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"Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens" published by *Nature,* February 9, 2011

Summary of the work

Normally, the immune system of our gut is constantly and closely scrutinizing all ingested proteins, making sure that no inflammatory reactions are generated upon their ingestion. One of the players inducing intestinal regulatory responses is retinoic acid, a metabolite of vitamin A.
A notable exception is celiac disease, where genetically susceptible individuals develop an inflammatory response (mediated by both, T cells and antibodies) against dietary gluten, a protein present in wheat. The mechanisms underlying this dysregulation have not been identified.
In this study, it was found that in the intestine of celiac disease patients, in conjunction with IL-15, a cytokine greatly upregulated in their gut, retinoic acid - contrary to its role in normal circumstances- rapidly activated dendritic cells to induce release of the inflammatory cytokines IL-12p70 and IL-23. As a result, the study showed that in a stressed intestinal environment, retinoic acid acted as an adjuvant that promoted rather than prevented inflammatory cellular and humoral responses to a fed antigen.
Altogether, these findings unveil an unexpected role for retinoic acid and IL-15 in the abrogation of tolerance to dietary antigens.

Comment

- Our study is the first to show that retinoic acid (RA) has - in the presence of IL-15 - unforeseen properties that induce cellular immunity to fed antigens. These observations caution against the use of vitamin A and RA for the treatment of autoimmunity and inflammatory intestinal disorders associated with high levels of IL-15. Indeed, a causal relationship between retinoids used for the treatment of acne and inflammatory bowel disease was suggested in a subset of patients. Conversely, these findings provide an explanation as to why children suffering from vitamin A deficiency in developing countries respond less efficiently to oral vaccines than children from developed countries and also suggest that engineering mucosal vaccines that induce IL-15 may be beneficial.
- More generally, our study supports the concept that there are no "unconditional" suppressive factors, and that integration of endogenous and exogenous signals determine the type of the immune response, which ultimately needs to be tailored to the tissue and the antigen.
- Additionally, we may have in hand a long-awaited relevant mouse model mimicking the early stages of celiac disease (CD), a unique model of paramount importance in light of future development of therapeutic strategies for celiac disease. Especially relevant to CD is the identification of IL-15 as a causative factor driving the differentiation of anti-gluten T cells in the intestinal mucosa, resulting in the break of tolerance to gluten.
- Our observations may also explain why oral tolerance is disrupted in patients with inflammatory bowel disease who also have dysregulated IL-15 expression in the gut.

Last but certainly not least, our results suggest that inhibiting IL-15 signaling may constitute a therapeutic intervention to restore mucosal tolerance to orally ingested food antigens.

Comment by S. Guandalini, February 9, 2011