

NEWS AND COMMENTARY

Oral tolerance

Passing CD11b on the way to tolerance

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The important role that CD11b plays in oral tolerance is revealed in a recent study on mice published in the *Journal of Experimental Medicine*.¹

Despite a large amount of research, we still only poorly understand how antigen-presenting cells (APCs) mediate the opposing effects of immune activation and tolerance. Oral tolerance is of special interest in this area, since it is a recurrent and natural immunologic event, which ultimately results in a symbiotic micro-environment of host mucosa, commensal bacteria and dietary antigens.

Current evidence suggests that bone marrow-derived APCs (which include macrophages, B cells and dendritic cells (DCs)) present orally fed antigens (as they do for antigens administered via other routes). These APCs control differentiation of naïve T cells into effector T cells and their subsequent secretion of cytokines. So it is not surprising that attempts to dissect the mechanisms that underlie tolerance induction have focused on APCs and in particular on DCs.

Nonetheless, DCs certainly do not act in isolation: they integrate a variety of micro- and macro-environmental stimuli before 'instructing' appropriate responses. Other cells found in the gut-associated lymphoid tissues (GALT), like $\gamma\delta$ T cells,² contribute significantly or are in some cases a key requirement in their own right. It is clear then that more than one mechanism mediates oral tolerance and that many cell types influence this active immunological process. One effector molecule has been inextricably linked with tolerance and reported to play a central role: TGF- β .

In their new paper, Driss Ehrichou and colleagues¹ focus on the role of the integrin

CD11b/Mac-1 in the induction of oral tolerance. CD11b's ligand, C3bi, was previously shown to be critical in the development of peripheral tolerance.³ Moreover, genetic inactivation of CD11b worsens inflammation and disease progression in disease models of autoimmune disorders such as asthma, arthritis and lupus erythematosus,⁴ indicative of a potential role for this integrin in peripheral tolerance.

In keeping with these previous findings, the authors of the new report show that CD11b-deficient mice have increased IL-6 production that results in defective antigen-induced oral tolerance and enhanced immune activation. CD11b-deficient mice also generate greater numbers of Th17 (a recently-described CD4⁺ T helper cell subset). Furthermore, the authors show that the Th17 cytokine IL-17 is sufficient to interfere with oral tolerance induction.

Following oral administration of ovalbumin (OVA), the CD11b^{-/-} mice that the authors studied had an increase in delayed-type hypersensitivity (DTH) reaction after priming with OVA in complete Freund's adjuvant (CFA), whereas tolerance was successfully restored upon transfer of wild-type adhesion-enriched total splenocytes. OVA-unfed wild-type and CD11b^{-/-} controls respond vigorously upon OVA-CFA challenge, indicating that CD11b deficiency does not prevent immune activation. Lymphocyte proliferation assays revealed an increased responsiveness of CD11b^{-/-} mice compared with wild-type mice under non-tolerizing conditions, accompanied by a twofold increase of IL-2 and IL-6 production.

The increase in IL-6 expression in these mice is significant. IL-6 can reverse the suppression of proliferation in co-cultured responder cells by naturally occurring FoxP3-positive regulatory T cells (nTreg).⁵ and is an essential differentiation factor in *de novo* generation of Th17.^{6,7} Low-dose oral tolerance induction has been associated with

the generation of Th3: CD4⁺ TGF- β -secreting cells with suppressive properties (see Faria and Weiner⁸ and Weiner⁹ for review). The relationship between nTreg and Th3 is not entirely clear. However, TGF- β is implicated in the generation of Th3 as well as the conversion of naïve CD4⁺CD25⁻ into CD4⁺CD25^{hi}FoxP3⁺ T cells, and might reflect the generation of inducible Treg (iTreg). At least *in vitro*, a dichotomy between generation of iTreg (Th3) and Th17 from naïve CD4⁺ T cells exists, under the control of IL-6.⁶

Ehrichou *et al.* now report that the absence of CD11b results in increased IL-6 expression and the inability to establish low-dose oral tolerance. Non-immunized CD11b^{-/-} mice harbour increased percentages of Th17, as shown by the outgrowth of this subset from total CD4⁺ cell populations with IL-23. Continuous contact with pathogens during the mouse's lifespan probably causes this pattern and might result in the accumulation of Th17, enhancing the susceptibility to autoimmune diseases as previously reported.⁴ Indeed, CD11b^{-/-} mice show increased IL-6 production after immunization, accompanied by increased percentages of Th17 and total IL-17 production. In the case of oral tolerance induction, one could hypothesize that Th3 generation has been redirected to that of Th17.

Unfortunately, the mechanism that underlies the role of CD11b in oral tolerance remains unclear. To help reveal this mechanism, several specific questions need to be addressed: are absolute numbers of Th3 and Treg reduced in the GALT-associated tissues in CD11b^{-/-} mice? Does CD11b deficiency lead to the absence of a specific cell population that may potentially regulate IL-6 expression? Does triggering of CD11b have a role in controlling IL-6 expression levels?

In the new study, as little as 60 pg/mouse per day of recombinant IL-17 was sufficient to block oral tolerance induction. This finding could confirm a previous suggestion that

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IL-17 enhances or strengthens the formation of tight junctions of epithelial cells and increases mucosal layer thickness.^{10,11} These effects would limit antigen absorbance in the small intestine, prevent access of the orally administered antigen to the GALT and so inhibit oral tolerance induction. This scenario would place IL-17 as an important player in homeostatic regulation of the symbiotic micro-environment of the intestine.

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