J Pediatr Care 2018, Volume 4
DOI: 10.21767/2471-805X-C4-015

Effects of DOCK8 deficiency on IL-10 producing regulatory B cells

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Dedicator of cytokinesis 8 (DOCK8) deficiencies are characterized by recurrent infections, increased serum IgE levels, eosinophilia, and a significantly high risk of allergic and autoimmune manifestations. DOCK8 is a regulating factor of actin cytoskeleton proteins involved in the development and differentiation of B cells. Regulatory B cells (Breg) are potent negative regulators of antigen-specific inflammation and T-cell-dependent autoimmune diseases mainly through producing inhibitory cytokine interleukin-10 (IL-10). The precise signaling mechanisms required for Breg functions remain unknown. We sought to elucidate the effects of DOCK8 deficiency on Breg function in patients and DOCK8KO mice. DOCK8 deficient patients (n=3) have decreased percentage of IL-10+CD19+regulatory B cells compared with healthy controls. In DOCK8KO mice, the percentage and number of IL-10+CD19+regulatory B cells were reduced compared with WT mice after induced by OVA. In DOCK8KO-WT bone marrow chimera mice, it showed the decreased number of Breg, but for DOCK8KO-μMT (B cell deficient mice) bone marrow chimera mice showed the normal number of Breg. Adoptive transfer of DOCK8-/-CD4+ naïve T cells to CD4KO mice exhibited decreased Breg percentage. Finally, In vitro and in vivo administration of recombinant IL-21could restores the percentage of Breg, it might be caused by LPS-driven, but not IL-21-driven, STAT3 phosphorylation was defective in DOCK8KO mice. In conclusion, DOCK8 deficiency causes Breg intrinsic defect, as a result of abnormalities of IL-21-producing CD4+ T cells in DOCK8 deficiency.

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