

Immunomodulatory Properties of Perinatal Tissue-Derived Stem Cells

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1 Immunogenicity and Immunomodulatory Properties of Wharton's Jelly-Derived Mesenchymal Stem Cells (WJ-MSCs)

The umbilical cord contains two arteries and a vein and a mucilaginous proteoglycan-rich connective tissue known as Wharton's Jelly that surrounds the umbilical vessels and covered by amniotic epithelium (Taghizadeh et al. 2011). MSCs can be isolated from the different compartments of the umbilical cord (Karahuseyinoglu et al. 2007; Troyer and Weiss 2008). Stem cells have been reported in umbilical cord blood, the Wharton's jelly, subendothelial layer of the umbilical vein, and in other layers of umbilical vessels' perivascular region (Fong et al. 2007). WJ-MSCs are primitive mesenchymal cells that trapped in the connective tissue matrix through the developing cord, during embryogenesis (Taghizadeh et al. 2011). WJ-MSCs have been isolated from different regions: the perivascular compartment surrounding the blood vessels, the intervacular zone, and the subamnion (Bongso and Fong 2013). However, derivation protocol for WJ-MSCs has not been standardized.

The phenotype of WJ-MSCs appears to be similar to bone marrow stromal and other MSCs. WJ-MSCs are negative for CD34, CD45, CD14, CD33, CD56, CD31, and human leukocyte antigen (HLA) class II and positive for CD73, CD90, CD105, CD10, CD13, CD29, CD44, CD146, CD271, and HLA-class I (Wang et al. 2004;

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Weiss et al. 2008; Subramanian et al. 2015). Immunogenicity WJ-MSCs have been characterized both *in vitro* and *in vivo*. Human UC-MSCs as well as WJ-MSCs do not express (HLA)-DR and the co-stimulatory molecules, CD40, CD80, and CD86 that are required for T cell activation (Weiss et al. 2008; Tipnis et al. 2010). HLA-DR expression increased after *in vitro* interferon- γ (IFN- γ) treatment. However, no significant change in the expression of co-stimulatory molecules was observed (Tipnis et al. 2010). Immunogenicity of human WJ-MSCs has been assessed by *in vitro* assays including mixed lymphocyte reaction (MLR). The results of Weiss et al. who assessed the effect of WJ-MSCs on one- and two-way MLR assays showed that they do not stimulate T cell proliferation in a one-way MLR, and that they inhibit the proliferation of stimulated T cells in a two-way MLR (Weiss et al. 2008). The immunogenicity of human WJ-MSCs has been reported to be lower than human BM-MSCs. *In vitro* activation of allogeneic lymphocytes or peripheral blood by human BM-MSCs was significantly stronger than WJ-MSCs (Prasanna et al. 2010; Deuse et al. 2011). *In vivo* immunogenicity of WJ-MSCs has been assessed by allogeneic and xenogeneic transplantation. WJ-MSCs has been reported to survive *in vivo* after xenogeneic and allogeneic transplantation.

It has been reported that xenogeneic *in vivo* immune activation of BM-MSCs was significantly stronger than WJ-MSCs. Although both BM-MSCs and umbilical cord lining MSCs are recognized by allogeneic and xenogeneic lymphocytes, umbilical cord lining MSCs are less immunogenic and were more slowly rejected in immunocompetent mice (Deuse et al. 2011).

After xenotransplantation of pig umbilical cord matrix MSCs into rat brain the cells engraft and proliferate without requiring immune suppression (Medicetty et al. 2004). In another study, human WJ-MSCs survived for 16 weeks in the spinal cord of immune competent rats in the absence of any immune suppressive drugs (Yang et al. 2008). In a recent study, the effects of intra-hippocampal transplantation of human WJ-MSCs on rat pilocarpine-induced epilepsy was evaluated (Huang et al. 2015). In addition to their effects in the central nervous system, xenotransplantation of human WJ-MSCs was reported in rat models of peritoneal fibrosis (Fan et al. 2016) and carbon tetrachloride (CCl₄)-induced liver fibrosis (Tsai et al. 2009). These results indicate that human WJ-MSCs are a good stem cell source for xenotransplantation.

WJ-MSCs are also capable of immune suppression and immune avoidance similar to other types of MSCs. Immunomodulatory properties of WJ-MSCs are mediated by soluble factors such as cytokines and immunosuppressive molecules. It has been shown that WJ-MSCs secreted a number of soluble suppressive cytokines such as transforming growth factor-beta (TGF- β), insulin like growth factor (IGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), leukemia inhibitory factor (LIF), and interleukin (IL)-10 (Liu et al. 2012; Wang et al. 2010a; Choi et al. 2013a). WJ-MSCs compared with MSC from other sources produce large amounts of IL-10, higher levels of TGF- β and HLA-G.

In addition, PGE₂, indoleamine 2, 3-dioxygenase (IDO), and NO have been reported to have immunoregulative functions in different types of MSCs. However, blocking experiment indicated that PGE₂ was more effective than TGF- β , IDO, and

NO in immunosuppressive effects of WJ-MSCs (Chen et al. 2010; Wang et al. 2010b; Choi et al. 2013b; Donders et al. 2015). In addition to immunomodulatory agents, WJ-MSCs have been reported to secrete angiogenic and wound healing promoting factors such as TGF- β , vascular endothelial growth factor (VEGF), PDGF, IGF, IL-6, and IL-8 (Choi et al. 2013b). Furthermore, WJ-MSCs express vascular endothelial growth factor (VEGF) and IL-6, which have been shown to modulate differentiation of lymphoid precursors and differentiation of monocytes to dendritic cells (Weiss et al. 2008). Recent studies suggest that immunomodulatory properties of WJ-MSCs were enhanced upon stimulation with proinflammatory cytokines, IFN- γ , TNF- α , and IL-1b (Donders et al. 2015; Prasanna et al. 2010; Tipnis et al. 2010). Moreover, IFN- γ and IL-1 β produced by activated peripheral blood mononuclear cell (PBMC) upregulated the expression of cyclooxygenase-2 (COX-2) and the production of PGE2 by human umbilical cord mesenchymal stem cells (hUCMSCs) (Chen et al. 2010). WJ-MSCs has suppressive effects on differentiation, proliferation, and function of immune cells such as T cells, dendritic cells (DC), and NK cells via contact-dependent mechanisms as well as through soluble molecules. WJ-MSCs are able to inhibit polyclonal T cell proliferation. They can functionally inhibit IFN- γ production by activated T cells and induce IL-10 secretion as well as induction of regulatory T cell (Treg) generation (Donders et al. 2015; Tipnis et al. 2010; Chen et al. 2010; Zhou et al. 2011).

It has been reported that MSCs induced CD4⁺ CD25⁺ FOXP3⁺ regulatory T cells after in vitro coculture with naïve T cells (Yousefi et al. 2016) and cell contact is more effective than soluble mediators.

Moreover, in vivo studies reveal that WJ-MSCs increasing the frequency of Treg cells (Tregs) and reestablishing the balance between Th1/Th2 and Th17/Treg-related cytokines (Alunno et al. 2014; Sun et al. 2010). Several studies reported that WJ-MSCs inhibit differentiation, maturation, and functionality of DCs. WJ-MSCs reduce the expression of HLA-DR, CD80, and CD83 and resulted in impaired allostimulatory ability of DCs (Donders et al. 2015; Saeidi et al. 2013; Tipnis et al. 2010). In several experimental models, such as type 1 diabetes, myocardial infarction, and Parkinson's disease, severe and refractory systemic lupus erythematosus, in vivo immunomodulatory, and anti-inflammatory effects of WJ-MSCs have been investigated (Chao et al. 2008; López et al. 2013; Wu et al. 2007; Sun et al. 2010). Low immunogenicity and immunomodulatory properties of WJ-MSCs make it promising to use in allogeneic clinical applications in inflammatory and autoimmune diseases (Fig. 1).

2 Immunomodulatory Properties of Umbilical Cord Blood-Derived Mesenchymal Stem Cells (UCB-MSCs)

Umbilical cord blood has been accepted as a well-established source for hematopoietic stem cells. However, it is still controversial whether MSCs can be isolated from cord blood.

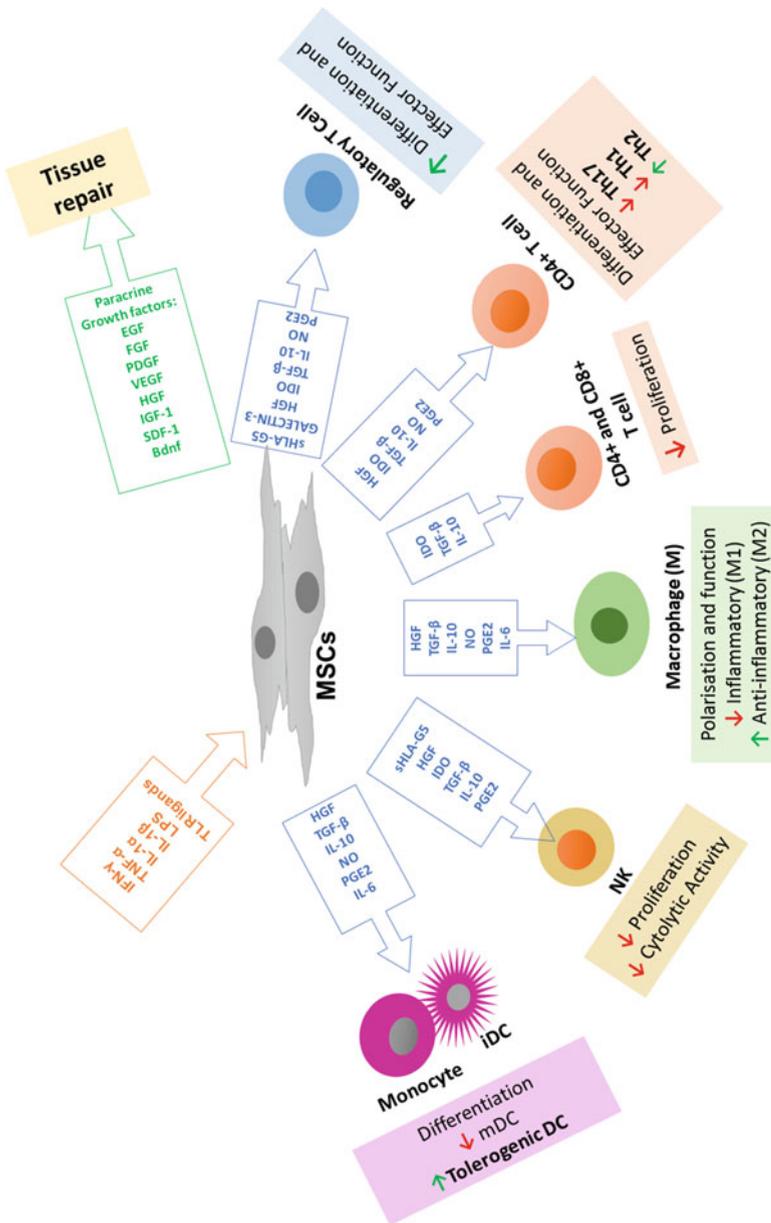


Fig. 1 Immunomodulatory effects of mesenchymal stem cells on differentiation and function of different types of immune cells such as helper T cell subsets, dendritic cells (DCs), regulatory T cells (T), natural killer (NK) cells, monocytes, and macrophages. Immunomodulatory effects of MSCs is dependent on cell-cell contact and soluble factors released by MSCs. *HGF* hepatocyte growth factor. *iDC* immature dendritic cell, *IDO* indoleamine 2, 3-dioxygenase, *IL* interleukin, *mDC* mature dendritic cell, *NO* nitric oxide, *PGE2* prostaglandin E2, *TGF-β* transforming growth factor β

The presence of MSCs in UCB has been reported in some studies (Lee et al. 2004; Bieback et al. 2004; Heo et al. 2016) whereas others have suggested that the UCB is not a rich source of MSCs due to very low frequency and MSC isolation protocol (Flynn et al. 2007; Secco et al. 2008; Mareschi et al. 2001; Wexler et al. 2003).

The cells were positive for CD29, CD44, CD73, CD90, and CD10 whereas MSCs were negative for CD14, CD31, CD34, CD45, and CD106, which are known markers of hematopoietic and endothelial cells (Lee et al. 2004; Bieback et al. 2004; Liu and Hwang 2005; Heo et al. 2016).

The cytokine expression profile of UCB-MSCs has been reported to be similar to that of BM-MSCs, except that UCB-MSCs expressed IL-12 but not G-CSF (Liu and Hwang 2005).

Using cytokine protein array Liu and Hwang et al. reported that UCB-MSCs produced cytokines including proinflammatory: IL-1b, IL-6; anti-inflammatory: TGF- β 2, TGF- β 3, MIF, LIF; growth factor: GM-CSF, VEGF, FGF-4, FGF-7, FGF-9, PIGF, oncostatin M; growth factor receptor: IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4; chemokines: GRO, IL-8, MCP-1, MIP-3a, PARC, IP10, ENA-78, GCP-2, osteoprotegerin; TIMP-1, TIMP-2 the natural inhibitors of matrix metalloproteinases (Liu and Hwang 2005). IL-6, IL-8 and TIMP-1, TIMP-2 are abundant CB-MSCs cytokines (Hwang et al. 2009; Flynn et al. 2007).

3 Immunogenicity and Immunomodulatory Properties of Amniotic Membrane-Derived MSCs (AM-MSCs)

The innermost layer that surrounded the embryo is amniotic membrane (AM) that is a fetal component of extra embryonic membranes. This multilayer membrane with 0.02–0.5 mm thickness has diverse clinical application because of both its physical and cellular structure. The physical aspect of AM application is related to an integrated translucent avascular membrane which provides a permeable barrier with high elasticity that resists against proteolytic factors and fractional forces. Basement membrane proteoglycans, laminins, different types of collagens, and cytoskeletal proteins are responsible for these physical properties. With regards to these characteristics AM is used in general surgery for treatment of corneal, conjunctival and limbal lesions, reconstitution of burned skins, and wound healing. The second aspect of AM application is its cellular component composed of two main cellular compartments which are separated by basement membrane. The inner layer adjacent to amniotic fluid (Rennie et al. 2012a; Mamede et al. 2012; Danforth and Hull 1958) is amniotic epithelial cells (AEC) and the outer layer of AM is amniotic mesenchymal stromal cells that according to agreement of “International Placenta Stem Cell Society” called amniotic mesenchymal stem cell (AMSC) (Parolini et al. 2008, 2009). Both of them are categorized as stem cells because of their ability to self-renewal and differentiation to other lineages (Insausti et al. 2010). Amniotic epithelial cells express pluripotency transcription factors such as Oct-4, Sox-2, Nanog, and Rex-1 (Parolini et al. 2008; Insausti et al. 2010) and can differentiate to the three

germinal layers: ectoderm, mesoderm, and endoderm (Tamagawa et al. 2004; Miki and Strom 2006). In addition, AEC show pluripotent cell surface markers such as SSEA-3 and SSEA-4 (stage-specific embryonic antigen 3 and 4), TRA 1-60 and TRA 1-81 (tumor rejection antigen 1-60 and 1-81) that is associated with embryonic stem cells. They also express cell–cell interaction molecules such as E-Cadherin, CD9, CD29, CD104, CD49e, CD49f, CD49d, and CD44 (Roubelakis et al. 2012; Insausti et al. 2010). Amniotic mesenchymal stem cells have adipogenic, chondrogenic, osteogenic, and angiogenic differentiation potential (Ilancheran et al. 2009; Alviano et al. 2007; Ilancheran et al. 2007; In't Anker et al. 2004) although hepatic, neurogenic, and myogenic differentiated lines have been reported too (Portmann-Lanz et al. 2006). Similar to bone marrow and other adult tissue isolated mesenchymal cells, they highly express CD90, CD73, CD105, and CD29 cell surface markers and do not express hematopoietic cell surface markers such as CD45, CD34, CD14, CD11b, and CD19 (Ilancheran et al. 2007; Roubelakis et al. 2012; Parolini et al. 2008). Human amniotic epithelial cells (hAEC) are separated by trypsin digestion of amniotic membrane which is mechanically separated from chorion. More enzymatic digestion with collagenase will terminate to complete isolation of AM-MSCs (In't Anker et al. 2004; Miki and Strom 2006; Wei et al. 2009; Bilic et al. 2004; Soncini et al. 2007). AM isolated stem cells are cultured in DMEM or α -MEM medium supplemented with fetal bovine serum (FBS) and epidermal growth factor (EGF) with or without leukemia inhibitory factor (LIF) according to the laboratory setup (Manochantr et al. 2010; Lisi et al. 2012; Tamagawa et al. 2007). The significant high ratio of stem cell to naïve population of AM (5–50%) compared to others somatic tissues (0.01–0.1%) is one of the main feature of AM for clinical application, as an average of 5×10^8 AM-MSCs (Bilic et al. 2008; Parolini et al. 2008) and 100×10^6 hAECs are obtained from one AM (Lagasse et al. 2000; Miki 2011).

To behave as an immunomodulatory agent, isolated cells should express and secrete immunoregulatory molecules, sense inflammatory and anti-inflammatory conditions, and interact with immune cells. AM-derived stem cells do not express polymorphic HLA-A, B, C, and DR antigens that demonstrated their low immunogenicity after allo- or xeno-transplantation (Li et al. 2005). Transplantation of a monolayer of human amniotic epithelial cells can survive for a long time without induction of any acute immune responses against transplant (Akle et al. 1981). Xenograft amniotic membranes transplanted to the limbal area, intracorneal space, and under the kidney capsule show no or low host cell infiltration and few host vessels formation (Kubo et al. 2001). Amnion-derived MSCs not only are low immunogenic but also are immunosuppressive. According to this feature, co-transplantation in conjunction with umbilical cord blood-derived hematopoietic stem cells reduces potential of graft-versus-host disease in recipients (Li et al. 2007). Although we do not know the complete immunosuppressive mechanisms of AM-MSCs, following inhibitory molecules are suggested as important ones. AM-MSCs express high level of IL-10 and IL-1 receptor agonists at transcriptional level and release the proteins to amnion where counteracts with inflammatory cytokine products such as TNF- α , IL-1, IL-8, and IL-6 and suppress their more production by immune cells. In addition, AM-MSCs

exert their inhibitory effect on T lymphocyte proliferation through self-secreted IL-10 or induction of IL-10 producing immune cells by its other inhibitory molecules like (Indoleamine 2,3-dioxygenase) IDO (Yang et al. 2009). (IDO) enzyme which catalyzes essential amino acid tryptophan through kynurenine pathway works as an immunoregulatory molecule through inhibition of T lymphocyte and NK cell populations' growth and activity (Kang et al. 2012; Spaggiari et al. 2008). Co-culturing of AM-MSCs with PBMC and other inhibitory molecules like Prostaglandin E (PGE) augmented IDO production (Kang et al. 2012). Prostaglandin E2 (PGE2) is an anti-inflammatory lipid mediator that is produced by arachidonic acid processing by COX-1 and COX-2 enzyme (Smith et al. 1996). PGE2 constitutively produced by AM-MSCs and increased when AM-MSCs were co-cultured with PBMCs (Kang et al. 2012). PGE2 are dominant immunosuppressive molecule of AM-MSCs, because it enhances its own production that result in complete suppression of surrounded inflammatory molecules (Kalinski 2012) PGE2 use different ways to play its immunosuppressive role on T lymphocytes. T lymphocyte proliferation and activation were suppressed by inhibition of IL-2 production and induction of cAMP production by PGE2, respectively (Walker et al. 1983). PGE2 promoted FOXP3⁺CD4⁺CD25⁺ regulatory T cell differentiation and affected T helper cell polarization to the benefit of Th2 subtype through induction of IL-10 and IL-4 cytokine production and inhibition of IL-12 and IL-2 production (Mahic et al. 2006; Demeure et al. 1997). PGE2 inhibit inflammatory cell migration and induce regulatory cell maintenance by modulation of chemokine production. In addition, it interacts with dendritic cells and suppressed DC-mediated T cell activation by suppression of antigen presentation and can inhibit activation of macrophages and NK cells (Yañez et al. 2010; Sreeramkumar et al. 2012).

Transforming growth factor beta (TGF- β) family are consisted from highly similar three isoforms (TGF- β 1, TGF- β 2, and TGF- β 3) that secreted in the inactive latent form to extracellular matrix. *Activation of TGF- β* will be primed by proteolytic function of matrix metalloproteases and reactive oxygen species (Barcellos-Hoff and Dix 1996; Yu and Stamenkovic 2000). Activated TGF- β interacts with TGF- β receptors on immune cells and triggers both anti-inflammatory and proinflammatory functions in the context-dependent manner. TGF- β is abundantly secreted by all types of MSCs like AM-MSCs. Amnion-derived MSCs exerted the most parts of its immunomodulatory effects through TGF- β that was abrogated with anti-TGF- β antibody. Different studies show increased level of TGF- β expression in AM-MSCs at both mRNA and protein level after co-culturing with immune cells (Kang et al. 2012; Chen et al. 2011a). Secreted TGF- β will suppress immune cell proliferation through cell cycle blocking. It ligates to TGF- β receptors on B lymphocytes and induces apoptosis (Spender et al. 2009). In addition, TGF- β suppressed B cell activation by inhibition of NF- κ B and cytokine production and interfere with antibody production (Cazac and Roes 2000). AM-MSCs can direct T helper cell differentiation to regulatory T cells or Th17 subtype through TGF- β 1. This induction suppresses Th1 or Th2 differentiation of helper T cells (Li and Flavell 2008), inhibit T cell proliferation, and suppress cytotoxic T cell activity by

inhibition of expression of cytolytic gene products. TGF- β production by AM-MSCs suppressed inflammatory cytokine production by classical macrophages and promotes alternative macrophage activation which secretes anti-inflammatory cytokines and help to tissue repair (Gong et al. 2012).

Beside the soluble factors, AM-MSCs express cell membrane bound suppressive molecules. Induction of nonclassical class I HLA-G molecules on the surface of AM-MSCs is among the immunosuppressive mechanisms. Physiological expression of HLA-G is restricted to AM and thymus in the body (Lefebvre et al. 2000). HLA-G transcripts can be alternatively spliced to membrane bound and soluble proteins. Cell bound HLA-G induces tolerance in natural killer cells especially through activation of killing inhibitory receptor ILT (*Ig-like transcript*) pathway. Soluble HLA-G interaction with CD8+ marker on T and NK cells upregulate FasL expression and induce apoptosis (Contini et al. 2003). In addition, soluble HLA-G redirect helper T lymphocyte to regulatory phenotype (Lila et al. 2001) and exerts immunosuppressive effect on DC maturation that in consequence terminated to less activation of NK cells and T lymphocytes (Gros et al. 2008). Increase in immunosuppressive cytokine production by mononuclear cells is another effect of soluble HLA-G on immune cells (Hunt et al. 2006).

Programmed death-ligand 1 (PD-L1) or B7 homolog 1 (B7-H1) is another transmembrane protein expressed on the AM-MSCs. This regulatory molecule interacts with PD-1 on T lymphocyte and disturbs TCR signaling pathway through attenuation of NF- κ B and AP-1 activation (Sheppard et al. 2004). This attenuation results in IL-2 reduction and suppression of T lymphocyte proliferation.

Fas ligand as a member of the tumor necrosis factor (TNF) family are located in transmembrane part of AM-MSCs and interacts with Fas(CD95) receptors on immune cells. Induction of apoptosis in Fas-expressing T lymphocytes is an immunoregulatory way that suppresses cytotoxic T cell function (Mazar et al. 2009). Uptake of apoptotic T cell particles by macrophages turn them to alternatively activated macrophages with high TGF- β production and tolerogenic function (Akiyama et al. 2012).

Although there is no doubt on immunoregulatory function of AM-MSCs that exerted by its membrane bound or soluble factors, different studies demonstrated that they are not spontaneous suppressors and should be excited under inflammatory condition (Shi et al. 2012). Inflammation may provide MSCs migration and homing to injured site. MSCs produce growth factors, chemokines, chemokine receptors, and other cell adhesion molecules in response to TNF- α , IL-1 β , and other inflammatory cytokines secreted by immune cells at inflammation site (Ullah et al. 2015). There are also reports that show the production of immunosuppressive molecules of AM-MSCs needs stimulation especially by IFN- γ or microbial ligands (Chang et al. 2006) (Nurmenniemi et al. 2010). Matrix metallo-proteases (MMPs) and chemokine receptors, chemokine receptor type 4 (CXCR4), are the main factors for MSCs migration to and homing in injured site (Ries et al. 2007). After migration, resident MSCs secrete chemokines (CCL2, CXCL9, CXCL10, and CXCL11) and express cell adhesion molecules like intercellular adhesion molecules (ICAM)-1 and vascular cell adhesion molecules (VCAM)-1 which attracted immune cells and facilitate close contact with them at inflammation site (Ren et al. 2010; Shi et al. 2012).

AM-MSCs apply all mentioned inhibitory mechanisms in direct interaction with innate and adaptive immune cells, to suppress their function (Insausti et al. 2014). According to Magatti et al. reports, AM-MSCs block DC maturation and differentiation from monocytes through inhibition of CD80, CD86, and HLA-DR expression and induction of cell cycle arrest at G0 phase (Magatti et al. 2009) AM-MSCs induce tolerogenic dendritic cells and macrophages by their soluble factors and direct transmembrane HLA-G interaction with ILT receptors which terminated to differentiation of regulatory T cells (LeMaoult et al. 2007). Natural killer cells are innate lymphoid cells that patrol the body and screen tumor, microbial infected or foreign cells ligands that interacted with activating NK receptors. Following activation, NK cells release the content of cytolytic granules including perforins and granzymes and kill involved cells (Vivier et al. 2008). However, NK cells express killing inhibitory receptors including KIR, NKG2A/CD94, ILT2, and so on, that recognize MHC class I (HLA-A, -B or -C) molecules on every normal cells in the body and tolerate them (Campbell and Purdy 2011). Because of the absence of MHC class I molecules on AM-MSCs, they can be killed by active NK cells while inhibiting their cytotoxic effect on other cells. PGE2 and IDO production by AM-MSCs downregulate NK cell killer activating receptors and inhibit their proliferation (Spaggiari et al. 2008). AM-MSCs interrupt NK cell communication with other immune cells via soluble or membrane bond HLA-G which ligated to the killing inhibitory receptors on dendritic cells, T and B lymphocytes and affected their cytokine production and ligand-receptor engagement with NK cells (Gros et al. 2008). T lymphocytes as the main player of adaptive immunity, respond to environmental stimulus after antigen recognition by their antigen-specific T cell receptors. Antigen-specific T lymphocytes are divided to two main categories according to how they act; 1) cytotoxic T lymphocyte which destroy and kill the cells who introduced antigens by class I MHC molecules in the cell-cell contact manner, and 2) helper T lymphocyte which recognize antigens on class II MHC molecules and produced the wide range of cytokines from regulatory to inflammatory and anti-inflammatory properties. AM-MSCs do not express MHC molecules and escape from T lymphocytes recognition system, however have reciprocal effect on each other. Kang et al. showed that AM-MSCs produce increased level of IL-10, TGF- β , hepatic growth factor (HGF), IDO, and COX-2 in co-culture with PBMCs or in the presence of PBMC supernatant (Kang et al. 2012). In the reciprocal interaction, AM-MSCs secreted factors that inhibit T cell proliferation in response to phytohemagglutinin or allogeneic stimulation in the dose-dependent manner (Li et al. 2007) (Banas et al. 2008). Researchers demonstrated that cytokine production of mitogen-stimulated T lymphocytes will be affected in the presence of AM-MSCs in the culture. According to analysis of cytokine level in the supernatant of AM-MSCs – PBMC co-culture, changes in level of IL-2, IL-4, IL-7, IL-10, IL-15, TGF- β , and IFN- γ production were observed while IL-10 and TGF- β had the significant increased level and IFN- γ showed the decreased level compared to PBMC culture alone (Li et al. 2007; Roelen et al. 2009). Differentiation to different subtypes of helper T lymphocytes is dependent on surrounded cytokines, so AM-MSCs can trigger TH2 and regulatory subtypes and suppress TH1 differentiation, because of augmentation of IL-10 and TGF- β production.

Different reports confirmed that placental MSCs support FOXP3+ regulatory T cell induction and proliferation through induction of tolerogenic antigen-presenting cells or regulatory cytokines (LeMaoult et al. 2007; Chen et al. 2011b).

4 Immunomodulatory Properties of Amniotic Fluid Mesenchymal Stem Cells (AF-Mscs)

Amniotic fluid (AF) is the secretion of chorio-amniotic membrane and fetal skin that provide water and nutrients in the amniotic bag to create a safe environment for embryo development (Ganatra 2003). Amniotic fluid volume increases during pregnancy as a result of active transport of sodium and chloride that induces water transport across membrane. Electrolytes, protein, lipid, carbohydrate, and embryo produced urine and respiratory fluid are soluble components of amniotic fluid (Zhao 2015; Westgren et al. 1995). Most of these soluble components are secreted by diverse cell population that separated from different tissues of developing embryo and immersed in amniotic fluid. The cells are derived from placenta, skin, digestive, urinary, and respiratory tracts of embryo and are used for prenatal genetic diagnosis by amniocentesis (Siegel et al. 2007). However, they have pluripotent and multipotent stem cell characteristics and are considered in clinics for their tissue regeneration and immunomodulatory properties (Rennie et al. 2012b).

Human amniotic fluid-derived MSCs (AF-MSCs) can be isolated from amnion fluid of pregnant woman at 16–20 weeks of gestation. This adherent fibroblastic-like cells is expanded in culture media containing 89 % DMEM-High Glucose or α -MEM, 10 % FBS, 1 % penicillin–streptomycin supplemented with/without 4–10 ng/ml bFGF (Liu et al. 2009; Li et al. 2015). AF-MSCs are not tumorigenic after injection to nude mice, however well growing AF-MSCs can be cultured up to more than 20 passages. The population doubling time will increase from 36 h at first passage to 48, 55, and 97 h for P5, P10, and P20, respectively (Li et al. 2015), so usually the cells are used up to 4–8 passages for experimental use. Immunophenotype analysis showed that AF-MSCs represented high expression of CD73, CD105, CD90, CD166, and HLA-ABC, while are negative for CD45, CD34, CD14, and HLA-DR cell surface markers (Parolini et al. 2009; Li et al. 2015). AF-MSCs express pluripotency markers of Oct-4, Nanog, Sox-2, and Rex-1 in different gestational age (Tsai et al. 2004). Although AF-MSCs have diverse differentiation potential to different cells like alveolar epithelial cells and hepatocytes (Li et al. 2014; Zheng et al. 2008), they are characterized by differentiation to adipogenic, chondrogenic, and osteogenic cells after in vitro culture in the presence of specific differentiation promoting media (Li et al. 2015). AF-MSCs create an immunoprivileged status in the amniotic cavity to protect fetus from rejection by mother immune system because of their low immunogenicity and immunosuppressive activity. Low immunogenicity of AF-MSCs is related to the absence of HLA-DR and positive co-stimulatory molecules of CD40, CD80, and CD86. In addition, they express high level of negative co-stimulatory

molecules of B7H1, B7H2, B7H3, B7H4, and BTLA in the cell surface (Moorefield et al. 2011). Low immunogenicity of AF-MSCs introduced them as a source of allogeneic MSC transplantation, while cell surface expression of HLA-ABC and probable low level expression of class II HLA molecules promoted allo-antibody production (Schu et al. 2012). So it seems that they are suitable for autologous not allogeneic transplantation. AF-MSCs like other MSCs take part in immunosuppressive processes through secretion of anti-inflammatory molecules that are one of the main soluble components of amniotic fluid. IL-10, IL-1 receptor agonists, and other inhibitory secretions counteract with inflammatory functions of immune cells that causes inhibition of neutrophil infiltration to damaged site (Cargnoni et al. 2009) or production of proinflammatory cytokines of TNF- α and C-X-C motif chemokine ligand 10 (CXCL10) by activated dendritic cells (Magatti et al. 2009). AF-MSCs can suppress T lymphocyte proliferation and activation by PGE2 and IDO as discussed earlier (Kang et al. 2012). AF-MSCs are one of the complex components of amniotic fluid contributed to wound healing and tissue regeneration (Silini et al. 2013). Fibroblast proliferation and differentiation to myofibroblasts are the primary step of wound repair that terminated to regeneration of epithelium, connective tissue, and vasculature. AF-MSCs have paracrine role by secretion of different growth factors containing vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), basic fibroblasts growth factors (bFGF), members of the insulin growth factor-binding protein (IGFBP) superfamily, and transforming growth factor beta (TGF- β) in wound repair (Skardal 2014; Sorrell and Caplan 2010). In addition, MSCs can differentiate directly to myofibroblasts and augment vascularization (Yamaguchi et al. 2005). AF-MSCs are also involved in the last step of wound repair that was accompanied by increase in matrix metalloproteases (MMPs) and decrease in TGF- β that terminated to collagen degradation, fibroblast apoptosis, and tissue-specific cell proliferation (Darby and Hewitson 2007). MSCs can bound MMPs at the cell surface and activate exogenous pro-MMPs which may further participate in extracellular matrix degradation and tissue remodeling (Lozito et al. 2014).

5 Immunomodulatory Properties of Chorion-Derived Mesenchymal Stem Cells (CMSCs)

Chorion is the outer layer of fetal part extraembryonic membrane that is connected to decidua as maternal part of placenta. Both decidua and chorion form the placenta membrane that separates maternal from fetal blood (Witkowska-Zimny and Wrobel 2011). Chorion is composed of chorionic plate and chorionic villi that are a rich source of mesenchymal stem cells that is known as CP-MSC and CV-CMSCs, respectively (Soncini et al. 2007; Jones et al. 2002). These fetal tissue-isolated MSCs are primitive than adult MSCs and have greater life span and self-renewal capacity. However, different studies demonstrated that maternal part isolated MSCs like decidua (D-MSC) have a greater life span than CP-MSC and CV-MSC (Soncini et al.

2007; Fukuchi et al. 2004). They showed an intermediate phenotype of adult MSCs and pluripotent stem cells and can differentiate into cells developed from three germ layers (Wang et al. 2014; Abumaree et al. 2013; Chang et al. 2007). Although pre-term-isolated chorion-derived mesenchymal stem cells (CMSCs) show higher stemness and expression level of NANOG, SOX2, c-MYC, and KLF4 and generates better embryoid body rather than term-isolated CMSCs, their application technically are impossible because of ethical problem (Jones et al. 2012). Although MSCs obtained from different fetal or adult tissues contribute the same phenotype and immunomodulatory properties, they have differences in magnitude and quality of these characteristics according to species origin, tissue source, and localization (Hass et al. 2011; Hashemi et al. 2013). CP-MSC and CV-MSC are negative for hematopoietic cell surface markers and express MSC-specific markers of CD105, CD73, CD90, and CD29. Their low immunogenicity and immunoprivileged phenotype are related to low or negative expression of HLA-DR that may be converted to immunogenic after differentiation or stimulation with IFN- γ (Huang et al. 2010; Chan et al. 2008). Expression of HLA-ABC and HLA-G is higher in CP-MSC and CV-MSC compared to adult MSCs. Strongly HLA-G positive CMSCs reflected their immunosuppressive role in pregnancy and their potential in graft tolerance (Hunt et al. 2005; Menier et al. 2010). As Bailo et al. demonstrated that engraftment of chorion-derived cells can be successfully transplanted into neonatal swine and rats and create tissues with human microchimerism (Bailo et al. 2004). Moreover, higher expression of HLA-G on human placenta-derived MSCs (hP-MSC) compared to adult MSCs makes them resistant to NK cytotoxicity and suppressed NK cells efficiently. Different studies demonstrated that hP-MSC suppress allogeneic T cell proliferation and activation through IL-10 and TGF- β production (Li et al. 2007) and induction of Treg cell increase (Chang et al. 2006). Recent study showed that CV-MSC have two subpopulation according to CD106 (VCAM-1) expression on the cell surface that affected their immunomodulatory capacity and biological activity. CD¹⁰⁶⁺CV-MSC demonstrated low colony forming capacity and proliferation potential compared to CD¹⁰⁶⁻CV-MSC, while exerts higher immunosuppressive activity (Yang et al. 2013). CD¹⁰⁶⁺CV-MSC have augmented inhibitory activity on T cell function through complete suppression of IFN- γ secretion by PHA-activated T lymphocyte and suppression of Tbet expression that directed Th1 polarization (Yang et al. 2013). Moreover, increased expression of COX-2, IL-1a, IL-1b, IL-6, and IL-8 appeared in CD¹⁰⁶⁺CV-MSC compared to CD¹⁰⁶⁻CV-MSC (Yang et al. 2013). CP-MSCs are also the active immunomodulator of T cell responses, as they suppress IFN- γ production and induce IL-4, IL-13, IL-2, and GM-CSF production if co-cultured with activated T cells in the dose-dependent manner (Lee et al. 2012). Like AF-MSC, CP-MSC has antifibrotic effect. They counteract with TGF- β in wound healing process and suppress collagen formation by production and activation of MMPs (Lee et al. 2010). However, different comparative studies on immunomodulatory function of F-MSCs and adult MSCs demonstrated the superior immunoregulatory function of F-MSCs beside their low immunogenicity (Lee et al. 2012; Chen et al. 2011a). In addition, F-MSCs function is different from adult MSCs in response to IFN- γ and TNF- α stimulation. IFN- γ stimulation will turn adult MSCs to active antigen-presenting cells (APCs) by

upregulation of MHC class II molecules while F-MSCs behave as poor APCs (Chang et al. 2006; Chan et al. 2008; Stagg et al. 2006). Finally, because of F-MSCs isolation has no ethical problem; they are an available source for therapeutic use in tissue regeneration and immunosuppression aspects.

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