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RelB-deficient dendritic cells have increased retinoic acid dehydrogenase activity and promote regulatory T cell differentiation in mice and humans

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Peripherally-derived Foxp3$^+$ regulatory T (pTreg) cell generation from naïve T cells in the TGF-β-enriched intestinal environment depends on specialized dendritic cells (DCs). RelB-deficient mice have an increased proportion of Treg cells in the spleen despite their thymic atrophy and lack of lymph nodes and Peyer´s patches. The mechanism by which RelB influences pTreg is incompletely understood. We demonstrate in RelB$^{-/-}$ mice, that antigen-exposed RelB$^{-/-}$ DCs induce significantly more Tregs from adoptively-transferred CD4$^+$CD25$^-$ precursors than RelB$^{+/-}$ mice. This was recapitulated *in vitro*. Treg induction was TGF-β- and retinoic acid (RA)-dependent. RA-metabolizing *Raldh2* enzyme expression and ALDH activity were increased in RelB$^{-/-}$ relative to RelB$^{+/-}$ splenic DCs. In naïve mice, these ALDH$^+$ DCs developing in the absence of RelB generated pTreg cells in the spleen in the context of high TGF-β production. To determine the relevance to immunotherapy, we compared human monocyte-derived DCs generated in the absence or presence of calcitriol, a selective suppressor of RelB. Similar to RelB$^{-/-}$ DCs, ALDH activity, *ALDH1A2* and RA-responsive transcription factors *RARA* and *RXRA* expression were increased and LPS-induced costimulatory molecule expression was decreased in calcitriol-modified human DCs. In allogeneic mixed lymphocyte cultures, T cell proliferation decreased and IL-10$^+$ regulatory T cells increased in response to calcitriol-modified, relative to untreated DCs. These data indicate that RelB deficiency or pharmacological inhibition promotes RA metabolism in DCs and RA- and TGF-β-dependent induction of regulatory T cells and support clinical application of DC targeting with RelB inhibitor and antigen.

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Developmental heterogeneity of splenic CD11b$^+$ dendritic cells

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Early life immune balance is essential for survival and establishment of healthy immunity in later life. In neonates, dendritic cells (DCs), which are versatile controllers of immunity, are qualitatively distinct from adults. Newborns have an underdeveloped DC compartment when compared to adults, containing not only fewer DCs, but also an altered ratio of DC subsets. Why such age-dependent differences exist is unclear but newborn DCs are considered underdeveloped and functionally immature.
We have recently generated a model to fate map conventional DC precursors (CDP) with yellow fluorescent protein (YFP) and have revisited the development of DCs during mouse embryogenesis, as well as in perinatal and adult mice. We found that cells resembling adult CD11c$^+$MHCII$^+$ DCs were present in spleen as early as embryonic day 17. Surprisingly, CD11c$^+$MHCII$^+$CD11b$^+$ splenocytes, which phenotypically resemble CDP-derived CD11b$^+$ DCs that label strongly with YFP in adult mice, were poorly labeled in embryonic and neonatal mice. However, the labeling frequency increased gradually overtime, reaching adult levels by five weeks of age, when the splenic DC pool is fully established. Thus, splenic CD11c$^+$MHCII$^+$CD11b$^+$ DCs are predominantly CDP-derived in adults, yet cells with similar phenotypic characteristics but distinct ontogeny populate the spleen in young mice. Preliminary data indicate that these ontogenetically distinct DCs exhibit functional differences. Thus, our studies reveal a previously unappreciated developmental heterogeneity of splenic CD11b$^+$ DCs in young mice. Characterizing how developmentally regulated DC poiesis shapes the unique features of early life immunity will provide novel insights into immune development.

