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Immunomodulatory properties of human placental mesenchymal stem/stromal cells

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ABSTRACT

Mesenchymal stem/stromal cells (MSCs) are isolated from various fetal and adult tissues such as bone marrow, adipose tissue, cord blood and placenta. Placental MSCs (pMSCs), the main focus of this review, are relatively new MSC types that are not as intensively studied compared with bone marrow-derived MSCs (BMMSCs). MSCs modulate the immune functions of important immune cells involved in alloantigen recognition and elimination, including antigen presenting cells (APCs), T cells, B cells and natural killer (NK) cells. Clinical trials, both completed and underway, employ MSCs to treat various human immunological diseases, such as multiple sclerosis (MS) and type 1 diabetes. However, the mechanisms that mediate the immunosuppressive effects of pMSCs are still largely unknown, and the safety of pMSC use in clinical settings needs further confirmation. Here, we review the current knowledge of the immunosuppressive properties of placental MSCs.

1. Introduction

Mesenchymal stem/stromal cells (MSCs) are multipotent adult stem cells that are isolated from different fetal and adult tissues, such as adipose tissue, umbilical cord, bone marrow and placenta [1–3]. MSCs are spindle-shaped cells that adhere to plastic and form colonies called colony-forming unit (CFU) [1–3]. MSCs differentiate into cell derivatives of the mesenchymal lineage, including adipocytes, osteocytes and chondrocytes [1–3]. In cell culture, MSCs can be stimulated to *trans*-differentiate into hepatocyte-, neuron- and astrocyte-like cells [4].

The therapeutic potential of MSCs has been attributed to their differentiation potential. In addition, their immunomodulatory properties make them highly attractive for treating immune disorders such as multiple sclerosis (MS) and graft versus host disease (GVHD). GVHD occurs when the transplanted donor's immune system attacks the recipient's immune system, usually after allogeneic bone marrow transplantation, but occasionally after homologous blood transfusion [5].

The placenta is a fetomaternal organ that allows the protection, and the growth of the developing fetus. It consists of chorionic and basal plates that are fetal and maternal surfaces, respectively [6]. The chorionic plate consists of the chorionic villous tree, and the basal plate consists of the decidua basalis, which is endometrial tissue transformed during pregnancy to allow attachment of the placenta [6,7]. Moreover, during pregnancy these plates merge to form the fetal membranes, which consists of the amnion and the chorion [1]. The amnion consists of an epithelial layer with an underlying stromal layer, and the chorion consists of a stromal layer

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[1]. As the fetus grows, the chorion of the fetal membranes adheres to the overlying decidua parietalis to form the choriodecidua [1]. MSCs can be isolated from each of these regions.

We are others isolated MSCs from various parts of human placenta (pMSCs) such as chorionic villous, *decidua basalis*, *decidua parietals* and amniotic membrane [1–3,8]. In common with MSCs from other sources, pMSCs display immunomodulatory properties, which make them potentially useful for immune-mediated diseases, and therefore pMSCs are intensively studied.

2. Immune tolerance of placental mesenchymal stem cells

2.1. pMSCs express major histocompatibility complex (MHC) class molecules

MSCs express major histocompatibility complex (MHC) class I but not MHC class II. Unstimulated MSCs from the placenta and other sources such as bone marrow (BMMSCs), umbilical cord (UCMSCs), adipose tissue (ADMSCs) express MHC class I but not MHC class II antigens [1–3, 9, 10]. However, following stimulation with interferon-γ; (IFN-γ), BMMSCs, UCMSCs, and ADMSCs upregulate the expression of MHC class II both *in vitro* and *in vivo* [10–17]. There is a single report showed that unlike BMMSCs, pMSCs treated with IFN-γ; for 3 days only very minimally upregulated MHC class II [18]. The exact role of IFN-γ in regulating pMSC immunomodulatory functions is still unclear and therefore a future study is necessary to determine this.

Human leukocyte antigen (HLA)-G is a non-classical MHC class I molecule, which induces immune tolerance through interactions with inhibitory receptors present on major immune effector cells. pMSCs express the membrane-bound HLA-G, which is known to inhibit T cell functions [19]. It has been shown that pMSCs suppress T-cell proliferation through HLA-G [20,21]. In addition, HLA-G expression is induced by IFN-γ on pMSCs and this mediated the immunosuppressive functions of pMSCs on natural killer (NK) cells [22]. However, there is no extensive studies on the role of HLA-G in mediating pMSC immunosuppressive functions on immune cells including dendritic cells (DCs), NK cells and cytotoxic or cytolytic T lymphocyte ($CD8^+$ T cells) mediated cytolysis, as well as allogeneic T-cell proliferation and therefore more research is needed to determine this role.

3. The immunosuppressive effects of pMSCs on immune cells

3.1. Immunosuppressive effects of pMSCs on lymphocytes

3.1.1. T cells

The immunosuppressive effects of pMSCs on T lymphocytes are the most commonly studied. T lymphocytes are part of the adaptive immune system and play an essential role in cell mediated immunity. Increasing reports show the potent immunosuppressive properties of pMSCs are dependent on their ability to inhibit the proliferation and cytokine production of allogeneic lymphocytes. pMSCs inhibit the proliferative response of allogeneic lymphocytes in a mixed lymphocyte reaction (Fig. 1) [23–32]. Similar to BMMSCs and ADMSCs, pMSCs inhibit the proliferation of allogeneic lymphocytes stimulated by anti-CD3 and CD28 monoclonal antibodies or by cytokines *in vitro* [18,20,23,24,33–36]. This anti-proliferative effect of pMSCs on lymphocyte proliferation is intensified following indoleamine 2,3 dioxygenase (IDO) induction by IFN-γ [33]. In addition, pMSCs inhibit the proliferation of phytohemagglutinin (PHA) and alloantigen-stimulated T lymphocytes in a dose-dependent manner [34]. Moreover, pMSCs inhibit the secretion of several cytokines, such as the T helper 1 (TH1) cytokines (i.e. IL-2, IL-12, TNF-α and IFN-γ), whereas they induce the expression and secretion of the T helper 2 (TH2) cytokines (i.e. IL-10) (Fig. 3) [27,35,37]. Furthermore, pMSCs induce the differentiation of T regulatory lymphocytes (Tregs), Th2 polarization associated with increased levels of IL-4 and IL-10 and Th17 induction (production of high concentrations of IL-6 and IL-17) (Fig. 3) [20,37].

Various mechanisms are proposed to account for pMSC immunosuppression on lymphocytes. pMSCs suppress the proliferation

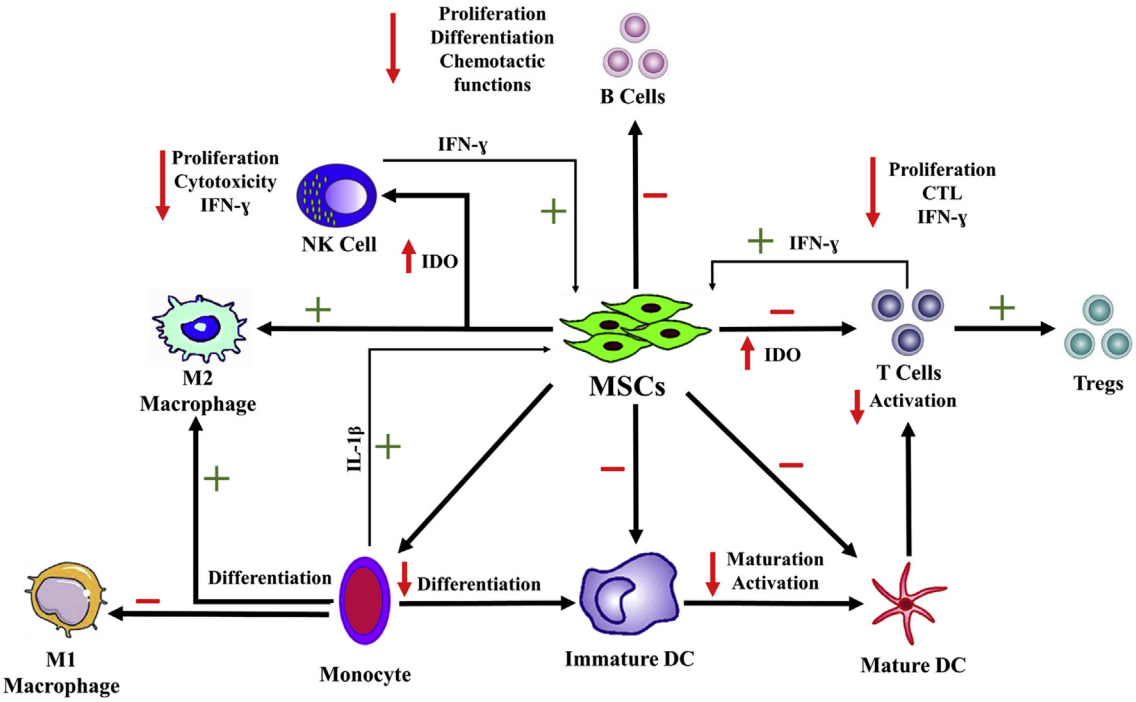

Fig. 1. Immunomodulation properties of MSCs on immune cells including T cells, NK cells, B cells, monocyte, dendritic cells (DCs) and macrophages.

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