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# The dichotomy of placenta-derived cells in cancer growth

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ABSTRACT

Placenta-derived mesenchymal stromal cells (MSC) have often been considered to linger behind their equivalents from other tissues, such as MSC from bone marrow, in many aspects including their therapeutic potential in regenerative medicine. Nowadays however, it is clear that certain aspects make placental MSC attractive as a cellular therapy, such as their lack of ethical concerns and ease of isolation from human term placenta, a material long regarded as biological waste. Moreover, placental MSC virtually lack expression of human leukocyte antigens and co-stimulatory molecules, making them very attractive for transplantation in allogeneic settings.

In the context of cancer, cell therapy remains an area of intense investigation whereby MSC have been shown to play opposing roles, and placental MSC are no exception. In this review, we will discuss dichotomy of placental MSC that underscores the challenges in understanding their therapeutic potential in oncology.



## 1. Introduction

### 1.1. Cellular therapy for cancer

An improved understanding of stem cell biology along with the emergence of targeted therapies have favored the investigation of stem-cell based therapeutic strategies for the treatment of different cancers [1].

Adult stem cells are the most commonly studied stem cells for potential applications as an anti-cancer treatment [2]. For example, hematopoietic stem cells (HSCs) are somatic stem cells found in bone marrow, umbilical cord, and in peripheral blood and their function is maintain the hematopoietic homeostasis. HSCs represent the only stem cell treatment currently being used in the clinical setting as a means to reconstitute the immune and hematopoietic systems of patients with lymphomas and leukemia [3–5]. The field of HSC transplantation has pioneered the concepts of stem cell therapy and immunotherapy as a tool against cancer [6].

Early research on stem cells was carried out using embryonic stem cells (ESCs) which are pluripotent stem cells, therefore able to differentiate into the three germ layers, with unlimited capacity for self-renewal. A therapeutic strategy using ESCs for cancer has been reported whereby ESCs were used to induce an antitumor cellular immune response [7]. However, isolation of ES cells leads to ethical issues because involves the destruction of blastocysts and, furthermore, these cells are immunogenic due to problems associated with histocompatibility. In addition, ES cells have been shown to be tumorigenic in mice [8,9]. Thus, the application of ES as a potential cancer treatment poses major obstacles and their use for research and therapeutic purposes are restricted and prohibited in many countries throughout the world. In the attempt to avoid such problems, new technologies offer a more pragmatic alternative by reprogramming tissue cells to become induced pluripotent stem cells (iPSCs). iPSCs can be generated from patient's somatic cells and have been proposed as a new source for cancer immunotherapy whereby they can be induced to differentiate into immune cells with the ability to activate an immune response against cancer cells [10].

More recently, adult stem cells from different tissues have been explored in the attempt to find an therapeutic strategy against solid tumors. Of particular interest, mesenchymal stem/stromal cells (MSC), are a non-hematopoietic fibroblast-like cell population residing in a large variety of tissues. They are a promising source for

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cell therapy in regenerative medicine owing to their self-renewal, multi-lineage differentiation potential, immune-modulatory actions, and trophic factor secretion. MSC can be isolated from various tissues including bone marrow, adipose tissue, dermis, skin, amniotic fluid, and also placenta. In the past decade, MSC isolated from placenta have attracted much attention in the field of regenerative medicine [11].

### 1.2. Placental MSC

MSC can be isolated from different placental regions [12], such as the amniotic membrane [13,14], umbilical cord (Wharton's jelly) [15], chorionic villi [16], and maternal decidua [17].

Moreover, iPSCs have been obtained from chorionic cells [18].

Placenta MSC have provided promising results in regenerative medicine. In fact, evidence has supported their beneficial properties in different preclinical disease models, for example in autoimmune diseases such as collagen-induced arthritis and experimental autoimmune encephalomyelitis [19,20], neurological diseases such as Parkinson's disease [21], multiple sclerosis [22], Alzheimer's disease [23], ischemic stroke [24], and traumatic brain injury [25], and lung [26,27] and liver [28,29] fibrosis, inflammatory bowel disease [19,30], graft versus host disease [31], and limb ischemia [32]. It has been widely demonstrated that the therapeutic effects of placental MSC are mediated by the release of bioactive factors [16,33–35], that can control the damaged tissue by modulating inflammatory conditions and by directly or indirectly stimulating resident target cells to proliferate or progenitor cells to differentiate. Of note, human term placenta cells are poorly immunogenic, making them attractive for allogeneic transplantation settings.

In this review, we will focus on another fertile, yet less discovered area concerning placental cells and their potential applications as an anti-cancer strategy. As with MSC from other sources, placental MSC have been described to have dual actions, possessing both anti-tumor and pro-tumor properties. Below we will discuss both properties and the attributed mechanisms of actions. We will also discuss some potential reasons for these contradictory roles.

### 1.3. Rationale for the use of placental MSC in cancer

MSC from placenta and other sources possess several characteristics which constitute the rationale for their potential applications as an anti-cancer strategy.

Tumors are considered wounds that do not heal and tumor microenvironments resemble wound environments [36]. Tumors are known to produce a variety of chemokines and cytokines, such as vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), hypoxia inducible factor (HIF), and hepatocyte growth factor (HGF), that could contribute to MSC migration [37–39]. Chemokines released from tumors can bind to their cognate receptors on MSC inducing their migration. In fact, several studies have shown that placental MSC migration is enhanced in presence of tumor cells, lysates, or their conditioned medium [40–42]. While the mechanism of MSC homing is poorly understood [43], the chemokine–chemokine receptor axis stromal cell-derived factor 1 (SDF1), also known as CXCL12, and its receptor CXC-chemokine receptor 4 (CXCR4) seem to play a major role [44].

The high tropism of MSC for injury sites has significant therapeutic implications. First, MSC could directly affect tumor biology through the secretion of factors and paracrine signaling locally at the tumor site (Fig. 1), and second, MSC could be exploited for the specific delivery of toxic agents to the tumor (Fig. 1), thus reducing doses administered to patients and side effects. Another noteworthy property is that MSC can be genetically modified to stably express or release various anticancer agents/mediators (Fig. 1), thereby circumventing the issues associated to unfavorable pharmacokinetics, and difficulty in producing sustained and efficacious concentrations in the vicinity of the tumor.

An important issue to consider in cell therapy is safety. Several studies have shown that placental MSC do not form tumors when injected, either subcutaneously or intravenously [45,46] in mice. In addition, MSC from the amniotic membrane [47], bone marrow [48], and adipose tissue [49] do not proliferate when loaded with the chemotherapeutic drug paclitaxel, which is relevant to suggest their lack of tumorigenicity and thus potentially safe applications.

## 2. Evidence of anti-tumor properties and suggested mechanisms

There is evidence demonstrating that unmodified placental MSC exert anti-proliferative effects versus tumor cells, mediated by factors that they secrete and physical interactions established with tumor cells, thereby opening the possibility of their application in cancer therapy. In addition, as mentioned previously, MSC can be modified in various ways to treat cancer, such as through genetic modifications for the secretion of anticancer proteins (e.g. IFN-alpha, IFN-beta, TRAIL, thymidine kinase). Furthermore, MSC can be loaded with oncolytic viruses or with chemotherapeutic drugs, thus enhancing tumor-destructing abilities. The multifaceted anti-tumor properties of MSC from different placental regions are discussed below (see Tables 1 and 2).

### 2.1. Umbilical cord MSC (hUC-MSC)

#### 2.1.1. In vitro studies

The most intensively studied placental MSC for their potential use in cancer therapy are those from the umbilical cord (hUC-MSC), and specifically Wharton's jelly (hWJ-MSC). The main mechanisms attributed to the in vitro anti-tumor properties of hUC-MSC are the induction of tumor suppressor and/or pro-apoptotic genes and proteins. Apoptosis usually involves different regulators, such as pro-apoptotic bcl-2 family proteins (e.g. bad, bax, bak, bcl-XS, bim), apoptosis inhibiting proteins (bcl-2, bcl-XL), and caspases (especially caspase 3). Several studies have shown that hUC/WJ-MSC decrease the proliferation and/or induce apoptosis of RPMI-8226 human multiple myeloma cells [50], HL60 and K562 human leukemic cells [51], MDA-MB-231 (highly metastatic) human breast carcinoma cells [52,53], PC3 human prostate cancer cells [54], and Mat B III rat mammary adenocarcinoma cells [55]. These effects in tumor cells were reported to be associated to either an increase of p38 MAPK phosphorylation [51], attenuation of Akt and ERK1/2 phosphorylation [55], or induced apoptosis as shown by induction of cleaved caspase 3 [55] and phosphorylation of JNK [54]. Furthermore, the expression of survival genes such as bcl-2, bcl-xL, survivin, and cellular inhibitor of apoptosis protein-1 (cIAP-1) have been shown to be attenuated in tumor cells co-cultured with hUC-MSC [54].

Other studies have shown that hUC/WJ-MSC can also affect cancer stem cells. Cancer stem cells are found within a tumor and possess characteristics associated with normal stem cells and can self-renew and drive tumorigenesis. Specifically, hUC-MSC have been shown to deliver exogenous miRNA mimics to U87 and A72 human glioma cells and stem cells via intercellular transfer (gap junctions and exosomes), ultimately reducing the migration of U87 cells and the self-renewal capability of the glioma stem cells [56].

#### 2.1.2. The role of bioactive factors from hUC/WJ-MSC

A remarkable amount of evidence suggests that the bioactive

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