The unique profile of cord blood natural killer cells balances incomplete maturation and effective killing function upon activation

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ABSTRACT

Cord blood (CB) is increasingly used as a source of stem cells for hematopoietic stem cell transplantation, and natural killer (NK) cells may be the effectors of the antileukemic response observed after CB transplantation. Here, we analyzed the phenotype and functions of CB NK cell subsets. We determined that the percentage of NK cells was higher in CB compared with peripheral blood (PB). Furthermore, there was a higher percentage of the CD56dim subset in CB. CB NK cells reached a late stage of differentiation, but exhibited higher expression of NKG2A and expressed fewer killer-cell immunoglobulin-like receptors, suggesting an incomplete maturation. CB NK cells highly expressed CXCR4, but did not express L-selectin, highlighting unique homing properties of CB NK cells. CB NK cells proliferated in response to interleukin-2 and degranulated in response to stimulation with tumor cells, but failed to lyse K562 cells in 51Cr-release assay. CB NK cells exhibited a lower interferon-γ production in comparison with PB NK cells. Culture with IL-2 increased CB NK cell functions. Our study sheds light on CB NK cell properties and highlights the potential of CB as a source of NK cells for immunotherapy.

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1. Introduction

Hematopoietic stem cell transplantation is most commonly indicated for leukemia, but is also used to treat different hematological and nonhematological malignancies, immunodeficiency, and autoimmunity [1]. Cord blood (CB) has been increasingly used as an alternative source of stem cells for hematopoietic stem cell transplantation in adults because it presents several advantages including faster availability, lower human leukocyte antigen matching requirement, lower incidence and severity of graft-versus-host disease [2–4], and preservation of the graft versus leukemia effect described after allogeneic bone marrow transplantation.

The use of intense immunosuppression after CB transplantation (CBT) in conjunction with the naivity of the T cells infused with the graft and the slow T cell reconstitution generate a long period of immunodeficiency after CBT. Natural killer (NK) cells constitute between 15 and 30% of CB lymphocytes [5,6], and after CBT, NK cell reconstitution occurs very early on, so NK cells constitute most of the lymphocytes in circulation. The observation that they are capable of killing leukemia cells ex vivo [7] supports the hypothesis that NK cells are most likely to be a main effector of the graft-versus-leukemia effect observed after CBT.

It has been reported that the phenotype of CB NK cells demonstrates some similarities to peripheral blood (PB) NK cells [8]. CB CD56− cells have been demonstrated to express CD94, some killer-cell immunoglobulin-like receptors (KIR), and activating receptors such as NKG2D and Nkp46 [6,9]. Nonetheless, the current literature relating to the phenotype and functions of CB NK cells indicated some inconsistencies [8]. CB NK cells have been reported to be mature by some investigators [6,8,10] and immature by others [11]. In some circumstances, they have been demonstrated to be as cytolytic as PB NK cells [6,10] or deficient in killing target cells, potentially because of an immature phenotype [11], a high expression of NKG2A [9], or a low expression of adhesion molecules [12]. However, incubation with interleukin-2 (IL-2), IL-12, or IL-15 can increase their cytolytic activity [6,11].

In addition to the CD56dim and CD56bright subsets, CB has been demonstrated to be characterized by the presence of CD16+CD56− cells, which are not typically present in healthy PB. Previous studies have reported that these cells are a unique cell subset present in CB [10,11,13] that exhibited reduced lytic activity and might be the precursor of mature NK cells. Tanaka et al. reported an increased