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Current opinion

Can we fix it? Evaluating the potential of placental stem cells for the treatment of pregnancy disorders

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ABSTRACT

In pregnancy disorders such as pre-eclampsia, intrauterine growth restriction (IUGR) and recurrent miscarriage a poorly functioning placenta is thought to be a major component of the disease process. However, despite their prevalence, we currently have no way to fix dysfunctional placentae or directly treat these disorders. Over the past two decades our understanding of the role that stem cells play in organ development and regeneration has expanded rapidly, and over the past 5 years the therapeutic use of stem cells to both regenerate damaged tissues, and act as potent modulators of diseased microenvironments, has become a reality in many organs including the heart, kidney, liver, skin and eye. Over its short lifespan the placenta undergoes rapid and continuous growth and differentiation, meaning that placental 'organogenesis' only truly ends at delivery, and thus stem cells are likely to play important roles in placental function for the duration of pregnancy. Two populations of stem cells exist in the placenta that contribute to this on-going growth and differentiation: trophoblast stem cells and mesenchymal stem cells. This review will address our current understanding of how each of these stem cell populations contributes to successful placental function, how epithelial and mesenchymal stem cell populations are being translated to the clinic in other fields, and whether these advances can teach us anything about how placental stem cells could be used to fix faulty placentae in the future.

1. Introduction

In diseases of pregnancy such as intrauterine growth restriction (IUGR) a poorly functioning placenta is thought to be a major component of the disease process. However, despite our absolute reliance on the placenta, we do not understand the basic biological processes that underpin placental formation, nor why these may fail, and we cannot effectively treat faulty placentae. Imagine that we could fix the failing placenta by redirecting cell lineage differentiation or, by implanting stem cells to replace poorly functioning parts of the placenta. To do this requires harvesting the enormous potential of stem cells to improve placental function. At present, stem cell therapies to treat placental disorders seem like a far-fetched idea, but in reality there are currently hundreds of clinical trials investigating the use of stem cells as therapeutics registered on the US clinical trial database (clinicaltrials.gov), and it is likely that advances in stem cell biology will lead to major changes in medical care in the future. As stem cell therapies become a significant and on-going part of medical practice in many different medical fields in the future, how do we ensure that obstetric medicine is not left behind? This review aims to address our current understanding of how stem cells contribute to successful placental function, how similar mesenchymal and epithelial stem cell populations are being translated to the clinic in other fields, and whether these advances can teach us anything about how placental stem cells could be used to fix faulty placentae in the future.

2. How do stem cells contribute to normal placental function?

Following conception the newly fertilised oocyte undergoes a series of divisions producing equipotent daughter cells until at the 32/64 cell stage the trophectoderm separates from the inner cell mass. At nidation, following contact with the decidua the outer trophectoderm layer begins to form the first primitive trophoblast populations – the primitive cytotrophoblast and primitive syncytiotrophoblast [1]. As the early cytotrophoblast populations proliferate they form invaginations into which mesenchymal cells derived from the differentiating inner cell mass invade, forming the first placental villi at around 12 days post-fertilisation [1]. Therefore, our current understanding is that the placenta is originally

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formed from two stem cell populations; 1) trophoblast stem cells (TSC) derived from the trophectoderm that go on to form all the differentiated trophoblast lineages of the placenta, and 2) mesenchymal stem cells (MSC) that form all non-trophoblast cells of the villous core. As the placenta continues to develop it undergoes an intricate programme of organogenesis well in advance of the development of individual fetal organs. Indeed, the placenta is the first fetal organ in which *de novo* blood vessel development occurs, with the first blood vessels evident in tertiary villi at just 15 days post-fertilisation, a time when the embryo exists only as the three ectodermal, endodermal and mesodermal layers and contains no blood vessels [1,2].

2.1. Mesenchymal stem cells

Mesenchymal Stem Cells (MSC) are multipotent cells that are precursors to tissues of mesodermal lineages. MSCs were first isolated from bone marrow in 1974 [3], and have now been identified in almost all tissues, including muscle, adipose tissue, lung, Wharton's Jelly, umbilical cord blood and placenta [4,5]. In order for cells to be characterised as MSCs they must be capable of adhering to plastic and differentiation into the three major mesenchymal lineages; adipocytes, chondrocytes or osteocytes [6]. MSCs must also express characteristic cell surface markers including CD73, CD90, CD105 and HLA-A2 and lack expression of makers of other cell lineages including CD34, CD45, CD14 or CD11b, CD79α or CD19 and HLA-DR [6].

Placental MSCs have been postulated to play an important role in placental development and function by developing the branching villus structure of the placenta and contributing to vasculogenesis and angiogenesis. Vasculogenesis (the *de novo* synthesis of blood vessels) begins in the placenta with a change in morphology of MSCs at around 15–20 days post-fertilisation, which coincides with the appearance of haemangiogenic stem cells that aggregate into cell cords [7,8]. These haemangiogenic stem cells then differentiate into CD34 positive endothelial cell cords in which primitive lumens are evident from 23 to 26 days post-fertilisation [7,8]. These vessels are connected by microvascular tubes, and by day 30 post-fertilisation (six and a half weeks of gestation) a connecting network of larger vascular structures with clear lumens are evident within the placenta [7]. In an adult, vasculogenesis occurs during tissue remodelling, wound healing and tumour growth and involves the differentiation of existing bone marrow derived endothelial progenitor cells into endothelial cells [9]. However, no bone marrow derived endothelial progenitor cells exist in the placenta at the beginning of pregnancy, and therefore placental vasculogenesis occurs under very different circumstances. Instead, it has been proposed that placental vasculogenesis is initiated by the differentiation of placental MSCs [8] (Fig. 1).

MSC plasticity is influenced by the tissue of origin, and correspondingly placental MSCs demonstrate limited potential to differentiate into unrelated cell types such as cardiomyocytes and skeletal muscle, and are less efficient at differentiating into osteocytes and adipocytes than their bone marrow derived counterparts [10]. However, several MSC populations, including those derived from bone marrow and amniotic membrane, have demonstrated an inherent predisposition to differentiate into an endothelial phenotype [11,12], and the pro-angiogenic environment generated by trophoblast secretion of angiogenic factors such as VEGF family members, angiopoietins, FGF and PDGF, strongly suggests that MSCs within placental villi are likely to have a similar predisposition [13]. Bone marrow-derived MSC treated with VEGF can be induced to differentiate into endothelial-like cells that express both vWF and Flt1 [14,15]. In a similar manner, MSC isolated from first trimester placental villi and cultured in commercial endothelial growth media also adopt an endothelial-like cobblestone morphology and up-regulate early endothelial lineage cell surface markers including VEGFR2, but to date conditions have not been established to induce the up-regulation of late endothelial markers such as CD31 or vWF by cells derived from placental MSC [10].

As placental MSC reside in a peri-vascular niche in the placenta throughout gestation, it is likely that they also continue to support the expansion of the placental vascular network by contributing to the process of angiogenesis, which takes over from vasculogenesis as the dominant mechanism for vascular development at around 32 days post-fertilisation [4,16,17]. This switch coincides with the onset of circulation between the placenta and fetus via the umbilical cord [17], thus opening up the possibility that both MSC originating in the placenta, and MSC circulating in fetal blood can begin to contribute to placental vascular development from that time point. There are two forms of angiogenesis that contribute to the placental vascular network. **Branching angiogenesis**, which involves the proliferation and migration of endothelial cells to elongate and form lateral extensions from existing endothelial tubes, leads to the formation of a branching vascular tree and is the predominant mechanism of angiogenesis in the placenta between weeks 6–24 of gestation. Branching angiogenesis results in the formation of terminal capillaries, which are evident as highly coiled blood vessels with a dilated lumen located close to the overlying trophoblast to ensure efficient exchange between the maternal and fetal circulations [17]. After 24 weeks of gestation **non-branching angiogenesis** predominates, which results in the elongation of vascular capillary loops as a result of endothelial cell proliferation, and ensures that the placenta is able to keep up with fetal growth demands during the third trimester of pregnancy [17].

2.2. Trophoblast stem cells

Trophoblasts are epithelial cells that are unique to the placenta. There are at least three mature subtypes of trophoblast in the human placenta; cytotrophoblasts, extravillous trophoblasts and the syncytiotrophoblast, each of which have separate functions that are required to ensure pregnancy success. All of these three mature trophoblast populations are derived initially from the trophectoderm lineage of the pre-implantation blastocyst. In the mouse, TSCs that give rise to all murine trophoblast types have been isolated from the trophectoderm, and as a result of experiments employing these TSCs we have a good understanding of murine trophoblast differentiation [18]. However, the murine placenta is anatomically very different to the human placenta and murine trophoblast lineages bear little resemblance to human trophoblast lineages [18]. Obtaining human TSCs would be of great value to better understand how mature trophoblast populations are formed in the human placenta and ultimately how human TSCs may be used to fix faulty placentae.

Traditionally villous cytotrophoblasts were termed 'stem like cells' that were believed to be multi-potent and give rise to all the mature trophoblast lineages. However, many groups including ours have presented evidence to challenge the multi-potent nature of villous cytotrophoblasts, and have instead suggested that different cytotrophoblast sub-populations primed to differentiate into syncytiotrophoblast or extravillous trophoblast exist [19–21]. Indeed, a feature of other epithelial stem cell populations is their generation of highly proliferative progeny, referred to as transiently amplifying cells, that are intermediate between stem and terminally differentiated cells. The transiently amplifying cells divide actively for a period of time to expand the pool of progenitor cells able to differentiate into the terminal cell lineages of the tissue, thus increasing the number of differentiated progeny a stem cell can produce, and enabling the stem cell itself to divide infrequently and