Chapter 2

Placenta-Derived Mesenchymal Stromal Cells: Modulation of Immunity and Inflammation

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Abstract

As an organ generally discarded after a normal full-term birth, the placenta is one of the most studied organs from the cellular standpoint. The placenta contains large numbers of immune cells, stem cells, and stromal cells. These cell types spurred the field of regenerative medicine by catalyzing the establishment of cord blood banks and hematopoietic stem cell reconstitution in the treatment of many diseases including cancer. Previously, many scientific articles and reviews have focused on the production, phenotype, and functional characterization of bone marrow-derived mesenchymal stromal cells. In this chapter, the focus will be solely on the biology, phenotype, and functional characterization of placenta-derived stromal cells. Modulation of the immune response, including T cell proliferation, dendritic cell maturation, and monocyte differentiation by placenta-derived stromal cells, will be discussed. This chapter will span in vitro functional analyses, animal models highlighting the in vitro data culminating in a summary of current clinical activity.

Keywords: placenta, stromal cells, immune modulation, inflammation, mesenchymal, stem cells, growth factors, cytokines

1. Introduction

The placenta is an organ that has evolved to accomplish one thing, promote fetal growth during gestation. This is not a new concept, but the concept has evolved with our understanding of the molecular and cellular components required. The fetal allograft is maintained by several mechanisms including, but not limited to physical sequestration, immune modulation by hormones, cells, and metabolites. In fact, the function of T cells and dendritic cells changes

during gestation [1]. In mid gestation, there were reduced antigen-specific T cell responses, upregulation of inhibitory molecules, and reduced myeloid maturation toward dendritic cells suggesting an immune tolerance state was achieved. These changes were reversed in the third trimester toward immune activation that participated in completing pregnancy. In fact, the observation of microchimerism in mothers postpartum indicated that there was a very strong tolerance inductive mechanism produced by the placenta and its physiology. Maternal-fetal chimerism has been recently reviewed [2]. A highlight from this review discussed pregnancy-associated progenitor cells that were proposed to be tissue resident stem cells with long-term survival that led to microchimerism that was detected for decades in some individuals. We propose that these types of tissue resident stem cells can be isolated and cultured from full-term postpartum placenta. After culture, we hypothesize that the immune modulatory properties that these cells exhibit in the placenta will be translated to in vitro and in vivo experiments that form the basis of many clinical development programs.

An example of the cells that can be isolated from the human placenta is the human placenta-derived adherent cells (PDAC). PDAC are a culture expanded, plastic-adherent undifferentiated MSC-like population derived from normal full-term postpartum placental tissue. PDAC exhibit a phenotype of CD34-, CD10+, CD105+, and CD200+. PDAC constitutively express low to moderate levels of HLA Class I and undetectable level of HLA Class II, and these cells do not express the costimulatory molecules CD80 and CD86. PDAC were isolated by mechanical and enzymatic digestion of human placental tissue obtained from a normal, full-term birth as described [3]. PDAC are currently in clinical development as two separate formulations, PDA-001 (infusion product) and PDA-002 (locally injected product). This chapter will focus on developing the connection between placental immune biology (observed microchimerism) and the phenotypic and functional properties of the cells isolated from placenta tissues. These cells regardless of placental tissue source (amnion, cord, and cord blood) can mediate at least some of the immune tolerance properties of the placenta.

2. Molecular and cellular mechanisms of action

2.1. T cell proliferation and differentiation

Placenta-derived mesenchymal stromal-like cells (pMSC), including PDAC, have been isolated from various anatomical sites of the placenta, including the umbilical cord, chorion, decidua, amniotic membrane, and amniotic fluid. Like their bone marrow counterparts, these cells possess potent immune suppressive properties and exert their effects on T lymphocytes through a multitude of mechanisms that include both cell contact mediated interactions and through the modulation of secreted soluble factors. pMSC have been shown to inhibit both the proliferation and cytokine production of T lymphocytes, as well as, modulate T cell differentiation [3–5].

Many investigators have demonstrated the immune suppressive effects of pMSC in vitro via co-cultures of pMSC with CFSE-labeled, mitogen stimulated, or allogeneic T cells, known as mixed lymphocyte reactions (MLR), or with CFSE-labeled T cells stimulated by anti-CD3/

anti-CD28 monoclonal antibodies/beads, known as bead T cell reactions (BTR). In all cases, in reactions where CFSE-labeled cells were co-cultured with pMSC, significant reductions in both CD4+ and CD8+ T cell proliferation were observed. Reduced levels of proliferation were accompanied by decreased levels of Th1 cytokines (IL-2, IL-12, TNF-α, and IFN-γ) and increased levels of Th2 cytokines (IL-4 and IL-10) [3, 4, 6, 7]. Furthermore, when pMSC were co-cultured with naïve T cells under Th1 or Th17 inducing conditions, inhibition of Th1 and Th17 differentiation was observed [3].

Several factors secreted from pMSC have been implicated in the immune suppressive activities observed and will be summarized below. Indolamine 2, 3 dioxygenase (IDO) has been identified as a key mediator of pMSC anti-proliferative effects in MLRs/BTRs. IDO is a heme-containing enzyme that catabolizes the essential amino acid tryptophan into L-kynurenine. IDO-induced tryptophan degradation results in T cell cycle arrest in the G1 phase and serves as an instrumental mechanism for maintaining immune cell homeostasis and peripheral tolerance [8]. IDO gene expression and activity were induced in co-cultures of pMSC with MLRs/BTRs [6, 7, 9] and replenishment of tryptophan or treatment with IDO blocking compounds were shown to impair the antiproliferative abilities of pMSC [9, 10]. In addition, IDO was induced and subsequent suppression of T cell proliferation was intensified following stimulation of pMSC with IFN-γ [9, 11].

In addition to IDO, increased production of prostaglandin E2 (PGE2) and transforming growth factor-β (TGF-β) by pMSC, and increased secretion of IL-10 by T lymphocytes have also been implicated as key soluble factors underlying pMSC's immunosuppressive mechanism. PGE2, a bioactive lipid that is synthesized from arachidonic acid by the COX-1 and COX-2 enzymes, inhibits T cell proliferation and regulates the maturation and antigen presentation function of dendritic cells [3, 12]. TGF-β is a potent immunoregulatory protein that controls the differentiation, proliferation, and activation of various immune cells [13]. IL-10 is a well-known anti-inflammatory cytokine that controls the growth and activation of regulatory and/or anti-inflammatory cells [7]. All three secreted factors have been shown to be significantly increased in pMSC co-cultured with MLRs/BTRs [6, 7, 14]. The addition of blocking or neutralizing agents against PGE2, TGF-β, or IL-10 partially reversed and impaired the inhibitory effects of pMSC on T cell proliferation [5, 10]. Stimulation of pMSC with IFN-γ significantly upregulated the release of the tolerogenic cytokines TGF-β and IL-10 [5, 11].

Moreover, the increased levels of PGE2, TGF-β, and IL-10 can also affect T cell differentiation and lead to selective induction of Tregs [15, 16]. Tregs are CD4 + CD25 + FoxP3+ T cells that specialize in inhibiting T cell responses, allergic reactions, autoimmune disease, and graft rejection, while maintaining immune homeostasis [4]. Numerous studies have described an increase in the frequency of Tregs from co-cultures of pMSC with MLRs/BTRs [5, 6, 10, 14].

The immune modulatory effects of pMSC on T cell proliferation and differentiation have also been shown in several animal models. We reported that PDAC suppressed T cell proliferation in an OT-II T cell adoptive transfer model [3]. OT-II transgenic mice, expressing the T cell receptor specific for ovalbumin, were used to evaluate the effects of PDAC on antigen-specific CD4+ T cell proliferation. PDAC at three different doses or vehicle were administered along with the adoptive transfer of CD4+ T cells isolated from OT-II mice into

wild-type recipient mice following ovalbumin peptide immunization. PDAC treatment showed a dose-dependent decrease in the ovalbumin-specific CD4+ T cell proliferation in the spleen as compared with vehicle-treated mice. In addition, PDAC treatment resulted in an increase in the percentage of IL-10-producing splenic CD4+ T cells in a dose-dependent manner. In a rat sciatic nerve neuritis model, we showed that PDAC enhanced IL-10, but suppressed IFN-γ and IL-17 gene expression in draining lymph node, indicating that PDAC suppresses Th1 and Th17 cell differentiation [17]. We postulated that immune modulation of T cells in the draining lymph node is the mechanism underlying PDAC mediated neuropathic pain relief. To test this hypothesis, we performed two draining lymph node adoptive transfer studies in rat sciatic nerve neuritis model. Neuritis was induced by surgery and application of 1% carrageenan around sciatic nerve [17]. As shown in **Figure 1**, donor rats were treated with PDAC or vehicle 3 days after neuritis induction. One day after treatment, donor rats were sacrificed, and the draining lymph node was isolated into a single cell suspension and subsequently administered intravenously into the recipient rats with sciatic nerve neuritis.

Mechanical hyperalgesia measurement in the recipient rats showed that the draining lymph node cells from PDAC-treated animals reduced neuropathic pain in a dose-dependent manner compared with the draining lymph node cells from vehicle-treated animals (**Figure 2**).

To further identify the role of PDAC-mediated T cell modulation in the reduction of neuropathic pain, draining lymph node cells were separated into T cells and non-T cells using magnetic Pan-T microbeads, and adoptively transferred the cells to recipient rats with sciatic nerve neuritis. As shown in **Figure 3**, the whole population of draining lymph node cells as well as, the T cell fraction reduced neuropathic pain at days 4, 6 and 8. Interestingly, the non-T cell fraction also reduced neuropathic pain, with a slight time-delayed effect. These results from adoptive transfer studies demonstrated that immune modulation of the draining lymph node cells is the underlying mechanism of PDAC-mediated neuropathic pain reduction. Additional studies will be needed to sort out the differing contributions of the lymph node cells and how PDAC mediate these effects.

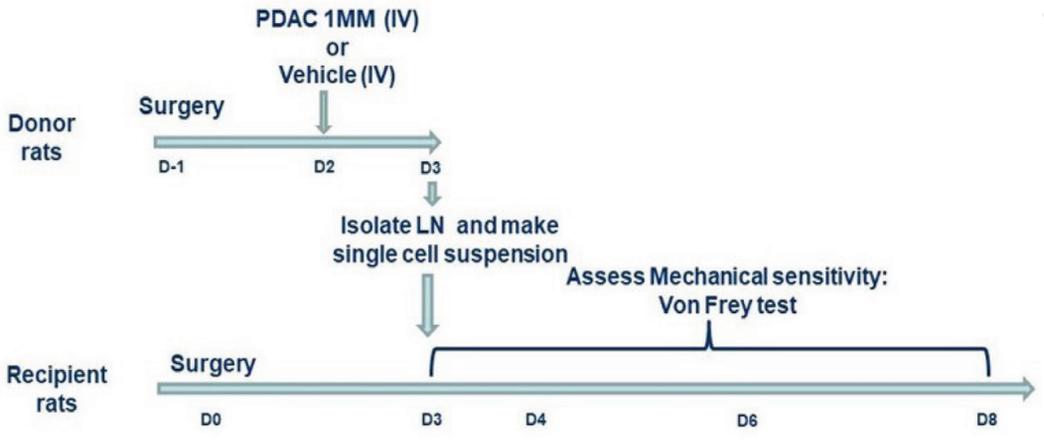

Figure 1. Schematic chart of draining lymph node cell adoptive transfer study.

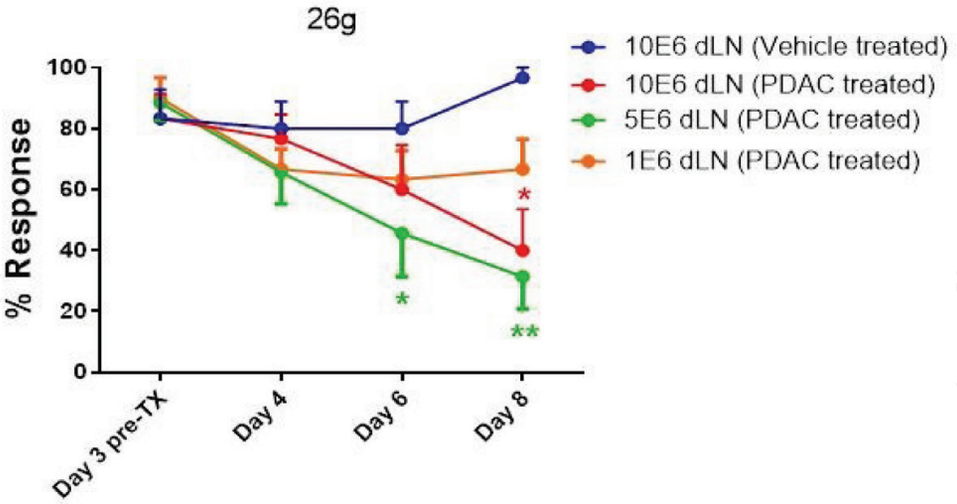

Figure 2. The effect of draining lymph node from PDAC-treated rats on mechanical hyperalgesia measured by 26 g force of von Frey fiber.

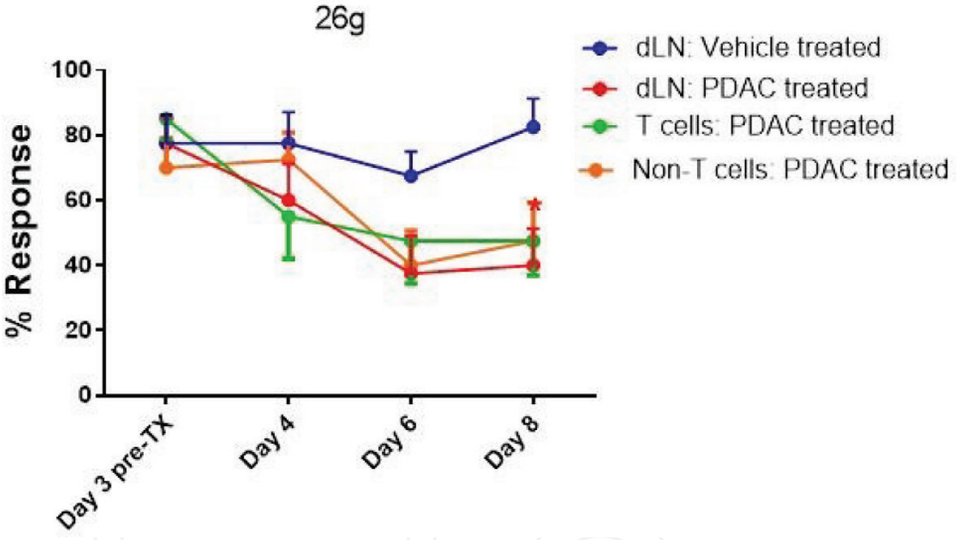

Figure 3. The effects of T cell, non-T cell subsets, and whole population of draining lymph node cells from PDAC-treated rats on mechanical hyperalgesia measured by 26 g force of von Frey fiber.

2.2. Macrophage maturation and differentiation

The migration of the monocytes to the wound site and the following maturation of monocytes to macrophages play key roles in the process of wound healing. Mesenchymal stem cells have been known to benefit the wound healing process since they have immune regulatory properties including an anti-inflammatory activity [18]. Mesenchymal stem cells derived from different placental tissues have been reported to modulate the maturation and differentiation of macrophages in both in vitro and in vivo studies. pMSC were shown to reduce the endotoxin induced activation of a mouse macrophage RAW264.7 cell line [19]. Human amnion mesenchymal cells, when co-cultured with human THP-1 macrophage cells, were shown to

inhibit the mRNA expression and secretion of TNF-α and IL-1β by THP-1 cells in vitro [20]. In addition, human placental mesenchymal stem cells shifted macrophage differentiation from inflammatory M1 to anti-inflammatory M2 macrophages presumably mediated by soluble molecules acting partially via glucocorticoid and progesterone receptors [21]. In a murine hind limb ischemia (HLI) model, a standard preclinical model of peripheral arterial disease (PAD), local administration of placenta tissue-derived mesenchymal stem cells to ischemic hind limb significantly reduced the infiltration of neutrophils and macrophages in the injured tissue compared to the sham-treated group [22].

In a separate report of studying PDAC in an HLI model, we showed that intramuscular administration of PDAC improved angiogenesis in the injured limb. Histological analysis revealed that PDAC-treated mice had an increased level of CD68+ arginase1+ M2-like macrophages in ischemic tissue. Moreover, we demonstrated that the effect of PDAC on macrophage differentiation was T cell dependent. The M2-like macrophage skewing was only observed in wild type and T cell reconstituted nude mice, but not in nude mice [23]. This observation is consistent with other reports that placental mesenchymal stem cells from amniotic membranes shifted macrophage differentiation from an inflammatory M1 to an anti-inflammatory M2 macrophage population [21, 24].

2.3. Dendritic cell maturation and differentiation

As discussed earlier, the human placenta plays a key role in maintaining immune tolerance between mother and fetus during normal pregnancy and is associated with the presence of Treg cells. It is also apparent that dendritic cells (DC) play a critical role in adaptive immunity and tolerance. While the multiple mechanisms of immune tolerance are not fully understood, it was first reported that amniotic mesenchymal tissue cells from human placenta (AMTC) can inhibit dendritic cell differentiation and maturation of monocytes from both peripheral blood and amniotic tissue [25]. When monocytes were cultured under the differentiation inducing condition, the presence of AMTC inhibited the expression of CD1a and reduced the expression of HLA-DR, CD80, and CD83. This finding suggested that placenta tissue mesenchymal stem cells could contribute to immune tolerance during pregnancy.

Another source of placenta-derived mesenchymal stem cells was reported to induce myeloid DC to a tolerogenic phenotype as demonstrated by its reduced migration in response to CCR7 and impaired ability to stimulate IFN-γ secretion from NK cells [26]. Placenta-derived mesenchymal stem cells were also shown to increase the secretion of IL-10 and reduce the secretion of IFN-γ from DC cells [27]. Placenta chorionic villous-derived mesenchymal stem cells were shown to inhibit the maturation of human dendritic cells induced by LPS in co-culture experiments. The DC cells co-cultured with placenta MSC not only expressed lower levels of costimulatory surface molecules, including CD40, CD80, CD83, and CD86 but, also reduced expressed a reduced ability to activate T cells [28].

Placental trophoblasts express a lower level of CD200 in preeclampsia and that is associated with an increase in production of Th1 cytokines, TNF-α, IL-6, IL-8, and IL-10 [29]. This result suggested that in normal placenta with higher CD200 levels on trophoblasts immune tolerance is favored [29]. Since PDAC express CD200, one can postulate that PDAC can also establish

immune tolerance. In the rat neuropathic pain model, when PDAC was administrated via tail vein, it was found that PDAC alleviates mechanical hyperalgesia [17]. This anti-neuroinflammatory activity appeared to be mediated by the suppression of dendritic cell recruitment, maturation and differentiation. Rat DC cells isolated from draining lymph nodes of the PDAC-treated animals showed reduced gene expression of CD11c, CD86, and CD80, markers of DC maturation. The relative expression of IL-12, a key pro-inflammatory cytokine secreted by differentiated DCs, was also significantly reduced in PDAC treated rats. Furthermore, the inhibition of DC infiltration and activation was observed at the ipsilateral sciatic nerve. In an in vitro co-culture experiment, PDAC inhibited differentiation of mouse DC [3], providing direct evidence of PDAC-mediated modulation of DC maturation and differentiation in vitro. In this work, mouse bone marrow cells were induced with GM-CSF and LPS to induce DC maturation with or without PDAC. The bone marrow DC exhibited a phenotype of CD86high and MHC I-A/I-E high, which was reduced in a PDAC cell dose-dependent manner. In addition, the expression of the tolerogenic DC marker, PD-L1, was enhanced. PDAC was further shown to affect the differentiation of human immature peripheral blood DC cells in vitro. When exposed to GM-CSF and IL-4, immature DC (CD1a+) differentiated to mature DC (CD86 high). The inhibition of DC differentiation and maturation by PDAC does not require cell–cell interaction since the co-culture was performed using a trans-well system separating mouse and human DC from PDAC. The conditioned medium from PDAC can also modulate DC differentiation and maturation. The DC modulation activity was in part mediated by PGE2 secreted by PDAC [3].

2.4. Clinical trial activity

In a recent review of advanced cell therapy clinical trials highlighting perinatal cells, the authors compiled data on the number of clinical trials conducted in different countries, with different cell types and in many different indications [30]. Since 2008, there was a more rapid advancement in the number of trials registered with most of the trials using cord blood or cord tissue. The use of perinatal mesenchymal stem cells has also increased to about 70% of

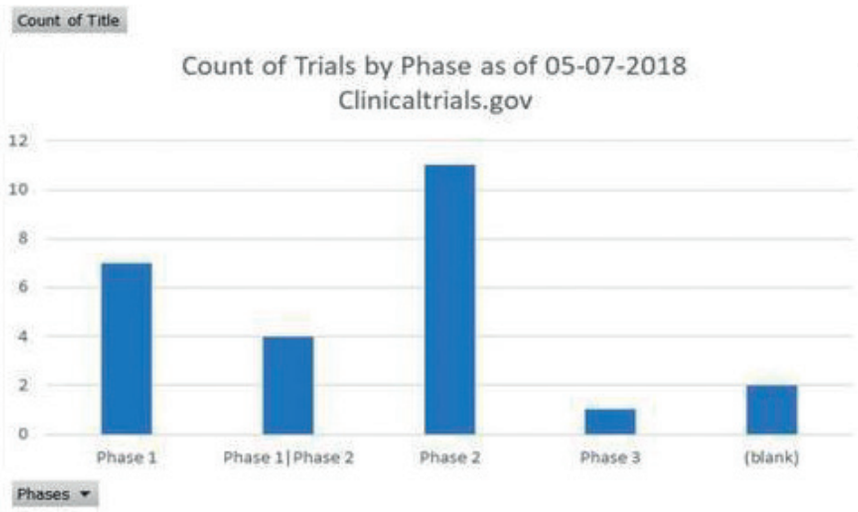

Figure 4. A narrow search on ClinicalTrials.gov with the search terms placenta derived cells.

Figure 5. A narrow search on ClinicalTrials.gov with the search terms placenta derived cells illustrating the diverse diseases investigated.

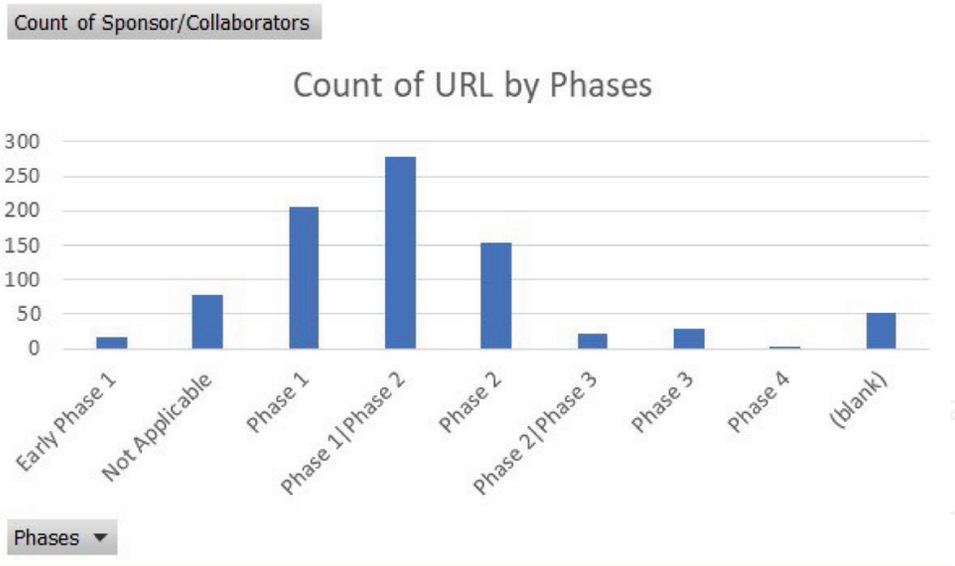

Figure 6. A search on ClinicalTrials.gov with the search terms mesenchymal stem cells illustrating the much greater numbers of clinical studies.

the annual trials registered and many of the trials were in the early phase of development (phase I or II). The cells from the amniotic membrane and placental tissue seem to be in a growth period for clinical trials. It will be important to track the progress of these trials and see which cells work in which indications.

In **Figure 4** below, the search terms on ClinicalTrials.gov included placenta-derived cells and were intentionally kept very narrow. The paucity of trials would suggest that the placenta is not an organ used to derive cells for clinical trials, however, this excluded cord tissue and cord blood as keywords in the search. As discussed above, these were the most cited trials over the last decade. The stage of development was consistent with the previous review in that the majority of studies were early phase clinical trials. The data depicted in **Figure 5** also corroborated the cited study above since there are many different diseases targeted in these trials and indicated that the search continues for the most appropriate clinical use for these cells. In **Figure 6**, the search encompassed the terms mesenchymal stem cell with no preference toward the source of cells and would include bone marrow-derived cells. As was evident, there were far more studies registered and the stage of development was slightly shifted to later stages, but still awaiting pivotal study readouts. As outlined in the sections of this review, the in vitro and in vivo data describe a broad array of immune modulation functions that suggest several pathways of clinical development and this is reflected in the number of indications pursued with these cells regardless of the biological source for the cells.

3. Conclusions

In this chapter, the observation of fetal-maternal microchimerism that can last for decades indicated that the placenta exhibited highly specific and strong immune tolerance to the host. In an attempt to explain the immune tolerance mechanisms, we highlighted several cell types from Tregs to dendritic cells and their interactions with placental derived cells using in vitro and in vivo models. There were several molecular mechanisms (examples, IDO, PGE2, T cell proliferation, and DC maturation) invoked to explain some of the interactions with T cells and dendritic cells, which included the effects of cytokine secretion on the activation and differentiation status of immune cells. The in vitro and in vivo data describe a broad array of immune modulation functions suggesting that cells of placental origin have immune modulatory and immune tolerance inducing properties that are independent of tissue source.

These immune modulatory properties highlight some of the possible ways in which the physiology of the placental graft is maintained during pregnancy and well after for microchimerism. To put these interesting results into some physiological context, a recent example of the immune system driving preterm labor described a pro-inflammatory environment at the fetal-maternal interface as a prerequisite for preterm labor [31]. In this study, the authors demonstrated that fetal T cells produced INF-γ and TNF-α which preceded myometrial cell contraction required for parturition. In addition, the authors demonstrated that fetal T cells (both CD4 and CD8) specifically proliferated in response to maternal antigen. It is interesting to speculate that the placental MSC present at the fetal-maternal interface could participate in suppressing the pro-inflammatory signals and the T cell proliferation that drive preterm labor.

This is a very active field of clinical and pre-clinical investigation and has generated huge excitement in the field of advanced cell therapy. The near future will bring us clinical results that allow the advancement of cell therapy to FDA approval and ultimately for the benefit of the patients that eagerly await these therapies.

Conflict of interest

All authors receive compensation from Celularity Incorporated.

Appendices and nomenclature

AMTC	amniotic mesenchymal tissue cells
BTR	bead T cell reactions
DC	dendritic cells
HLI	hind limb ischemia
IDO	indolamine 2, 3 dioxygenase
MLR	mixed lymphocyte reactions
PAD	peripheral arterial disease
PDAC	placenta-derived adherent cells
pMSC	placenta-derived mesenchymal stromal-like cells
PGE2	prostaglandin E2
TGF-β	transforming growth factor-β

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