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Retinoic acid signalling is required for the efficient differentiation of CD4⁺ T cells into pathogenic effector cells during the development of intestinal inflammation

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Epidemiological studies of vitamin A-deficient populations have illustrated the importance of the vitamin A metabolite retinoic acid (RA) in mucosal immune responses. However, RA seems to be a double-edge sword in CD4⁺ T cell biology. While it sustains the development of foxp3⁺ regulatory T cells, it was also very recently reported to be essential for the stability of the Th1 lineage and to prevent transition to a Th17 program.

Here we explored the role of RA signalling in CD4⁺ T cells during the development of intestinal inflammation in the T cell transfer colitis model. We found that RA signalling-deficient CD4⁺ T cells are less potent at inducing intestinal inflammation compared to their RA signalling-competent counterparts and exhibit a differentiation skewing towards more IFN γ ⁻ IL-17⁺, IL-17⁺IFN γ ⁺ and foxp3⁺ cells, while their capacity to differentiate into IL-17⁻ IFN γ ⁺ Th1 cells is compromised. *In vitro* studies confirm the inefficacy of RA signalling-deficient T cells to generate *bona fide* Th1 cells and demonstrate their aberrant increased ROR γ t expression while their differentiation into Th17 remains unaffected. Surprisingly, RA signalling-deficient CD45RB^{lo} regulatory T cells (Tregs) are however as efficient as their RA signalling-competent counterparts to inhibit colitis development.

Together our results indicate that RA, through its receptor RAR α , negatively regulates the early expansion of CD4⁺ T cells during colitis and is necessary for the generation of colitogenic Th1/Th17 cells, while it is dispensable for the protective function of Treg cells. We are currently deciphering the mechanisms of these effects of RA on CD4⁺ T cells.