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The anatomy of mucosal immune responses.

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Abstract

It remains unclear how and where unresponsiveness to fed antigens is induced. This "oral tolerance" is probably necessary to prevent the array of immune effector mechanisms required to counteract pathogens of the mucosae from being misdirected against food antigens or commensal flora. It will obviously be important to dissect where, when, and how such immunological homeostasis is maintained in the gut, but it will also be necessary to determine whether similar inductive and effector mechanisms are required for the therapeutic applications of oral tolerance systemically. This may be influenced by anatomical and microenvironmental effects on the phenotype and/or activation state of the antigen-presenting cell (APC), which presents orally delivered antigen. Fed antigen passes from the intestinal lumen either via the villus epithelium and M cells in the Peyer's patches (PP) or the mucosal lamina propria to the organized lymphoid tissues of the PP and mesenteric lymph nodes (MLN). In addition, there is evidence that mucosally administered antigen also gains access directly to peripheral lymphoid organs. Each of these sites contains distinctive populations of APCs and has unique local microenvironments that may influence the immune response in different ways. We propose that feeding antigen in high doses may induce clonal anergy, deletion, or altered differentiation because it gains direct access to resting APCs in the T cell areas of both the gut-associated lymphoid tissues (GALT) and peripheral lymphoid organs, with presentation occurring in the absence of productive costimulation. By contrast, low doses of tolerizing antigen may be taken up and presented preferentially by APCs in the GALT, where the local environment may favor the induction of regulatory T cells. This is consistent with our own and others findings, using adoptive transfer of TcR tg T cells. These studies have shown that antigen-specific CD4(+) T cells are activated simultaneously in all peripheral and gut-associated lymphoid organs after feeding high doses of proteins, but that this may be more restricted to local tissues when lower doses are used. Another level of anatomical control is imposed within lymphoid organs, where migration of T cells through distinct anatomical compartments can affect their differentiation. We find that, in contrast to orally primed T cells, orally tolerized T cells are unable to migrate into B cell follicles during their initial exposure to antigen. This affects their differentiation as upon subsequent challenge with antigen in adjuvant, tolerized T cells can be found in follicles but are unable to provide the B cell help that primed T cells can deliver. We hypothesize that the initial defective migration of tolerized T cells prevents them from receiving signals from antigen-specific B cells in follicles and results in abortive differentiation. Thus, both gross and fine anatomical location of fed antigen presentation may be important in mucosal immunoregulation.

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