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Retinoic acid signalling is required for the efficient differentiation of CD4<sup>+</sup> 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<sup>+</sup> T cell biology. While it sustains the development of foxp3<sup>+</sup> 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<sup>+</sup> T cells during the development of intestinal inflammation in the T cell transfer colitis model. We found that RA signalling-deficient CD4<sup>+</sup> T cells are less potent at inducing intestinal inflammation compared to their RA signalling-competent counterparts and exhibit a differentiation skewing towards more IFN $\gamma$ <sup>-</sup> IL-17<sup>+</sup>, IL-17<sup>+</sup>IFN $\gamma$ <sup>+</sup> and foxp3<sup>+</sup> cells, while their capacity to differentiate into IL-17<sup>-</sup> IFN $\gamma$ <sup>+</sup> 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 $\gamma$ t expression while their differentiation into Th17 remains unaffected. Surprisingly, RA signalling-deficient CD45RB<sup>lo</sup> 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 $\alpha$ , negatively regulates the early expansion of CD4<sup>+</sup> 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<sup>+</sup> T cells.