REGULATORY T CELLS

Stabilizing immune regulation in the gut

The results indicate that miR-10a limits the ability of T_{Reg} cells to become T_{FH} cells by targeting BCL-6.

John O'Shea and colleagues describe a new pathway that could contribute to the regulatory environment induced by high levels of retinoic acid in the gut. They show that retinoic acid, together with transforming growth factor- β (TGF β), induces the expression by regulatory T (T_{Reg}) cells of a microRNA (miRNA) that can restrict T cell plasticity and attenuate differentiation to a T follicular helper (T_{FH}) cell phenotype.

Deficiency of Drosha or Dicer — which are required for the generation of miRNAs — results in the instability and altered differentiation of CD4⁺ T cells, but little is known about the specific miRNAs involved. The authors identified miR-10a-5p (referred to here as miR-10a) as being selectively expressed by natural T_{Reg} cells — and to a lesser extent by induced T_{Reg} cells — but not by naive T cells or T helper (T_H) cells. Retinoic acid and TGF β together induced the expression of miR-10a by induced T_{Reg} cells in a dose-dependent manner, and blockade of either signalling pathway prevented miR-10a induction. That retinoic acid and TGF β are both required for optimal induction of miR-10a was explained by TGF β -induced expression of retinoic acid receptor- α

(RAR α).

Potential target sequences for miR-10a were identified in the 3' untranslated regions of B cell lymphoma 6 (*Bcl6*) and nuclear receptor co-repressor 2 (*Ncor2*) mRNAs. Overexpression of miR-10a resulted in significantly decreased expression of reporter constructs containing these target sequences *in vitro*, whereas sequestration of miR-10a through the expression of a decoy target sequence could restore the expression of a *Bcl6* reporter construct. Similar effects on the expression of NCOR2 were observed, and the authors confirmed that endogenous miR-10a in induced T_{Reg} cells inhibits the expression of endogenous BCL-6 and NCOR2 proteins. NCOR2 is a co-repressor of RARA expression, and the authors showed that this forms

a positive-feedback loop whereby miR-10a increases the sensitivity of cells to signalling through RAR α , which results in increased levels of miR-10a.

The transcriptional repressor BCL-6 is a crucial factor in the generation of T_{FH} cells, which can arise from T_{Reg} cells in Peyer's patches. To assess this process further,

naive CD4⁺ T cells were differentiated *in vitro* into induced T_{Reg} cells, transferred into T cell-deficient mice and assessed 6 weeks later for the expression of T_{FH} cell markers in Peyer's patches. When the induced T_{Reg} cells were transduced with the miR-10a decoy sequence, they more readily acquired T_{FH} cell markers, whereas overexpression of miR-10a decreased their differentiation to T_{FH} cells. The levels of miR-10a and BCL-6 in these cells were inversely correlated. The results indicate that miR-10a limits the ability of T_{Reg} cells to become T_{FH} cells by targeting BCL-6. High levels of miR-10a were observed in 'follicular regulatory T cells', which express both forkhead box P3 (FOXP3) and BCL-6; the authors suggest that miR-10a might be particularly important in these cells to constrain the 'helper' effects of BCL-6 and allow the 'regulatory' effects of FOXP3.

In further experiments, the authors also showed that miR-10a can inhibit T_H17 cell differentiation in the presence of retinoic acid by increasing the levels of T-bet (which is a negative regulator of T_H17 cells) through decreased expression of BCL-6. Thus, the induction of miR-10a by retinoic acid in the gut maintains the phenotype of T_{Reg} cells by targeting multiple factors that could induce conversion to other T cell fates.

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ORIGINAL RESEARCH PAPER Takahashi, H. *et al.* TGF- β and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. *Nature Immunol.* 29 Apr 2012 (doi:10.1038/ni.2286)

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