An Example of Peripheral Tolerance – Regulation of Mucosal Immunity

Immune Response versus Tolerance Induction

It remains unclear how pathogens are identified and differentiated from commensals at the mucosal surface; however, once recognition occurs, the immune response at the inductive sites follows similar steps to that of the systemic immune response. Antigen presentation by APCs is followed by the activation and proliferation of specific T cells (and B cells directly recognizing antigen) at the inductive sites. The microenvironmental cytokines influence the outcome of the response, where APCs and accessory cells drive Th0 T cells toward a Th1 or Th2 phenotype. T cells engage in a cognate interaction with antigen-specific B cells, and then activated lymphocytes circulate throughout the body and seed the effector mucosal site and/or remote mucosal sites where final differentiation into effector or memory cells takes place.

The mechanism(s) by which tolerance is induced to harmless molecules and microorganisms by the mucosal immune system is much less well defined, but there are some clues from animal models. A principal mechanism is the elimination of pathogens without engendering an inflammatory response that might not only result in disruption of the barrier epithelium, but also provide cytokine signals and upregulation of costimulatory molecules to activate the immune system.

Several levels of control of the immune response can be identified. The nature of the antigen is the first level of control. Microorganisms contain PAMPs, which engage PRRs on

APCs of the innate immune system, bringing about upregulation of MHC-I and MHC-II and costimulatory molecules. Replicating microorganisms are much more likely to induce productive immune responses than nonreplicating, inactivated organisms—presumably related to their ability to react with immunoreactive APCs. Soluble antigens, in contrast, are handled differently by pathways that stimulate immune tolerance, e.g.Treg cells. This may explain, in part, the failure to induce immunity by oral and nasal immunization using soluble antigens. A second level of control is at the level of the APCs, since immature DCs or nonprofessional APCs (epithelial cells) lack costimulatory molecules needed for proper T cell activation. The final outcome may be anergy, unresponsiveness (Chapters 7 and 19 in Immunology IV), or apoptosis (Chapter 9 in Immunology IV) of T cells.

Another level of control is affected by the cytokines in the mucosal microenvironment, some of which are released by "accessory" cells. These cells (DCs, mast cells, eosinophils, macrophages, NK cells, and TCR1 T γδ cells) are known to populate most mucosal surfaces and to react to antigen stimulation by releasing preformed mediators and synthesizing new ones. In this way, accessory cells became "quick response cells," providing a particular cytokine microenvironment able to direct the T cell-mediated immune response. Among these mediators are the "suppressor" cytokines, IL-10 and TGF-β, that downregulate the inflammatory immune response. DCs in PPs produce IL-10 and little IL-12, controlling the immune response and allowing the development of Th2-type responses.

Immune regulation at mucosal surfaces is thus a complex interplay between innate and adaptive immune mechanisms. Antigen presentation by DCs and microenvironmental cytokines released by quick response cells like intraepithelial lymphocytes (IEL), mast cells (MCs), and macrophages, have a profound impact in the outcome of the immune response, either inducing cell-mediated immunity (CMI) with Th1 cells,

antibody-mediated immunity through Th2 cells, or immune regulation and tolerance with T regulatory cells (Tregs). Activated macrophages are able to break tolerance by releasing IL-12 and IFN-γ.

T-cell anergy is a state of unresponsiveness characterized by a lack of proliferation and IL-2 synthesis (Chapter 19 in Immunology IV). Oral tolerance may be achieved by anergized CD4+ T cells. It is thought that anergic T cells may retain some functional activity and are able to upregulate IL-10 and TGF-β production, downregulating DC expression of CD80/86 (Chapter 9 in Immunology IV). Therefore, anergic T cells could also function as regulatory cells by releasing TGF-β resembling Treg cells that suppress immune responses. In the scenario, where Th1 or Th2 cells become anergic, subsets of these cells may switch to become Treg cells producing IL-10 and/or TGF-β. Oral and nasal tolerance also have been shown to block mast cell function in animal models and may be a route for the control of allergies and inflammatory responses in the human. Furthermore, antigen presentation by DCs regulates tolerance by the deletion of self-reactive T cells, the induction of nonresponsiveness by immature DCs expressing low levels of costimulatory molecules, and the expansion of Tregs. In humans, two major subpopulations of DCs have been described: $CD11c^{hi}$ (myeloid DCs or **mDC**) and $CD11c^{lo}$ (plasmacytoidDCs [**pDC**] or lymphoid DCs). In the mouse, three major functionally distinct types exist: pDCs (B220+, Gr1+, and IFN-α production), mDCs (CD11b+CD8α−), and lymphoid DCs (CD8α+). Activated DCs influence the generation of polarized IL-12 (Th1) and IL-4 (Th2) lymphocytes. Tregs may be stimulated in vivo by specific subsets of IL-10-producing DCs. Two different pulmonary subsets of DCs exhibiting plasmacytoid morphology induce Tr1-type Tregs in vitro and in vivo. Th1-type Tregs are induced by pulmonary CD8α+ DCs, and Th2-type Tregs are induced by pulmonary CD8α− DCs secreting IL-10. These Tregs produced IL-10 and blocked the development of asthma in mice. CD4+CD25+ Tregs can be expanded in vivo by

mature DCs secreting IL-10.

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