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*J Immunol* 2010; 184:5368-5374; Prepublished online 31 March 2010;
doi: 10.4049/jimmunol.0903662
http://www.jimmunol.org/content/184/9/5368

Supplementary Material http://www.jimmunol.org/content/suppl/2010/03/31/jimmunol.0903662.DC1

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An Imbalance of Two Functionally and Phenotypically Different Subsets of Plasmacytoid Dendritic Cells Characterizes the Dysfunctional Immune Regulation in Multiple Sclerosis

Nicholas Schwab,*1 Alla L. Zozulya,*1,2 Bernd C. Kieseier,† Klaus V. Toyka,* and Heinz Wiendl§

Plasmacytoid dendritic cells (pDCs) are instrumental in peripheral T cell tolerance and innate immunity. How pDCs control peripheral immunotolerance and local parenchymal immune response and contribute to the altered immunoregulation in autoimmune disorders in humans is poorly understood. Based on their surface markers, cytokine production, and ability to prime naïve allogenic T cells, we found that purified BDCA-2^BDCA-4^ pDCs consist of at least two separate populations, which differed in their response to oligodeoxynucleotides and IFNs (IFN-β), and differently induced IL-17– or IL-10–producing T cells. To evaluate the potential immunoregulatory role of these two types of pDCs in multiple sclerosis (MS) and other human autoimmune disorders (myasthenia gravis), we studied the phenotype and regulatory function of pDCs isolated from clinically stable, untreated patients with MS (n=16). Patients with MS showed a reversed ratio of pDC1/pDC2 in peripheral blood (4.4:1 in healthy controls, 0.69:1 in MS), a phenomenon not observed in the other autoimmune disorders. As a consequence, MS pDCs had an overall propensity to prime IL-17–secreting cells over IL-10–secreting CD4^ T cells. Immunomodulatory therapy with IFN-β induced an increase of the pDC1 population in vivo (n=5). Our data offer a plausible explanation for the disturbed immune tolerance in MS patients and provide evidence that immunomodulatory therapy acts at the level of reconstituting homeostasis of pDC, thus reconstituting the disturbed balance. The Journal of Immunology, 2010, 184: 5368–5374.

Plasmacytoid dendritic cells (pDCs) are considered to be safeguards of peripheral T cell tolerance and key players in innate immunity (1, 2). During immunoregulation, pDCs have both stimulatory (3, 4) and regulatory (5–7) effects on T cells. However, little is known regarding the contribution of pDCs to the balance of T cell activation during autoimmunity in the periphery or in the local control of immune reactions in inflamed tissue.

Multiple sclerosis (MS) is a chronic inflammatory disease of the CNS and is thought to be autoimmune in nature (8–10). The combination of genetic and environmental factors predisposes to disease susceptibility, severity, and course. Because of their tolerogenic and immunogenic functions, pDCs are assumed to play an important role in the immunoregulatory network in MS. A first hint to functional abnormalities of pDCs isolated from the peripheral blood of MS patients has been described previously (11).

pDCs are rarely detected in the CNS under nonpathologic conditions, but they are elevated under neuroinflammatory conditions (including MS) in the cerebrospinal fluid (12). Active recruitment of pDCs into the CNS and their accumulation in white matter lesions and leptomeninges of MS brains has also been demonstrated (13). In experimental autoimmune encephalomyelitis, an animal model of human MS, a critical tolerogenic effect of pDCs was demonstrated (14). Unlike myeloid DCs, pDCs had only a minor role in T cell activation and epitope spreading, but negatively regulated pathogenic CNS CD4^ T cell responses, suggesting a regulatory role during experimental neuroinflammation (14). However, it has to be noted critically that the exact mechanism of pDC accumulation and their role during CNS inflammation are not well understood.

In this study, we provide a detailed characterization of two phenotypically and functionally different subsets of pDCs in human peripheral blood using specific markers for pDCs (15). These subsets (pDC1 and pDC2) clearly differ in their properties to induce proinflammatory versus regulatory T cell responses. We noted that MS is characterized by a different distribution of those pDC subsets in the periphery, which results in a high propensity of MS-derived pDCs to generate IL-17 over IL-10–producing CD4^ T cells in vitro. Immunomodulatory therapy with IFN-β (an established standard treatment of MS) was capable to reverse the altered pDC distribution in vivo. Our data therefore suggest that the alterations in pDC subsets might be responsible for the failure of immunotolerance in MS patients.
Materials and Methods

Patients
Fresh blood samples were obtained from 16 patients referred to the Department of Neuroradiology (University of Wuerzburg). Diagnoses of MS were made according to the criteria of McDonald et al. (16). Patients included in the study were clinically stable and had not yet received immunomodulatory treatment except for corticosteroids, with the last dose at least 6 mo prior to sampling (Fig. 1A). In addition, we included five patients who were in remission (no relapse for at least 6 mo). IFN-β and were followed for 12 mo. All patients gave informed consent in accordance with the Declaration of Helsinki and a protocol approved by the Ethics Committee of the University of Wuerzburg Medical School.

Isolation and stimulation of pDCs

pDCs were purified from freshly collected peripheral blood samples (~24 h processing time). PBMCs were isolated by density gradient centrifugation using lymphocyte separation medium (PAA Laboratories, Linz, Austria) followed by positive sorting using anti–BDCA-4–conjugated magnetic beads (Miltenyi Biotec, Bergisch-Gladbach, Germany). The purity of the recovered pDCs was determined by flow cytometry and was >90%. Where indicated, BDCA-4–isolated pDCs were stained with anti-CD123/anti-CD58 and sorted by flow cytometry based on CD123highCD58low (named pDC1) expression and CD123lowCD58high (named pDC2) using a fluorescence-activated cell sorter (MoFlo; Cytomation, Freiburg, Germany).

Ex vivo isolated or cultured pDCs were washed with FACS-buffer (PBS supplemented with 1% BSA and 0.1% sodium azide) and stained with fluorescence-labeled mAbs together with blocking mouse IgG (Sigma-Aldrich, Munich, Germany) at a concentration of 2 × 10^5 per well in RPMI 1640 (PAA, Linz, Austria) supplemented with 2 mmol/l L-glutamine, 1% penicillin/streptomycin (Invitrogen, Karlsruhe, Germany), and 10% human AB serum (AB serum; PAA) for 30 min. Cells then were analyzed using CellQuest software with a FACSCalibur (Becton Dickinson Biosciences, Heidelberg, Germany) and FlowJo (Tree Star, Ashland, OR) software. The following mAbs were used for counterstaining of BDCA-4+–isolated pDCs: anti–HLA-DR (L243; BD Biosciences), anti–CD123 (9F5, BD Pharmingen), anti–ILT2 (L243; BD Biosciences), anti–ILT3, anti–ILT4, anti–CD80, CD86, MHCII, TLRs, ICOS-L), this population was not specified otherwise in results. IFN-β concentration was 1000 U/ml.

Flow cytometry

Ex vivo isolated or cultured pDCs were washed with FACS-buffer (PBS supplemented with 1% BSA and 0.1% sodium azide) and stained with fluorescence-labeled mAbs together with blocking mouse IgG (Sigma-Aldrich, Munich, Germany) at 4˚C for 30 min. Cells then were analyzed using CellQuest software with a FACSCalibur (Becton Dickinson Biosciences, Heidelberg, Germany) and FlowJo (Tree Star, Ashland, OR) software. The following mAbs were used for counterstaining of BDCA-4+–isolated pDCs: anti–HLA-DR (L243; BD Biosciences), anti–CD123 (9F5, BD Pharmingen), anti–ILT2 (HF-PI), anti–ILT3 (ZM 3.8), anti–ILT4 (4D21), all Beckman Coulter, Krefeld, Germany, and anti–CD86 (2363, BD Pharmingen), anti–CD58 (1C3, BD Pharmingen), anti–BDCA-1 (AD5-8E7, Miltenyi Biotec), anti–BDCA-2 (AC144; Miltenyi Biotec), anti–BDCA-3 (AD5-14H2; Miltenyi Biotec), and anti–BDCA-4 (AD5-17F6, Miltenyi Biotec).

Immature pDCs, cells that were fixed and permeabilized (BD Biosciences) according to the manufacturer’s protocol and then stained for 30 min at 4˚C. The following mAbs were used for intracellular staining: anti–IFN-α (LT27; 295; Miltenyi Biotec), anti–TNF-α (cA2; Miltenyi Biotec), and anti–IL-6 (A512; BD Biosciences), anti–IL-10 (B-T10, Miltenyi Biotec), anti–IL-17 (eBio64DEC17; eBiosciences, Frankfurt, Germany), anti–IFN-γ (45-15, Miltenyi), anti–TLR3 (TLR3.7, eBiosciences), anti–TLR7 (IMGENEX via Biomol, Hamburg, Germany), anti–TLR8 (44C143, IMGENEX), and anti–TLR9 (eB72-1665, eBiosciences). Before fixation, the cells were counterstained with anti–CD123 (9F5, BD Pharmingen).

T cell priming assays

PBMCs from HDs were isolated using lymphocyte separation medium (PAA) and washed twice with PBS. CD4+ T cells were purified by negative isolation from PBMCs using magnetic beads (Miltenyi Biotec) and following the manufacturer’s instructions. CD54RA+T cells (allogenic) were isolated from the purified CD4+ T cell population using anti-CD54RA microbeads (Miltenyi Biotec). T cell subsets were >95% pure as controlled by flow cytometry analysis (the contaminating cells were CD4+CD45RA+). Cells were cultured in 96-well plates (6 × 10^4 per well) with or without allogeneic sorted pDCs (3 × 10^4 per well). Either the entire population of BDCA4+ pDCs or the flow cytometry–sorted subpopulations (pDC1 or pDC2) were used as APCs for the priming of T cells. After 7 d, cells were collected and the secretion of IFN-γ, IL-17, and IL-10 was detected by intracellular cytokine staining following a 4 h T cell restimulation with 50 ng/ml PMA plus 2 μg/ml ionomycin together with 10 μg/ml brefeldin A (BD Pharmingen).

Statistical analysis

Statistical significance of differences was determined by ANOVAs without assuming Gaussian distribution (Kruskal-Wallis test) and subsequent Dunn’s multiple comparison test. Differences were considered statistically significant with p values < 0.05 and highly significant with *p < 0.01 and **p < 0.001. Software for statistical assessment was Prism 5 (GraphPad).

Results

Purified pDCs contain at least two phenotypically different subsets

pDCs represent a population of DCs with relatively low frequency (~0.4%) in human peripheral blood (1). Recently, two additional markers (BDCA-2 and BDCA-4) were identified with a restriction to human pDCs in peripheral blood and bone marrow (15). Since then, these markers have been used widely to identify and purify pDCs from human blood. We found that pDCs purified by BDCA-4+ contain at least two distinct subpopulations in the peripheral blood of HDs that can be identified based on the cell size and granularity (Fig. 1A, left panel). Using mAb to CD123 (IL-3Rα) we could distinguish between CD123high (pDC1 subset) and CD123low cells (pDC2 subset). A subpopulation that was negative for CD123 expression could also be identified (Fig. 1A, left panel). Because CD123 negative cells were also negative for other important cell surface proteins (e.g., CD80, CD86, HMCII, TLRs, ICOS-L), this population was not studied in detail here.

Further phenotypic analysis revealed a lower expression of HIC class II and other markers associated with DC maturation (e.g., CD86, TLR2, and CD58) by pDC1 in comparison with pDC2 (Fig. 1A, right panel). In addition to MHCII, CD123, and CD86, pDC1 and pDC2 differed in the expression of CD58, ILT2, ILT3, ILT4, CD1c, CD303, and TLR2 (Fig. 1A, right panel). No differences between pDC1 and pDC2 could be observed in the expression of TLR1, TLR3, TLR4, TLR5, TLR7, TLR8, and TLR9 (data not shown). To rule out the autofluorescence-nonspecific Ab binding common for matured DCs, isotype stains were performed differentially on pDC1 and pDC2 (Supplemental Fig. 1). The stains revealed a weak increase in the fluorochromes FITC, PE, and APC and some increase on pDC2 in the PE-Cy5-channel.

Functional differences in pDC1 and pDC2 subsets in response to stimulation

We also observed profound differences in the cytokine secretion by both pDC subsets (Fig. 1B). pDCs were analyzed either directly (no stimulus) or after stimulation using CpG4α (ODN 2216), which was shown to induce high amounts of IFN-α/β in pDCs, or CpG8 (ODN 2006), which strongly promotes pDC maturation and activation but induces only small amounts of IFN-α/β (17–19). Unlike CpG4α, pDC stimulation with CpG8 altered the pDC1/pDC2 ratio observed under noninflammatory conditions. CpG8 treatment stimulated a profound shift of total pDCs into pDC2, as indicated by lower expression of CD123 (Fig. 1B) and high expression of various maturation markers (not shown). In our assays, pDC1 was the main source of IFN-α under both steady state and proinflammatory stimulus delivered by CpGs, whereas pDC2 was a poor cytokine producer at a steady state and produced TNF-α upon CpG treatment (Fig. 1C, left and middle rows). TNF-α could be differentially induced in pDC1 in response to CpG4α and in pDC2 by CpG8 (Fig. 1C, middle and lower rows). pDC2 also produced more IL-6 than did pDC1 (data not shown). This behavior further corroborates our finding that pDCs in human blood contain at least two phenotypically different subsets.

We next studied whether the two identified pDC populations would change phenotype and/or function in response to CpGs. As already indicated in Fig. 1, pDC1 displayed a more immature

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phenotype with low expression of MHCII, CD86, and CD58 molecules. As a result, this cell population was more prone to mature upon CpG stimulation. CpG A and CpGB treatments both resulted in an increase of CD86 and MHCII expression by pDC1 with a percentage of double-positive cells increasing from 36% (unstimulated) to 58% (upon CpG A) and 83% (upon CpG B) (data not shown). pDC2 consistently revealed CD86 and MHCII expression before or after CpGs treatment (data not shown). Therefore, we suggest that CpG A activated total pDCs, but did not induce their maturation, whereas CpG B appeared to result in maturation of pDC1 into cells with pDC2 phenotype. Thus, blood-derived pDCs could be converted by CpGB into pDC2, whereas the immunomodulatory agent IFN-γ, had an opposite effect on pDCs, inducing a pDC1 phenotype (Fig. 2A).

After demonstrating the behaviors of pDC1 (CD123^{high}CD58^{low}) and pDC2 (CD123^{low}CD58^{high}) in response to different stimuli, and their relative changes, we were interested in the effects these cells could have under conditions of allogeneic T cell priming. Thus, we sorted pDC1 (CD123^{high}CD58^{low}) and pDC2 (CD123^{low}CD58^{high}) by flow cytometry from human blood-derived pDCs and directly cocultured them with allogeneic naive T cells. Interestingly, pDC1 induced 3.8-fold more IL-10–producing T cells (Tr1) (Fig. 2B) than did pDC2, whereas pDC2 induced 4.8-fold more IL-17–secreting IL-17–producing T cells (T H17) than did pDC1 (Fig. 2B). Because matured DCs are generally prone to reduced viability, we included 7-AAD staining to control the ability of pDC subsets to survive over time and under different experimental conditions. Although both pDC1 and pDC2 were stable and viable in culture under all conditions, CpGA treatment resulted in reduced viability of mainly pDC2 (Supplemental Fig. 2 and data not shown).
are representative of five independent experiments performed.

We next investigated the influence of prestimulated total pDCs (containing pDC1 and pDC2 subsets) on T cell priming in vitro to corroborate our previous observations. Total pDCs were isolated and treated with CpG A or CpG B for 48 h prior to coculture with allogeneic naive CD4+ T cells. After showing that CpG A does not alter the composition of pDCs (Fig. 2A), we compared how in vitro-shifted pDCs differed in the generation of Th17 type T cells when compared between HD and MS (Supplemental Fig. 3).

**pDC1/pDC2 distribution influences the generation of IL-10–producing T cells versus Tr1**

We next investigated the influence of prestimulated total pDCs (containing pDC1 and pDC2 subsets) on T cell priming in vitro to corroborate our previous observations. Total pDCs were isolated and treated with CpG A or CpG B for 48 h prior to coculture with allogeneic naive T cells. After showing that CpG A does not alter the composition of pDCs (Fig. 2A), we compared how in vitro-shifted pDCs differed in the T cell priming assay. CpG B-treated pDCs (therefore mainly consisting of pDC2; Fig. 2C, left panel) induced no Tr1 (Fig. 2C, right panel), and IFN-β–driven pDCs (therefore mainly consisting of pDC1) induced Tr1.

Moreover, we challenged the capability of general pDCs as well as pDC1 versus pDC2 differentially to induce FoxP3 regulatory T cells, as previously suggested (20). As a positive control, we used TGFβ, which has been reported to induce FoxP3-expressing cells under in vitro conditions (21). In our experimental settings, we did not observe the induction of FoxP3-expressing cells by pDC (data not shown).

**The ratio of pDC1 versus pDC2 is inverted in peripheral blood-derived pDCs of patients with MS**

To investigate whether MS might be associated with a disturbance of the pDC1/pDC2 ratio, we next evaluated phenotype and distribution of pDC1/pDC2 in peripheral blood of patients with MS. pDCs isolated from human peripheral blood of stable, untreated, relapsing-remitting MS cases were compared with HDs and another autoimmune disease (OD), MG. In HDs, the ratio of pDC1 to pDC2 was rather stable at an average number of 4.4 to 1 (pDC1 to pDC2: n = 21, range, 0.6:1–18.2:1; Fig. 3A). Interestingly, pDCs of patients with MS showed a reversed ratio of pDC1 to pDC2 (n = 16; average, 0.69:1; range, 0:1–1.81:1), which was not observed in OD. Patients with MG (n = 15), a prototypic Ab-mediated neurologic disorder, had a slightly altered pDC1/pDC2 balance in the same direction as MS (average ratio, 0.9:1), but this ratio did not reach the level of significance and the pDC1/pDC2 distribution was not as apparent as in MS blood samples (Fig. 3A). In addition, we investigated several patients with rheumatoid arthritis, where the pDC1/pDC2 ratio was not altered (data not shown). We did not observe significant differences in cell surface markers expression for both pDC1 and pDC2 when compared between HD and MS (Supplemental Fig. 3).

**Immunomodulatory treatment with IFN-β reconstitutes the pDC1/pDC2 imbalance in MS**

Because an inverted ratio of pDC1 to pDC2 toward pDC2 could be shown for patients with MS (Fig. 3A) and IFN-β treatment could induce a pDC1 phenotype in vitro (Fig. 2A), we finally questioned whether immunomodulatory therapy with IFN-β, a well-established basic therapy in clinical practice, would exert its effects by influencing the pDC phenotype. We investigated samples from MS cases that were serially acquired before and at different times during clinical treatment. Blood-derived pDCs were analyzed in the samples before IFN-β therapy and at 6 and 12 mo after treatment. Analogous to our observations in vitro, systemic IFN-β therapy resulted in
genic and tolerogenic properties during various immune responses.

showing a mature phenotype.

rather immature DC, whereas pDC2 behave similar to DC

g positive and IL-17/IFN-γ
cocultured directly with HD- or MS-derived pDCs (n = 4)
in whom this shift could be observed in differing frequencies (Fig. 6).

Acytokines by T cells.

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have not yet been analyzed in detail. Based on the size and acti-

23), distinct populations of pDCs as identified by specific markers

the overall pDC population in human blood (15, 22) and MS (11,

proinflammatory versus anti-inflammatory or regulatory T cell

in a certain ratio and have different effects on the generation of

pDC2 subsets. Under basal conditions, these subpopulations exist

a long-lasting effect on the pDC1 to pDC2 distribution, shifting

a high percentage of the pDC1 subset under steady-state conditions.

Thus, pDCs can induce Tr1 (26) and FoxP3+ (20) regulatory T cells in
direct coculture assays. Although we could not induce FoxP3
expression in naive T cells by pDC (data not shown), we observed
a generation of Tr1-type T cells through direct, cell-to-cell contact
dependent pDC interaction. Specifically, our results proved to be in
accordance with other work (26) showing that the pDC1 subset could
induce Tr1.

It is generally accepted that the functions of pDCs are not fixed,
but can be modulated by a variety of environmental factors (e.g.,
innate stimuli). Thus, pDC act as immune regulators and contain
a high percentage of the pDC1 subset under steady-state conditions.
However, under pathogenic conditions (e.g., with viral or other
inflammatory stimuli resulting in pDC maturation) pDCs effec-
tively switch into pDC2-containing immunogenic cell population
to presumably fight pathogens during infection (27).

IFN-β, an approved immunomodulatory drug for MS (28), had
a long-lasting effect on the pDC1 to pDC2 distribution, shifting
the ratio of the two subsets to a pDC1 phenotype in MS blood
samples. IFN-β–modulated pDCs with enhanced CD123 expression
and IL-10 production were previously described as a subset of
myeloid DCs (29–31). Interestingly, these cells resemble the
pDC1 subset described in this study and suggest that both pDC1
and pDC2 are a subset of plasmacytoid DCs and not, as hypoth-
esized earlier (22), a possible subtype of myeloid DCs.

An impaired maturation profile and a lower cytokine secretion
in response to innate stimulation of pDCs derived from patients
with MS have been demonstrated recently (11, 23). However, the
factors responsible for this impairment remained elusive, as was
the link with the disordered immunoregulation in MS. We found
a remarkable imbalance in the distribution of pDC1 versus pDC2
subsets in MS. Although the overall frequency of pDCs in per-
ipheral blood did not differ between MS and HDs, and the cell

Discussion

Our study addressed the questions of how human pDCs contribute
to the immune regulatory networks and how phenotype and func-
tion of blood-derived pDCs might differ in a common autoimmune
disorder of the CNS (i.e., MS) from healthy volunteers, thereby
providing a further hint to the immunopathogenesis of MS.

We could show that human peripheral pDCs contain at least two
major subpopulations, which we propose to be called pDC1 and
pDC2 subsets. Under basal conditions, these subpopulations exist
in a certain ratio and have different effects on the generation of
proinflammatory versus anti-inflammatory or regulatory T cell
responses. Although previous reports have recognized differences in
the overall pDC population in human blood (15, 22) and MS (11,
23), distinct populations of pDCs as identified by specific markers
have not yet been analyzed in detail. Based on the size and activ-
ation marker expression of pDCs under basal conditions (24, 25),
our data suggest that pDC1 (CD123highCD86 MHCIIm+)+
resemble rather immature DC, whereas pDC2 behave similar to DC
showing a mature phenotype.

Accumulating evidence suggests that pDCs exert both immuno-
genic and tolerogenic properties during various immune responses.

a recovery of the underrepresented pDC1 population in MS blood
(Fig. 4). In an extreme case, before therapy, there was no detectable
pDC1 population (Fig. 4A). The pDC1 population reached 39% after
6 mo and 52% after 12 mo of treatment. We examined five patients
in whom this shift could be observed in differing frequencies (Fig. 4B,
C). The first sign of a recovery of the pDC1-to-pDC2 ratio
could be observed as early as after 2 mo of therapy (data not shown).
Similar to earlier observations (11), this finding rules out that
the subset imbalance is a fixed abnormality not amenable to therapeutic
modification.

FIGURE 3. An inverted ratio of MS-derived pDC1 and pDC2 pop-
ulations directly correlates with increased production of IL-17 and IFN-γ
cytokines by T cells. A, The percentage of pDC1 (closed circle) and pDC2
(open circle) subpopulations within total pDCs from samples of HDs (n = 21),
clinically stable, untreated MS (n = 16), and MG (n = 15). The black
bars represent the mean for each group. B and C, The percentage of IL-17–
positive and IL-17/IFN-γ–double positive T cells was calculated in T cells
cocultured directly with HD- or MS-derived pDCs (n = 3).

FIGURE 4. IFN-β therapy restores pDC1 population in the blood of
patients with MS. Blood was analyzed before and after 6 and 12 mo of
IFN-β therapy. A, The pDC distribution in the blood of one especially
interesting patient is shown. The dot plots demonstrate the percentage of
pDC1 and pDC2 based on the expression of CD58 and CD123. B, The
pDC1 percentages in five analyzed patients are shown for 0, 6, and 12
mo on IFN-β treatment. Different symbols represent individual patients. C,
The pDC2 percentages in five analyzed patients are shown for 0, 6, and 12
mo on IFN-β treatment. Different symbols represent individual patients.

Thus, pDCs can induce Tr1 (26) and FoxP3+ (20) regulatory T cells in
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subsets in MS. Although the overall frequency of pDCs in per-
ipheral blood did not differ between MS and HDs, and the cell
As a note of caution, we did not purify and test the remaining pDC population with negative CD123 expression. It cannot be excluded that this subset has also some regulatory functions in the disordered immune network of MS.

Our work identifies and characterizes that human blood-derived pDCs contain at least two different subpopulations. These subpopulations differ in cell surface markers, cytokine expression, and their ability to prime naive T cells toward tolerogenic or immunogenic/inflammatory directions. The phenotype of these pDC subpopulations can be modulated in vitro. There is a clear underrepresentation of immature pDC1 in conjunction with functional evidence in MS, and immunomodulatory therapy IFN-β recovers the pDC1 population, regenerating a pDC1/pDC2 ratio as observed in healthy controls. Our work provides an additional mechanism of action for IFN-β in vivo and shows how immunomodulatory therapy can act at the cellular level in recovering immunoregulatory dysfunctions in patients with MS.

Acknowledgments

We thank Barbara Reuter, Barbara Wrobel, Andrea Staudigel, and Theresa Moritz for technical assistance and the blood donors for cooperation. We are grateful to our MS patients for donating blood.

Disclosures

The authors have no financial conflicts of interest.

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