Published in final edited form as:

Placenta. 2011 October ; 32S4: S298–S303. doi:10.1016/j.placenta.2011.04.007.

Pregnancy-associated progenitor cells: An under-recognized potential source of stem cells in maternal lung

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Abstract

Novel therapies are needed for the treatment of acute and chronic lung diseases, many of which are incurable. The use of exogenous stem cells has shown promise in both animal models and clinical trials. However, to date, the stem cell literature has under-recognized naturally acquired pregnancy-associated progenitor cells (PAPCs). These cells are found at sites of injury or disease in female tissues. They persist for decades after parturition in maternal blood and organs, with the largest number being found in the maternal lungs. Their presence there may be one explanation for the sex differences observed in the prevalence and prognosis of some lung diseases. Although the clinical significance of these cells is as yet unknown, the literature suggests that some of the PAPCs are stem cells or have stem cell-like properties. PAPCs harvested from the blood or organs of parous women could potentially be used as an alternate source of cells with regenerative properties for the woman herself or her children. Because PAPCs preferentially traffic to the maternal lung they may play a significant role in recovery or protection from lung disease. In this review article, we discuss ongoing research investigating the administration of both adult and placenta-derived stem cells to treat lung disease, and how PAPCs may also play an important future therapeutic role.

Introduction

Transplacental bidirectional trafficking of cells from the fetus to the mother occurs in all human pregnancies [1, 2, 3]. Although the exact purpose of this cellular exchange is unknown, it is thought to be important in development of immune tolerance of the mother to the fetus and vice versa [3, 4, 5]. Substantial numbers of maternal cells cross the placenta and travel to the fetal lymph nodes where they induce production of fetal T-regulatory cells (T-regs). The anti-maternal fetal T-regs persist into adulthood [3].

Similarly, microchimeric fetal cells persist in the maternal circulation and/or tissue without evidence of graft rejection. This has given rise to the term *fetal cell microchimerism* [6]. Fetal cells can be identified for decades after the pregnancy [2, 7, 8]. Therefore, as a result of pregnancy, females acquire populations of cells that have unknown effects on their health.

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One hypothesis is that fetal cells might trigger a graft-versus-host reaction leading to autoimmune disease. This offers a potential explanation for why many autoimmune diseases are more prevalent in middle-aged women [9]. The other main theory is that fetal cells home to injured or diseased maternal tissue where they act as stem cells and participate in repair [10, 11]. It is also possible that the fetal cells are merely innocent bystanders and have no effect on maternal health [12].

Despite the fact that the specific health implications of fetal cell microchimerism have yet to be definitively determined, a growing body of literature points towards disproportionately increased fetal cell presence at sites of injury. Khosrotehrani et al. [13] showed in a pregnant murine model that the number of fetal cells in the maternal liver increased in response to a chemical injury induced by carbon tetrachloride. Other researchers showed that skin and spinal cord injuries in pregnant mice resulted in significantly more fetal cells at the site of injury [14].

Taken together, the current literature suggests that a sub-population of microchimeric fetal cells possess properties similar to stem cells. They have been called “pregnancy-associated progenitor cells,” or PAPCs [10]. Evidence exists to suggest that at least some of the fetal cells are hematopoietic stem cells, while other research suggests that some are mesenchymal stem cells [15]. If such studies are validated, fetal cells could potentially be harvested, expanded *in vitro*, and reintroduced to the mother to aid in tissue repair. Together with the exogenous stem cell therapies currently being studied, PAPCs should be explored as a novel source of stem cells. Because PAPCs preferentially traffic to the maternal lung [16] they may play an especially important role in lung disease.

Many acute and chronic lung diseases are currently incurable. Despite significant advances in symptomatic care, the only option for many patients is transplantation. This is not a guaranteed cure, as lung transplantation has a 50% mortality rate at 5 years [17]. Innovative therapies could have a significant impact on the morbidity and mortality of lung diseases. Exogenously administered stem cells are currently being investigated as novel therapeutic approaches for many lung diseases, including chronic obstructive pulmonary disease (COPD), emphysema, pulmonary fibrosis, pulmonary hypertension and acute respiratory distress syndrome [18]. Although there is currently little experience using stem cells for treatment of lung diseases, preliminary results from animal models and clinical trials are promising.

Physicians and researchers alike have long recognized the presence of sex differences in lung diseases. Idiopathic pulmonary fibrosis, idiopathic pulmonary arterial hypertension and lymphangiomyomatosis (LAM) are all more prevalent in females [18]. Emphysema in males is typically more extensive and characterized by greater peripheral involvement and larger emphysematous areas compared to females [19]. Additionally, there are sex differences in the prognosis of acute respiratory distress syndrome, with men having a much higher mortality rate [20]. Most studies addressing this issue have focused on the effects of sex hormones on lung development and progression of disease. Although differences in sex hormones may be responsible for some of these discrepancies, the field has overlooked the potential role of pregnancy and fetal cell microchimerism. This is especially important, given the high concentration of PAPCs found in the maternal lung [16]. In this review we present the current state of stem cell therapies and discuss PAPCs, an under-appreciated and potentially powerful alternative type of stem cell.

Current Knowledge Regarding Stem Cell Therapy in the Lung

Studies performed in numerous animal models suggest that stem cell therapies may be a promising approach for the treatment of lung diseases [21]. Intravenous delivery of stem

cells results in significant trapping of cells within the lung, making cell-based therapies even more attractive for treatment [22]. In developing potential therapies, the type of stem cell to be used must be considered, as each has different characteristics and potential uses.

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) differentiate into all blood cell lineages [23]. HSCs have been used for the treatment of cancer, myelodysplastic syndromes, and hereditary immunodeficiency disorders [24]. It is generally accepted that HSCs are CD34⁺, CD38⁻, CD133⁺ and negative for lineage-specific markers (lin⁻) [25].

Bone marrow-derived stem cells (BMSC) can reconstitute the hematopoietic system of an irradiated mouse, and contribute to the epithelium of the liver, lung, GI tract and skin [23]. In early studies that administered exogenous BMSCs to individuals, researchers noticed increased engraftment at sites of chronic lung injury. This led them to hypothesize that the injured lung was actively recruiting bone marrow-derived stem cells in order to aid repair [26].

Subsequent studies had conflicting results, with some demonstrating substantial engraftment while others showed none [26]. Transplantation of BMSCs into emphysematous mice resulted in decrease, and even reversal, of emphysematous structural changes within the damaged lungs, despite lack of apparent engraftment. This suggests that a paracrine effect may play a critical role [17]. BMSCs interact with endothelial cells in the lung to prevent thrombin-induced endothelial hyperpermeability. The mechanism involves activation of Cdc42, resulting in increased integrity of adherens junctions, leading to decreased inflammation and edema [27].

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are stromal cells that adhere to plastic, are negative for hematopoietic lineage antigens, and have the potential for differentiation into adipocytes, chondrocytes and osteocytes in culture [28]. More recently MSCs have been shown to be capable of neuronal, epithelial and muscular differentiation *in vitro* [29]. Because MSCs possess the features of stromal cells that support growth and maintenance of a variety of cell types in tissues, they are good candidates for cell-based therapies for lung disease. Additionally, MSCs have decreased immunogenicity due to low expression of major histocompatibility (MHC) I proteins, and lack of MHC II proteins and T-cell co-stimulatory molecules, such as CD80, CD86 and CD40. This allows administration of allogenic MSCs without generation of a significant host immune response [28].

Administration of bone marrow derived MSCs (BM-MSCs) have already demonstrated potential clinical benefits in mouse models of asthma, acute lung injury, fibrotic lung disease, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension [17]. Similarly to HSCs, MSCs are suspected to work through a paracrine effect. For example, MSC administration was shown to reduce the extent of fibrosis in bleomycin-induced lung injury with minimal engraftment [30]. It has also been demonstrated that the MSC culture medium can replicate the beneficial effect [28].

Rather than engraftment, modulation of inflammation and immune cells may be the primary cause of the beneficial effects of BM-MSCs. MSCs are known to be able to alter the functions of B and T lymphocytes as well as neutrophils, in part by the release of cytokines. Compared to controls, mice that receive BM-MSCs after lung injury have decreased levels of pro-inflammatory cytokines, increased levels of anti-inflammatory cytokines (such as IL-10 and IL-13) [28], and an overall decrease in histological evidence of inflammation. Similar results are seen in murine models for asthma, pulmonary fibrosis, radiation-induced

injury, and pulmonary vascular disease [17]. The use of allogenic MSCs in patients with moderate to severe COPD is already in Phase II clinical trials in the United States [17].

Endothelial progenitor cells

Endothelial progenitor cells (EPCs) are bone marrow-derived cells that contribute to vascular repair and homeostasis [31]. EPCs express surface markers of both hematopoietic and endothelial cell lineages, such as CD31 (PECAM), CD34, CD133 (Prominin), VEGFR-2 (KDR, Flk-1), and vWf. These cells expand in culture and differentiate into mature, functional endothelial cells [31, 32].

There are several reasons to believe that EPCs may be useful in the treatment of lung diseases. Through maintenance of the necessary vascular scaffold, these cells contribute to the homeostasis of the lung parenchyma [32]. Additionally, EPCs can be transduced to express pro-angiogenic factors or inhibitors of smooth muscle cell proliferation to minimize disease progression [33].

EPCs play a role in vasculogenesis and vascular repair in rodent models of pulmonary hypertension. These cells may act via a paracrine effect to diminish inflammation and by secretion of angiogenic and other growth factors such as SDF-1 (CXCL12), VEGF and PDGF [26, 32]. As with other types of stem cells, EPCs home to areas of injury after systemic administration [17].

A human clinical trial testing the effect of administration of autologous EPCs for the treatment of pulmonary hypertension is already underway. Preliminary results show improved clinical measures such as 6-minute walk, mean pulmonary artery pressure, pulmonary vascular resistance and cardiac output [34].

Placenta-Derived Stem Cells

The placenta and fetal membranes have recently been demonstrated to contain cells with stem cell-like properties, including amniotic epithelial and mesenchymal stromal cells (hAEC and hAMSC, respectively), chorionic mesenchymal stromal and trophoblastic cells (hCMSC and hCTC, respectively) and HSCs [22].

Placenta-derived stem cells have significant plasticity [21] and low immunogenicity [35]. They are able to engraft in solid organs, including the lung, brain and bone marrow [35]. The placenta can be readily obtained without invasive procedures and it does not have many of the ethical concerns that are associated with other sources of stem cells [36].

The use of placenta-derived stem cells for the treatment of pulmonary diseases is being tested in animal models. In a bleomycin-induced model of pulmonary fibrosis, investigators showed that either intratracheal or intraperitoneal administration of placenta-derived stem cells, whether allogenic or xenogenic, reduced the amount of fibrosis when compared to controls [21]. There was also decreased neutrophil infiltration and attenuated expression of pro-inflammatory cytokines [37]. This is consistent with existing hypotheses regarding the immunomodulatory properties of fetal membrane-derived cells [22].

Fetal membrane- and tissue-derived stem cells may have other benefits. For example, fetal MSCs have growth advantages over their adult counterparts, including expression of pluripotency markers, more rapid growth and longer telomeres maintained during passaging [38]. Isolation of stem cells directly from fetuses, however, would require performing unnecessary procedures on pregnant women and their fetuses. Remarkably, fetal cells are naturally present in the blood and organs of women who have been pregnant.

Pregnancy associated progenitor cells (PAPCs)

The presence of fetal cells in maternal organs was first reported in 1893 by the German pathologist Georg Schmorl. He observed multi-nucleated syncytial giant cells in the pulmonary circulation of women who had died of eclampsia. He correctly hypothesized that fetomaternal cell trafficking might also occur in normal pregnancies [39] although this was not demonstrated for another 76 years [40].

In the human, the number of fetal cells in the maternal circulation increases throughout gestation and decreases rapidly after parturition [1], although a population persists for several decades [2, 7, 8]. Male cells with an osteocyte-like morphology can also be found in the lamellae of cortical bone in postpartum females. These results suggest that PAPCs enter the maternal blood as progenitors and engraft within bone where they persist for decades [2]. PAPCs are also present in healthy lung, thyroid, skin and lymph node tissues [10, 41, 42].

Due to the challenges associated with human research, including limited access to appropriate tissues in living subjects, and lack of a complete reproductive history in deceased subjects, more recent efforts have focused on murine models. Animal studies typically involve mating a wild-type female to a male transgenic for green fluorescent protein (GFP). The fetal cells can be easily identified by their green color. This model system was employed to perform histological studies of the placenta to observe fetal cell trafficking. Fetal cells could be visualized in the decidua as early as 10 days post conception [43]. The frequency of PAPC detection increased during the second half of gestation. In other experiments, maternal lung, liver and spleen were used to trace the natural history of fetal cell trafficking [16]. PAPCs are detectable at day e11, increase to a maximum at day e18–19, and then are cleared rapidly in the immediate postpartum period.

PAPCs in the Maternal Lung

PAPCs may have a unique impact on lung disease. In conjunction with the GFP mouse model described above, researchers use a variety of methods to detect PAPCs in the maternal lung. Fetal cells can be directly visualized by fluorescent stereomicroscopy as discrete green fluorescent foci that are widely distributed throughout the lung [16]. They can also be detected using flow cytometry, PCR and immunofluorescence [16, 44] (Figure 1). No matter which method is used, the highest frequency of PAPCs is consistently observed in the lung as opposed to other maternal organs. This is also independent of gestational age or whether the mating was allogenic or congenic [16, 44]. Fetal and placental cells have also been consistently detected in human lungs, starting with the initial discovery of syncytiotrophoblasts in the lungs of pregnant women who died of eclampsia [39]. More recent reports show that fetal cells are present even in the healthy lungs of women at autopsy [41]. In diseased lungs, fetal cells preferentially cluster at the site of lung tumors when compared to healthy surrounding lung [42].

The reason for the high concentration of PAPCs in the maternal lung is currently unknown. It might be due to the high rate of blood flow through the lung or that the pulmonary capillary bed is the first encountered by PAPCs after flowing through the uterine vein into the inferior vena cava (i.e. passive mechanisms). Alternatively, it is possible that the lungs (e.g. capillary endothelium) present a receptive microenvironment for retention and engraftment of these cells, or that homing to the lungs is stimulated by an as yet undetermined chemical axis [45], such as SDF-1/CXCR4, which promotes retention of a variety of cells in tissues.

PAPCs Increase at the Site of Injury and Differentiate

Previously, researchers hypothesized that fetal cells might be capable of triggering a graft-versus-host disease, leading to autoimmune disease [9]. This was supported by the fact that the number of fetal cells is often increased in tissues affected by autoimmune diseases [12]. More recent research suggests that the fetal cells home to areas of injury and inflammation [10]. In a murine model of contact dermatitis initiated during pregnancy, fetal cells preferentially trafficked to the injured skin [46]. Using histochemistry, fetal cells were identified as CD45⁺ leukocytes in the maternal blood vessels and CD31⁺ cells that contributed to the development of angiogenesis. This last finding supports the hypothesis that fetal cells cross as progenitors and differentiate within the maternal tissues.

Other studies have demonstrated similar results in the murine brain. PAPCs crossed the blood-brain barrier and integrated within the maternal brain for up to 7 months postpartum [47]. The number of cells increased significantly during the postpartum period, with the highest frequency of cells detected at 60 days after parturition. PAPCs had morphologies similar to neurons, showed axonal and dendritic projections that became more complex over time, and expressed neuron-specific genes such as NeuN and β 3-tubulin. The numbers of PAPCs in the brain was higher in a model of Parkinson's disease.

Analogous results have been observed in human studies. Fetal cells have been demonstrated to contribute to thyroid follicles in a postpartum woman with an adenomatous goiter [48], the liver parenchyma in a postpartum woman with hepatitis C [49], and the appendices of pregnant women with appendicitis [50]. In all of these reports, the fetal cells were morphologically indistinguishable from and continuous with the maternal tissue, identifiable as fetal only by the presence of a Y chromosome.

One of the biggest questions surrounding fetal cell microchimerism is the type or types of cells that make up the population. It was originally hypothesized that PAPCs are a uniform population of cells that have characteristics somewhere between that of embryonic and adult stem cells [51, 52]. Since then it has been demonstrated that fetal cells, especially within the lungs of pregnant female mice, are a diverse group, expressing a variety of surface markers found on both immature and mature cell types [53] (Table 1). The differentiation state of these cells may have implications for maternal health. More mature cells would be more likely to initiate a host immune response, while immature cells would be more likely to contribute to tissue repair [12]. Further research is needed to clarify whether these cells cross the placenta as a non-uniform population with respect to lineage, a homogenous population at various stages of differentiation (e.g. fibroblast vs. myofibroblast), or if they trans-differentiate once in they arrive in maternal organs.

Conclusions

Fetomaternal cell trafficking is a well-described phenomenon occurring during all pregnancies. Fetal cells are present in maternal organs; the largest number is in the maternal lungs. PAPCs can be detected for decades after parturition. The clinical significance of these cells is unknown, but they include a population of progenitor cells that may contribute to tissue repair and regeneration. Their presence in the maternal lung may be one explanation for the sex differences observed in the prevalence and prognosis of lung disease.

Novel therapies are needed for the treatment of acute and chronic lung diseases. The use of exogenous stem cells has shown promise in both animal models and clinical trials. With stem cell research there is controversy surrounding the use of embryos as a stem cell source, while the use of adult stem cells is restricted by their limited plasticity. The use of placenta-derived stem cells has been recently described. These cells have significant plasticity and are

readily obtained without invasive procedures. To date, the stem cell literature has under-emphasized the contribution of PAPCs, which concentrate in the maternal lung and are disproportionately present in areas of injury. Fetal cells harvested from the blood or organs of parous women could potentially be used as an alternate source of stem cells with potential therapeutic properties for the woman herself or her children.

Since they are naturally-acquired, fetal progenitor cells may have advantages over other types of stem cells with therapeutic promise. Induced pluripotent stem (iPS) cells, which require cell culture and exposure to viruses and transcription factors, embryonic stem cells, which require destruction of embryos, and adult stem cells, which have limited plasticity, all have significant disadvantages not shared by PAPCs [6]. Because PAPCs are haploidentical with the mother, they are less likely to be rejected than exogenously administered stem cells. They may also be less likely to be engulfed by macrophages. Future research should focus on clarifying the identity of PAPCs in the maternal lung, their isolation and expansion in culture, and determining if parous females experience health benefits or consequences from the presence of these cells.

Acknowledgments

The authors would like to thank Helene Stroh who produced the images in Figure 1. The project described was supported by Award Number R01 HD04946-05 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (to DWB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health. The authors have no conflicts of interest to disclose.

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Figure 1.

Fetal cells expressing the green fluorescent protein (GFP) transgene are clearly visible within the murine maternal lung at gestational day 18. Nuclei were counterstained with 4',6-diamidino-2-phenylindole. *Left: 400×, Right: 1000× magnification.*

Evidence from studies in both humans and mice suggests that PAPCs may be stem cells or have stem-like properties. It is currently unknown whether one type of cell crosses the placenta and then differentiates, or whether the trafficking fetal cell population consists of multiple different progenitors.

Table 1

	HSC	MSC	EPC	Placental
HUMAN STUDIES	Male cells in CD34-enriched apheresis products from non-pregnant female bone marrow donors [15]	Male cells detected in maternal bone marrow identified as MSCs by morphology, immunophenotype, self-renewal <i>in vitro</i> and osteogenic and adipogenic differentiation [2]	Fetal cells expressing vWF, CD34 and CD31 in the intervillous space [54]	Trophoblasts, as identified by morphology, in the lungs of women with eclampsia [39]
	Fetal HSCs in the placenta could migrate to the mother [15]			
MURINE STUDIES	CD45+ fetal cells within the maternal blood vessels [46]	Fetal cells expressing CD29 (integrin $\beta 1$), CD44, and CD105 (endoglin) in the maternal lung [53]	CD31+ (PECAM) fetal cells within the vascular wall in areas of inflammation [46]	Fetal cells with large nuclei in the placental decidua [43]
	CD34+ fetal cells in the maternal lung and liver [53]		CD31+ fetal cells in the maternal lung, liver, spleen and kidney [53]	