Blocking miR-212/132 in T cells is a potential therapy for treating colitis

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, is thought to be caused by aberrant immune response to host intestinal microbiota, leading inflammation in gastrointestinal tract. The symptoms such as diarrhea, rectal bleeding, anemia, abdominal pain, or weight loss can be observed in the patients. Dysregulated T lymphocytes differentiation has been considered to be a trigger of IBD pathogenesis. Type 1 regulatory T (Tr1) cells producing IL-10, an anti-inflammatory subset of T lymphocytes, can prevent colitis. However, it remains unclear how Tr1 cell differentiation was controlled under intestinal inflammation.

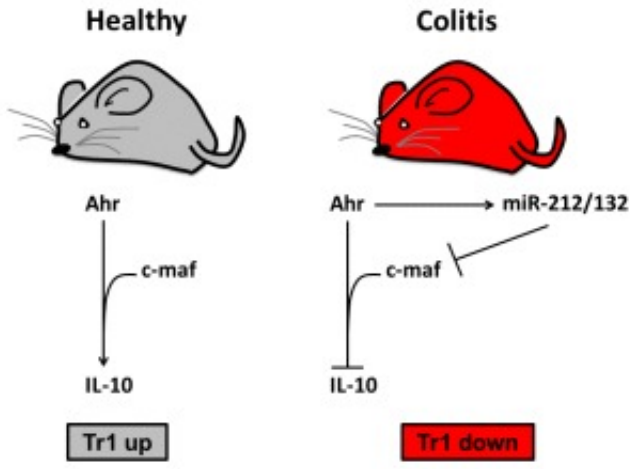

Fig. 1. miR212/132 regulates Tr1 induction via c-maf expression.

MicroRNA is around 22nt non-cording RNA that binds 3' untranslated region (3'UTR) of its target mRNAs, leading degradation and/or translational inhibition of these mRNAs. We previously reported that miR-212/132 expression is dependent on Aryl hydrocarbon receptor (Ahr). Recently, several groups showed that Ahr mediates suppressive immune response in IBD. In addition, it's reported that Ahr positively regulates Tr1 cell induction via interacting with c-maf, a transcription factor for IL-10. On the basis of these findings, we hypothesize that Ahr-mediated miR-212/132 expression is involved in the pathogenesis of intestinal inflammation via regulating Tr1 cell generation.

In this study, we found that miR-212/132-KO mice are resistant to DSS-induced colitis, a mouse model of IBD with increased Tr1 cells. We found that lymphocytes isolated from colon of colitic mice abundantly express miR-212/132. Consistent with our previous findings, miR-212/132 expression was low in lymphocytes from colon of Ahr-KO mice. These results indicate that miR-212/132 is induced by Ahr under intestinal inflammation. To investigate the significance of Ahr-

mediated miR-132/212 induction in intestinal inflammation, miR-212/132 KO mice and T cell-specific Ahr-deficient mice were subjected to DSS-induced colitis. Contrary to the observation in which Ahr KO mice show severe colitis, we found that miR-212/132 KO mice as well as T cell-specific Ahr-deficient mice exhibited less severe symptoms of the disease. In addition, the frequency of Tr1 cells in colon was significantly high in miR-212/132 KO mice, compared to that of control. Next, to examine whether miR-212/132 expression in T cells directly affects Tr1 cell differentiation, naïve T cells of miR-212/132 KO mice were cultured under Tr1 cell-polarizing condition. We found that Tr1 cell induction was significantly elevated by miR-212/132 loss. The computational analysis showed potential interaction between 3?-UTR of c-maf and miR-212/132. We found that c-maf expression was elevated at the protein level in miR-212/132-deficient T cells.

Our findings emphasize the important role of miR-212/132 in Tr1 cell differentiation under intestinal inflammation and suggest that inhibition of miR-212/132 represents a potential therapy for treating colitis.

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