes the T-cell paradigm (TREG) caused by the previously explained dendritic cells (DC).[15] Pre-eclampsia begins with the introduction of a maternal pro-inflammatory state due to the upregulation of Th1. Th1 is a part of the $CD4^+$ effector T-cell lineage and promotes an increase in plasma levels of pro-inflammatory cytokines.[16] The increase in pro-inflammatory cytokines causes an upregulation of Th17. Th17 is also a part of the $CD4^+$ effector T-cell lineage and is commonly seen in chronic inflammatory disease. Its upregulation causes the cell to over produce IL-17, an inflammatory cytokine. Th1 and Th17 have now created an extremely concentrated cytokine environment disrupting TREG proliferation.[15]

TREG is crucial for developing and maintaining peripheral tissues, a key component in maternal-fetal tolerance.[17] A decrease in TREG cells is common in pre-eclampsia patients. In order for these cells to proliferate, they must be able to meet the antigens on immature DCs but this can only be done in a controlled cytokine environment. The role of MSCs would be to provide this optimal environment. MSCs would inhibit maturation of DCs allowing cytokine secretion involved in maternal-fetal tolerance development to be controlled.[18] The stem cells control over the Th1/Th2/Th17 imbalance and T-cell paradigm suggest that they would then be able to regulate and correct abnormal placentation seen in pre-eclampsia.[12]

Current research of mesenchymal stem cells involved with pre-eclampsia

There is a functional similarity between pulmonary circulation and the placenta. Mesenchymal stem cells have been shown to treat pulmonary hypertension, therefore ambitious research is being done to apply these properties to the placenta and reduce hypertension during pregnancy.[20] Even though the main cause of pre-eclampsia goes unknown, it is understood that it is due to a flaw in blood vessel formation of the placenta. There is current research being done to try

and see if there are genetic factors involved. Since there are multiple ways to acquire pre-eclampsia it opens up various avenues for research to try and cure it. The imbalance between the Th1/Th2 paradigm in pre-eclampsia is a highlighted area in current research. The specific cytokines produced by these T-helper cells are responsible for different immunopathology reactions[21] making them ideal candidates for immune-modulation.

An experiment published in 2015 by Fu Lihua and his team, was done to investigate umbilical cord-derived mesenchymal stem cells on endotoxin-induced hypertension during pregnancy.[21] The experiment was done to 3 groups of 7 rats: control, endotoxin-treated, and endotoxin-treated +MSCs. The pre-eclampsia was induced via intravenous injection of endotoxins to 2 of the 3 groups. The researchers measured the differences in blood pressure, urine protein levels, and number of white blood cells; as well as, protein expression levels of pro-inflammatory cytokines (IL-1β), tumor necrosis factor-α (TNF-α), and anti-inflammatory cytokine (IL-10). The endotoxin-treated rats were used to model a pre-eclamptic pregnancy against the control. After the MSCs were added to the pre-eclamptic rats, they began to form a monolayer of long cells showing strong proliferation activity and complete symmetry to its surrounding surface antigens.

As shown in Figure 5, the endotoxin treated rats showed an increase in blood pressure, urine protein levels, and white blood cell count. This shows an established pre-eclamptic state in the rats was achieved. Then when compared to the rats that had the addition of MSCs, blood pressure and protein urine levels decreased. It can be seen in Figure 6, that in the pre-eclamptic rat there was an increase in IL-1β and TNF-α but decreased levels of IL-10. When the stem cells were added, these conditions were reversed. The results were consistent with human pre-eclamptic pregnancies. The increased levels of Th1 in PE patients caused the release of these pro-inflammatory cytokines. It can be shown through this experiment that placenta-derived mesenchymal stems have a protective effect on endotoxin-induced pre-eclampsia through suppression of the inflammatory factors.[20]

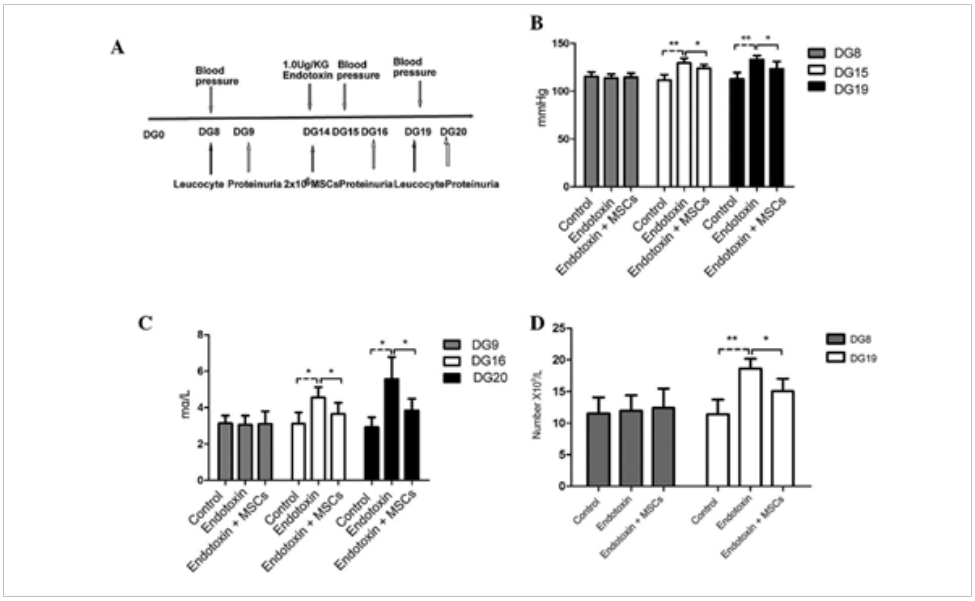

Figure 5 Umbilical cord-derived mesenchymal stem cells on endotoxin-induced hypertension in mice. (A) Diagram of the experimental design. (B) Blood pressure measured. (C) Proteinuria measured. (D) Number of white blood cells measured. All the data is representative of three independent experiments. MSC: mesenchymal stem cell, DG: gestation day.

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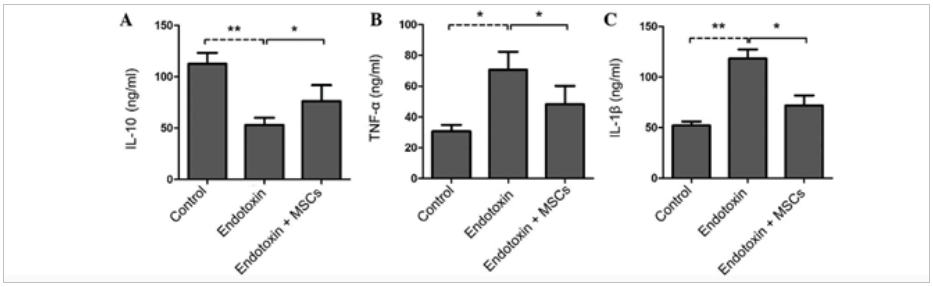

Figure 6 Cytokine protein levels in control, endotoxin-treated, and endotoxin-treated + MSCs rats. (A) Serum levels of IL-10. (B) Serum levels of TNF-α. (C) Serum levels of 1β. All data represent three independent experiments.

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Another experiment published in 2014 by Liu Liu and team, researched the improvement of Th1 induced eclampsia symptoms by suppressing the expression of TNF-α; a Th1 pro-inflammatory cytokine. This was done by extracting MSC's from the membrane that lines the uterus during pregnancy called the decidua. The decidua is the maternal-fetal interface where the white blood cells and other supporting cells work together to create an affective placenta.[23] During a healthy pregnancy, circulating TNF-α levels are increased and are even more elevated in a pre-eclamptic pregnancy.[24] This indicates TNF-α to be one of the key causations of the disorder by its ability to cause an immune imbalance. The experiment was done using Th1 cell-induced PE mouse models that showed high levels of the pathogenesis factor, TNF-α.[22] MSCs-based therapy was carried out to see its reversing effects on TNF-α.

As shown in Figure 7, blood pressure of the placenta was taken. The mice with Th1 induced PE (increase in TNF-α) showed an increase in blood pressure while the introduction of mesenchymal stem cells was able to restore the blood pressure almost back to baseline. It can also be seen that proteinuria levels were increased with Th1 induced rats and decreased with the addition of MSC therapy. In Figure 8, the histopathological analysis of the placenta, mice that received Th1 activated cells showed large areas of blood in the placenta (black arrow). The MSCs infusion was able to reverse the hemorrhage condition in PE. In conclusion, it can be shown that MSCs-based therapy ameliorate symptoms caused by Th1 cell-induced PE by decreased blood pressure and proteinuria. The MSCs protect the feto-placental development by maintaining the immune balance and suppressing the Th1 pro-inflammatory cytokine, TNF-α.

Research done by Dan Zhang and his team, summarize similar therapeutic benefits of mesenchymal stem cells that are being seen across multiple labs. The goal was to reverse angiotensin receptor agonistic autoantibody (AT1-AA)-induced hypertension on rats through administered human umbilical cord-derived mesenchymal stem cells (HU-MSCs).[25] Their effect on systolic blood pressure, fetal weight, and spiral artery remodeling was measured along with the expression of TNF-α and IL-10. Within just 19 days of gestation the systolic blood pressure had decreased. The change in blood pressure allowed for improvement of spiral artery remodeling and ameliorated the reduced fetal weight.[25] The injection of HU-MSCs into AT1-AA-induced rats upregulated IL-10 levels and downregulated TNF-α levels. The chain of improvements seems to be attributable to intervention of the pathogenic immune system response.

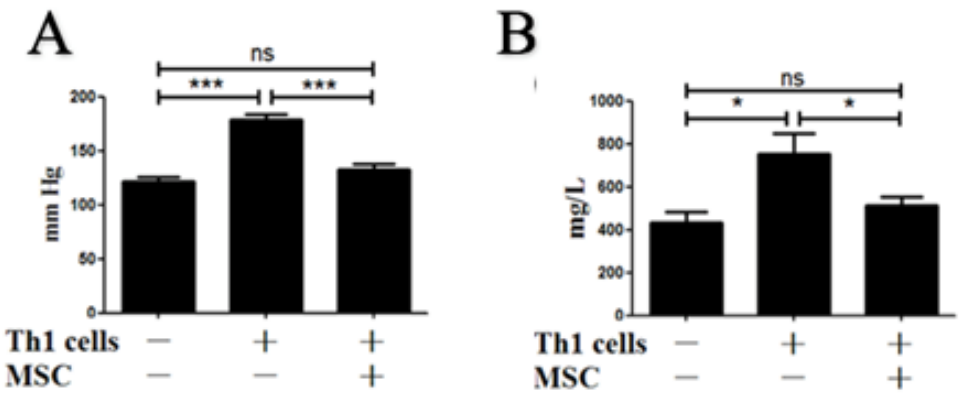

Figure 7 MSCs – based therapy improves TH1 induced PE in mice. (A) Blood pressure detected on control group, PE induced mice, and MSCs treated mice. (B) Proteinuria detected on control group, PE induced mice, and MSCs treated mice.

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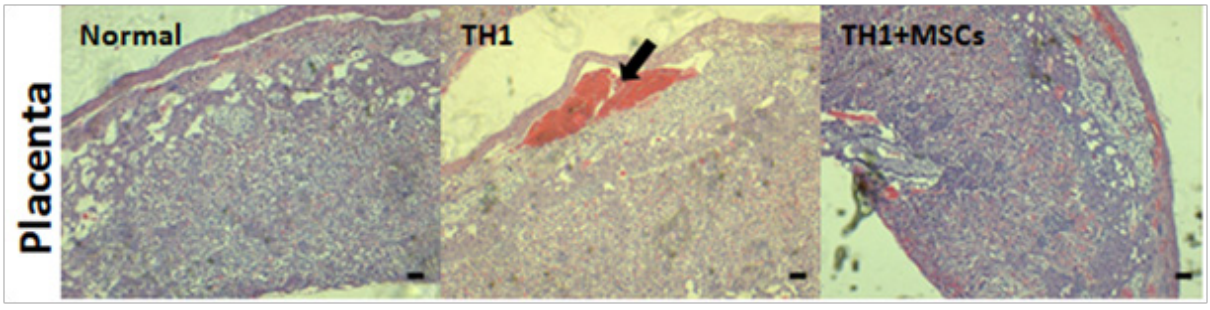

Figure 8 MSCs – based therapy improves TH1 induced PE in mice. Histopathological analysis of placenta. Mice with Th1 induced PE developed large a hemorrhage in placenta represented by the black arrow. Addition of MSCs reversed the adverse effects. Objective lens used for picture: (10X).

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Conclusion

Immune system vs. mesenchymal stem cells. Effects on preeclampsia.

Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine produced by macrophages during acute inflammation and signals events leading to necrosis or apoptosis.[26] Specifically, it inhibits proliferation of trophoblast cells in preeclampsia and more increased soluble TNF-α receptors are found in the plasma of patients with preeclampsia. This increase in receptors throughout the systematic circulation increases the cells sensitivity and responsiveness to elevated levels of TNF-α as well as other vasoactive factors. This elevation causes endothelial dysfunctions that ultimately lead to hypertension.[28] It can be a useful prediction, in the early third trimester of pregnancy, for preeclampsia.[27] Since it is a key mediator of inflammation, it tends to have a negative effect on tissue generative processes, such as development of the placenta; making it a key player for MSC therapy on preeclampsia.

Interleukin (IL-)1β is another regulatory of the inflammatory cascade. There are increases in IL-1β commonly found in pre-eclampsia. The increase in this cytokine can cause functional and structural damages.[30] Specifically, it interrupts and changes vascular integrity and coagulation. Interleukin (IL-)10 is shown to be downregulated in preeclampsia. Normally, it promotes positive cellular communication between the maternal-fetal interface and uses its immunomodulatory activity to directly benefit vasculature.[31] Downregulation of this cytokine can have detrimental effects leading to preeclampsia.

Both, TNF-α and IL-1β, have been identified in the trophoblast of the placenta and the decidua and are shown to be produced and secreted by both.[29] These pro-inflammatory cytokines are thought to be involved with the pathogenesis of preeclampsia when levels are increased. The immunological imbalance shifts the maternal immune response towards promoting inflammation and endothelial dysfunction.[31] This event can also occur when there is a decrease in IL-10. The loss of production of these cytokines in trophoblasts can lead to an inadequate placental development in preeclampsia.[32]

Based on the experiments discussed, it can be seen that mesenchymal stem cells have an effect on the pro-inflammatory cytokines; which then results in an improvement of the subject's preeclampsia. The depression of TNF-α and upregulation IL-1β is a probable solution to preeclamptic symptoms.

Ethics and controversary

General use of stem cells as a potential treatment

Throughout different branches of medicine there has been numerous experiments conducted in order to find a safe and effective way to use stem cells as a regenerative treatment. Even through the success, it is no lie that it brings forward ethical controversies. There are a lot of concerns voiced when it comes to stem cells based on procedures, funding, regulation, and safety. The derivation method of the stem cells varies from reprogramming of somatic cells to produced induced pluripotent stem cells to extraction of pluripotent stem cells from the lining of oocytes and embryos. Strong ethical disputes tend to regard the extraction from oocytes and embryos for its risk of interfering with human personhood and reproduction.[33] These embryonic stem cells can be derived from the inner cell mass starting as early as a 5-7-day old blastocyst.[33] This raises the debate on when a human's life begins and if the procedure is disrupting an embryos ability to develop into a live-born child.

To date, seven states offer stem cell research funding.[34] This statistic alone shows the pressure to develop an adequate method of oversight in order to identify and regulate the financial conflict of interest. This includes considering both the state and federal level; most importantly the taxpayer. It is often wondered if there is even an ethical way to put a price on something like embryonic stem cells. Accepting payment for participating or donating in/for research is very common in U.S. medicine but if it becomes a routine treatment there needs to be regulation so the justifications aren't solely for financial gain.[35] This creates an unethical influence to donate.

Future recommendations

Future studies may want to examine more on immune response when it comes to patients with preeclampsia. There are still many grey areas when it comes to determining the root of preeclampsia, therefore, exploring a way to recognize the early onset symptoms would provide more time for successful mesenchymal stem cell therapy. Unfortunately, preeclampsia can have detrimental effects if not discovered early enough, harming both the mother and fetus. In order to prevent this fate, we need to learn more about what is causing it in the first place.

As discussed earlier, many clinical trials have been successfully conducted on animals. Another future recommendation would be to continue to grow and expand on the trials in place and work towards making a safe and effective therapy for humans specifically. Human clinical trials would be new to preeclamptic research and a step towards confirming the therapeutic potential of stem cell treatment on preeclampsia.

Additionally, working towards creating universal regulation policies on stem cell therapy would only strengthen research in the field. It is a growing technique that needs a large amount of funding support as well as consistency in order to be successful. Creating guidelines would help to keep the research organized and provide different foundations to build upon.

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