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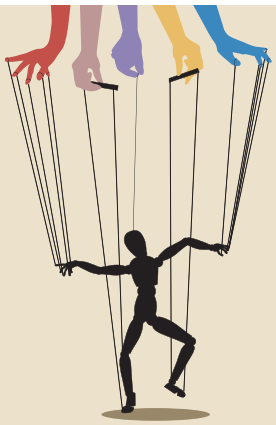

REGULATORY T CELLS

Collaborative control of induced regulators

Two related papers published in *Nature Immunology* show that the ligand-activated transcription factor aryl hydrocarbon receptor (AHR) functions with MAF (also known as c-Maf) or other transcription factors to induce the development of mouse and human type 1 regulatory T cells (T_R1 cells).

T_R1 cells are an inducible subset of regulatory T cells that produce interleukin-10 (IL-10) and are involved in the prevention of inflammatory and autoimmune disorders. Although it is known that IL-27 drives the expansion of mouse T_R1 cell subsets, the molecular mechanisms of their induction are not fully defined.

Apetoh *et al*. first observed that AHR expression was upregulated in mouse T_R1 cells that had been differentiated *in vitro* with IL-27 and transforming growth factor-β (TGFβ). MAF expression was also upregulated in these cells, consistent with previous studies that showed a role for this transcription factor in T_R1 cell differentiation and the activation of *Il10* and *Il21* transcription. Moreover, IL-10 production was increased when T_R1 cells were generated in the presence of AHR ligands, whereas it was reduced when *Ahr* expression by T_R1 cells was downregulated through the use of small interfering RNA (siRNA). When T cells that overexpressed a *Maf* transgene were cultured in the presence of IL-27, TGFβ and AHR ligands, even more IL-10 was produced, suggesting that MAF and AHR act together to enhance IL-10 production. AHR and MAF also increased the expression of IL-21 by T_R1 cells. Indeed, the *Il10* and *Il21* promoters were both found to contain AHR- and MAF-binding sites, and chromatin immunoprecipitation studies and reporter assays confirmed direct interaction of AHR and MAF with the *Il10* and *Il21* promoters in T_R1 cells, indicating that they control the transcriptional activity of both promoters. IL-21 is an autocrine T_R1 cell growth factor that was shown to promote expression of IL-10, AHR and MAF, thereby acting as a positive feedback mechanism in T_R1 cell development. Last, Apetoh *et al*. showed that AHR is also required *in vivo* for the induction of IL-27-driven T_R1 cells, which could inhibit the incidence of experimental autoimmune encephalomyelitis.

Similar to the observations in mouse T_R1 cells, Gandhi *et al*. found that AHR activation also promotes the *in vitro* differentiation of human IL-10-producing T_R1 cells by acting with MAF to transactivate the *IL10* promoter. Human T_R1 cells that were generated in the presence of AHR ligands suppressed responder T cells in a cell contact-dependent manner involving the cytotoxic effector granzyme B (rather than through IL-10 production). When naive human T cells were cultured with both AHR ligand and TGFβ, they differentiated into forkhead box P3 $(FOXP3)^+$ regulatory T cells that expressed high levels of AHR and the ectonucleotidase CD39. CD39, which hydrolyses ATP, was shown to be responsible for the suppression mediated by these induced $FOXP3^+$ regulatory T cells. Further analysis revealed that in the $FOXP3^+$ cells AHR activation enhanced expression of the transcription factors SMAD1 and Aiolos. SMAD1, which is involved in TGFβ signalling, was found to interact with the *FOXP3* enhancer in T cells that were treated with TGFβ and AHR ligand and to promote *FOXP3* transcription. Aiolos, which is a member of the Ikaros family, was shown to interact with the FOXP3 protein and repress *IL2* transcription.

Together these papers provide important insights into the factors that synergize to control the generation of inducible regulatory T cells, which could prove useful for the therapeutic application of these cells in autoimmune disorders.

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ORIGINAL RESEARCH PAPERS Apetoh, L. *et al.* The aryl hydrocarbon receptor interacts with c-Maf to promote the differentiation of type 1 regulatory T cells induced by IL-27. *Nature Immunol.* 1 Aug 2010 (doi:10.1038/ni.1912) | Gandhi, R. *et al.* Activation of the aryl hydrocarbon receptor induces human type 1 regulatory T cell-like and $Foxp3^+$ regulatory T cells. *Nature Immunol.* 1 Aug 2010 (doi:10.1038/ni.1915)