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Cell intrinsic characteristics of human cord blood naïve CD4 T cells

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Abstract

It has been generally considered that the perinatal immune system is less inflammatory compared to the adult system and type 2 responses predominate perinatal immune responses against antigens. Indeed, previous studies in mice showed that there are cell-intrinsic differences between neonatal and adult CD4 T cells. However, studies on human cord blood and infant blood demonstrated that human perinatal T cells do not produce elevated levels of Th2 cytokines with the exception of IL-13. These data raise the question if human T cells in the perinatal blood fundamentally differ from adult T cells. To decipher differences between human perinatal and adult T cells, we performed a focused comparative analysis on purified naïve CD4 T cells from umbilical cord blood (UCB) and adult peripheral blood. Our data demonstrate naïve CD4 T cells from UCB differ from adult naïve CD4 T cells in surface expression of CD26, dipeptidyl peptidase-4. While only a fraction of effector/memory T cells from adult blood express CD26, practically all T cells from UCB express high levels of CD26. We also determined that Th1/Th2 polarizing conditions induce UCB CD4 T cells to produce higher levels of IFN- γ and IL -5 compared to adult CD4 T cells, respectively. These data demonstrate intrinsic differences between

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UCB and adult naïve CD4 T cells and suggest that human perinatal immune responses involve more complex mechanisms than the previously thought Th2-dominant responses.

1. Introduction

The neonatal immune system is phenotypically and functionally distinct from the mature, adult immune system [1, 2]. The overall response of the perinatal immune system is tolerogenic, as shown by the landmark works by the groups of Owen and Medawar [1, 2]. Multiple factors are considered to contribute the tolerogenic conditions of the perinatal immune system (reviewed by [3, 4]). Studies using mouse models showed that one of the unique features of the fetal/neonatal immune system is a cell intrinsic propensity of T cells to produce elevated levels of Th2 type cytokines while producing reduced Th1 type cytokines compared to adult T cells [5, 6]. Th2 bias in neonatal CD4 T cells is in part due to an intrinsic property whereby they are endogenously poised to produce Th2 like cytokines, and this profile is not found in CD4 T cells from adult blood [7]. However, others showed that both IFN- γ and IL-4 gene expression are suppressed in perinatal T cells [8].

In contrast to their murine counterpart, human perinatal T cell responses are less clearly characterized. In response to tetanus toxoid vaccination, neonate memory T cells from mice produced more Th2 type cytokines than Th1 cytokines [9]. However, a large cohort analysis of cord blood and 3 month old infants revealed that perinatal total T cells do not show an increased propensity of Th2 cytokine production except for IL-13 [10]. *In vitro* studies using purified human UCB T cells express elevated levels of IL-13 but not IL-4 [11, 12]. These data strongly suggest that the human perinatal immune system responds differently from the mouse perinatal immune system. A more detailed analysis on human perinatal T cells is needed to understand how the human fetal/neonatal immune systems respond to antigenic stimuli and infections.

The goal of this study is to determine the cellular and molecular differences between perinatal and adult immune systems. The cellular composition of the perinatal immune system differs significantly from adult. The majority of T cells in adult blood are effector/memory T cells while a predominant fraction of cord blood T cells are naïve T cells. To understand perinatal responses and to avoid the complex influences that arise from analyzing multiple populations of cells, we focused on naïve CD4 T cells to elucidate cell intrinsic differences between human umbilical cord blood (UCB) and adult peripheral blood. We found that cord blood T cells differ from adult naïve T cells in surface antigen expression, homeostatic expansion, and cytokine production. These data strongly suggest that perinatal T cells are programmed differently from adult T cells in homeostasis and their reactivity against antigens.

2. Materials and Methods

2.1 Naïve CD4 T Cell Isolation

Whole umbilical cord blood (UCB) was kindly donated from Gottlieb Memorial Hospital and Loyola University Medical Center from donors that meet our collection criteria

(Exclusion criteria: 1. Evidence of active malignancies; 2. Use of medications that affect the immune system- such as glucocorticoids and immunosuppressants; 3. Uncontrolled hyper or hypothyroidism; 4. Presence of an autoimmune disease; 5. Presence of active infection). Adult peripheral blood were obtained from National Institute of Health. Naïve CD4 T cells were isolated from mononuclear cells enriched from UCB or adult blood via negative selection using an EasySep Human Naïve CD4⁺ T Cell Enrichment Kit (Stem Cell Technologies, Vancouver, BC, Canada).

2.2 Phenotype analysis of naïve CD4 T Cells

Isolated naïve CD4 T cells from UCB and adult blood were seeded at 0.3×10^6 cells per 96 well round bottom in the presence of recombinant human IL-7 (20 ng/mL; PeproTech, Rocky Hill, NJ). Media was changed every 2–3 days and IL-7 concentrations were maintained throughout. On the day of isolation (day 0) and day 7 of maintenance in IL-7 the naïve phenotype was assessed by staining with anti-CD4, anti-CD45RA (BioLegend, San Diego, CA), anti-CD45RO (BD Biosciences, San Jose, CA), anti-CD26, and anti-CD31 (BioLegend, San Diego, CA) antibodies and analyzed on a BD FACSCANTO II Flow Cytometer (BD Biosciences). Additionally, on day 0, 1×10^6 cells were stimulated in the presence of fresh media, phorbol 12-myristate 13-acetate (PMA) (50 ng/mL; Fisher Scientific, Hampton, NH) and ionomycin (1 μ M; Sigma-Aldrich, St. Louis, MO) for 4 hours. After stimulation, cell supernatants were harvested and analyzed for the expression of IFN- γ , TNF- α , IL-2, IL-4, IL-5 and IL-13 using the LEGENDplex Human Th Cytokine Panel (BioLegend) on a BD FACSCANTO II Flow Cytometer (BD Biosciences).

2.3 Th1 and Th2 Differentiation Assays

Isolated naïve CD4 T cells from UCB and adult blood were maintained in IL-7 for 7 days, then were stimulated with anti-CD3 (OKT3; 5 μ g/mL; BioLegend) and anti-CD28 (28.2; 5 μ g/mL; BioLegend) and differentiated in the presence of IL-2 alone (neutral), T helper type 1 (Th1), or T helper type 2 (Th2) inducing reagents using a Human Th1 or Th2 Differentiation Kit (R&D Systems, Minneapolis, MN) according to the manufacturer's protocol. Cells were harvested on day 5 for the Th1 differentiation assay and day 13 for the Th2 differentiation assay and washed once in media. 1×10^6 cells from each assay were then stimulated in the presence of fresh media, PMA and ionomycin for 4 hours. After stimulation cell supernatants were harvested and analyzed for the expression of IFN- γ , TNF- α , IL-2, IL-4, IL-5 and IL-13 using the LEGENDplex Human Th Cytokine Panel (BioLegend) on a BD FACSCANTO II Flow Cytometer.

3. Results

3.1 Expression of CD26 by cord blood naïve CD4 T cells

To determine the cell intrinsic differences between cord blood and adult blood, we determined surface antigen expression by each group of T cells. We defined naïve T cells as a group of cells expressing CD45RA but not expressing CD45RO [9]. Among the surface antigens known to be expressed by T cells, we identified a significant difference in expression of CD26 between cord blood and adult peripheral blood naïve CD4 T cells (Fig. 1A and B). A fraction of adult CD45RA⁺ naïve CD4 T cells express low levels of CD26.

CD26^{hi} cells are mostly CD45RA⁻ CD45RO⁺. In a striking contrast, close to 100 % of cord blood naïve CD4 T cells express high levels of CD26. CD26 is also known as dipeptidyl peptidase 4 (DPPIV) and cleaves multiple ligands (e.g. chemokines) that contain proline or alanine at the N-terminus [13, 14].

One explanation for the elevated levels of CD26 expression by cord blood T cells is the high frequency of Recent Thymic Emigrants (RTE) in cord blood. CD31 is a cell surface antigen expressed by naïve CD45RA⁺ cells and is considered a marker for RTEs [15]. If cord blood naïve T cells express CD26 because they are enriched for RTE, then we expect that CD26^{hi} T cells co-express CD31 both for cord and adult naïve T cells. CD31 expression is found among CD45RA⁺ cells both in adult and cord blood, unlike CD26 (Fig. 1C). While cord blood CD26^{hi} cells express CD31, adult T cells do not co-express CD26 and CD31 (Fig. 1D and 1E). These data show that CD26 expression is not *a priori* associated with RTE.

CD26 expression was reported to be induced by antigen receptor stimulation [16]. Thus, we next tested if anti-TCR stimulation changes CD26 expression. We stimulated total CD4 T cells with plate-bound anti-CD3 and anti-CD28 antibodies (Fig. 1F). While adult naïve CD4 T cells increased expression of CD26 after stimulation, cord blood naïve CD4 T cells did not significantly change CD26 expression. Together, these data strongly suggest that CD26 is a unique surface antigen expressed by cord blood naïve CD4 T cells and is regulated differently in cord blood naïve CD4 T cells than in adult naïve CD4 T cells.

3.2 IL-7 induced an elevated expansion of naïve CD4 T cells from cord blood

Next, we compared the ability of naïve CD4 T cells to respond to IL-7. IL-7 is a critical anti-apoptosis and survival cytokine for naïve T cells and plays a pivotal role in homeostatic expansion of T cells [17]. Previous studies have shown that IL-7 is required for *ex vivo* expansion of naïve and memory T cells [18]. CD31⁺ human naïve T cells also proliferate in response to IL-7 [19]. Since cord blood T cells are mostly CD31⁺ while only a fraction of adult naïve T cells are CD31⁺, we investigated if human cord blood naïve T cells and adult PBMC naïve CD4 T cells respond differently to IL-7. We purified naïve CD4 T cells from cord blood and adult blood and maintained them *in vitro* in the presence of IL-7. After 7 days of culture, T cells were harvested and analyzed for their surface antigen expression and cellularity (Fig. 2A,B). Both cord blood and adult blood naïve T cells maintained their expression of CD45RA/CD45RO after 7 days of culture with IL-7. As reported, adult naïve CD4 T cells did not proliferate after 1 week and maintained their cellularity. In contrast, cord blood naïve CD4 T cells expanded approximately 2 fold after 7 days, confirming that cord blood naïve T cells have different requirements for IL-7 induced homeostatic expansions compared to adult naïve CD4 T cells, potentially due to their short duration after thymic emigration.

3.3 Cytokine production by cord blood CD4 T cells

Previous reports on mouse T cells showed that perinatal T cells have an elevated propensity to express Th2 type cytokines (e.g. IL-4, IL-10) compared to adult T cells [5, 6]. A report on human T cells showed that CD26⁺ T cells express IL-17 [20]. Thus, we investigated the type of cytokines human cord blood naïve T cells produce. To test this, we stimulated purified

naïve CD4 T cells from cord blood and adult blood by PMA and ionomycin and assessed cytokine profiles. Adult naïve CD4 T cells produce IL-2, TNF and IFN- γ (Fig 3). Naïve CD4 T cells from cord blood also produce IL-2 and TNF but a significantly lower level of IFN- γ (Fig. 3). In addition, cord blood naïve CD4 T cells did not produce IL-4, IL-5, and IL-13 (not shown). While human CD26⁺ cells were reported to express IL-17 [20], we did not observe detectable levels of IL-17 production by cord or adult blood T cells. These data demonstrate that cord blood naïve CD4 T cells do not produce either Th1 or Th2 type cytokines to the level comparable to adult naïve CD4 T cells and are not pre-programmed to produce Th2 cytokines..

We next hypothesized that cord blood naïve T cells have an elevated propensity to become Th2 type T cells compared to adult naïve CD4 T cells. To test this, we used *in vitro* culture systems that promote Th1 or Th2 differentiation. *In vitro* maintained naïve T cells were stimulated under the neutral, Th1, or Th2 inducing conditions. Cells were harvested and re-stimulated by PMA and ionomycin. After stimulation, the supernatant was collected and the cytokine profile was assessed (Fig. 3B–D).

While no significant difference was observed between cord and adult naïve CD4 T cells cultured under the Th0 conditions, the Th1 polarizing conditions induced much higher levels of IFN- γ production by cord blood T cells compared to adult blood T cells (Fig. 3C). Th1 conditions also induce TNF production by cord blood T cells at the comparable level to adult T cells. In contrast, Th2 skewing conditions induced lower levels of IL-4 production by cord blood T cells compared to adult blood T cells (Fig. 3D). Interestingly, cord blood T cells expressed higher levels of IL-5 (statistically significant) and IL-13 compared to adult naïve T cells, showing a dichotomy among the Th2 cytokines. These data suggest that naïve CD4 T cells from cord blood differ from adult naïve CD4 T cells in their effector cell differentiation ability. While cord blood naïve T cells are less effective in producing cytokines in the early stage of antigen stimulation, they can acquire the higher capacity than adult T cells to produce both Th1 (IFN- γ) and Th2 (IL-5, IL-13) type cytokines when exposed to the effector T cell differentiation conditions.

4. Discussion

Our data demonstrate that high levels of CD26 expression is a unique surface marker for cord blood derived naïve CD4 T cells. These data also depict that, while cord blood naïve CD4 T cells do not produce cytokines comparable to adult naïve CD4 T cells under neutral conditions, they can acquire the ability to produce elevated levels of both Th1 (IFN- γ) and Th2 (IL-5 and IL-13) cytokines when they are stimulated under the conditions that promote effector T cell differentiation. Together, the data strongly suggest that cord blood naïve CD4 T cells are programmed differently from adult naïve CD4 T cells.

Previous works showed that CD45RA expression correlated positively with CD26 expression in T cells from cord blood, thus identifying immature T cells [21]. Conversely, other reports showed that memory, but not naïve, T cells express CD26 [22]. Our data show that antigen receptor stimulation of adult naïve CD4 T cells induces expression of CD26 (Fig. 1). In contrast, cord blood naïve CD4 T cells maintain or slightly reduce expression of

CD26 after antigen receptor stimulation. In addition, most of adult CD26⁺ T cells are in the CD45RO⁺ and CD45RA⁻ population while cord blood CD26⁺ T cells are exclusively CD45RA⁺. Thus, expression of CD26 by cord blood naïve T cells differ fundamentally from adult blood naïve CD4 T cells.

CD26 is a regulator of glucose metabolism and inactivates a group of insulinotropic proteins such as glucagon like peptide 1 (GLP1) [23] and its inhibitor has been used clinically for treatment of insulin resistant diabetic patients [24]. CD26 also binds adenosine deaminase, an essential factor for immune competence of neonates [25]. The functions of CD26 in T cells are currently not well understood. Knockout mice for CD26 show an increase in the severity of Experimental Autoimmune Encephalomyelitis (EAE) [26]. CD26 deficient mouse T cells showed significantly elevated responses to antigens as assessed by their proliferation and cytokine production (IFN- γ , TNF), suggesting that CD26 plays an inhibitory role in T cell activation. However, studies in humans demonstrate that CD26 can deliver a strong co-stimulatory signal and contribute to activation in CD4⁺ helper/memory T cells [27, 28]. Furthermore, previous studies suggest that CD26 is more efficient in responding to stimulation and promoting activation in CD45RO⁺ effector/memory T cells when compared to CD45RA⁺ naïve T cells [28]. Clinical analysis demonstrated that a CD4⁺ CD45RO⁺ CD26^{hi} T cell subset is correlated with Multiple Sclerosis (MS) disease severity, as this subset was found to be enriched for Th1 effector functions [29]. Altogether, there are species-specific differences in the function of CD26. Indeed, previous works demonstrated that CD26 in T cells from mice is not directly linked to T cell activation [30]. In light of data obtained in humans T cells in combination with our own, it is possible that CD26 functions to enhance CD45RO⁺ T cell effector functions while inhibiting T cell activation in CD45RA⁺ T cells. While the mechanism of how CD26 inhibits activation in CD45RA⁺ T cells is currently not well characterized, a reduced cytokine production by cord blood naïve CD4 T cells may be in part due to the highly elevated CD26 expression.

An unexpected outcome of this study is the enhanced effector cytokine production by cord blood CD4 T cells when differentiated *ex vivo* under the Th1/Th2 polarizing conditions. Previous reports from mice suggest that there is a Th2 bias in neonates culminating in a reduced capacity of neonatal T cells to produce IFN- γ and TNF- α [6, 7, 14]. However, an epidemiological study involving over 400 children showed no significant bias toward Th2 cytokine production by freshly isolated PBMC T cells except for IL-13 [10]. Our data are in line with these outcomes from human studies and demonstrate no bias in Th2 cytokine production by freshly stimulated naïve CD4 T cells from cord blood. However, naïve cells from cord blood produced significantly elevated levels of IFN- γ and IL-5 when they are expanded under the Th1/Th2 polarizing conditions, respectively. It should be noted that cord blood T cells did not produce appreciable levels of IL-4. Unlike IL-4, IL-5 does not affect T cell differentiation into Th2. Instead, IL-5 promotes eosinophils and B cell differentiation and growth [31]. Thus, elevated expression of IL-5 does not directly promote Th2 development. These data support the epidemiological study's results, showing that the human perinatal immune system is not skewed toward canonical Th2 responses.

In conclusion, human cord blood naïve CD4 T cells are intrinsically different from adult naïve CD4 T cells in CD26 expression and their cytokine production. Perinatal T cells are

not pre-programmed to produce Th2 type cytokines, but they are able to produce both Th1 and Th2 type cytokines with the exception of IL-4. These data suggest that the presence of environmental factors and innate immune cells could contribute to the overall outcomes of perinatal immune responses upon antigen exposure.

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Highlights

- Human cord blood naïve CD4 T cells constitutively express high levels of CD26.
- Cord blood naïve CD4 T cells do not have an intrinsic propensity to produce Th2 type cytokines.
- Cord blood naïve CD4 T cells produce significantly more IFN- γ /IL -5 than adult naïve CD4 T cells when they are cultured under Th1/Th2 differentiation conditions, respectively.
- Cord blood naïve T cells proliferate in response to IL-7 without TCR engagement.

Figure 1.

Figure 2.

Figure 3.