

CELIAC DISEASE

Retinoic acid and IL-15 jointly implicated in reversal of oral tolerance

The vitamin A metabolite retinoic acid has a crucial role in the induction of regulatory T (T_{REG}) cell responses in the gastrointestinal tract. DePaolo and colleagues now show, however, that retinoic acid can also act synergistically with high levels of IL-15 to promote a proinflammatory T-cell response to dietary antigens. “These observations caution against the use of vitamin A and retinoic acid for the treatment of autoimmunity and inflammatory intestinal disorders associated with high levels of IL-15,” explain the authors.

The normal T-cell response to a dietary antigen is tolerogenic; however, in individuals with celiac disease an inflammatory T-cell response to gluten is induced instead. These individuals also express markedly high levels of IL-15 in the gut epithelium and lamina propria.

As a model of early celiac disease, the researchers created *HLA-DQ8-IL15*

transgenic mice that overexpressed IL-15 in the lamina propria to a similar extent to patients with celiac disease. Oral administration of chicken ovalbumin, a model dietary antigen, led to reduced conversion of naive T cells into T_{REG} cells in IL-15 transgenic mice compared with wild-type animals. Retinoic acid resulted in a further decrease in the numbers of T_{REG} cells generated in these ovalbumin-fed transgenic mice, whereas blockade of IL-15 signaling restored oral tolerance to ovalbumin.

“Our results also indicate that inhibiting IL-15 signaling may constitute a therapeutic intervention to restore mucosal tolerance to dietary antigens,” the researchers write.

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Original article DePaolo, R. W. *et al.* Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. *Nature* doi:10.1038/nature09849