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Histone deacetylase inhibitor valproic acid affects plasmacytoid dendritic cells phenotype and function

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ABSTRACT

Objective: Plasmacytoid dendritic cells (PDC) represent a rare subset of dendritic cells specialized in the production of type I IFN in response to microbial pathogens. Recent data suggested that histone deacetylase (HDAC) inhibitors possess potent immunomodulatory properties both *in vitro* and *in vivo*. In this study, we assayed the ability of the HDAC inhibitor, valproic acid (VPA), to influence the phenotype and functional properties of human PDC isolated from peripheral blood.

Methods and results: We showed that VPA inhibited the production of IFN-α and the proinflammatory cytokines TNF-α and IL-6 by CpG-activated PDC. VPA also affected the phenotype of PDC by reducing the expression of costimulatory molecules induced by CpG activation. Moreover, VPA reduced the capacity of CpG-stimulated PDC to promote $CD4^+$ T cell proliferation and IFN-γ production, while enhancing the proportion of IL-10 positive T cells.

Conclusion: These results suggest that HDAC inhibition by VPA alters essential human PDC functions, highlighting the need for monitoring immune functions in cancer patients receiving HDAC inhibitors, but also making these drugs attractive therapies in inflammatory, and autoimmune diseases implicating PDC.

Introduction

Plasmacytoid dendritic cells (PDC) represent a rare subset of dendritic cells specialized in the production of type I IFN in response to microbial pathogens (Rissoan et al., 1999; Cella et al., 1999; Siegal et al., 1999). Human PDC express Toll-like receptors (TLR), namely TLR-7 and TLR-9 that sense viral single-stranded RNA and unmethylated CpG DNA, respectively (Gilliet et al., 2008). Thus, IFN type I signature is associated with the pathogenesis of several autoimmune diseases such as systemic lupus erythematosus (SLE), psoriasis, Sjögren's syndrome and rheumatoid arthritis (Banchereau and Pascual, 2006; Farkas et al., 2001; Nestle et al., 2005; Ronnblom and Eloranta, 2013). Moreover, PDC can be activated by self-DNA coupled to antimicrobial peptides, a mechanism contributing to the pathogenesis of psoriasis (Lande et al., 2007). The functional capacity of PDC to induce immune responses may depend on the local microenvironnement. Thus, PDC can be immunostimulatory, and induce potent Th1 responses (Cella et al., 2000). In contrast, PDC have been shown to promote tolerogenic T cells responses by inducing regulatory T (Treg) cells, especially in cancers (Sisirak et al., 2012). Acetylation of histones is an essential epigenetic mechanism controlling chromatin structure, DNA accessibility for transcription factors and gene expression. Histone deacetylases (HDAC) are enzymes involved in the compaction of the chromatin structure favoring gene silencing. Dysregulated HDAC expression has been linked to the pathogenesis of cancer and chronic inflammatory and autoimmune diseases (Rodriguez-Paredes and Esteller, 2011). HDAC inhibitors have been shown to exert anticancer activities notably in patients with hematologic malignancies (Minucci and Pelicci, 2006; Pratt, 2013; Lane and Chabner, 2009). In addition to the antitumor activities, HDAC inhibitors have been reported to have immunomodulatory properties both *in vitro* and *in vivo* (Leoni et al., 2002; Reddy et al., 2008).

We and others have previously reported the effect of HDAC inhibitors on the function of human monocyte-derived dendritic

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cells (Mo-DC) (Reddy et al., 2008; Frikeche et al., 2012a,b; Song et al., 2011). Thus, we reported that valproic acid (VPA) treatment of Mo-DC reduced their costimulatory activity and inflammatory cytokine release upon stimulation with TLR4 ligands (Frikeche et al., 2012a,b). In this study, we analyzed the effect of VPA on the phenotype and function of PDC.

Materials and methods

Media and reagents

RPMI-1640 supplemented with Sodium Pyruvate (Sigma–Aldrich, Saint-Quentin Fallavier, France), non-essential

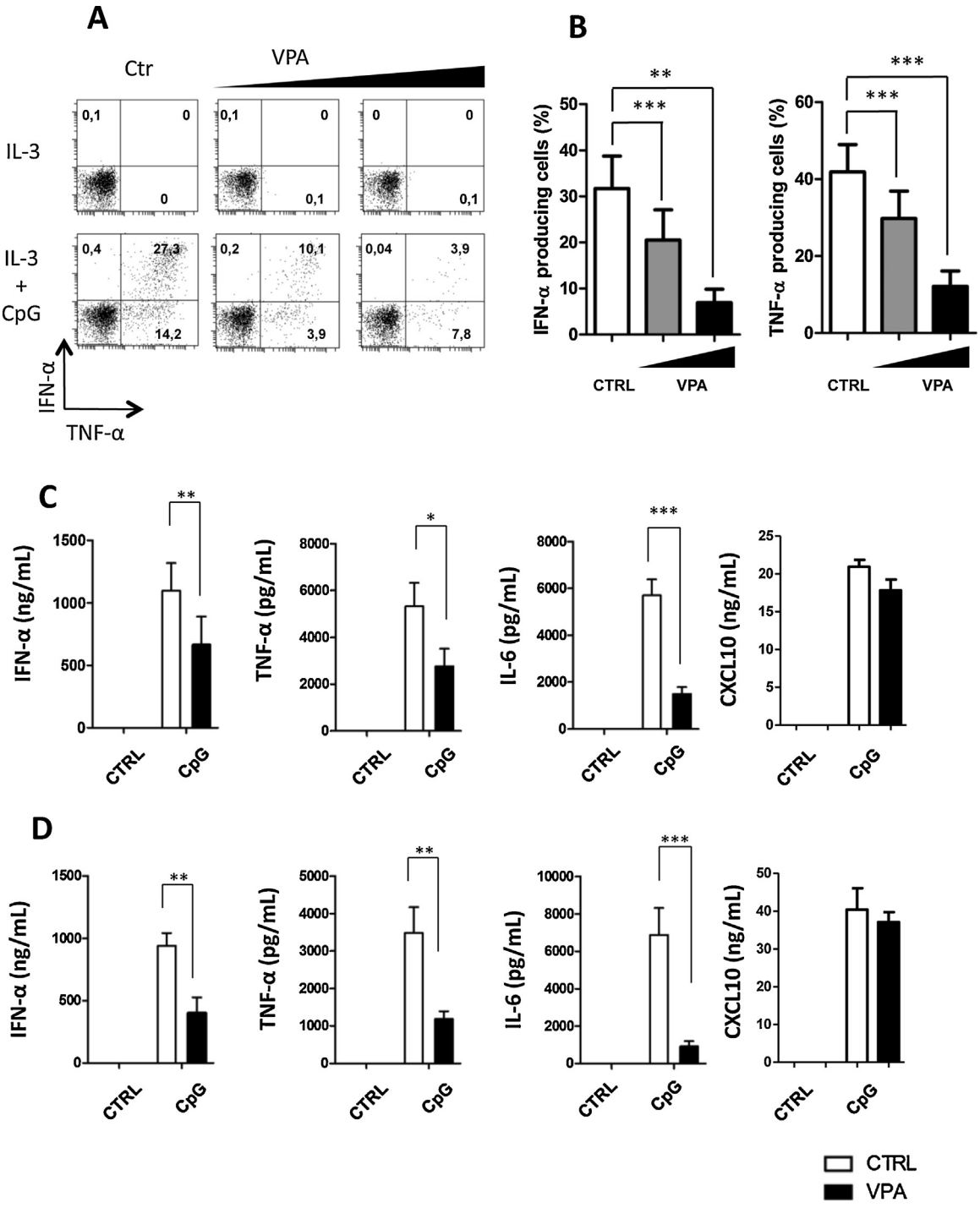

Fig. 1. VPA decreases IFN-α and proinflammatory cytokines by PDC. (A and B) Analysis of intracellular cytokines produced by PDC in the presence of 0.1 mM or 0.5 mM VPA. Total PBMC were stimulated with IL-3 and CpG2216 (IL-3$^+$CpG) or IL-3 alone (IL-3). After 6 h, intracellular IFN-α and TNF-α were analyzed by flow cytometry by gating on BDCA2 and CD123 positive cells. (A) A representative experiment is shown. (B) Results are expressed as mean ± SEM of the percentage of IFN-α (left panel) and TNF-α positive cells (right panel) (4 independent experiments). (C and D) Freshly isolated PDC were cultured for 24 h (C) or 48 h (D) in the presence of 0.5 mM VPA and activated by CpG (CpG) or not (Ctrl). Supernatants were harvested before quantification by CBA for IFN-α, TNF-α and IL-6 or by Elisa for CXCL10. Mean ± SEM are indicated ($n = 4$); $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.