Oral Tolerance: Not Simple But more Complex

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ABSTRACT

The intestinal immune system can discriminate between harmful and unharmful antigens and do not provoke productive immunity to unharmful antigen. Thus oral administration of antigen is one of classical methods for inducing antigen-specific immune tolerance in the periphery. Furthermore, oral tolerance has been investigated for the treatment of autoimmune disorders in human clinical trials. However, the detail mechanism of oral tolerance and contributing factors are not defined clearly at this time. Recent studies demonstrate unique types of immune cell that suppressing immune response, such as regulatory T cell and tolerogenic dendritic cell. This article reviews the factors involved in oral tolerance and discusses our current understanding base on the recent literatures and our works. **(Immune Network 2003;3(3):169-175)**

Key Words: Oral tolerance, antigen presenting cell, regulatory T cell, gut-associated lymphoid tissue

Introduction

Immunological tolerance means a state of unresponsiveness to a particular antigen. Oral administration of antigen is a long-recognized method to induce immune tolerance to the antigen, termed oral tolerance. Oral tolerance was first described by Wells in 1911 as a state in which systemic anaphylaxis in guinea pigs was prevented by previous feeding of hen's egg protein (1). It has been well described that oral Ag can induce suppression in Ab production, Th1/2 response, and the cytotoxic T lymphocytes (CTL) response against the Ag (2-5). Subsequently, oral tolerance has been employed for the treatment of autoimmune diseases in both animals and humans (Table I).

It has been well described that oral administration of relevant Ag effeciently prevents the onset of autoimmune and allergic disorders in experimental animals in various experimental disease models (6-12). We also reported that both high-dose and low-dose administration of allergen via oral route completely prevented the development of eosinophilia in a murine model of asthma (Fig. 1). However, application of oral tolerance after disease onset yielded conflict results. There are several clinical trials with oral tolerance (13-15). It has been tested whether oral tolerance could affect the clinical course and immune responses in patients with relapsing remitting multiple sclerosis (MS). MS is an autoimmune disorder and self-Ag such as myelin protein is speculated as the causing Ag. Results demonstrated a decrease in myelin basic protein reactive cells in the bloodstream of MS patients fed myelin as compared to that taking placebo. A 60-patient double-blind trial of oral col-

Table I. Trials for application of oral tolerance in immunopathogenic disorders

Species	Diseases or disease models
Mouse	Experimental autoimmune Encephalomyelitis
	Experimental arthritis
	Experimental anti-phospholipid syndrome
	Experimental autoimmune uveoretinitis
	Experimental insulin dependent diabetes mellitus
	Experimental autoimmune myasthenia gravis
	Experimental allergic asthma
Human	Multiple sclerosis
	Rheumatoid arthritis
	Uveitis
	Insulin dependent diabetes mellitus

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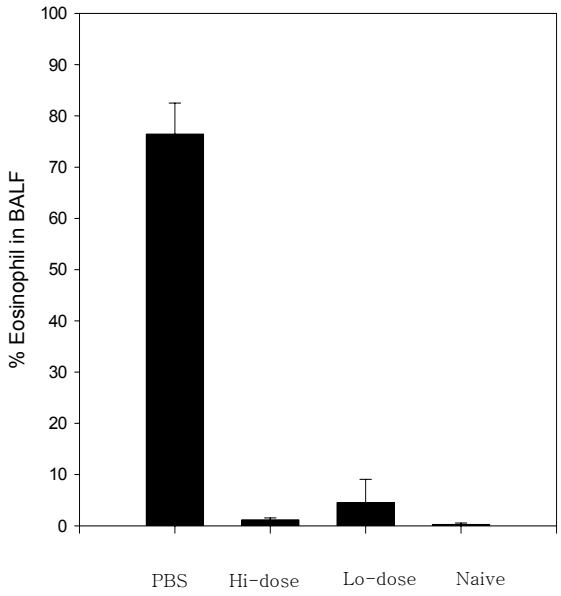

Figure 1. Effect of oral tolerance in development of eosinophilia in mice. Groups of BALB/c mice were given 20 mg or 2 mg of model allergen (Ovalbumin) or PBS as a control. Then these mice were sensitized with OVA in alum and inhaled aerosol OVA to induce allergic asthma. Cells from the bronchoalveolar lavage fluid (BALF) were stained, counted and the percentage of eosinophils calculated. Note the complete blocking of the infiltration of eosinophil in mice fed high or low dose of allergen.

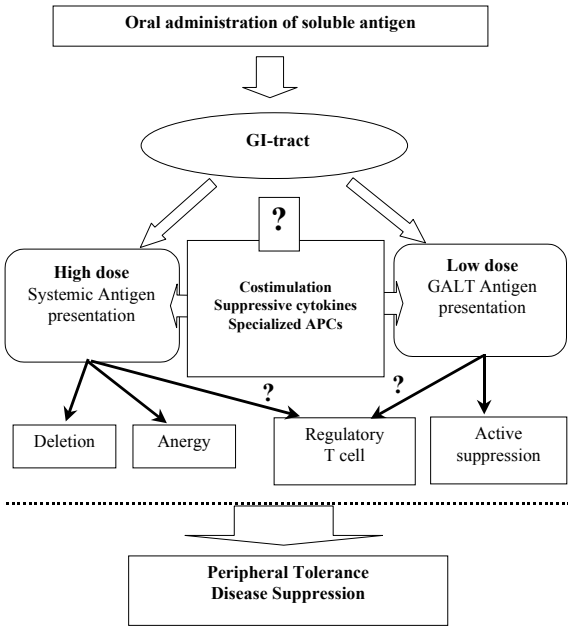

Figure 2. Proposed mechanism of oral tolerance. The primary factor determining which form of oral tolerance develops following oral tolerance is the dose of antigen that is fed, low doses of antigen favor the generation of active suppression, whereas high doses of antigen favor deletion or anergy.

lagen administration to patients with rheumatoid arthritis demonstrated a decrease in joint swelling and disease index in those patient fed collagen compared to those given the placebo. More clinical trials are under investigation including allergy as well as autoimmune disease. However, several studies demonstrated that oral administration of autoantigen in mice induces a cytotoxic T lymphocyte response that could lead to the onset of autoimmunity, which suggests that caution should be used when applying this approach to the treatment of human autoimmune diseases (16,17).

Mechanisms of Oral Tolerance

Peripheral tolerance is not programmed in the germ line but is acquired during maturation of immune system. Three basic mechanisms explain antigen-driven tolerance: clonal deletion, clonal anergy, active suppression. The primary factor determining which form of oral tolerance develops is the dose of antigen that is fed (2,18-20). It has been suggested that low doses of antigen favor the generation of active suppression-driven tolerance, whereas high doses of antigen favor deletion or anergy-driven tolerance (Fig. 2). However, the mechanism of oral tolerance seems to be more complex. They are not mutually exclusive and may occur simultaneously, and the frequency of antigen administration is also involved. Recent studies showed that multiple high dose of oral Ag induced antigen-specific regulatory T cells (Tr) in mouse models. Moreover, oral Ag induces regulatory cells which secreted suppressive cytokines TGF-β and IL-10. Furthermore, although the type and status of APCs that uptake and process fed-Ag is important in the induction of oral tolerance, it is not described clearly at this time. We will discuss our current understanding regarding the role of each factor in inducing oral tolerance from recent literatures and our studies.

Gut-Associated Lymphoid Tissue (GALT)

Mucus area, especially GALT, has been investigated as a target for both vaccine development and tolerance induction. Orally administered antigen meets immune system via GALT throughout the gut. The GALT can be divided into inductive sites, which consists of Peyers patches and mesenteric lymph nodes (MLN), and effector sites, which consists of lamina propria and intraepithelial lymphocytes (IEL).

Peyer's patches and MLNs are the sites where Ag-specific T cells primarily respond against orally-fed Ag (Fig. 3). Peyer's patches are well-organized lymphoid nodules containing T cells, macrophage, den-

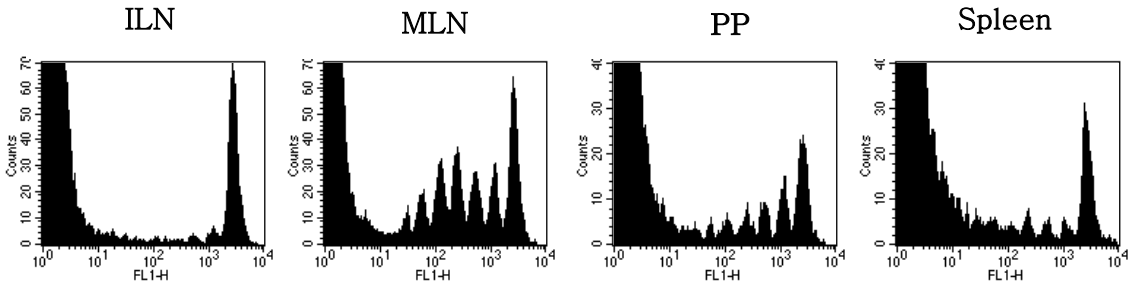

Figure 3. Mesenteric lymph nodes (MLN) and Peyer's patches (PP) are the primary sites for T cells to respond against intestinal antigen. CFSE-labeled DO11 T cells, expressing OVA-specific TCR, were adoptively transferred into syngenic mice. Then recipient mice were fed OVA and lymphoid cells from secondary lymphoid organs were harvested and analyzed by flow cytometer. Note the vigorous division of DO11 T cells in response to fed-OVA in MLN and PP.

dritic cells, and a germinal center with B lymphocytes. They are overlaid by M cells which function for antigen uptake and transfer. A recent report indicates that M cells are not the only cell type capable of transporting Ag across the epithelial barrier but the dendritic cells (DC) might sample luminal Ag directly (21). Although Peyer's patches have been thought to be a site where active suppression of oral tolerance is generated, several studies demonstrated that oral tolerance could be induced in mice lack of Peyer's patches (22-24).

Mesenteric lymph nodes (MLN) is known as a main draining lymph nodes of orally administered Ag (Fig. 3). The majority of MLN is CD4 T cells. Their development is distinct from that of both Peyer's patches and peripheral lymph nodes. As a result of the unique anatomical features, the MLNs might be a crossroads for lymphocytes between the peripheral and mucosal recirculation. There is little doubt that MLNs play a pivotal role in oral tolerance since it is impossible to induce oral tolerance in mice lack of MLNs (24,25). The involvement of each lymphoid tissue in oral tolerance is not clear at this time.

Antigen Presenting Cells in Oral Tolerance

APCs are the platform of the immune response. Especially DCs are sentinels of immune system. They sense 'danger signal' such as invasive pathogens and tissue damage and initiate immunity to remove such danger (26,27). It seems evident that DCs also regulate tolerance as well as immunity (28-30).

There might be a unique subset of APC that specialized for inducing and maintaining tolerance. In this case, this subset of APC (tolerogenic DCs) may overcome other APC (immunogenic DCs) and lead tolerance to oral Ag. Wakkach *et al* reported that a subpopulation of DCs specifically induce tolerance in vivo through the differentiation of Tr1 cells (31). Furthermore, recent study reported that there are several inhibitory receptors on DCs rendering these cells tolerogenic to CD4 T cells (32). Characterization of DC subtype responsible for tolerance in mucosal tissue would be interesting.

There is growing evidence that dendritic cells lead T cell to be anergic by regulating tryptophan metabolism. In a certain microenvironment, such as placenta, DCs express tryptophan-degrading enzyme indoleamine 2,3 dioxygenase (IDO) on the surface (33,34). By depleting tryptophan or by its metabolites, induction of IDO blocks clonal expansion of T cells and finally T cells become anergic. Originally, IDO was thought as a mechanism for fetus protection from attacks of mother's T lymphocytes. However, IDO expression was also reported in non-pregnant condition, suggesting this enzyme may have a role in immunoregulation (35). Dissecting the role of IDO in mucosal tolerance will be interesting.

One of the most interesting characteristics of GALT is the presence of distinctive subsets of DCs (36). In addition to the conventional subsets of myeloid and lymphoid dendritic cells, $CD8a^{-}CD11b^{-}$ DCs are found in MLNs and Peyer's patches although roles of this subset of DCs remain unclear. For its unique environment, DCs in GALT are thought to have distinctive properties. For example, splenic $CD8a^{-}CD11b^{+}$ DCs (myeloid) produce IL-12 in response to RANK stimulation whereas the same subset of Peyer's patch DCs produce IL-10 in response to the same stimulus (37). Thus it seems apparent that Ag-loaded APCs (especially DCs) have a crucial role in induction of oral tolerance.

Several recent studies proposed the role of APCs in mucosal tolerance. Alpan et al demonstrated that Ag-loaded dendritic cells from MLNs induce T cells to produce IL-4 and IL-10 (24). Akbari *et al* showed that Ag-loaded dendritic cells in MLNs produce TGF-β and stimulate T cell to produce both IL-10 and TGF-β (38).

It is widely accepted that peripheral tolerance to an exogenous Ag might be caused by the lack of costimulatory molecules on APCs. Therefore, it seems feasible to assume that providing costimulatory molecules on APCs would overcome oral tolerance. Nevertheless, our recent work has indicated that stimulation of APCs by CD40 ligation fails to overcome the induction of oral tolerance (unpublished data). CD40 ligation induced costimulatory molecules such as CD40, CD80, and CD86 on APCs efficiently and enhanced the division of Ag-specific T cells in MLNs, however, tolerance can be established in anti-CD40 mAb treated mice as well as control Ab treated mice by oral administration of Ag. Our results propose that providing costimulatory molecules on Ag-loaded APCs is not sufficient to reverse the induction of oral tolerance.

Regulatory T Cells in Oral Tolerance

It is well described that a population of CD4+ T cells producing transforming growth factor-β (TGF-β) can be generated by repeated administration of low doses of oral Ag, and this population was termed Th3 cells (2,20,38). These cells have been suggested to suppress immune response *in vivo* and *in vitro*. Recently, a population of CD4 T cells that produce IL-10 (termed Tr1 cells) can be generated in vivo as well as in vitro by intranasal administration of soluble Ag (38). Pulmonary dendritic cells producing IL-10 have been shown to be crucial to generate Tr1 cells. These Tr1 cells have been shown to suppress autoimmunity *in vivo*. However, this type of cells has not been isolated in orally-tolerized mice at this time. Accumulating evidence showed that $CD25^+$ $CD4^+$ regulatory T cells (termed Tr cells) are generated in the thymus and suppress immune response in vitro via cell-contact dependent manner. Transfer of $CD4^+$ T cells depleted of Tr cells caused a variety of autoimmunity in scid mice indicating that Tr cells prevent autoimmunity *in vivo*. Most recently, two papers described that Tr cells are also generated in the periphery by administration of tolerogeic Ag, especially oral Ag (40,41). In accordance with these papers, we observed that the percentage of Tr cells in $CD4^+$ T cells increased in DO11 mice by oral administration of OVA (unpublished observation). Increase of Tr cells is not restricted in lymphoid organs in GALT but through all secondary lymphoid organs including spleen and distal lymph nodes. Tr cells generated in the periphery possess regulatory properties *in vitro* as the same way described in thymus-derived Tr cells. It has also been shown that transfer of Tr from orally tolerized mice into syngenic mice can suppress Ag- specific immune response *in vivo* (41). Based on the described observation, it seems reasonable to assume that Tr cells are crucial to induce and maintain tolerance by oral administration of Ag. However, our recent experiments demonstrated that oral administration of a high dose of antigen was able to suppress antigen-specific immune response in mice depleted of $CD25^+$ cells. In contrast, the unresponsiveness induced by lower doses of OVA was partially blocked by CD25-depletion prior to feeding. Depletion of $CD4^+CD25^+$ cells after mice were orally-tolerized did not reverse the tolerant status. These observations imply that $CD4^+CD25^+$ T cells are not necessary for maintenance of tolerance to oral Ag, but in limited circumstances may contribute to tolerance induction by oral Ag. Interestingly, anti-TGF-β neutralizing Ab in mice depleted of $CD25^+$ cells blocked the induction of tolerance by oral OVA, suggesting that Tr cell and TGF-β play a compensatory role for each other in inducing oral tolerance unpublished data.

CTLA-4 and Immunosuppressive Cytokines in Oral Tolerance

There are several immunoregulatory molecules on the surface of lymphocytes and one of the crucial roles of these molecules is regulation of the size of the immune response by delivering negative signals into the cell. The most well studied immunoregulatory molecule is CTLA-4. The critical role of CTLA-4 in regulating homeostasis in the immune system is described by CTLA-4-deficient mice. One study reported that CTLA-4 is required for induction of oral tolerance by multiple high doses of Ag (42). Interestingly, blockade of B-7.2 but not B-7.1 reversed the induction of low dose oral tolerance, suggesting different contribution of these two molecules *in vivo* in oral tolerance induction (43). A lot of studies showed that CTLA-4 is highly expressed on Tr cells although the role of CTLA-4 in suppressive property of Tr cell is still controversial (39). Recently, several molecules, such as PD-1, were suggested as new immunoregulatory molecules. Dissecting the role of such molecule in oral tolerance will be interesting.

Several cytokines are also involved in homeostasis of the immune system, especially TGF-β and IL-10 are known as suppressive cytokines. As mentioned above, TGF-β seems to be involved in oral tolerance. Weiner and colleagues were demonstrated that TGF-β secreting T cells, termed Th3 cells, were generated by oral Ag and suppressed the Ag-specific response. They also showed that transfer of Th3 cells prevented the induction of autoimmune disease and

this suppression was abrogated by neutralizing TGF-β (20). The production of TGF-β is not restricted by Th3 cells. Several reports showed that Tr cells produced TGF-β and expressed TGF-β as a cell-surface bound form (39). In addition, a recent study described that TGF-β was released by apoptotic cells (44). TGF-β secreted from apoptotic T cells inhibits proinflammatory cytokine production and contributes to regulation of immune system. Given that apoptosis is occurred continuously in the epithelial cells of the gut, the involvement of TGF-β in the immune response of GALT seems to be reasonable. Nevertheless, oral tolerance could be induced in TGF-β knockout mice regardless of Ag-dose suggesting that multiple mechanisms of tolerance coexist (45). We also observed that neutralization of TGF-β alone did not overcome the induction of oral tolerance.

IL-10 is also known as suppressive cytokine. It has been reported that intranasal administration of antigen induced antigen-specific Tr1 cells producing IL-10 (38). They also showed that IL-10 producing pulmonary dendritic cells loaded intranasal Ag are crucial to generate Tr1 cells. However, oral tolerance established normally in IL-10 deficient T cells, suggesting secretion of this cytokine by Ag-specific T cell is not required for induction of oral tolerance (46). In addition, Tsitoura *et al* showed that neutralization of the immunosuppressive cytokines IL-10 and TGF-β did not abrogate the induction of mucosal tolerance (47).

Cross-presentation of Orally Administered Antigen

Oral administration of soluble antigen can lead to hyporesponsiveness of cytotoxic T cells to a subsequent challenge with the same antigen. However, it has been reported that oral OVA primed cytotoxic T cells capable of inducing autoimmune diabetes (16,17). It has been proposed that oral administration of antigen primarily lead Ag-specific T cells to activate and proliferate followed by becoming anergic. However, in a certain condition, these primarily activated T cells gained effector function and lead to the onset of autoimmunity. Although oral tolerance was applied to clinical trials, this strategy is not successful yet. Failure of human trial is at least partially due to the induction of Ag-specific CTLs. Induction of CTL by oral administration of antigen was shown to be dependent on CD40-CD40L interaction (48). However, the phenotype of DC responsible for cross-presentation of oral Ag has not been defined yet. More studies should be accompanied in terms of cross-presentation of oral Ag since it will rovide crucial information for human clinical trials.

Concluding Remarks

For decades, the mechanism of oral tolerance was simply described as clonal deletion, clonal anergy or active suppression according to the dose of Ag. As we described above, multiple factors are involved in mucosal immunity. In most cases, modulation of a single factor failed to reverse oral tolerance. Thus it seems dangerous to assume that one single factor determine immunity versus tolerance against oral antigen. Multiple factors are probably playing complementary role for each other and balance between immunity and tolerance (Fig. 4). For example, de-

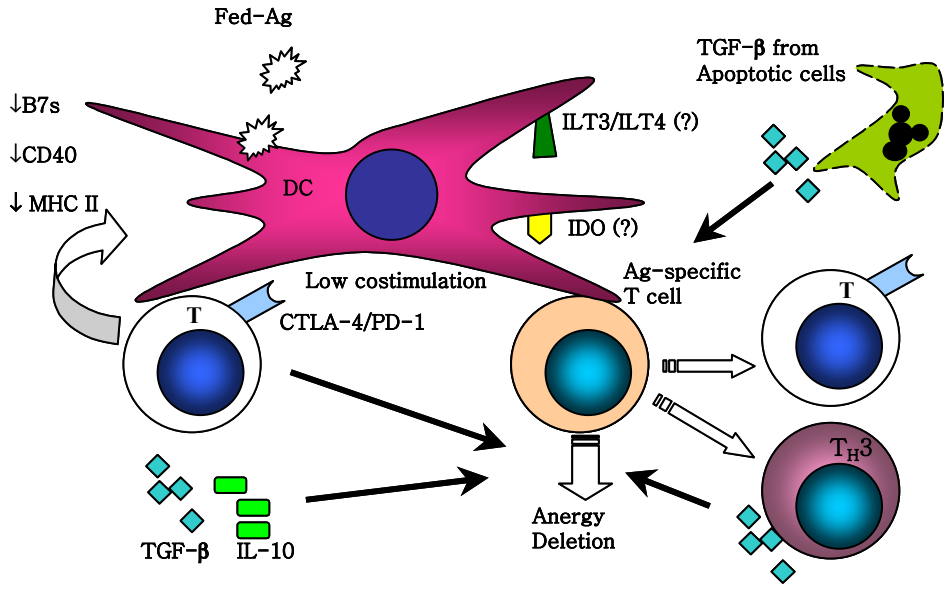

Figure 4. Multiple factors are involved in the induction and maintenance of oral tolerance. Both cell-intrinsic and extrinsic elements are involved in T cell response, especially in GALT. We propose that not one factor but multiple factors determine between tolerance and immunity in response to intestinal antigen.

pletion of Tr or TGF-β does not overcome the induction of oral tolerance. However, depletion of both factors completely abrogates the induction of oral tolerance (unpublished observation). Since GALT has unique anatomical features and has distinct phenotype of immune cells, the role of molecules and cells described in other organ or tissues should be redefined in GALT environment.

Dysregulation of immune response to food or commensals can cause diseases such as Crohn's disease and coeliac disease. In addition, it is apparent that oral administration of autoantigen or allergen with appropriate regimen can prevent or reduce severity of autoimmune and allergic disorders. Hence, delineating the precise mechanism of immune response in GALT will provide insights on treating this regime for human clinical trials.

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