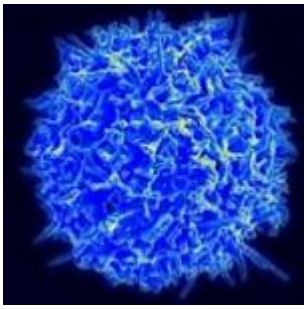
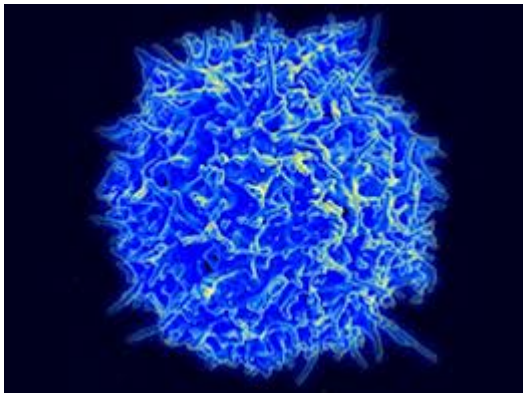
T cell differentiation regulated by methyltransferase G9A during murine intestinal inflammation





Th cells differentiate into one of several effector lineages, including Th17, and Tregs. Th17 and Tregs are unique among the Th cell subsets in that they are found in high numbers in intestinal tissues in the steady state and their differentiation is controlled by the cytokine TGF-beta1. Activation of naive Th cells in the presence of TGF-beta1 and IL-6 leads to the development of Th17 cells, while activation of naive Th cells in the presence of TGF-beta1 and IL-2 leads to the development of Tregs that express Foxp3. The balance between Th17 and Tregs is critical for intestinal homeostasis. Thus, understanding the molecular mechanisms that control Th17 and Treg differentiation is important for identifying how

dysregulated Th cell responses contribute to the development of intestinal inflammation. Using a murine T cell transfer model of colitis, this study found that T cell–intrinsic expression of the histone lysine methyltransferase G9A was required for development of pathogenic T cells and intestinal inflammation. G9A-mediated dimethylation of histone H3 lysine 9 (H3K9me2) restricted Th17 and Treg differentiation in vitro and in vivo. H3K9me2 was found at high levels in naive Th cells and was lost following Th cell activation. Loss of G9A in naive T cells was associated with increased chromatin accessibility and heightened sensitivity to TGF-beta1. Pharmacological inhibition of G9A methyltransferase activity in wild type T cells promoted Th17 and Treg differentiation. Indicating that G9A-dependent H3K9me2 is a homeostatic epigenetic checkpoint that regulates Th17 and Treg responses by limiting chromatin accessibility and TGF-beta1 responsiveness. Thus making G9A a therapeutic target for treating intestinal inflammation.

Antignano, F. et al. 2014. Methyltransferase G9A regulates T cell differentiation during murine intestinal inflammation. *The Journal of Clinical Investigation.*