How the immune system is regulated by small RNAs called microRNAs to prevent self-attacks leading to autoimmunity

The ability to properly engage the different arms of the immune response is essential for protection from pathogens but also for preventing autoimmune reactions against normal tissue. Central to autoimmune prevention are a class of white blood cells called regulatory helper T cells or Tregs for short. Tregs, as their name implies, regulate the activity of other classes of helper T cells and suppress immune responses against normal tissue. Individuals with defects in Tregs suffer acute autoimmunity that is lethal in the most severe cases. In contrast, an over-reaction of Tregs is thought to facilitate cancer progression by suppressing the immune response to tumors. Therefore, understanding the mechanisms controlling the development and function of Tregs will be essential for creating new strategies to combat these immune related diseases.

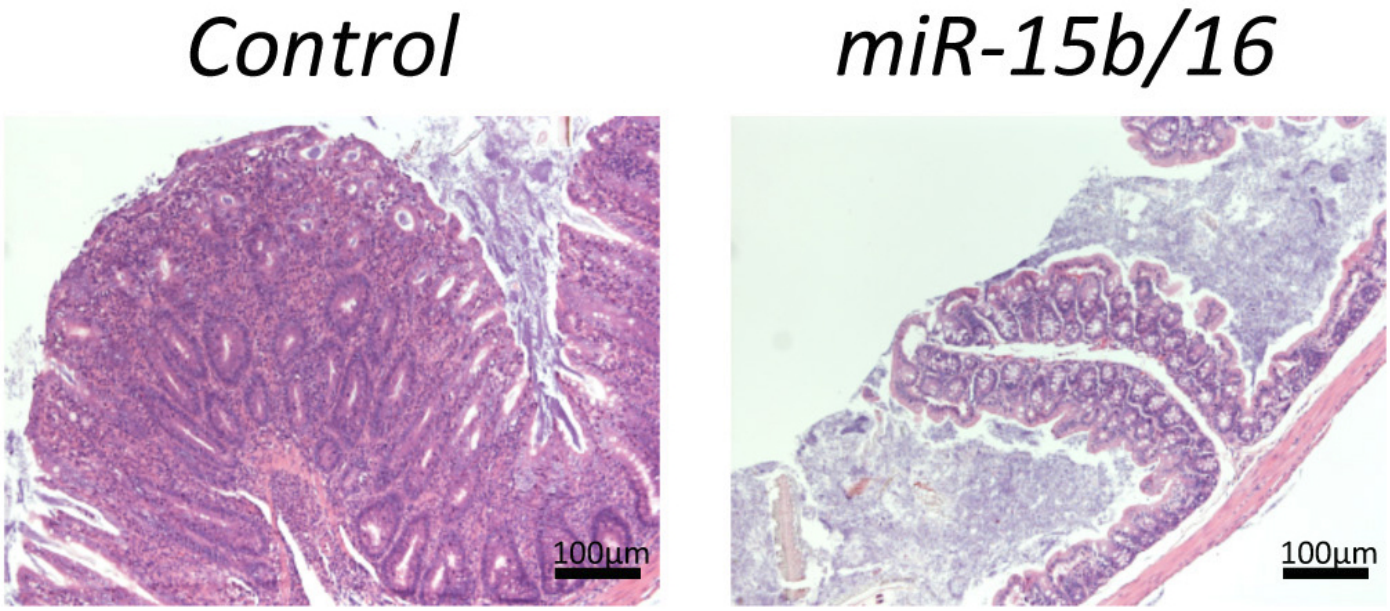

Fig. 1. Histology sections from the colons of mice prone to autoimmunity. Overexpression of miR-15b and miR-16 in T cells results in a significant reduction in the thickening of colon tissue and its inflammation.

Previously we discovered that a class of RNAs called microRNAs (miRNAs) is important for regulating gene expression that leads to Treg development. miRNAs are small RNAs encoded within the genome that are approximately 22 nucleotides in length. They negatively regulate gene expression by targeting homologous sequences in protein encoding messenger RNAs and inhibiting translation into proteins. miRNAs play important roles in many developmental systems and typically function by fine-tuning gene expression levels required for development and function

of a specific cell type. However, it was unknown why miRNAs were important in the development of Tregs.

We set out to understand miRNA function by identifying important miRNAs and the relevant genes they regulate. We hypothesized that important miRNAs would be highly expressed in Tregs so we tested the most abundant using a genetic approach. This involved overexpressing or blocking individual miRNAs in isolated naïve murine helper T cells and measuring the effect on differentiation into Tregs under specific cell culture conditions. Most effective in these assays were two highly related miRNAs called miR-15b and miR-16. Their overexpression enhanced, whereas their blocking inhibited Treg differentiation. miR-15b and miR-16 regulation of Treg differentiation was also apparent in the whole mouse, as their overexpression in T cells enhanced Treg differentiation and suppressed the immune response in a mouse model of autoimmunity against the colon (as shown in figure 1). Therefore, these miRNAs were important for both the *in vitro* and *in vivo* differentiation of Tregs.

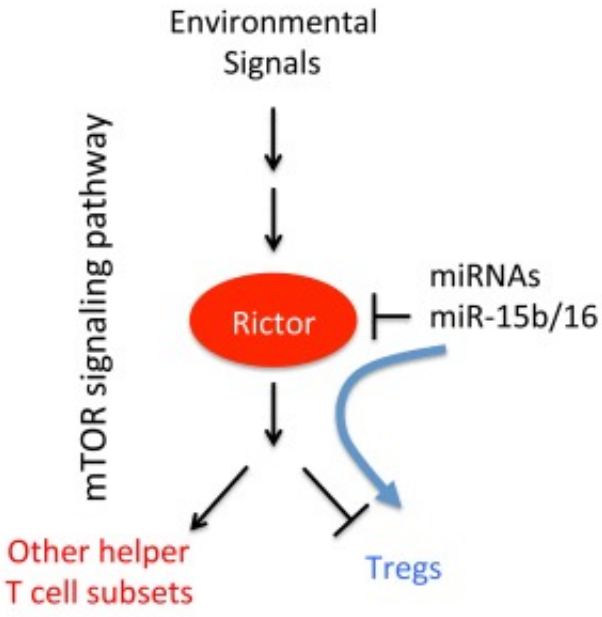

Fig. 2. Summary of miRNA regulation of mTOR signaling in helper T cell differentiation. miR-15b and miR-16 enhance Treg differentiation by suppressing the expression of Rictor, which Inhibits the signaling through the mTOR pathway that would otherwise impede Treg differentiation and lead to other helper T cell subsets.

To identify relevant genes regulated by miR-15b and miR-16, we used a bioinformatics approach based on the complementarity of miRNAs to sequences within messenger RNAs. One gene that stood out in this analysis encodes a protein called Rictor, which is a central member of a series of

regulatory proteins that make up what is called the mTOR-signaling pathway. This pathway is important for many cell types, as it is a key mechanism for responding to environmental changes that influence developmental and functional programs. In helper T cells, the mTOR-signaling pathway plays a critical role in regulating differentiation, and its inhibition boosts Tregs. Here we found that miR-15b and miR-16 suppress the expression of Rictor and mTOR signaling, and this level of regulation was sufficient to enhance Treg differentiation (summarized in figure 2). Therefore, fine-tuning of mTOR signaling by these miRNAs is important in helper T cells.

With these discoveries we have illustrated a novel mechanism controlling the differentiation of helper T cells. In the future, the use of these miRNAs or other pharmacological agents targeting the MTOR signaling pathway could be the basis for new clinical approaches to immune related diseases. However, much remains to be understood prior to these therapies becoming a reality, especially regarding any additional effects on the development and function of helper T cells and also other cell types outside of the immune system. Nevertheless, we have uncovered a new and interesting way of regulating the immune response.

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Publication

MicroRNA-15b/16 Enhances the Induction of Regulatory T Cells by Regulating the Expression of Rictor and mTOR.
Singh Y, Garden OA, Lang F, Cobb BS
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