**Review**

**Umbilical cord blood stem cell and its immunoregulatory properties initiative towards clinical application**

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The lack of maternal rejection of the allogenic fetus, suggests that adaptation of the immune system occurs during normal pregnancy. Umbilical cord blood (UCB) cells have unique properties to overcome the maternal rejection of allogenic fetus. Currently, UCB cells are being used as a good source of various types of stem cells for the development of allogenic stem cell therapy to treat intractable diseases. Many clinicians and scientists have concern to use human UCB cells as a choice of cell for clinical applications due to its limited availability and concern for graft-versus-host disease (GVHD) due to allogenic transplantation (UCBT) (Tilburgs et al., 2009). However, umbilical cord blood cells (UCBC) is chosen as alternative source for stem cells to bone marrow and peripheral blood stem cells transplantation, especially when HLA matched donor is not available (Kurtzberg et al., 1996; Gluckman et al., 1997). Several studies have shown decreased risk of graft versus host disease after umbilical cord blood transplantation. (Locatelli et al., 2003; Jaing et al., 2009). However, there is limited information regarding mechanisms that cause decreased GVHD following UCB transplantation (Kanda et al., 2013; Narimatsu et al., 2008).

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UCB-Mesenchymal stem cells (MSCs) mainly express
non-classical major histocompatibility complex (MHC)-I and do not express MHC-II Human Leukocyte antigen (HLA)-DR or any co-stimulatory molecules such as CD80 (B7-1), CD86, (B7-2), CD40, and CD40 ligand, which are generally expressed on Antigen Presenting Cells (APCs) and other tissues which causes immune reactions to foreign antigens (Wang et al., 2009). UCB-MSCs also fails to induce allogenic T-cell proliferation under in vitro conditions (Cutler et al., 2010; LeMaoult et al., 2004; Deuse et al., 2011) which demonstrates the immunosuppressive nature of human UCB cells. This immunosuppressive activity of UCB cells occurs via its non-classical MHC interactions and this activity may be enhanced by presence of interferon gamma (IFN-γ) treatment (Tipnis et al., 2010).

Human UCB cells are highly positive for non-classical HLA molecules like HLA-E, HLA-F and HLA-G and unlike classical HLA-1 molecules; HLA-E, HLA-F and HLA-G do not seem to possess considerable immune stimulatory functions. However, these molecules help in the immunosuppressive action via non-classical MHC interactions and a classical MHC-restricted immune response. HLA-G confers down regulation of the natural killer (NK) cells during normal pregnancy (Tilburgs et al., 2009) and mediates NK cell regulation via inhibitory receptors on NK cells. This inhibitory effect on NK cells leads to less immune reactions due to deactivation of NK cells, thereby leading to immunoregulation and immunomodulation (Figure 1). Around (50 – 90)% of leukocytes in the decidua are NK cells and uterine natural killer (uNK) cells may perhaps be involved in the regulation of the extent of trophoblast cell growth and differentiation (Caumartin et al., 2007; Le Bouteiller et al., 2011) and invasion of trophoblast cells may be countered by HLA-E and HLA-G, which are ligand for killer inhibitory receptors (KIR), on NK cells by non-classical MHC interactions. HLA-E antigens are identified as ligand of a subset of immunoglobulin super family of NK cell receptors and their interaction with KIR on NK cells may be responsible for inhibition of killer activities of NK cells (Valés-Gómez et al., 2000). HLA-E specifically interacts with CD94/NKG2A receptors that leads to the recruitment of the phosphatase SHP-1 to phosphorylated tyrosine of NKG2A and results in the inhibition of NK cells (Carretero et al., 1998). The leader peptides are transported into the endoplasmic reticulum (ER) by the Transporter associated with antigen processing (TAP) transporter. The binding of leader sequences to HLA-E leads to the stabilization of HLA-E which then moves to the surface of cell. The interaction of HLA-E interacts with CD94/NKG2 receptors on NK cells cause inhibitory signal which protects the cell from killing by NK cell (Figure 1). In tumor or virally infected cells, obstruction of the normal phenomenon of antigen processing, such as inhibition of HLA-A, HLA-B and HLA-C synthesis or inhibition of TAP activity, leads to reduction in the delivery of leader peptide. The amount of HLA-E reaching the cell surface is therefore reduced causing decrease in the inhibitory signal to the NK cell. These changes may facilitate virally infected or tumour cells being vulnerable to NK-cell-mediated lysis. Therefore, functionally HLA non-classical interaction caused inhibition of cytolytic function of uterine NK cells.

Some molecular and genetics studies also supported role of HLA E and HLA-G molecules in immunoregulation and immunomodulation by its role in maintenance of normal pregnancy (Szekeres-Bartho 2002; Agrawal and Pandey 2003; Tripathi et al., 2006; Tripathi and Agrawal 2007). The expression patterns of HLA-G at fetal-maternal interface are quite relevant key contributor of fetus tolerance by the immune system of the mother. In fact, HLA-G can protect fetal trophoblast cells from maternal NK cells through interaction with their inhibitory receptors, and HLA-G expression by embryos seems to be a prerequisite to their implantation and the subsequent pregnancy. Because of broad inhibitory function of non classical MHC molecules, these cells may be used as therapeutic tool (Hviid, 2006). In the perspective of transplantation, HLA-G expression might be favorable and promote the acceptance to graft. Several studies have shown HLA-G expression after heart (Lisa et al., 2000; Luque et al., 2006), kidney (Qiu et al., 2006), liver (Naji et al., 2007), kidney-liver (Créput et al., 2003; Naji et al., 2007) transplantation, with those expressing HLA-G in the graft and/or plasma exhibiting significantly better graft acceptance. Therefore, titration of HLA-G in transplanted patients might be used as monitoring tool to determine the tolerance level of graft in transplanted patients which could be helpful to determine the

Figure 1. Pathway of NK cell inhibitory response by non-classical interaction of HLAs interactions
requirement of immunosuppressive therapies. In view of this context patents with high HLA-G titer could be selected for low immunosuppressive agents whereas patients with low HLA-G titer higher dose of immunosuppressive drugs may be provided. Furthermore, HLA-G itself could be used as therapeutic agent for toleration of graft and exogenously provided to HLA-G-negative patients as alternative therapy for better graft tolerance (Carosella et al., 2008).

A retrospective survey report published from Japan included 1072 patients with hematological malignancies also demonstrated that incidence of chronic GVHD after UCBT is probably lower than unrelated Bone marrow transplantation (BMT) and are associated with improved survival (Narimatsu et al., 2008). This mild GVHD reaction may be related to immature and immunologically tolerant lymphocytes in UCB cells (Subramaniam et al., 2007; Chen et al. 2002). Although the complete basic mechanism is still unknown and hence further intensive research are required. Interaction of non-classical MHC may be related to immunoregulatory properties and awaits further investigations in basic and clinical research. These immunoregulatory properties of UCB cell can provide an approach for its usage and testing in preclinical and clinical trials.

UCB cells have advantages over bone marrow-derived mesenchymal stem cells in therapeutic potential for regenerative medicine and cell therapy. In contrast, bone marrow mononuclear stem cells therapy requires aspiration of bone marrow which is an invasive procedure. The potential of differentiation properties of BM-MSC decreases significantly with increasing age of the patients, however, in the case of UCB cells, are naive cell and have greater potential for differentiation (Lv et al., 2012; Biancotti and Town 2013). Mesenchymal stem cells have been isolated from several alternative sources including trabecular bone, fetal pancreas, amniotic fluid, skin, adipose tissue, muscle, placenta; cord blood (Yu et al., 2013; An et al. 2013). Among these, cord blood may be an ideal source because of its easy accessibility without risk to mother or infant and has less ethical barriers. It is also a painless procedure to donors and minor risk of viral contamination.

Some necessary precautions should be taken at the time of collection of the UCB cells, i.e. it should be collected from the healthy women who have not had spontaneous abortion during her lifetime to ensure the collection of healthy UCB cells. Several studies have shown that abnormality in immunomodulation properties of UCB cells may leads to abnormal pregnancy (Wagner et al., 2002; Wagner et al. 2013). MSC isolated from UCB have the potential to be expanded and cryopreserved for future use as an ‘off-the-shelf’ therapy. Cells from UCB have many advantages because of the immature nature of newborn cells compared to adult cells (Pereira-Cunha et al. 2013). Moreover, UCB cells have less ethical barriers for basic research and its clinical applications. In view of above, there is need to explore role of UCB cell immunosuppressive marker particularly HLA-E, HLA-F and HLA-G, so that improved treatment strategies could be followed for clinical applications. UCB-MSCs express a negative regulator of T-cell activation, B7-H1, and its expression may be increased after IFN-γ treatment. These immunomodulatory properties of UC-MSCs could potentially improve the outcome of allogenic stem cell therapy. There is also the need for more studies to fully evaluate the immunosuppressive markers of UCB cells, and identify chemical substances and basic mechanisms that could enhance their immunoregulatory and immunomodulatory functions so that further improvement in UCB cell therapy could be achieved.

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