The Egyptian Journal of Hospital Medicine (January 2024) Vol. 94, Page 1127-1132

Immunological Difference between Cord and Peripheral Blood: Review Article

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ABSTRACT

Most people feel that transplanting Cord Blood (CB) is a promising substitute for bone marrow transplants. There are several causes for this, the two most contentious of which are (1) whether graft-versus-host disease is lower in CB transplantation than in bone marrow (BM) transplantation, and (2) whether or not more human leukocyte antigen (HLA) mismatches can be used in CB transplantation. The most widely accepted theory explaining decreased CB cell function is that it is naïve in comparison to populations of adult mononuclear cells, there are more polyclonal T cell receptor repertoires, decrease in T cell proliferation specific to antigens and mitogens, greater CD4+ CD45RA+ cells levels, decreased cytokine production upon stimulation, and decrease levels of T cell proliferation. Though it's possible that certain naïve characteristics, observed in vitro, are circumvented in vivo, lymphocyte naiveté may not be the entire explanation. We have proof that variations in the soluble components released into the serum have changed the way adult and cord lymphocytes function.

Given its logistical benefits and similar clinical results to other hematopoietic stem cell transplantations (HCTs), Umbilical cord blood transplantation (UCBT) has been a useful A viable substitute donor for allogeneic transplantation since it was first introduced for use in adults and children. The lymphocytes in UCB grafts have a distinct cell makeup, and the immunological reconstitution of T and natural killer cells after UCBT seems to differ slightly from that of other donor kinds.

Keywords: Cord blood, Peripheral blood, Neonatal immune cells, Umbilical cord blood transplantation

INTRODUCTION

For neonatal immune cells, CB has been the favored source. The low frequency of graft versus host illness in recipients of cord blood transplants may be partially explained by the impact that CB dendritic cells can promote the formation of T regulatory (Treg) cells, despite their inability to produce Th-1 type environment that would aid in immune responses against pathogens. In past ten years, efforts have been undertaken to identify functional distinctions among immune systems of grownups and newborns. The most popular method has been to gather neonatal cord blood, which hospitals frequently still discard because they believe it to be close to the neonate's blood (because collecting neonatal blood would traumatize the newborn). The majority of the time, scientists have taken mononuclear cells from CB and adult peripheral blood (APB) and grown them with mitogens and toll-like receptor ligands; in a few cases, they have even grown the entire CB **(1).**

There are well-established distinctions between the LPS-responsiveness of CB and APB leukocytes. As a TLR4 ligand, LPS stimulates APB leukocytes, which results in the release of IFN-b. On the other hand, there was a marked reduction in IFN-b production in response to LPS stimulation of CB cells. Cells' incapacity to secrete IFN-b was linked to their incapacity to secrete IL-12p70, which prevented them from inducing a Th1-type response **(2).**

Since it was found that CB is a potent supplier of hematopoietic stem cells, there has been a surge in interest in CB. As a result, CB banks were established to preserve CB for use in scenarios when the hematopoietic system needs to be reconstituted. The recipients of CB stem cells exhibit lower rates of graft vs host illness compared to those of APB stem cells. This benefit may be attributed to the higher concentration of naïve regulatory cells in cord blood or the higher quantity of immature NK cells. It's interesting to note that reports have also indicated that natural killer cells in cord blood are developed, with a percentage larger than in bone marrow and adult leukapheresis products. Additionally, it has been suggested that cord blood -derived natural killer cells have the capacity to lyse any residual tumour cells following transplantation; this would enhance the technique's success **(3).**

Given its logistical benefits and similar clinical results to other hematopoietic stem cell transplantations (HCTs), UCBT has been a useful and viable substitute donor for allogeneic transplantation since it was first introduced for use in adults and children. The lymphocytes in UCB grafts have a distinct cell makeup, and the immunological reconstitution (IR) of T and natural killer cells after umbilical cord blood transportation seems vary slightly from that of other donor kinds**(4)**. Here we discuss the immune cell makeup in umbilical cord blood, the clinical significance of IR in

Received: 24/10/2023
Accepted: 24/12/2023

UCBT results, and IR with particular attention to T and NK cells.

Lymphocyte Subsets in the UCB Graft

UCB units have a various immune cell composition and set of characteristics than bone marrow or peripheral blood. One way to evaluate the functional and physiological significance of the lymphocytes in a UCB graft is to compare them to peripheral blood (PB) from adults [4]. In UCB, the median T, NK, and B cell counts are 61 percent, twenty-three percent, and sixteen percent, respectively, while in PB, they are seventy-five percent, thirteen percent, and twelve percent. Whereas all of the lymphocytes in PB are CD45bright, there are two distinct lymphocyte populations in UCB: CD45bright and CD45dim. In UCB, the proportion of B and NK cells in CD45dim lymphocyte population is larger than that of CD45bright lymphocytes [5].

1. CD3+ T cells

The quantity of natural killer-T and TCRγδ+ T cells in the UCB CD3+ compartment is smaller than in the PB. In UCB, there are 72 percent and 28 percent CD4+ and CD8 T cells, respectively, while in PB, there are sixty-five percent and 35 percent. In UCB, the median number of naïve T cells is eighty-five percent while in PB, it is fifty percent. Compared to memory CD8+ T cells, UCB has a notably higher proportion of CD45+/CD62L+ "recent thymic emigrants," naïve CD4 and naïve CD8 T cell subsets. There are less effector (CD8+CD11b+), activated (HLA-DR+), Th1-type (CCR-5+), and suppressor T cells (CD8+/CD57+/CD28−) compared to cytotoxic T lymphocyte (CTL, CD8+/CD45RA+/CD27−) T cells [6].
T lymphocytes that specifically target inflamed skin regions express cutaneous lymphoid antigen. Remarkably, UCB T cells do not express CLA, which may be related to a decreased prevalence of GVHD in UCBT. Newborn CD4+CD45RA+ naïve T cells convert more quickly than their adult counterparts into CD4+CD45RO+ memory T cells in response to phytohemagglutinin and interleukin-2 (IL-2). This suggests that UCB naïve T cells have a higher potential for memory T cell transformation [7].
However, UCB cells produce significantly less IFNγ and TNFα as well as IL interleukin-2 than adult PB lymphocytes, probably as a result of decreased expression of NFAT-dependent genes. In comparison to adult PB T cells, UCB T cells exhibit potent allogeneic anticancer activity, including a greater tumor-infiltrating CD8/Treg ratio and faster development into memory/effector cells [8].

2.-A: **Tregs**

The term "Tregs" refers to subset of CD4+CD25+ T cells that sustain immunological suppression and self-tolerance. The main transcription factor for Treg formation is Forkhead box protein P3 (FoxP3) [8,9]. Tregs can be produced in the thymus (nTregs) or in peripheral lymphoid tissues (iTregs) by converting CD4+CD25− naïve T lymphocytes in existence of TGFβ. A unique CD25+ population is present in CD4+ T cell compartment of umbilical cord blood [9].
Since most UCB regulatory T cells (Tregs) have never been stimulated by an antigen, they are unable to suppress T cells that are "antigen-specific" alloreactive. However, the suppressive ability of UCB Tregs on allogeneic T cells is significantly greater than that of Tregs from APB when they are expanded and activated by TCR contact and cytokine stimulation, such as using anti-CD3/CD28 mAb-coated beads and IL-2. Additionally, UCB Tregs have a greater potential for growth, and Tregs (CD4+CD25+CTLA4+) can be induced from CD4+CD25− T cells in umbilical cord blood more easily than from adult PB. Notably, promising therapeutic efficacy to prevent acute GVHD has been demonstrated in early stage clinical research utilizing ex vivo umbilical cord blood-derived nTreg expansion [10].

2-B: **NK Cells**

Early on after HCT, natural killer cells are recognised to be the primary mediator of graft-versus-leukemia reactions. They can make up to thirty percent of the enriched UCB graft. UCB NK cells have a CD56bright/CD56dim ratio that is either slightly greater or comparable to PB NK cells. Notably, in the umbilical cord blood graft, cytotoxicity of the CD56dim natural killer subset is inferior to that of the CD56bright natural killer cells, while in PB, cytotoxicity of the CD56dim NK cells is more pronounced. While the cytotoxicity of umbilical cord blood's CD56dim NK cells is significantly less than that of PB's counterpart, that of the CD56bright subset of UCB- NK cells is similar to that of PB natural killer cells. There was a significant drop in the binding ability of CD56dim NK cells of UCB to leukemic targets, as evidenced by the results of an experiment that involved conjugate formation. This reduction in binding ability was related to a decrease in the expression of adhesion molecules such as CD11a, CD18, CD2, and DNAM-1. NK cells derived from UCB were found to exhibit significantly lower levels of L-selectin and ICAM-1 expression contrasted to those derived from PB [6].

In comparison to PB NK cells, UCB - NK cells express distinct chemokine receptors. UCB CD56dim NK cells exhibit a significant decrease in CXCR1 expression, while both CD56dim and CD56bright NK cells exhibit an increase in CXCR4 expression. Therefore, it's possible that umbilical cord blood NK cells have greater homing ability to BM (CXCR4) but are less sensitive to inflammatory activation (involved in CXCR1 expression), which could explain the successful GVL of UCBT [11].

While UCB NK cells show more of the phenotypic marker of NK cell immaturity, NKG2A/CD94, than PB NK cells do, maturation markers including KIR, CD16, and CD57 are less expressed by umbilical cord blood natural killer cells. When it comes to NK cell activation receptors, UCB NK cells express more GITR, 2B4, TLR-4, and CD48 (in CD56bright) than PB NK cells. NKG2C/CD94 and NKp46 (in CD56bright) expression is lower [12].

Although they are a unique population observed in UCB grafts, immature CD56−/CD16+ natural killer cells are rarely detected in healthy persons. Under IL-2 or IL-15 treatment, CD56−/CD16+ NK cells can develop into CD56+/CD16+ NK cells, gaining increased cytotoxicity. In comparison to PB NK cells, growth of umbilical cord blood natural killer cells is less sensitive to low-dose interleukin-2 stimulation (200 IU/mL). This is probably secondary to CD56dim NK cells in UCB expressing less CD25 (IL-2Rα). In comparison to PB NK cells, UCB CD56dim NK cells exhibit less cytotoxicity while at rest due to their decreased expression of CD107a, IFNγ, granzyme B, perforin, and FAS-L. By stimulating UCB NK cells with large doses of IL-2 (1000 IU/mL), they can develop a robust cytotoxicity with increased production of IFNγ and cytotoxic granules. Moreover, UCB NK cells exhibit a greater response than PB natural killer cells to IL-12 and IL-18 stimulation as indicated by IFNγ production and CD69 expression [13].

3. Immune Reconstitution in UCBT

Clinical results include the frequency of GVHD and transplant-related mortality, dangers of infections and recurrence, and, eventually, survival may be impacted by immune reconstitution following HCT. Numerous factors, such as the graft source, the cell makeup of the graft, the immune suppression regimen, viral infections in HCT, and conditioning regimens (nonmyeloablative vs. myeloablative, use of, total body irradiation and antithymocyte globulin), influence IR following HCT [14].

3-A: T cells

When UCBT is used instead of PB stem cell transplantation otherwise BM transplantation, T cell reconstitution takes longer [15]. T Following HCT, there are two different processes that lead to cell reconstitution: (1) mature T cell growth in the periphery (a thymus-independent pathway); and (2) thymopoiesis from donor hematopoietic progenitors (a thymus-dependent approach) [16]. T cell reconstitution occurs in the early stages following HCT via peripheral expansion facilitated via T cells transmitted from the graft otherwise recipient that have survived conditioning therapy (thymus-independent pathway). Homeostatic cytokines, including IL-7 and IL-15, as well as self-MHC molecules delivered through antigen-presenting cells, are in competition among mature T cells [17].

IL-7 and IL-15 are considered continuously created by non-immune and immune cells in the lymphopenic condition, but they are not ingested in significant amounts. Early after HCT, therefore, plasma concentrations of these cytokines are elevated. In the context of lymphopenia, the increased availability of IL-7 otherwise IL-15 and self-MHC on APCs to mature T cells transferred from the graft facilitates expansion with limited competition. T cells endure several cell divisions during their natural expansion, which results in a quicker telomere shortening during the initial year following HCT. Naïve T cells, as opposed to memory T cells, necessitate TCR interaction with MHC molecules offered by antigen-presenting cells, apart from cytokine stimulation, to ensure their survival and proliferation [17].

Consequently, memory T cells proliferate more extensively in periphery than naïve T cells following HCT. Another unique feature of early immunological recovery is the reversed CD4/CD8 ratio, caused by increased proliferation of memory CD8 T cells in the outer regions of the body [14]. Seropositivity to viral pathogens such as CMV in specific donor-recipient pairings can polarise T cell expansion towards viral antigens, thereby restricting polyclonal expansion and restricting the repertoire of T cells, of which antigen-specific memory T cells proliferate primarily [18].

Early T cell reconstitution in UCBT is predominantly reliant on peripheral expansion, and the T cell repertoire may be comparatively limited in adults because of delayed thymopoiesis, in contrast to other donor kinds. In addition, CD8+ and CD4+T cells have a diminished capacity to produce IFNγ in response to superantigen and CMV stimulation on day +100 after UCBT. This may suggest that T cell functions were compromised early after UCBT [14].

The thymus is responsible for the reconstitution of diversity of T cell repertoire from naïve T cells derived from donors, which occurs after mature T cells have expanded peripherally after HCT (thymus-dependent pathway). Thymopoiesis, the process by which lymphoid progenitors derived from donors enter the thymus and endure maturation processes (negative selection and positive), requires an extended period of time. Thymopoiesis can persist for as long as six years and arises weeks after HCT. Following a series of positive and negative selections, only minute proportions of T cells are able to survive and depart the thymus; these are referred to as "recent thymus emigrants [19].

3-B: **NK Cells**

Following HCT, the initial lymphocytes to reconstitute are NK cells. Due to the meagre absolute counts and functional immaturity of T cells transmitted

with umbilical cord blood graft, natural killer cell immunity is particularly important in GVL in the early stages following UCBT. When both UCBT (one month) and unrelated BMT (1.4 months) received ATG as part of conditioning regimen, the time to natural killer cell reconstitution (>0.1 × 109/L) was comparable. The natural killer cell count reconstitution one month post UCBT was comparable to that of healthy controls, notably, in the lack of ATG in the conditioning regimen following UCB. Furthermore, UCBT demonstrated superior NK cell reconstitution compared to PBSCT over a 24-month duration, as evidenced by increased NK cell counts [(20)].

In comparison to healthy donor controls, NK cell reconstitution occurs 1 to three months after UCBT and is polarised towards CD56bright natural killer cells (approximately forty percent of the total natural killer cells) [(20)]. NK cells exhibit elevated NKG2A and CD62L levels and diminished levels of CD8, CD16, and CD57 three months after UCBT. Despite this, the expression of CD94/NKG2A, an inhibitory receptor that recognises HLA-E antigen, is initially elevated in CD56dim NK cells one year after UCBT [(21)].

Subsequently, the levels of CD94/NKG2A return to those of healthy controls. NK cell expression of KIR2DL2/3 and KIR3DL1 is substantially reduced in UCB graft, but reaches levels comparable to healthy donors three months after umbilical UCBT, indicating that natural killer cells have been educated. Nonetheless, during the first six months following UCBT, KIR2DL1 levels of CD56dim natural killer cells remain persistently below those of healthy controls. This finding is consistent with the sequential acquisition of KIR that is frequently noted in other types of HCT [(22)].

Following the administration of UCBT, natural killer cells gain distinct functional properties, as evidenced by the significant production of interferon-gamma within the first one to three months thereafter [(20)]. The direct cytotoxicity of natural killer cells against K562 targets and HLA mismatched primary AML samples is strong and equivalent to that found in healthy controls over the initial six months following UCBT. On the other hand, the antibody-dependent cellular cytotoxicity of natural killer cells is significantly impaired three months after UCBT. This finding is in line with the low expression of CD16 that occurs early on after UCBT [(4)].

There were numerous distinctions among the T- and B-cell lineages among individuals who received UBMT and CBT. The absolute number of CD8+ T cells was considerably greater in UBMT group in comparison to CD4+ T cells, where no significant variation was noted. As a consequence, the UBMT group exhibited a significantly reduced CD4/CD8 ratio. The absolute cell number of B cells was considerably reduced in the UBMT collection. Additionally, the absolute number of naive B cells was marginally reduced in the UBMT group. Different immune reconstitution among CBT and UBMT individuals may persist for at least two years following allo-HCT, according to these findings [(23)].

Mobilized PB versus CB:

Combined inflammatory cytokines were able to increase in vitro survival of CD34+ cells that were generated from CBs. This was accomplished by preventing apoptosis. On the contrary, it was observed that particular combinations of inflammatory cytokines, specifically IL-1β+ TNF-α, IL-6+ TNF-α, and IL-1β+ TNF-α+ TIMP-1, mostly facilitated in vitro migration of CD34+ cells that were obtained from mesenchymal peritoneal fluid through the receptor CXCR4. There was an increase in the expression of CD44 and CD13 in both sources when TNF- was present, either individually or in combination. Furthermore, the coexistence of BMSCs and inflammatory cytokines did not demonstrate any synergistic or additive effect. In conclusion, BMSCs by themselves promoted the survival and migration of CD34+ cells produced from CBs and mPBs to the same degree as the combined inflammatory cytokines. Based on these findings, it has been determined that neonatal or adult normal HSPCs experience unique in vitro functional activation as a consequence of the combined proinflammatory stimuli [(24)].

Cytokines that promote inflammation are becoming more important regulators of both steady-state and infection-induced hemopoiesis that are emerging. Inflammatory variables in the bone marrow microenvironment have been shown to have the capacity to alter the fate of HSPCs, according to study that was conducted not too long ago. The reason for this is because HSPCs have the potential to actively react to proinflammatory cytokines and the indications of danger. On the other hand, persistent excessive signaling can have a negative impact on the regulation and function of HSPC [(25)].

Furthermore, it has been observed that inflammation-related signalling pathway abnormalities are present in both preleukemic and leukemic conditions. BMSCs, or bone marrow mesenchymal stromal cells, are an essential component of the bone marrow microenvironment. By directly or indirectly producing indoleamine 2,3-dioxygenase, prostaglandin E-2, IL-10, and soluble receptors for IL-1 and TNF-α, the cells demonstrate immune-suppressive activity. This occurs in response to an assortment of stimuli that are present in the microenvironment [(26)].

Cross-communication among HSPCs and stromal cells may, nevertheless, foster a proinflammatory milieu that facilitates the advancement of malignant transformation and illness [(27)]. Numerous pathways and factors have been implicated in this process; however,

the precise manner in which inflammation may impact or alter HSPCs remains obscure. It is essential to identify the direct cellular targets of proinflammatory cytokines in order to gain a clearer understanding of how HSCs/HSPCs are regulated in bone marrow niche [28].

At present, mPB and UCB that have been mobilised by granulocyte colony-stimulating factor are two of HSPCs utilised for transplantation in hematological malignancies. Nevertheless, there is a lack of understanding regarding the mechanisms by which inflammation influences HSPCs in neonates and adults. Several phenotypic and functional distinctions among HSPCs derived from CB and mPB have been identified in recent years [29].

Pleiotropic proinflammatory cytokine IL-6 exerts its effects on hemopoietic cells, among other cell types. It has been recommended that it has crucial role in stimulating myelopoiesis in responding to chronic inflammation and pathogen infection [30]. IL-1β is highly effective inflammatory cytokine that regulates thrombocytosis and leukocytosis in the presence of inflammation through the stimulation of cytokine production (involving granulocyte colony-stimulating factor and IL-6) [31].

Furthermore, recent research by **Pietras *et al.*** [32] provided evidence that although IL-1β is not required for steady-state hemopoiesis, acute exposure to it stimulates the proliferation of HSCs and directs them to prime themselves for a myeloid destiny. Finally, it plays a role in the advance of hematological malignancies and solid tumors; TNF-α inhibits the growth and renewal of HSPCs. On the contrary, alternative evidence indicates that TNF signaling might augment the functionality of HSCs. TIMP-1 is involved in various biological processes, such as immune regulation and inflammation, via receptor (CD63) binding. It has been recently shown to exhibit cytokine-like characteristics in both the normal and leukemic HSPC compartments [33].

DECLARATIONS

- **Consent for publication:** I certify that each author has granted permission for the work to be submitted.
- **Funding:** No fund
- **Availability of data and material:** Available
- **Conflicts of interest:** No conflicts of interest.
- **Competing interests:** None

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