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Immunomodulating effect of vitamin D3 derivatives on type-1 cellular immunity

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ABSTRACT

1α,25-dihydroxyvitamin D3 [Calcitriol or 1,25$(OH)_2D_3$] is an important active metabolite involved in multiple functions but its calcemic effect in vivo limits its therapeutic applications. On the other hand, 22-oxa-1α,25-dihydroxyvitamin D_3 (22-oxacalcitriol or 22-Oxa-1α,25-D_3), a low calcemic analog of vitamin D3 (VitD3), has been widely used as a drug for the secondary hyperparathyroidism. Here, we investigated immunomodulating effect of these two VitD3 derivatives on the differentiation of type-1 immunoregulatory cells such as dendritic cells (DC1), cytotoxic T cells (Tc1) and helper T cells (Th1). BALB/c mouse bone marrow-derived DC (BMDC1) induced by culture with Th1 condition (GM-CSF, IL-3, IL-12 and IFN-γ) expressed higher levels of MHC Class I and Class II molecules and co-stimulatory molecules compared with BMDC0 induced by neutral condition (GM-CSF + IL-3). In addition, BMDC1 showed stronger immunostimulating activity to induce alloantigen ($H\text{-}2^d$)-specific cytotoxic T lymphocytes (CTL) compared with BMDC0. However, if VitD3 derivatives were added into the culture for BMDC1 induction, the expression of functional molecules and type-1 IFNs were greatly inhibited. Moreover, VitD3 derivative-treated BMDC1 lost their immunostimulating activity to induce alloantigen-specific IFN-γ-producing Tc1. In addition, it was demonstrated that the addition of VitD3 derivatives inhibited the differentiation of IFN-γ-producing Th1 cells from ovalbumin (OVA)-specific naive Th cells, while it rather augmented the differentiation of IL-4- or IL-10-producing Th2 cells. There was no significant difference in immunomodulating activity between 1,25$(OH)_2D_3$ and 22-Oxa-1α,25-D_3. Thus, VitD3 derivatives are demonstrated

to inhibit the functional differentiation of DC1, Tc1 and Th1 cells, which play a critical role in type-1 cellular immune responses.

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