Common variable immunodeficiency (CVID) is characterized by hypogammaglobulinemia and defects in T-cell functions that could be primary or secondary. We addressed whether CVID is associated with impairment in the dendritic cell (DC) compartment, as DCs play a central role in the development of adaptive immunity. We demonstrate that DCs from CVID patients display severely perturbed differentiation, maturation, and function, and express markedly reduced levels of the costimulatory molecules that are critical for T-cell stimulation. Patients’ DCs induced weak proliferation of allogeneic T cells and produced significantly low amounts of interleukin-12 (IL-12) upon CD40 signaling. Multiple defects in the immune system, including malfunctioning of DCs, appear to be prominent features of CVID patients. Impairment in both the innate and adaptive compartments of the immune system may thus cumulatively account for the inability of CVID patients to eradicate pathogens through conventional immune pathways, thus resulting in an increased risk for recurrent bacterial infections. (Blood. 2004;104: 2441-2443)

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Results and discussion

DCs of CVID patients expressed lower levels of CD1a (15.7 ± 10.6%) compared with DCs of healthy donors (46.1 ± 18.4%) and of control patients (42.3 ± 15.8%). The percentage of DCs from CVID patients expressing CD83 and CD80 was also significantly lower than in control groups (P ≤ .01, Mann-Whitney test) (Figure 1A-B). The expression of HLA-DR (mean fluorescence intensity [MFI], 131.6 ± 58.4), CD11c
(224.4 ± 150.7), and CD40 (160.6 ± 72.4) (Figure 1C) on CVID patients' DCs was also significantly lower than that of DCs from healthy donors (n = 6) (201.5 ± 108.5, 397.7 ± 189.8, and 269.5 ± 112.9 for HLA-DR, CD11c, and CD40, respectively) and control patients (n = 4) (312.5 ± 182.7, 262.5 ± 27.4, and 323.8 ± 240.6 for HLA-DR, CD11c, and CD40, respectively) (P < .05; Mann-Whitney test) indicative of an impaired differentiation of DCs in patients with CVID. The defective differentiation of DCs from CVID patients was also observed in the presence of AB serum or serum-free medium, thus excluding the possible influence of patients' plasma components on differentiation. The defects in DCs were not due to IVIg replacement therapy since defects were also observed in newly diagnosed naive CVID patients, and in a patient having received IVIg 6 months prior to obtaining blood sample (patient 8). In addition, lymphoid DCs of CVID patients also presented with down-regulated CD86 and HLA-DR expression, while other markers were not altered (not shown).

A major function of DCs is their ability to trigger the activation and proliferation of T cells.13 DCs from CVID patients displayed a markedly weaker stimulatory effect on allogeneic T cells than DCs from healthy donors (Figure 2A). To further investigate the functional properties of CVID patients' DCs, we tested their ability to mature and produce interleukin-12 (IL-12) upon stimulation with CD40 ligand (CD40L)-transfected fibroblasts. There was a striking up-regulation of markers on DCs from control patients (Figure 2B), whereas DCs from CVID patients failed to up-regulate the maturation markers and costimulatory molecules (Figure 2B). We then measured the secretion of bioactive IL-12 (p70) from DCs of CVID patients upon stimulation with CD40L. A significantly low amount of IL-12 was produced by DCs of CVID patients compared with healthy donors and control patients (Figure 2C). Defective IL-12 production was observed in DCs of CVID patients whether naive or under IVIg therapy. Together, our results demonstrate that despite heterogeneous clinical presentation, CVID is
DENDRITIC CELLS ARE DEFECTIVE IN CVID PATIENTS

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References

Common variable immunodeficiency is associated with defective functions of dendritic cells

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