Introduction
Mucosa-associated organs represent the physical interface to the environment. They are, therefore, particularly vulnerable to damage by infectious pathogens or noxious agents. This is why all mucosae are under constant surveillance by a specifically organized mucosa-associated lymphoid tissue (MALT). Notably, mucosal immune responses differ functionally from systemic immunity against blood-borne antigens. For example, mucosal antigen uptake and handling induce antigen-specific mucosal immune responses, but normally suppress systemic immunity against most orally ingested antigens. An explanation of these differences is given in the following sections.

Oral tolerance
The above-mentioned difference between systemic and mucosal immune responses reflects the distinct challenges that mucosal surfaces face from being directly exposed to the external environment. To protect mucosal surfaces from injury and subsequently from organ damage and severe diseases, the mucosal immune system must be able to discriminate efficiently between potential pathogens on one side and to tolerate the tremendous number of commensal microbes and harmless food antigens on the other side. This phenomenon, called oral tolerance, has emerged as a fundamental aspect of mucosal immunity, contributing highly to intestinal homeostasis and human health.

Structural properties of the mucosal immune system
Oral tolerance is defined as a state of "systemic hyporesponsiveness" to orally administered harmless antigen(s) on subsequent antigen challenge. The breakdown of this delicate balance provokes uncontrolled mucosal inflammation due to unlimited antigen contact with the MALT. For example, in newborns, some regulatory pathways of mucosal immunity might not be fully matured, allowing for greater sensitization to harmless dietary antigens instead of suppression. Therefore, food allergies can occur. Presumably, probiotic bacteria, with their numerous mechanisms of action, may represent a hopeful therapy to treat allergic disorders, as recently reviewed. The complexity of the mucosal barrier deserves some attention, considering the anatomical aspects of tolerance against luminal antigens. Both cellular and noncellular components cooperate to maintain mucosal barrier function. Among noncellular components, luminal enzyme activities, antimicrobial factors (e.g., defensins), and secretory IgA antibodies are present in large amounts in the mucous layer covering the mucosal surface. These components neutralize bacteria and viruses. The proteolytic cleavage of food antigens from egg, soy, fish, or nuts minimizes their immunogenic properties. Mucin glycoproteins lining the intestinal epithelium contribute substantially to mucosal barrier function. Remarkably, intestinal epithelial cells and luminal commensal bacteria closely interact to terminate and/or limit mucosal immune responses at a complex molecular level. For example, it has been demonstrated that recognition by intestinal epithelial cells of selected probiotic bacteria strongly down-regulates an important proinflammatory signaling cascade, the nuclear factor-κB pathway. Even the composition and functional activities of the gut microbiota crucially affect the structure and functions of the mucosal immune system.

Immunological networks
The efficient recognition of potential pathogens as one task of mucosal immunity includes inductive sites, such as Peyer's patches, where T-helper type 2 (Th2) cells provide cytokine help for B lymphocytes to switch to IgA antibody production. The lamina propria, as an effector site of mucosal tissues, contains many mature B plasma cells secreting secretory IgA delivered for mucosal protection against potential pathogens. Numerous T-helper cells and cytotoxic T cells in the lamina propria mediate cell-mediated immunity against microbes and viruses. For active oral tolerance to occur,
more than one mechanism presumably prevents uncontrolled mucosal immune responses against harmless antigens. Functionally distinct T-cell populations interact with differently specialized subtypes of antigen-presenting cells (APCs) in distinct mucosal compartments. In this context, it is reasonable to assume that the maturation and activation stage of locally present APCs, such as dendritic cells, dictates the fate of mucosal T-cell activation.11 Additional T cells with profound immunosuppressive functions, summarized under the term regulatory T cells, have been identified (Table).12 These include T-regulatory 1 (Tr1) cells and Th3 cells. From experimental models for autoimmune encephalomyelitis (EAE), Weiner and colleagues13 coined the term Th3 cells to explain their results. In mice orally fed myelin basic protein as an autoantigen for multiple sclerosis in humans, the peripheral immune response against the same antigen was inhibited on challenge. As responsible cell types, Th3 regulatory cells were detected, secreting large amounts of the cytokine transforming growth factor β. Interestingly, higher antigen doses favored T-cell anergy and/or depletion, whereas lower antigen doses seemed to generate tolerance mediated by these Th3 cells.13 Other regulatory T-cell populations such as Tr1 cells differed from classic Th1 cells by their secretion of larger amounts of the immunosuppressive cytokine interleukin 10. Interleukin 10 controls Th1 cell activation and several macrophage functions.

Clinical implications for oral tolerance

Altogether, oral tolerance mechanisms represent a continuous natural immunological event driven by exogenous antigens. For therapeutic purposes, it seems logical to assume that some human autoimmune diseases, such as multiple sclerosis or type 1 diabetes mellitus, may be prevented by orally given self-antigens. However, recently reviewed work on this topic indicated that this immunological concept functions well in animal disease models, but yielded inconsistent results in human clinical trials.14 In contrast, sublingual immunotherapy (SLIT) with oral allergen extracts for allergic rhinitis and conjunctivitis considerably improved symptom relief of these disorders.15 Ongoing research efforts on the basic mechanisms of this fascinating part of mucosal immunity hopefully will help prevent some pitfalls, so that the use of oral tolerance pathways may in the future become an inherent part of immune therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>“Natural” T reg Cells</th>
<th>“Induced” T reg Cells</th>
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<tbody>
<tr>
<td>Inducing stimuli</td>
<td>TCR stimulation with self-peptides</td>
<td>TCR stimulation with peripheral (auto) antigens, foreign antigens, dietary antigens, or pathogens</td>
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<td></td>
<td>Type of APC, mode of antigen presentation, and cytokine milieu are also important</td>
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<tr>
<td>Origin</td>
<td>Derived from the thymus</td>
<td>Conversion and/or expansion of nonregulatory peripheral CD4⁺ naive, memory, or effector T cells</td>
</tr>
<tr>
<td>Phenotype</td>
<td>FOXP3 positive, CD25 positive</td>
<td>Highly variable coexpression of FOXP3 and CD25</td>
</tr>
<tr>
<td>Mechanisms of suppression</td>
<td>T-cell–T-cell–contact and/or T-cell–APC–contact dependent</td>
<td>Cell-contact–dependent, cell-bound TGF-β and, in some cases, soluble TGF-β</td>
</tr>
<tr>
<td></td>
<td>Cytokines (IL-10 and TGF-β)</td>
<td>Other cytokines (IL-2, IL-4, IL-6, IL-13, IFN-γ, and TGF-β)</td>
</tr>
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<td></td>
<td>Accessory molecules (e.g., CTLA-4 and GITR)</td>
<td>Th3 cells (soluble TGF-β and/or IL-10)</td>
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<td></td>
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<td>Tr1 cells (IL-10)</td>
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<td></td>
<td></td>
<td>CD8⁺ Treg cells (not well defined, cell-contact–dependent, ILT3 and ILT4)</td>
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</tbody>
</table>

**Abbreviations:** APC, antigen-presenting cell; CTLA, cytotoxic T-lymphocyte antigen; FOX, fork head box; GITR, glucocorticoid-induced tumor necrosis factor receptor; IFN, interferon; IL, interleukin; ILT, immunoglobulinlike transcript; TCR, T-cell receptor; TGF, transforming growth factor; Th, T-helper cell; Treg, T regulatory; Tr1, T-regulatory cell type 1.
References:

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