Eur J Pediatr
DOI 10.1007/s00431-010-1210-y

ORIGINAL PAPER

Age-dependent changes in peripheral blood dendritic cell subsets in normal children and children with specific polysaccharide antibody deficiency (SPAD)

Harumi Jyonouchi · Chongwei Cui · Lee Geng · Zhiwei Yin · Patricia Fitzgerald-Bocarsly

Received: 17 February 2010 / Accepted: 24 April 2010
© Springer-Verlag 2010

Abstract Myeloid and plasmacytoid dendritic cells (MDC/PDC) play crucial roles in bridging adaptive and innate immunity by affecting development of both cellular and humoral immunity. The immune system evolves after birth as reflected in dynamic changes in numbers and functions of various immune cells with age. However, age-associated changes in DC subsets in children have not been elucidated despite the fact that such normative data are crucial for evaluating alternations of DC subsets in various pediatric diseases. This study addressed age-associated changes in DC subsets and CD40/86 expression on PDC (markers of maturation/activation) in 50 healthy children in comparison with 25 children with specific polysaccharide antibody deficiency (SPAD). Our results revealed age-dependent decrease of PDC numbers ($p<0.0001$), although there was no age-associated changes in CD40/CD86 expression. MDC1/MDC2 numbers did not reveal such linear age-dependent changes and MDC1/PDC ratio reached around 2 as typically seen in young adults after 10 years of age. In contrast, SPAD patients did not reveal such age-associated changes and showed decreased fluorescence intensity of CD86 in PDC cells. These results indicate lineage specific, age-dependent changes in DC subsets in normal children and possible altered development of these cells in SPAD children, emphasizing the importance of age-appropriate controls.

Keywords Dendritic cells (DCs) · Plasmacytoid DC · Myeloid DC · Specific polysaccharide antibody deficiency (SPAD) · CD86

H. Jyonouchi (✉) · L. Geng
Division of Allergy/Immunology and Infectious Diseases,
Department of Pediatrics, UMDNJ-NJMS,
185 South Orange Ave.,
Newark, NJ, USA
e-mail: jyanouha@umdnj.edu

C. Cui · Z. Yin · P. Fitzgerald-Bocarsly
Department of Pathology and Laboratory Medicine,
UMDNJ-NJMS,
185 South Orange Ave.,
Newark, NJ, USA

Introduction

Dendritic cells (DCs) were initially recognized as professional antigen-presenting cells (APC) that engage in antigen (Ag) uptake, processing, and transport to the peripheral lymphoid organs where they present the processed Ag to T lymphocytes. DCs play a crucial role in initiating adaptive immune responses and are also essential for controlling the magnitude and the quality of adaptive immune responses [30]. Human DCs are negative for markers specific for T, B, natural killer (NK), and monocyte lineage cells and are human leukocyte antigen (HLA)-DR^{+}. There are two major subsets of peripheral blood (PB) DCs that can be identified both by their expression of cell surface markers and by their functions: myeloid DCs (MDCs) and plasmacytoid DCs (PDCs).

MDCs function very effectively as professional APC and reside in the tissue, peripheral lymphoid organs, and PB [30]. Within the MDC population, there are two subpopulations characterized as MDC1 which express CD1c (BDCA-1) and MDC2 which express CD141 (BDCA-3, a C-type lectin also known as thrombomodulin), although the precise differences in the function of these subsets are not well-defined [7].

As opposed to MDCs, PDCs that express CD303 (BDCA-2) and CD123 are the most potent producers of

Published online: 15 May 2010

type 1 and III interferons (IFNs), sensing pathogen derived RNA and DNA via toll-like receptors (TLR) 7 and 9, as reviewed elsewhere [9, 30]. PDCs can also present Ags to T cells, albeit less effectively than MDCs. The PDCs' capability of producing vast amounts of type I IFNs has been implicated in their crucial role in anti-viral immunity, autoimmunity, and humoral immunodeficiency [2, 9, 30, 37].

DCs also play critical roles in B cell differentiation. MDCs are capable of directly presenting Ag to B cells in the extra-follicular region in the lymph node [3]. IL-12 secreted from MDCs can drive B cells into antibody (Ab)-secreting plasma cells along with IL-6 [30]. Isotype switching of B cells is promoted by molecules such as APRIL and BAFF expressed on MDCs [15, 17, 30]. PDCs can also affect B cell differentiation via production of type 1 IFNs and IL-6; type I IFNs initiate differentiation of B cells to plasmablasts and IL-6 promotes differentiation of B cells into Ab-secreting cells as reviewed by Fitzgerald-Bocarsly et al. [9]. Considering the critical roles of DCs in bridging innate and adaptive immunity, it is hardly surprising that changes in PB DCs occur in immunological disorders as reviewed elsewhere [5, 9, 30]. Likewise, decreased numbers of circulating DCs are reported in adult patients with primary immunodeficiency (PID) exhibiting impaired Ab production [34, 37].

A role of innate immunity in immune defense is especially important in the first few years of life until adaptive immunity develops fully upon gradual exposure to numerous antigens. With development of immune memory, the role of adaptive immunity increases as reflected in changes of numbers of PB T and B cell subsets. Given the different roles of the PDC and MDC subsets as described above, age-dependent changes of DC subsets are also likely to occur in children. However, although normative numbers of PDC and MDC have been established in adults, few studies have addressed development of DC subsets in children.

In this study, we hypothesized that age-associated changes in PDCs and MDCs differ considerably, given their roles in innate and adaptive immunity with PDCs bearing major first line defense against viral infection, while MDCs aid development of adaptive immunity by serving as professional APCs. We also hypothesized that such ‘presumed’ age-dependent changes are crucial for evaluating the disease-associated changes of DC subsets in children. In this study, we analyzed age-associated changes of DC subsets in normal children as well as children with specific polysaccharide Ab deficiency (SPAD). SPAD patients are characterized by impaired Ab formation against polysaccharide antigens with normal immunoglobulin (Ig) levels. Considering roles of DC subsets on B cell maturation, these children may exhibit significant changes in DC subsets as compared to age-appropriate controls. Our results revealed PDC- and MDC-specific age-associated changes in normal children, which appeared altered in SPAD children.

Materials and methods

Study subjects The study subjects included control children [N=50, 41 male and 9 female children; median age, 8.1 years (range, 0.5–18.8 years), 5 African Americans (AA), 6 Asians, 22 Caucasians, 14 Hispanics, and 3 mixed races] and children with SPAD [N=25, 15 male and 9 female children; median age, 13.0 years (range, 5.1–18.9 years), 7 AA, 2 Asians, 10 Caucasians, 5 Hispanics, and 1 mixed race]. These study subjects were recruited in the Pediatric Specialty Clinic at our institution. The blood samples were obtained after obtainment of the signed consent forms approved by the institutional review board at our institution. Prior to venipuncture, each study subject underwent physical examination to ensure that each individual is free from acute illnesses such as viral syndrome, asthma exacerbation, active ear infection/sinusitis, or active allergic symptoms. In these study subjects, 13/50 (26.0%) normal controls and 3/25 (12.0%) SPAD children were diagnosed with allergic rhinoconjunctivitis (AR) on the basis of the diagnostic criteria described elsewhere [4, 19]. In these subjects, the allergic condition was under control at the time of venipuncture. We did not observe significant changes in DC subsets between non-AR and AR controls when compared in three age groups (<5, 5–9, and 10–18 years).

Evaluation of SPAD Evaluation of SPAD included measurement of serum levels of Ig, IgG subclasses, Ab titers to polysaccharide/protein Ags, and enumeration of T and B cell subsets including memory B cell numbers (IgD^-, $CD27^+$, and $CD19^+$ cells) [1, 33, 34]. SPAD was defined as a lack of Ab responses against 23-valent pneumococcal vaccine (Pneumovax®) despite normal Ig levels and B cell numbers [12, 20]. All these SPAD patients revealed >2 fold increase of Ab titers in less than three serotypes among 14 serotypes tested. All these patients failed prophylactic antibiosis and are currently on supplemental Ig treatment intravenously or subcutaneously. Supplemental Ig treatment successfully controlled infectious diseases in these children. SPAD patients suffering from non-atopic asthma were off oral corticosteroid for at least 2 weeks prior to blood sampling. It is of note that three of these SPAD patients developed hypogammaglobulinemia over 2–3 years after SPAD diagnosis, fulfilling the diagnostic criteria of common variable immunodeficiency (CVID) [36].

Flow cytometry DCs in whole blood were enumerated using a commercially available kit according to the manufacturer's recommendations (Blood Dendritic Cell Enumeration Kit, Miltenyi Biotc, Auburn, CA, USA) [7]. MDC1, PDC, and MDC2 subsets were identified by staining them with the monoclonal antibodies BDCA1 (CD1c)-PE, BDCA-2 (CD303)-FITC, and BDCA-3-APC, respectively. A total of 6×10^5 cells were enumerated in each sample by flow cytometry. Absolute numbers of DCs of each subset per milliliter of blood were calculated on the basis of WBC count/ml blood and percentages of DC subsets. For CD40 and CD86 expressions by PDC, PDC were first identified with CD123-PE (BioLegend, San Diego CA) and BDCA2-APC (Miltenyi). CD40 and CD86 expressions were assessed by staining cells with CD40-FITC or CD86-FITC along with IgG-FITC isotype control (BioLegend). Memory B cells (IgD^-, $CD27^+$, and $CD19^+$ B cells) were detected by staining with anti-CD45-PITC, anti-CD19-APC-Cy7, CD27-APC (all from BD biosciences, San Jose CA), and IgD-PE (DAKO, Carpinteria, CA) monoclonal antibodies [36]. All flow cytometry was conducted by using FACS Caliber (BD Biosciences), and the data were analyzed with the CellQuest software (BD Biosciences).

Statistics For comparison of test values with control values, a Wilcoxon signed rank test was used. For comparison of values of multiple groups, a Kruskal–Wallis test was used. Assessment of difference of frequency was tested with a Chi square (χ^2) test. Correlation was tested by using a linear regression analysis. These tests were performed using R.2.10.1 (R-Development Core Team 2009). A p value of <0.05 was considered to be statistically significant.

Results

Normal children PDC numbers were higher in young children than older children, revealing an age-dependent decrease (RR=0.3831, $p<0.0001$ by linear regression analysis) (Fig. 1). MDC1 and MDC2 numbers did not reveal such linear age-dependent changes, but MDC1 cell numbers were higher in children with 3–6 years of age than older children ($p<0.01$). After 10 years of age, their levels tended to stabilize to the levels typically seen in young adults [8] (Figs. 2 and 3). As a result, the ratio of MDC1/PCD was low in young children and seemed to stabilize at around 2.0 after 10 years of age (Fig. 4), ratios typically seen in young adults [8]. Expression or fluorescence intensity of CD40, an activation/maturation marker, on PDCs varied considerably in individuals, but no age-dependent changes were observed (data not shown). Frequency of expression of activation marker (CD86) was generally less than 10% in PDCs without age-dependent changes (data not shown). Fluorescence intensity of CD86 expression did not change with age either (Fig. 6).

SPAD patients No age-dependent changes were observed in DC subsets or MDC1/PDC ratio (Figs. 1, 2, 3, and 4) in the SPAD children (age, 5–18 years). This may be associated with the fact that the median age of SPAD children was higher than normal control children (8.1 vs 13.0 years). When we compared the numbers of MDC/PDC cells with age-appropriate normal controls (5–9 and 10–18 years), there was no statistical difference in PDC and MDC1 cell numbers between SPAD and control children. We observed a positive association between PDC/MDC2 cell and isotype-switched memory B cell numbers in SPAD children (Fig. 5); three subjects who developed CVID were excluded in this analysis. Neither expression nor fluorescence intensity of CD40 and CD86 changed with age in SPAD children. However, fluorescence intensity of CD86 was lower in SPAD children as compared to age-appropriate normal controls (5–17 years) (Fig. 6 $p<0.05$).

Discussion

The recent availability of a commercial DC staining kit has made it possible to analyze DC subsets in a standardized

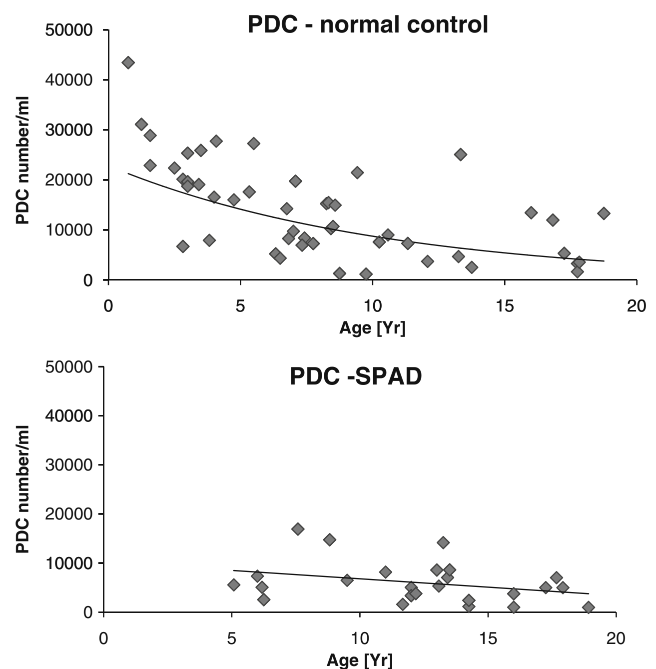

Fig. 1 Changes of PDC numbers in normal and SPAD children. PDC cell numbers declined with age in normal children (R-square= 0.4758, $p<0.0001$ by linear regression analysis)

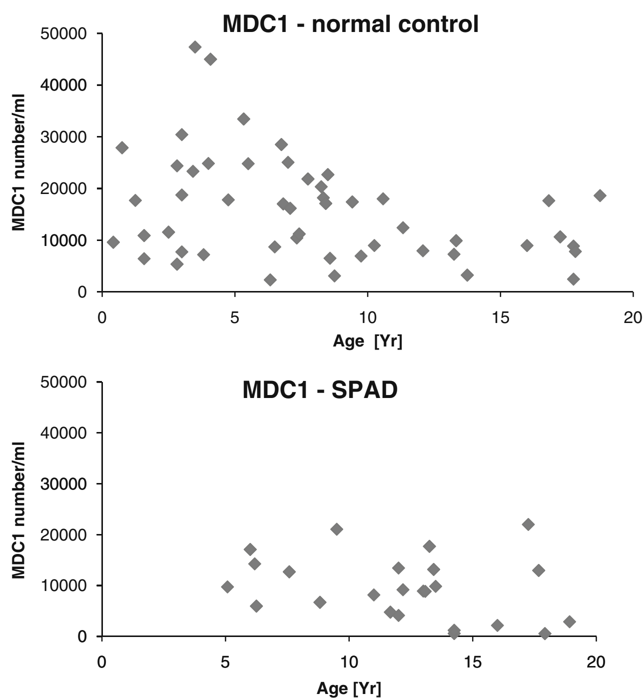

Fig. 2 Changes of MDC1 numbers with age in normal children and SPAD children. MDC1 cell numbers did not reveal linear decline with age unlike PDC cells in either normal or SPAD children

manner for various medical conditions. PDCs, MDC1s, and MDC2s identified on the basis of expression of BDCA2, BDCA1, and BDCA3 has been characterized in human PB [7, 14, 16]. In contrast to PDCs vs MDCs, distinct functional difference between MDC1 and MDC2 subsets

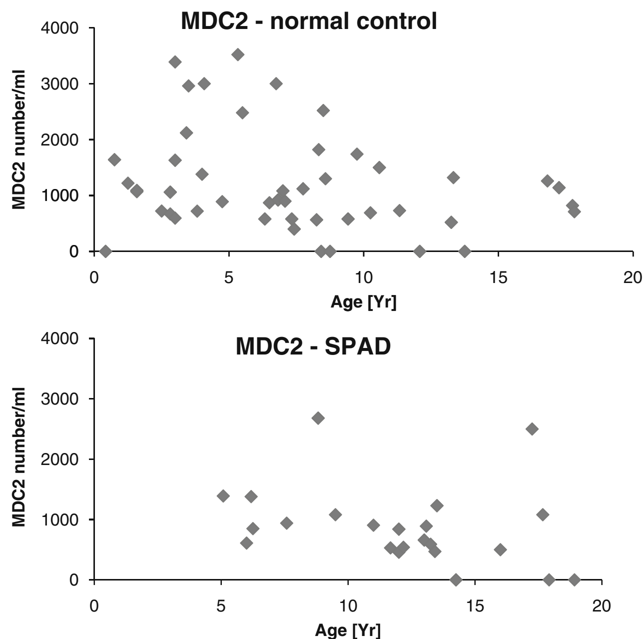

Fig. 3 Changes in MDC2 numbers in normal children and SPAD children. Changes of MDC2 cells are similar to those of MDC1 cells in control children

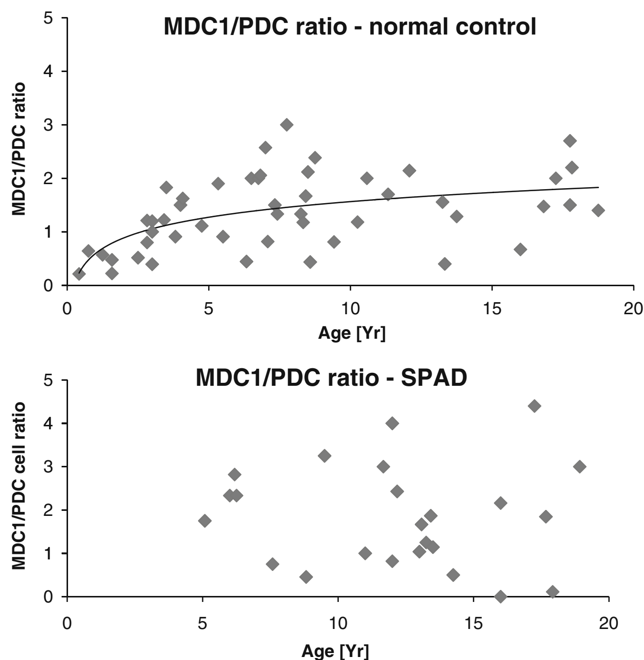

Fig. 4 Changes in MDC1/PDC ratio in normal control and SPAD children

are not well understood. Nevertheless, despite significant overlap of gene expression between the MDC1 and MDC2 subsets, there exists selective transcription of several genes specific for each of the MDC1 and MDC2 subsets [14].

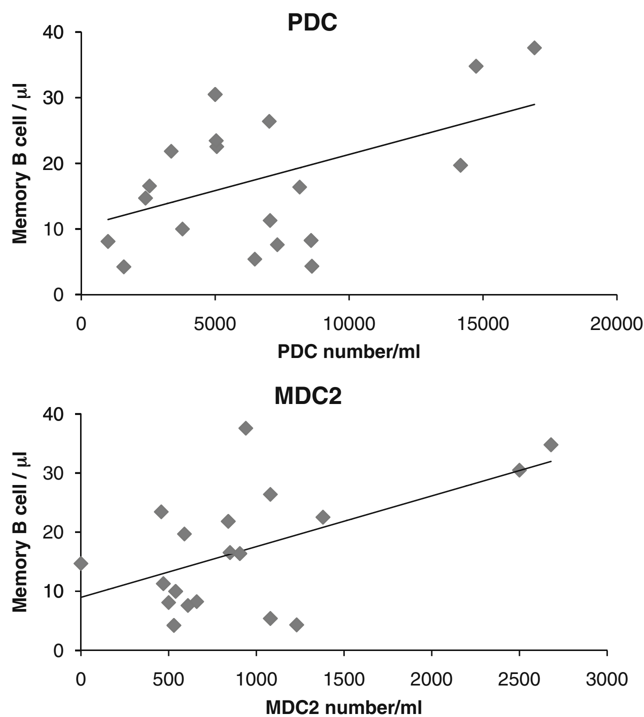

Fig. 5 Positive association between PDC/MDC2 cell and isotype-switched memory (IgD^-, $CD27^+$, $CD19^+$) B cell numbers in children with SPAD (R-square=0.2102, p<0.05 for PDC and R-square=0.308, p<0.02 for MDC1 by linear regression analysis)

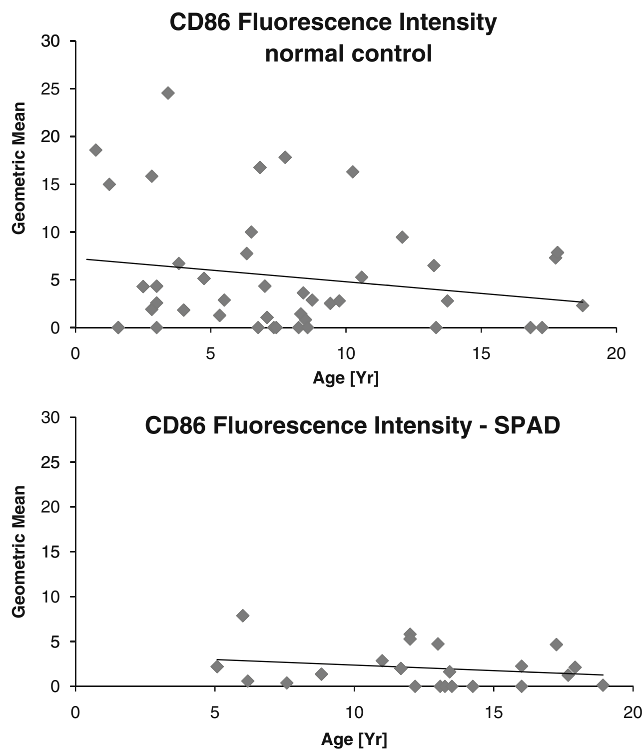

Fig. 6 Changes in CD86 fluorescence intensity (geometric mean) with age in normal control children and patients with Ab deficiency. No age-associated changes were observed but fluorescence intensity is lower in patients with Ab deficiency ($p<0.02$ Wilcoxon signed rank test)

This methodology has been used to assess the distribution of DC subsets in individuals with autoimmune diseases and immunodeficiency and yielded significant results [5, 10, 11, 13, 22, 24, 37]. In autoimmune diseases, decreased numbers of circulating DC subsets are generally observed, which is attributed to migration of DC subsets to the site of inflammation [13, 22]. In addition, decreased circulating DC cell subsets in patients with kidney transplants and diabetes are implicated with long-term immunosuppression by immunomodulating agents and/or metabolic impairment [10, 11, 24].

The primary role that the PDC subset plays in viral infection is well-established. In patients with human immunodeficiency virus (HIV) 1 infection that have undergone antiviral treatment, incomplete reconstitution of the PDC subset has been associated with the decreased production of type 1 IFNs and increased susceptibility to opportunistic infection [23]; this is consistent with our previous results [8, 26]. Thus, the enumeration of DC cell subsets in pediatric immunological diseases will likely provide important information and be helpful for assessing the roles of MDC1 and MDC2 subsets. However, to assess changes in circulating DC subsets properly, age-appropriate controls are essential. This is particularly important in the youngest patients due to rapid evolution of the immune system in the first few years of life.

To date, age-dependent DC subsets in pediatric population have not been well elucidated. Two previous reports that examined only numbers of PDCs and utilized different methodology for detection of PDCs revealed decline of PDC numbers with age [29, 33]. Using the same methodology employed in our study, Chen et al. reported a decline in the frequency (%) of PDCs but not MDCs with age in 75 normal controls (age, 1–65 years) [5]. However, the number of children tested in their study was limited, since 42 subjects were reported to be under 30 years old without specification of age ranges of children included in the study. A study involving young children (0.5–5 year) also reported a higher frequency of PDCs than MDCs in infants of 6 months of age [31]. However, in these studies, changes in absolute numbers of DC subsets were not explored. Secondary to higher WBC counts in young children, absolute numbers of DC subsets are likely to change more drastically than frequency of DC subsets and will be more informative for evaluation of alternation of DC subsets in various diseases in children.

In the current study, we observed a decline in PDC numbers (absolute number) with age in 50 normal children (age, 0.5–18.8 years), consistent with previous reports [5, 29, 33]. In contrast to PDCs, we did not observe such linear age-associated changes in MDC1/MDC2 numbers. Numbers of MDC subsets appeared to be higher at 3–6 years of age and then stabilize at the levels typically seen in young adults around 10 years of age. However, larger numbers of normal controls will be required to further address detailed age-related changes in MDC subsets. As a consequence, the MDC1/PDC ratio stabilized at approximately 2.0 after 10 years of age. Due to this age-dependent decline of PDCs, we also examined markers of activation/maturation (CD40) and activation (CD86) in PDCs. However, we did not observe age-dependent changes in expression of CD40 or CD86. Taken together, our results revealed significant age-dependent changes of numbers in DC subsets, differing in PDC and MDC subsets. Our results are consistent with previous evidence that PDC and MDC subsets belong to different cell lineages [18]. The difference in age-dependent changes in PDC vs MDC subsets may reflect their physiological roles in immune defense [9, 30].

Changes in circulating DC subsets in pediatric immunological diseases have been reported in a few conditions. In patients with juvenile idiopathic arthritis, circulating DC subsets decreased in parallel to enrichment of DCs in synovial fluid [28]. In 23 children with HIV-1 infection, persistently decreased PB PDC and MDC numbers were reported as compared to age-matched uninfected controls [32]. In the study addressing a role of RSV bronchiolitis in early life in the development of asthma, a lower frequency of circulating PDCs in severe RSV bronchiolitis was associated with a diagnosis of asthma 6 years after [27].

In these studies, neither age-associated changes nor absolute numbers of DC subsets were examined in the study subjects. This may be due to the ages of the study population or insufficient numbers of normal controls.

To address the importance of age-appropriate controls, we studied the distribution of circulating DC subsets in SPAD patients (age, 5–18 years). Consistent with roles of PDC and MDC subsets in B cell development, DC subsets are reported to be lower in common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) as described in the "Introduction" section [37]. They also reported a positive association between numbers of the DC cells and memory B cells in CVID patients [37]. However, this is not the case in adult SPAD patients [37]. Thus, we hypothesized that we may observe alterations in age-associated changes in circulating DC subsets in SPAD children, even if their absolute numbers remain in normal range.

Our results revealed noticeably different patterns in the distribution of circulating DC subsets in SPAD patients. First, age-associated changes were not observed in SPAD children (age, 5–18 years). This may be associated with the fact that the SPAD patients studied are older; SPAD is not typically diagnosed until 4–5 years of age, and this reflects the older age of SPAD children in this study. PDC/MDC numbers remained within normal range in SPAD children as compared to age-appropriate controls, although older SPAD children (10–18 years) revealed a tendency of low normal levels of PDC/MDC numbers. In addition, the SPAD patients (5–18 years) did not reveal stabilization of MDC1/PDC ratio at around 2.0 after 10 years of age as opposed to normal controls. In our study population, 19/24 SPAD patients suffered from non-atopic asthma, and many of them had a history of chronic rhinosinusitis. Thus, a lack of age-dependent changes in DC subsets in SPAD patients may reflect the recruitment of DC cells to the site of inflammation in some SPAD patients. However, it should be noted that at the time of blood sampling, all the study subjects were all in stable condition without active infection or asthma exacerbation. Alternatively, these findings may be associated with the heterogeneity of the pediatric SPAD patients. In some children, SPAD may be the initial diagnosis, but immunoglobulin levels may decline over time, evolving into CVID. We observed three such cases in our SPAD study population.

CVID patients with lower isotype-switched B cell numbers are known to reveal more severe clinical features along with frequent autoimmune complications [1, 35, 36]. In SPAD, severe clinical features were also associated with lower numbers of isotype-switched memory B cells in both children and adults [1, 36]. Thus, some of our SPAD patients, especially those with lower isotype-switched memory B cell numbers may eventually progress to profound hypogammaglobulinemia or CVID. Our results indicating a positive association between PDC and isotype-switched memory B cell numbers support this possibility.

In SPAD patients (5–18 years), a decrease in fluorescence intensity of CD86 in PDCs were observed despite the fact that these patients had a history of frequent infection and were likely to be exposed to more pathogens than normal controls (Fig. 6). This finding may indicate impaired PDC cell functions in the SPAD children. However, it should be cautioned that our study as well as those cited addressing DC subsets in CVID/SPAD patients are all cross-sectional studies. Prospective studies evaluating functions and numbers of DC subsets and memory B cells may be more informative in assessing roles of DC subsets in SPAD children.

In summary, our results demonstrated the importance of addressing age-associated differences in DC subsets in children. Decline of DC subsets was also reported in elderly population [5, 6, 21, 25]. Therefore, when evaluating DC subsets, it may be necessary to have age-appropriate controls in both adults and children.

Acknowledgement This study was partly supported by Jonty Foundation, St. Paul, MN and the NIH (AI26806 funded to PFB).

References

1. Alachkar H, Taubenheim N, Haeney MR et al (2006) Memory switched B cell percentage and not serum immunoglobulin concentration is associated with clinical complications in children and adults with specific antibody deficiency and common variable immunodeficiency. Clin Immunol 120:310–318
2. Banchereau J, Pascual V (2006) Type I interferon in systemic lupus erythematosus and other autoimmune diseases. Immunity 25:383–392
3. Batista FD, Harwood NE (2009) The who, how and where of antigen presentation to B cells. Nat Rev Immunol 9:15–27
4. Butrus S, Portela R (2005) Ocular allergy: diagnosis and treatment. Ophthalmol Clin North Am 18:485–492
5. Chen X, Makala LH, Jin Y et al (2008) Type 1 diabetes patients have significantly lower frequency of plasmacytoid dendritic cells in the peripheral blood. Clin Immunol 129:413–418
6. Della Bella S, Bierti L, Presicce P et al (2007) Peripheral blood dendritic cells and monocytes are differently regulated in the elderly. Clin Immunol 122:220–228
7. Dzionek A, Fuchs A, Schmidt P et al (2000) BDCA-2, BDCA-3, and BDCA-4: three markers for distinct subsets of dendritic cells in human peripheral blood. J Immunol 165:6037–6046
8. Feldman S, Stein D, Amrute S et al (2001) Decreased interferon-alpha production in HIV-infected patients correlates with numerical and functional deficiencies in circulating type 2 dendritic cell precursors. Clin Immunol 101:201–210
9. Fitzgerald-Bocarsly P, Dai J, Singh S (2008) Plasmacytoid dendritic cells and type I IFN: 50 years of convergent history. Cytokine Growth Factor Rev 19:3–19
10. Hackstein H, Renner FC, Bohnert A et al (2005) Dendritic cell deficiency in the blood of kidney transplant patients on long-term immunosuppression: results of a prospective matched-cohort study. Am J Transplant 5:2945–2953

11. Hinkmann C, Knerr I, Hahn EG et al (2008) Reduced frequency of peripheral plasmacytoid dendritic cells in type 1 diabetes. Horm Metab Res 40:767–771
12. IUIS Scientific Committee Committee (1999) Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. Clin Exp Immunol 118(Suppl 1):1–28
13. Jongbloed SL, Lebre MC, Fraser AR et al (2006) Enumeration and phenotypical analysis of distinct dendritic cell subsets in psoriatic arthritis and rheumatoid arthritis. Arthritis Res Ther 8: R15
14. Lindstedt M, Lundberg K, Borrebaeck CA (2005) Gene family clustering identifies functionally associated subsets of human in vivo blood and tonsillar dendritic cells. J Immunol 175:4839–4846
15. Litinskiy MB, Nardelli B, Hilbert DM (2002) DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat Immunol 3:822–829
16. MacDonald KP, Munster DJ, Clark GJ et al (2002) Characterization of human blood dendritic cell subsets. Blood 100:4512–4520
17. MacLennan I, Vinuesa C (2002) Dendritic cells, BAFF, and APRIL: innate players in adaptive antibody responses. Immunity 17:235–238
18. Naik SH (2008) Demystifying the development of dendritic cell subtypes, a little. Immunol Cell Biol 86:439–452
19. Nassef M, Shapiro G, Casale TB (2006) Identifying and managing rhinitis and its subtypes: allergic and nonallergic components—a consensus report and materials from the Respiratory and Allergic Disease Foundation. Curr Med Res Opin 22:2541–2548
20. Paris K, Sorensen RU (2007) Assessment and clinical interpretation of polysaccharide antibody responses. Ann Allergy Asthma Immunol 99:462–464
21. Perez-Cabezas B, Naranjo-Gomez M, Fernandez MA et al (2007) Reduced numbers of plasmacytoid dendritic cells in aged blood donors. Exp Gerontol 42:1033–1038
22. Robak E, Smolewski P, Wozniacka A et al (2004) Clinical significance of circulating dendritic cells in patients with systemic lupus erythematosus. Mediators Inflamm 13:171–180
23. Sachdeva N, Asthana V, Brewer TH et al (2008) Impaired restoration of plasmacytoid dendritic cells in HIV-1-infected patients with poor CD4 T cell reconstitution is associated with decrease in capacity to produce IFN-alpha but not proinflammatory cytokines. J Immunol 181:2887–2897
24. Seifarth CC, Hinkmann C, Hahn EG et al (2008) Reduced frequency of peripheral dendritic cells in type 2 diabetes. Exp Clin Endocrinol Diabetes 116:162–166
25. Shodell M, Siegal FP (2002) Circulating, interferon-producing plasmacytoid dendritic cells decline during human ageing. Scand J Immunol 56:518–521
26. Siegal FP, Fitzgerald-Bocarsly P, Holland BK, Shodell M (2001) Interferon-alpha generation and immune reconstitution during antiretroviral therapy for human immunodeficiency virus infection. AIDS 15:1603–1612
27. Silver E, Yin-DeClue H, Schechtman MB et al (2009) Lower levels of plasmacytoid dendritic cells in peripheral blood are associated with a diagnosis of asthma 6 yr after severe respiratory syncytial virus bronchiolitis. Pediatr Allergy Immunol 20:471–476
28. Smolewska E, Stanczyk J, Brozik H et al (2008) Distribution and clinical significance of blood dendritic cells in children with juvenile idiopathic arthritis. Ann Rheum Dis 67:762–768
29. Teig N, Moses D, Gieseler S, Schauer U (2002) Age-related changes in human blood dendritic cell subpopulations. Scand J Immunol 55:453–457
30. Ueno H, Klechevsky E, Morita R et al (2007) Dendritic cell subsets in health and disease. Immunol Rev 219:118–142
31. Upham JW, Zhang Z, Rate A et al (2009) Plasmacytoid dendritic cells during infancy are inversely associated with childhood respiratory tract infections and wheezing. J Allergy Clin Immunol 124:7070–713
32. Usuga X, Montoya CJ, Landay AL, Rugeles MT (2008) Characterization of quantitative and functional innate immune parameters in HIV-1-infected Colombian children receiving stable highly active antiretroviral therapy. J Acquir Immune Defic Syndr 49:348–357
33. Vakkila J, Thomson AW, Vettenranta K et al (2004) Dendritic cell subsets in childhood and in children with cancer: relation to age and disease prognosis. Clin Exp Immunol 135:455–461
34. Viallard JF, Camou F, Andre M et al (2005) Altered dendritic cell distribution in patients with common variable immunodeficiency. Arthritis Res Ther 7:R1052–R1055
35. Warnatz K, Denz A, Drager R et al (2002) Severe deficiency of switched memory B cells (CD27(+)IgM(−)IgD(−)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood 99:1544–1551
36. Wehr C, Kivioja T, Schmitt C et al (2008) The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood 111:77–85
37. Yong PF, Workman S, Wahid F et al (2008) Selective deficits in blood dendritic cell subsets in common variable immunodeficiency and X-linked agammaglobulinaemia but not specific polysaccharide antibody deficiency. Clin Immunol 127:34–42