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Review

History and mechanisms of oral tolerance

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ABSTRACT

Since its first description by Wells and Osbourne in 1911, oral tolerance has intrigued researchers due to its potential for therapeutic applications. Oral tolerance can be defined as an inhibition of specific immune responsiveness to subsequent parenteral injections of proteins to which an individual or animal has been previously exposed via the oral route. Tolerance induction to commensal bacteria and dietary proteins represents the major immunological event taking place in the gut in physiological conditions. Multiple mechanisms have been proposed to explain the immune hyporesponsiveness to fed antigens: low doses of orally administered antigen are reported to favor active suppression with the generation of regulatory cells, whereas high doses would favor clonal anergy/deletion. In this review, we highlight historical aspects and the mechanisms proposed for oral tolerance induction.

1. Introduction

In 1953, Peter Medawar coined the term "tolerance" [1]. It was then incorporated by Burnet [2] in his classical Clonal Selection Theory. Burnet's concept of tolerance involves three basic assumptions, where (i) the primary function of the immune system is to protect the organism from pathogens or from non-self materials; (ii) to perform this function, the immunologic response must be an inflammatory response; and (iii) tolerance is a negative counterpart of the immune system due to neonatal deletion of "forbidden clones." Thus, oral tolerance has classically been defined as the specific suppression of cellular and/or humoral immune responses to an antigen by prior administration of the antigen by the oral route [3]. It presumably evolved as an analog of self-tolerance to prevent hypersensitivity reactions to food proteins and bacterial antigens present in the mucosal microbiota.

Oral tolerance is of paramount importance because it contributes to the balance between exogenous antigens that come from diet and commensal bacteria, and the self-components of the body at the mucosal surface. The mucosa of the small intestine alone is estimated to be 300 m^2 in humans and there are 10^{12} lymphoid cells per meter of human intestine [4]. Approximately 130–190 g of dietary proteins is absorbed daily in the gut [5] and the number of bacteria colonizing the colonic mucosa can reach 10^{12} microorganisms/g of stool [6]. These antigens are crucial for the maturation of the immune system in the post-weaning period and oral tolerance rather than inflammatory immune response is established in order to keep homeostasis. Thus, oral tolerance is a form of peripheral tolerance that evolved to treat external agents that gain access to the body via a natural route as internal components that then become part of self. In this review, historical aspects of oral tolerance as well as the mechanisms involved in its induction are highlighted.

2. Historical aspects

2.1. Immunological tolerance

"Immunological tolerance" has often been defined as a mechanism by which the immune system prevents pathologic auto-reactivity against self and thus prevents autoimmune diseases. A classical study published in Nature in 1953 by Billingham, Brent, and Medawar demonstrated that immune responses against a defined set of antigens could be abolished, or at least attenuated, using a biological approach [1]. This work was inspired by the study of Ray Owen [7], who for the first time observed the phenomenon of immunological tolerance in vivo by showing the coexistence of two types of erythrocytes in the blood of dizygotic cattle twins: each calf contained a proportion of red blood cells belonging genetically to itself, mixed with red blood cells belonging to the zygote lineage of its twin. For different proposes, Billingham and Medawar were investigating the fate of skin allografts in young cattle in order to develop a test to distinguish between fraternal and identical twins. Surprisingly, they found that skin grafts transplanted from one twin to the other were accepted, irrespective of the origin of the twins [8]. Next, to further prove that tolerance to a known antigen could be induced in vivo, they demonstrated, by inoculating *in*

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uterus a suspension of living cells from an adult mouse of a given strain to a fetal mouse of another strain, that when the inoculated mouse grew up, it was found to be partially or completely tolerant of skin grafts transplanted from any mouse belonging to the strain of the original donor. Thus, the hypothesis underlying this experiment is that "mammals and birds never develop, or develop to only a limited degree, the power to react immunologically against foreign homologous tissue cells to which they have been exposed sufficiently early in fetal life" [1].

This classic work, together with those from Owen and Hasek [7,9], defined our current understanding of the immunological basis of tolerance to self and foreign antigens. The definition of tolerance as a negative counterpart of immunity comes from the work of Burnet who first proposed self/non-self discrimination as a major principle driving the operation of the immune system and tolerance to self-components as a deletional event taking place at early periods of development [2]. According to Burnet's "Clonal Selection Theory", self-tolerance was based on the blindness of the mature immune system to body components. However, the description of the thymic selection of T lymphocytes, the subsets of T cells, including the regulatory T (Treg) cells, and their distinct actions, as well as the demonstration of autoreactive B and T cells in normal individuals contributed to change this scenario [10–13]. It became clear that natural tolerance to auto-components is a more complex phenomenon. Studies derived from this new approach clearly demonstrated that natural tolerance to self is an active process that depends on the activity of non-inflammatory/regulatory auto-reactive T lymphocytes present at a stable frequency in the normal repertoire [14–16]. In analogy to the natural non-inflammatory reactivity that the immune system mounts to self-components, the name "oral tolerance" has been given in the seventies to the immunological tolerance to antigens that access the body via the oral route [3].

2.2. Oral tolerance

In the beginning of the 20th century, Wells and Osbourne [17] demonstrated for the first time the phenomenon of immunological tolerance through oral fed antigens by showing that guinea pigs fed corn-containing diet, but not corn-free diets, were not anaphylactically sensitized to zen, a major protein of corn. Subsequently, several researchers showed that when mammals are exposed to foreign macromolecules by digestive route, delivered either by gastric intubation or ingested with maternal milk, they became immunologically tolerant to these proteins [18,19]. Moreover, David [20] showed that rats fed horse serum or pollen extracts were made tolerant to those antigens; Thomas and Parrot [21] tolerized rats by repeated feeding of bovine serum albumin; and Andre and co-workers [22] showed oral tolerance induction in mice fed sheep red blood cells. In the context of allergic disease, Vaz et al. [3] contributed significantly to the field by showing that intense and prolonged states of specific immunologic tolerance with profound specific IgE reduction could be induced in adult mice by a single exposure to OVA. Thus, these works demonstrated that, despite the fact that the vast majority of the macromolecules ingested as food are degraded within the gut, antigenically intact materials are absorbed in amounts sufficient to induce significant modifications in the immune responsiveness of the organism.

The demonstration of transferable cellular suppression associated with oral tolerance is a recurrent theme reported by many investigators [23]. Mowat et al. [24] reported that high doses of ovalbumin-induced tolerance were not abrogated by cyclophosphamide, which is believed to block active suppression, and that such tolerance affected antibody responses. Low doses of ovalbumin induced a state of tolerance that could be reversed by cyclophosphamide and primarily affected cell-mediated responses. Thus, this study already seemed to delineate active suppression vs. anergy depending on the dose of antigen (discussed below). Moreover, Hanson & Miller [25] reported two components of oral tolerance following oral administration of ovalbumin: tolerance was observed in both cyclophosphamide-treated and untreated animals, but tolerance from cyclophosphamide-treated animals could not be transferred.

Our early studies of oral tolerance in autoimmune models have found active suppression to be an important mechanism, and we have identified regulatory cells generated following oral tolerance that act via the secretion of antigen-non-specific regulatory cytokines triggered by the fed antigen [26]. Such cells were first characterized in the Lewis rat model of experimental autoimmune encephalomyelitis (EAE) orally tolerized to low doses of guinea pig MBP. The regulatory cells identified in that model were CD8+ T cells [27]; they transferred suppression in vivo and also suppressed in vitro; and acted via the secretion of TGF-β following antigen-specific triggering [28]. Further studies demonstrated that the epitopes of guinea pig MBP triggering CD8+ T regulatory cells following orally administered MBP were different from the encephalitogenic determinant [29]. Moreover, TGF-β-secreting regulatory cells could be found in Peyer's patches 24–48 h after one feeding of low doses of MBP, and these cells did not proliferate in response to 1 mg MBP even though they release TGF-β upon in vitro stimulation [30].

When similar studies were extended to a mouse system, it was found that CD4+ T cells were also responsible for active suppression, both in vivo and in vitro [31,32]. Thus, when a low dose of MBP was administered orally to SJL/J mice, Th1 but not Th2 immune responses were suppressed. In fact, Th2 cytokines (IL-4, IL-10) and TGF-β were significantly increased in mice fed with low doses of MBP. Furthermore, if animals were fed MBP and then immunized intraperitoneally with the same antigen, one enhanced the production of IL-4 and IL-10, as well as TGF-β. McGhee and colleagues also found that exposure of soluble antigens to the gut preferentially generated Th2-type responses as judged by increased IL-4 and IL-5 production [33]. Thus, in the gut, immune responses to soluble antigen are preferentially of a Th2 type and involve the generation of cells that secrete TGF-β. When cells from mice fed and immunized with MBP were further studied in vitro, it was found that both CD4+ and CD8+ T cells secreted TGF-β, whereas only CD4+ T cells secreted IL-4 and IL-10 [31]. However, it was clear in the SJL model that a population of TGF-β-secreting CD4+ T cells were also generated and amplified in the gut following the feeding and subsequent immunization with MBP.

CD4+ T cells were then cloned from the mesenteric lymph nodes of MBP-fed mice, and it was found that the majority of T-cell clones produced active TGF-β in addition to varying amounts of one or the other of the Th2-type cytokines (IL-4 and IL-10). However, it appeared that the TGF-β clones were different from classic Th2-type cells, as there was a general correlation between the secretion of IL-4 and IL-10 in an individual clone, whereas this was dissociated for TGF-β and IL-4/IL10. We named these cells as Th3 cells. Mucosal-derived CD4+ T cell clones were further characterized for their epitope specificity, MHC restriction and TCR usage. Sequence analysis of their cDNA revealed that they used Vα1 or Vα3, and Vβ4 or Vβ17, all of which were also used by encephalitogenic Th1 cells. Most interestingly, one of these mucosal Th3 clones used identical TCR Vα and Vβ chains as one of the encephalitogenic Th1 clones. The regulatory T cell clones generated in this study had striking similarities to the encephalitogenic CD4+ Th1-cell clones in terms of their specificity, TCR usage and MHC restriction. However, they could be distinguished from the encephalitogenic CD4+ Th1-cell clones by the fact that they produced suppressive cytokines (TGF-β, IL-4 and IL-10) following antigen-specific activation. The clones inhibited the proliferation and cytokine production of MBP-specific Th1 cells, and they suppressed the development of MBP-induced EAE and proteolipid protein-induced EAE, and this suppression was abrogated by in vivo injection of anti-TGF-β antibodies. This demonstrated that these clones were able to mediate bystander suppression in vivo mediated by TGF-β production [31].

The identification of the master transcription factor regulator Foxp3 in 2003 by Sakaguchi's group [34] (discussed below) shed light on how a CD4+ T cell, using identical variable TCR chains to an effector CD4+

T cells, can become committed to a regulatory phenotype. This is particularly important in mucosal sites due to the necessity of constant regulation. In fact, CD4 + Foxp3 + regulatory T (Treg) cells have been shown to be crucial for oral tolerance induction, and they suppress in a cell-cell contact manner, but also through the release of TGF-β and IL-10 [35]. Because Th3 cells were described before the Foxp3 era, and Foxp3 + T cells share many suppressive properties with Th3 cells, it is possible that these cells may give rise to each other depending on the environment where they encounter the cognate antigen.

3. Mechanisms of oral tolerance induction

3.1. The gut mucosa as a specialized site for oral tolerance induction

Although it is generally assumed that our major surface of contact with the external milieu is the skin, the area of the mucosa exceeds in several folds the skin area. The mucosa of the small intestine alone is estimated to be 300 m^2 in humans [4]. Moreover, mucosal surfaces, differently from the skin, are more permeable to antigens, and a majority of the contacts with foreign antigenic materials occur at the mucosal sites. Approximately 30 kg of food proteins reach the human intestine during a year, and 130–190 g of these proteins are absorbed daily in the gut [5]. The microbiota in the small intestine is also an additional source of natural antigenic stimulation, and the number of bacteria colonizing the human intestinal mucosa is approximately 10^{12} microorganisms/g of stool [6]. It is also known that intestine lodges the most abundant lymphoid tissue in the body. There are 10^{12} lymphoid cells per meter of human small intestine [36,37]. The number of immunoglobulin (Ig)-secreting cells located in the murine and human gut exceeds by several fold the number found in all other lymphoid organs together [35,36]. Thus, it is reasonable to assume that antigenic contact initiated in the intestinal mucosa has an important impact in the activation of the immune system and in the consequent induction of oral tolerance. The three major consequences of oral antigen administration have been reported. It includes the local secretion of non-inflammatory IgA in the gut mucosa; the induction of systemic humoral and cellular immunity; and the development of systemic and/or local immunological tolerance, which prevent the potentially damage caused by active immunity when the offending antigen is encountered on subsequent occasions. The first two of these situations comprise the protective immune response to invasive pathogens, whereas dietary proteins and commensal bacteria predominantly induce immunological tolerance.

There are consistent evidences that the organized structures of the GALT (Gut-Associated Lymphoid Tissue), such as Peyer's patches (PP) and isolated lymphoid follicles (ILF) play an important role in the immune recognition of particulate antigens. However, the involvement of PP and ILF in the induction of oral tolerance is debatable [38]. One study demonstrated that inhibition of PP development during gestation impaired oral tolerance induction to protein but not haptens in adult mice [39]. On the other hand, some studies reported that oral tolerance could be induced in the absence of PP [40,41] and even in ligated small bowel loops regardless the presence or absence of PP in the respective gut fragment [42]. Nevertheless, it is becoming clear that antigen uptake by dendritic cells (DCs) underlying regular villus epithelium is critical for the development of tolerance by soluble antigens in the small intestine [43]. After taking up the antigen, CD103-expressing DCs migrate to the mesenteric lymph node (mLN), induce regulatory T (Treg) cells, which through the expression of gut-homing molecules, such as CCR9 and α4β7 integrin, migrate to the gut lamina propria and evoke tolerance. Importantly, the ability of CD103 + DCs to induce Tregs and the gut-homing molecules is directly linked to the production of retinoic acid from vitamin A by these DCs [44–47]. Moreover, mLN has been shown to be crucial for oral tolerance induction, because mice deficient for CCR7, a crucial chemokine receptor for cell migration to lymph nodes, failed to induce oral tolerance [48,49]. Furthermore, lymphotoxin-α-deficient mice lacking all lymph nodes and PP did not develop oral tolerance, but this was reversed by selective rescue of mLN development [50]. Consistent with this, surgical removal of mLN was shown to abrogate oral tolerance induction [49]. Thus, antigen uptake in the GALT, DC migration to the mLN and induction of gut homing imprinted Treg cells appear to be the pathway by which oral tolerance is induced.

3.2. Systemic tolerance after oral fed antigens

One of the important characteristics of oral tolerance is that it can spread out to the entire animal. This is somehow difficult to understand because antigen uptake and recognition are restricted to gut lamina propria, GALT and mLNs. It is possible that orally administered antigens can reach the circulation and activate the immune system. In fact, food proteins can be found in the blood of mice and humans soon after eating [51,52]. Moreover, food antigens can simultaneously activate T cells in the mLN and in the peripheral lymph nodes [53,54], and serum from protein-fed mice can induce antigen-specific tolerance in naïve recipients [55], suggesting that tolerogenic material is found in the circulation after protein feeding. Of note, antigens that reach secondary lymphoid organs may induce systemic tolerance because they are sampled by dendritic cells and presented to T cells in a non-inflamed environment. However, how proteins from the diet that reach the bloodstream are involved in oral tolerance induction remains elusive.

Another explanation for the systemic tolerance after oral fed antigens comes from the tolerogenic environment of the liver. The liver is located in a strategic position, where it receives blood from the hepatic artery and from the portal veins. Blood coming from the portal veins is rich in gut-derived antigens and due to the tolerogenicity of the liver, systemic tolerance to proteins that were not processed in the gut, and therefore reached the circulation, can be induced [56]. In fact, antigens injected directly into the portal veins induce tolerance [57], and preventing antigen from reaching the liver by portocaval shunting blocks oral tolerance induction [58]. Furthermore, liver sinusoidal epithelial cells can sample and present antigens to T cells, and it is known to induce tolerance rather than active immunity. Kuppfer cells and conventional liver dendritic cells also present antigens to T cells, rendering these lymphocytes tolerogenic (reviewed in [56]). Plasmocytoid dendritic cells, which are abundant in the liver, have also been shown to induce systemic tolerance to fed proteins and haptens [59]. Thus, the tolerant environment of the gut and the liver may contribute together to the systemic tolerance induced by fed antigens.

3.3. High vs. low dose of antigen in the oral tolerance induction

The phenomenon of oral tolerance can be explained by different mechanisms, which are primarily dependent on the dose, type and administration form of the antigen [24,60]. Anergy or clonal deletion occurs mainly with high doses of antigen whereas low and repeated doses of the antigen promote active regulation of suppressor cells (Tregs) [61]. Once oral tolerance is induced, various aspects of antigen-specific immune responses Th1 and Th2 are inhibited, such as production of immunoglobulins (IgM, IgG) [3,62,63] and synthesis and release of immunoregulatory cytokines, such as TGF-β, IL-10 and IL-4 [61,63].

A major conceptual advance in the oral tolerance field is the fact that TGF-β plays a central role in oral tolerance by being a primary link between distinct populations of Treg cells that are induced by feeding. Thus, conversion of CD4 + CD25- into CD4 + CD25 + T cells by the expression of Foxp3 involves TGF-β [35]. A membrane-bound form of TGF-β (containing latency-associated peptide − LAP) has also been described and CD4 + LAP + T cells mediate suppression in a TGF-β-dependent mechanism [64–66]. Thus, it appears that TGF-β-producing cells are not only crucial for oral tolerance, but they may be master regulators of most of the mechanisms triggered by antigen feeding.

3.3.1. Clonal deletion and anergy

We have shown that feeding increasing doses of OVA (0.5–500 mg) into OVA-T cell receptor (TCR) transgenic mice induced either a decrease or an increase in the frequency of CD4 + Vβ8.2 + OVA-specific T cells in the PP of fed mice [67]. In mice fed 500 mg OVA, there was a reduction of 10–20% of these clonotypic T cells in the PP, spleen, thymus and peripheral lymph nodes [67]. Clonal deletion of antigen-specific CD4 + T cells has been found after feeding high doses to fully transgenic mice [68–70]. However, feeding high doses of antigen to normal animals also seems to increase the susceptibility of their lymphocytes to die by apoptosis after systemic challenge with antigen in adjuvant [71]. In these experiments, lymphocytes from mice fed single high dose of OVA died rapidly when cultured in vitro in the absence of antigen, showing morphological and cytological evidence of apoptosis. Consistent with this, increased caspase activity and decreased levels of caspase-sensitive proteins in antigen-specific CD4 + T cells after long-term feeding of OVA to TCR transgenic mice were demonstrated [72]. Low number of transgenic cells adoptively transferred into wild type mice [73] was deleted after high dose feeding of OVA peptide [74] and cytochrome c [75]. However, clonal deletion could not be directly demonstrated in a study using normal animals that were adoptively transferred with limited numbers of identifiable TCR transgenic T cells [76].

Association between susceptibility to apoptosis and induction of oral tolerance is still unclear. Although there is evidence in normal mice that T cell resistance to apoptosis contributes to perpetuation of inflammatory bowel disease (IBD) and suppression of disease activity involves induction of T-cell apoptosis in the gut [77], oral tolerance is normal in Fas-deficient lpr mice [78]. An important connection between these reports on deletional events in oral tolerance induction and the generation of Tregs comes from the research on apoptosis. It has been reported that apoptotic cells are usually taken up by macrophages, and the phagocytosis of these dying cells through macrophage αvβ3 integrin results in the downregulation of pro-inflammatory cytokines and the induction of TGF-β production [79]. Therefore, antigen presentation that follows phagocytosis of these cells will take place in a regulatory milieu provided by TGF-β secretion. Apoptotic T cells can also release TGF-β, both in latent and bioactive form [80]. Uptake and presentation of apoptotic cells in the gut mucosa by lamina propria macrophages have been described as a physiological pathway for cellular renewal [81]. Interestingly, human lamina propria T cells exhibit an increased susceptibility to Fas-mediated apoptosis following CD2 pathway stimulation [82]. In addition, a subpopulation of DCs in the intestinal lymph, which contains fragments of apoptotic enterocytes, has been described. These DCs have relatively low stimulatory activity for T cells [83]. Thus, apoptosis of T cells [80] and clearance of apoptotic cells by macrophages [84] and DCs [83] may contribute to the generation of an immunosuppressive milieu. We can therefore hypothesize that clonal deletion of T cells at mucosal sites, as described in some high-dose oral tolerance experiments, may involve apoptosis, which results in both direct release of TGF-β by dying T cells and engulfment and presentation of apoptotic cell bodies by surrounding macrophages and DCs. Both processes may result in the induction of regulatory T cells, because TGF-β induces Th3 cells [26,85,86] and CD4 + Foxp3 + Tregs [16,87,88].

Another explanation for lack of T cell function in the absence of regulatory mechanisms is anergy of specific T cells. The upregulation of anergy-associated genes is largely nuclear factor of activated T cells (NFAT) dependent [89], and the transmembrane E3 ubiquitin ligase GRAIL is highly upregulated during anergy induction. Related to this, high-dose oral tolerance is abrogated in Grail −/− mice [90]. Furthermore, investigators have found that although orally tolerized T cells can form conjugates with APCs, they are defective in immunologic synapse formation, which appears related to the hyporesponsive state of orally tolerized T cells [91]. This appears to be the basis of peripheral tolerance to many self-antigens and its presence in oral tolerance was first suggested by experiments in which T cell tolerance was reversed in vitro by exogenous IL-2 [92]. Responsiveness to IL-2 and the absence of transferrable suppression were then used as the criteria for defining clonal anergy as the principal mechanism underlying oral tolerance to high doses of fed antigen [61,93–97]. This conclusion has also been supported by the studies in which adoptively transferred transgenic T cells were examined [74,76]. The dicotomy between anergy and active suppression may not be complete as there have been several reports on “anergic” regulatory cells [98–100]. Earlier studies on the cells rendered anergic have already raised the possibility that these cells do not function in a totally passive fashion in the tolerance they evoke [101,102]. It is now clear that anergic cells can retain other functions, such as production of cytokines, including IL-4 and IL-10 [103,104]. Moreover, anergic CD4 + T cells seem to act as suppressor cells in vivo and in vitro and to produce cytokines such as IL-4, IFN-γ and TGF-β [96,98,102,105–108]. Because these cytokines have been implicated as active mediators of oral tolerance, anergic T cells could function as regulatory cells in orally tolerized mice by releasing such mediators. This is supported by the fact that anergic CD4 + T cells from mice tolerized by feeding casein can mediate active suppression when transferred to SCID mice [96]. Thus, with our current understanding on regulatory T cells and their mechanisms of suppression, the word “anergy” as it has been used to characterize unresponsive cells induced during tolerance may not be an appropriated terminology anymore.

3.3.2. Regulatory T cells

Regulatory T (Treg) cells were first described in the 1970s, when they were considered to be mainly CD8 + and were referred as ‘suppressor’ T cells. The recent wave of research on CD4 + CD25 + Tregs rehabilitated the old concept of suppressor cells and brought important new insights into the tolerance field as a whole and to oral tolerance studies as a consequence. Initially reported by Nishizuka [109,110] and further explored by Sakaguchi, Nishizuka, and coworkers [111–113], studies on animals thymectomized as neonates showed that autoimmune pathology, characterized by gastritis, oophoritis, and orquitis, arises as a result of the ablation of a subpopulation of thymic T cells. These cells are able to restore immunoregulatory function in diseased mice upon adoptive transfer, and they have been characterized as CD4 + T cells that express the high affinity receptor for IL-2 (IL-2Ra or CD25) [114] and the transcription factor Foxp3 [34]. In fact, a mutation of the gene encoding Foxp3 results in manifestation of a disease known as IPEX or Syndrome immunodysregulation polyendocrinopathy and enteropathy associated to the X chromosome, characterized by autoimmune enteropathy, psoriasiform or eczematous dermatitis, nail dystrophy, and autoimmune skin conditions such as alopecia universalis and bullous pemphigoid [115].

Treg cells can be divided into two main classes: natural or nTregs and induced or iTregs. nTregs are generated in the thymus and express CD25 and Foxp3. These cells are anergic and therefore do not proliferate nor secrete IL-2, but depend on IL-2 produced by other lymphocytes to survive [116]. The regulatory mechanism of action of Treg cells involves cell-cell contact more than the secretion of cytokines [116]. This evidence was corroborated by experiments in which the two-photon intravital microscopy was used. It was shown that the contact between T cells and antigen-loaded DCs is shorter in the presence of Tregs than in its absence [117]. Molecules that contribute to the regulatory function of Treg cells include CTLA-4, GITR, CD39, CD73, latency-associated peptide (LAP), a membrane-bound TGF-β, and its anchoring molecule glycoprotein A repetitions predominant (GARP or LRRC32) [35].

In addition to nTregs, CD4 + CD25-Foxp3- naive T cells can be converted into functional CD4 + CD25 + Foxp3 + iTreg in the periphery. Importantly, iTregs, but not nTregs, are crucial for oral tolerance induction, because oral tolerance could be induced in mice devoided of naturally occuring Treg cells [118]. Consistent with this, a recent work has shown that under normal conditions, the vast majority of the small

intestinal iTreg cells are induced by dietary antigens from solid foods, have a limited life span, are distinguishable from microbiota-induced iTreg cells, and repress underlying strong immunity to ingested protein antigens [119]. Such intestinal iTreg cells are likely to be induced in the mLNs by specialized DCs that migrate form the gut to the mLNs, through a mechanism dependent on TGF-β and retinoic acid, a metabolite vitamin A [120]. However, in the presence of TGF-β and IL-6, as in an inflammatory process, naive CD4 + CD25-Foxp3- T cells can be differentiated into IL-17-producing CD4 + T (Th17) cells and favour inflammation [121,122]. Thus, TGF-β has a paradoxical effect of inducing distinct subsets of T cells with opposite effects on the immune response.

Peripherally-induced regulatory T cells may not only comprise those cells expressing the transcription factor Foxp3. In 1994, we described a subtype of CD4 T cells (Th3 cells) originated during oral tolerance induction to myelin basic protein (MBP) that secrets high amounts of TGF-β, IL-4 and IL-10 that suppress experimental autoimmune encephalomyelitis (EAE), a rodent model for Multiple Sclerosis [31]. Th3 regulatory cells form a unique T-cell subset, which primarily secretes TGF-β, provides help for IgA class switch and has suppressive properties for Th1, Th2 and Th17 cells. Th3 cells are distinct from the Th2 cells, as CD4 + TGF-β-secreting cells with suppressive properties have been generated from interleukin (IL)-4-deficient animals. Th3 cells are triggered in an antigen-specific fashion, but suppress in a non-antigen-specific manner, and thus mediate “bystander suppression” when they encounter the fed antigen at the target organ [123]. In addition to the secreted form of TGF-β, an active membrane-bound form was described. Murine CD4 + CD25 + Foxp3 + Tregs have been reported to express latency-associated peptide (LAP) and TGF-β on the surface after activation and to exert regulatory function by the membrane- bound TGF-β [64–66]. Blockage of TGF-β1 by anti-TGF-β monoclonal antibodies curtails the ability of these cells to suppress CD4 + CD25- T cell proliferation and B-cell immunoglobulin production in vitro [64]. We also have detected LAP on CD4 + CD25-Foxp3- cells in normal mice and these cell compartment increase after oral tolerance induction [65,124]. We therefore believe that Th3 cells are CD4 + CD25-Foxp3-LAP + cells that exist in the peripheral immune compartment and that is triggered by TCR signaling in the gut by oral antigen.

Although the investigation of oral tolerance has classically involved the administration of antigens, we have found that oral administration of anti-CD3 monoclonal antibody induces oral tolerance through a mechanism dependent on Treg generation [124]. By giving hamster anti-mouse CD3 (2C11 clone) to SJL mice and immunizing them with PLP emulsified in CFA to induce EAE, we found that oral anti-CD3 suppressed both clinical and pathological features of EAE [124,125]. Oral anti-CD3 administration was also found to ameliorate other autoimmune and inflammatory diseases, such as streptozotocin-induced and NOD autoimmune diabetes [126–128], type 2 diabetes in the Ob/Ob mouse [129], lupus prone SNF1 mice [130] and atherosclerosis in mice [131]. It is still elusive our current knowledge on how oral anti-CD3 works. Mechanistically, oral administration of anti-CD3 induced both CD4 + CD25 + LAP + and CD4 + CD25-LAP + Tregs in mLN and spleen [66]. Induction of Tregs by oral anti-CD3 is seen with lower doses rather than higher doses, suggesting that this effect is not simply related to administering higher doses of anti-CD3 to overcome degradation of the antibody in the gut. Indeed, we isolated biologically active anti-CD3 from intestinal eluates of animals orally dosed with anti-CD3 [126] and could visualize anti-CD3 being taken up by gut epithelial cells and binding to gut DCs in intestinal loop experiments [132]. Studies are in progress to test possible factors that may enhance oral tolerance induced by anti-CD3, including the combination of anti-CD3 and antigens, and anti-CD3 with pro-inflammatory cytokine-blocking monoclonal antibodies.

Another subtype of peripherally induced Tregs is the type 1 regulatory T (Tr1) cells. Tr1 cells are memory CD4 + T lymphocytes that express the surface markers CD49b and LAG-3, but are Foxp3 negative. Upon activation, Tr1 cells secrete high amounts of IL-10 and TGF-β, variable levels of IFN-γ, IL-5 and GM-CSF, and no IL-17. Tr1 cell suppressive properties are related to the release of IL-10 and TGF-β upon TCR activation by a cognate antigen [133], and like Th3 cells, they can mediate bystander suppression to other antigens [134]. Interestingly, Tr1 cells are better induced upon nasal tolerance [135] rather than oral tolerance, which preferentially gives rise to Th3 cells, as discussed above. Indeed, we have shown that nasal administration of anti-CD3 in mice induced suppressive Tr1 cells that were dependent on IL-27 produced by the upper airway dendritic cells [135]. Moreover, we have recently shown that nasal administration of anti-CD3 ameliorated disease in a progressive model of multiple sclerosis in mice by inducing Tr1 cells that suppress the astrocyte inflammatory transcriptional program [136]. Thus, the site of antigen exposition is crucial for the subtype of regulatory T cell to be expanded and to the mechanism of tolerance induction.

3.3.3. γδ T cells and oral tolerance

Gamma-delta (γδ) T cells are lymphocytes bearing a T cell receptor composed of gamma and delta chains as opposed to alpha and beta chains found in conventional CD4 + /CD8 + T cells. Despite comprising the majority of immune cells in niches associated with epithelial surfaces such as the intestine, only 1–2% of γδ T cells are present in secondary lymphoid tissues [137]. γδ T cells are considered the first line of defense against pathogens as they can rapidly respond to TCR signals in an MHC-independent manner [138] and to pattern recognition receptors signals such as toll-like receptors [139]. However, regulatory properties of γδ T cells have also been described. For example, in inflammatory bowel disease models, γδ T cell-deficient mice develop spontaneous colitis and are susceptible to 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis [140]. Transfer of intraepithelial γδ lymphocytes (IEL-γδ) ameliorates colitis in this model. In dextran sodium sulfate (DSS)-induced colitis in mice, IEL-γδ T cells help preserve the integrity of damaged epithelial surfaces by the localized delivery of keratinocyte growth factor, a potent intestinal epithelial cell mitogen [141]. Also, by secreting IL-22 as well as anti-microbial products in a retinoic acid-dependent fashion, γδ T cells play an important role in the attenuation of intestinal inflammation induced by DSS or *Citrobacter rodentium* infection in mice [142]. Consistent with this, γδ T cell population attached to the intestinal lumen is constitutively activated even by normal commensal bacteria [143], indicating the importance of γδ T cells in gut homeostasis maintenance.

We have recently shown that γδ T cells from the Peyer’s patches and small intestine lamina propria can express LAP and this LAP + γδ T (TCRγδ + LAP +) cells function as antigen presenting cells that induce CD4 + Foxp3 + regulatory T cells though TCRγδ + LAP + cells do not themselves express Foxp3. Moreover, in a T cell model of colitis induced by CD4 + CD45RBhigh cell transfer into immunodeficient mice (a rodent model for Crohn’s disease) or in an innate immune-mediated model of colitis induced by oral administration of DSS, transfer of TCRγδ + LAP + cells ameliorated the waist disease by promoting the induction of Foxp3 Treg cells [144]. Again, these data point out to a crucial role of γδ T cells in the control of gut homeostasis. Importantly, oral tolerance is impaired in mice depleted of γδ T cells [145] and in γδ T cell deficient mice [146]. However, low dose, but not high dose, of antigen-induced oral tolerance was affected by the absence of γδ T cells and this was associated with reduced levels of IL-10 in oral fed OVA to TCRδ mice [146]. Thus, γδ T cells appear to be crucial for oral tolerance induction, but the mechanisms underlying this effect remains to be determined.

3.4. Other mechanisms of oral tolerance induction

Although active mechanisms of oral tolerance are mainly T cell mediated, other regulatory mechanisms have been reported. Tolerance to sheep red blood cells (SRBC) and certain contact-sensitizing agents

can be transferred using serum from antigen-fed mice [22,147–149]. Regulation of immunity by anti-idiotypic antibody, i.e., antibodies against the variable region of other antibody molecules, also has been described in mice tolerized by portal vein inoculation of allogeneic lymphocytes [150]. Although it is generally not possible to transfer tolerance to proteins using immunoglobulin [151], milk from mice tolerized orally or parenterally during pregnancy can induce tolerance in the neonate by transfer of anti-idiotypic antibodies [152]. The possibility remains that this mechanism confers tolerance on the neonate at a time when susceptibility to food sensitivity is high. Blocking and cross-reactive antibodies have been demonstrated as a suppressive mechanism on oral tolerance to grass pollen [153].

4. Concluding remarks

Although it is clear that oral fed antigens can suppress autoimmunity and inflammatory diseases in animals, several factors need to be carefully considered for oral tolerance to be effective in human disease: (i) the dose and frequency of dosing of antigen is crucial; (ii) a clear immunological marker or immunological effect has to be established as a parameter for dosing in each disease; (iii) mucosal adjuvants that enhance induction of tolerance have been described and may be required; (iv) purified proteins are more effective oral tolerogens than protein mixtures; (v) in some instances nasal antigen may be more effective; (vi) combination therapy using conventional anti-inflammatory and immunosuppressive drugs may be required; and (vii) early therapy after disease onset. Taking all these factors into account, oral tolerance as a therapy for the treatment of allergy and autoimmune diseases, has been moving forward. Studies have successfully demonstrated that oral administration of peanut to peanut-allergic children/adolescents led to a substantial increase in the dose threshold, conferring protection against peanuts. This effect was accompanied by reduction in skin prick tests, decreased levels of IL-5 and IL-13, and increased ratio of FOXP3high:FOXP3intermediate CD25 + CD4+ T cells in treated patients compared to placebo controls [154,155]. Moreover, two single blind randomized placebo controlled phase IIa studies of oral anti-CD3 antibody in patients with resistant chronic hepatitis C infection (HCV) [156] or nonalcoholic steatohepatitis (NASH) [157] reported positive effects on disease and immunological markers including an increase of regulatory T cells. Interestingly, a recent study by Herzog and Daniell's groups, using two different hemophilia mouse strains, reported that oral administration of plant cell extracts expressing factor VIII (FVIII) antigens induced unresponsiveness to FVIII challenge [158]. This is an important approach that can be rapidly translated into clinic to treat hemophilic patients because it does not require large amounts of FVIII, which is highly expensive, and can be delivered as bioencapsulated antigen in plant cells and consumed as a vegetable.

Many aspects of the mechanisms involved in mucosal tolerance induction need to be further investigated. Cell-surface molecules and cytokines associated with inductive events in the gut that generate and modulate oral tolerance are not completely understood. Important areas of investigation include cytokine milieu, antigen presentation and co-stimulation requirements, routes of antigen processing, form of the antigen, role of the liver, the effect of oral antigens on antibody and IgE responses and on cytotoxic T lymphocytes, and the role of γδ T cells. As the molecular events associated with the generation and modulation of oral tolerance are better understood, we hope that the ability to successfully apply mucosal tolerance for the treatment of human autoimmune and other diseases will be soon achieved.

References

[1] R.E. Billingham, L. Brent, P.B. Medawar, Actively acquired tolerance of foreign cells, Nature 172 (4379) (1953) 603–606.
[2] M.F. Burnet, The Clonal Selection Theory of Immunity, 1st ed., The Vanderbilt and Cambridge University Presses, Nashiville/London, 1959 (200).
[3] N.M. Vaz, L.C. Maia, D.G. Hanson, J.M. Lynch, Inhibition of homocytotropic antibody responses in adult inbred mice by previous feeding of the specific antigen, J. Allergy Clin. Immunol. 60 (2) (1977) 110–115.
[4] F. Moog, The lining of the small intestine, Sci. Am. 245 (5) (1981) 154–158 (160, 162 et passiom.).
[5] P. Brandtzaeg, Development and basic mechanisms of human gut immunity, Nutr. Rev. 56 (1 Pt 2) (1998) S5–S18.
[6] G.T. Macfarlane, S. Macfarlane, Human colonic microbiota: ecology, physiology and metabolic potential of intestinal bacteria, Scand. J. Gastroenterol. 32 (Suppl. 222) (1997) 3–9.
[7] R.D. Owen, Immunogenetic consequences of vascular anastomoses between bovine twins, Science 102 (2651) (1945) 400–401.
[8] < TOLERANCE TO HOMOGRAFTS, TWIN, DIAGNOSIS, AND THE FREEMARTIN CONDITION IN CATTLE.pdf > .
[9] M. Hasek, Parabiosis of birds during their embryonic development, Chekhoslovatskaia Biol. 2 (1) (1953) 29–31.
[10] S. Avrameas, Natural autoantibodies: from 'horror autotoxicus' to 'gnothi seauton', Immunol. Today 12 (5) (1991) 154–159.
[11] N. Kerlero de Rosbo, R. Milo, M.B. Lees, D. Burger, C.C. Bernard, A. Ben-Nun, Reactivity to myelin antigens in multiple sclerosis. Peripheral blood lymphocytes respond predominantly to myelin oligodendrocyte glycoprotein, J. Clin. Invest. 92 (6) (1993) 2602–2608.
[12] J. Zhang, S. Markovic-Plese, B. Lacet, J. Raus, H.L. Weiner, D.A. Hafler, Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis, J. Exp. Med. 179 (3) (1994) 973–984.
[13] S. Lacroix-Desmazes, S.V. Kaveri, L. Mouthon, A. Ayouba, E. Malanchere, A. Coutinho, M.D. Kazatchkine, Self-reactive antibodies (natural autoantibodies) in healthy individuals, J. Immunol. Methods 216 (1–2) (1998) 117–137.
[14] I.R. Cohen, D.B. Young, Autoimmunity, microbial immunity and the immunological homunculus, Immunol. Today 12 (4) (1991) 105–110.
[15] Y. Modigliani, A. Coutinho, P. Pereira, N. Le Douarin, V. Thomas-Vaslin, O. Burlen-Defranoux, J. Salaun, A. Bandeira, Establishment of tissue-specific tolerance is driven by regulatory T cells selected by thymic epithelium, Eur. J. Immunol. 26 (8) (1996) 1807–1815.
[16] S. Sakaguchi, Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune responses, Annu. Rev. Immunol. 22 (2004) 531–562.
[17] H.G. Wells, T.B. Osborne, The biological reactions of the vegetable proteins, J. Infect. Dis. 8 (1911) 66.
[18] G. Filipp, B. von Boros, The induction of immunological tolerance by antigen feeding. The effect of thymectomy on orally induced tolerance, J. Allergy 39 (3) (1967) 167–170.
[19] R. Auerbach, S. Clark, Immunological tolerance: transmission from mother to offspring, Science 189 (4205) (1975) 811–813.
[20] M.F. David, Prevention of homocytotropic antibody formation and anaphylactic sensitization by prefeeding antigen, J. Allergy Clin. Immunol. 60 (3) (1977) 180–187.
[21] H.C. Thomas, M.V. Parrott, The induction of tolerance to a soluble protein antigen by oral administration, Immunology 27 (4) (1974) 631–639.
[22] C. Andre, J.F. Heremans, J.P. Vaerman, C.L. Cambiaso, A mechanism for the induction of immunological tolerance by antigen feeding: antigen-antibody complexes, J. Exp. Med. 142 (6) (1975) 1509–1519.
[23] A.M. Mowat, The regulation of immune responses to dietary protein antigens, Immunol. Today 8 (3) (1987) 93–98.
[24] A.M. Mowat, S. Strobel, H.E. Drummond, A. Ferguson, Immunological responses to fed protein antigens in mice. I. Reversal of oral tolerance to ovalbumin by cyclophosphamide, Immunology 45 (1) (1982) 105–113.
[25] D.G. Hanson, S.D. Miller, Inhibition of specific immune responses by feeding protein antigens. V. Induction of the tolerant state in the absence of specific suppressor T cells, J. Immunol. 128 (5) (1982) 2378–2381.
[26] A.M. Faria, H.L. Weiner, Oral tolerance: mechanisms and therapeutic applications, Adv. Immunol. 73 (1999) 153–264.
[27] O. Lider, L.M. Santos, C.S. Lee, P.J. Higgins, H.L. Weiner, Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein. II. Suppression of disease and in vitro immune responses is mediated by antigen-specific CD8+ T lymphocytes, J. Immunol. 142 (3) (1989) 748–752.
[28] A. Miller, O. Lider, A.B. Roberts, M.B. Sporn, H.L. Weiner, Suppressor T cells generated by oral tolerization to myelin basic protein suppress both in vitro and in vivo immune responses by the release of transforming growth factor beta after antigen-specific triggering, Proc. Natl. Acad. Sci. U. S. A. 89 (1) (1992) 421–425.
[29] A. Miller, A. al-Sabbagh, L.M. Santos, M.P. Das, H.L. Weiner, Epitopes of myelin basic protein that trigger TGF-beta release after oral tolerization are distinct from encephalitogenic epitopes and mediate epitope-driven bystander suppression, J. Immunol. 151 (12) (1993) 7307–7315.
[30] L.M. Santos, A. al-Sabbagh, A. Londono, H.L. Weiner, Oral tolerance to myelin basic protein induces regulatory TGF-beta-secreting T cells in Peyer's patches of SJL mice, Cell. Immunol. 157 (2) (1994) 439–447.
[31] Y. Chen, V.K. Kuchroo, J. Inobe, D.A. Hafler, H.L. Weiner, Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis, Science 265 (5176) (1994) 1237–1240.
[32] Y. Chen, J. Inobe, H.L. Weiner, Induction of oral tolerance to myelin basic protein in CD8-depleted mice: both CD4+ and CD8+ cells mediate active suppression, J. Immunol. 155 (2) (1995) 910–916.
[33] J. Xu-Amano, W.K. Aicher, T. Taguchi, H. Kiyono, J.R. McGhee, Selective induction of Th2 cells in murine Peyer's patches by oral immunization, Int. Immunol. 4

(4) (1992) 433–445.
[34] S. Hori, T. Nomura, S. Sakaguchi, Control of regulatory T cell development by the transcription factor Foxp3, Science 299 (5609) (2003) 1057–1061.
[35] E.M. Shevach, Mechanisms of foxp3+ T regulatory cell-mediated suppression, Immunity 30 (5) (2009) 636–645.
[36] J. Mestecky, J.R. McGhee, Immunoglobulin A (IgA): molecular and cellular interactions involved in IgA biosynthesis and immune response, Adv. Immunol. 40 (1987) 153–245.
[37] P.J. van der Heijden, W. Stok, A.T. Bianchi, Contribution of immunoglobulin-secreting cells in the murine small intestine to the total 'background' immunoglobulin production, Immunology 62 (4) (1987) 551–555.
[38] A.J. Macpherson, K.D. McCoy, F.E. Johansen, P. Brandtzaeg, The immune geography of IgA induction and function, Mucosal Immunol. 1 (1) (2008) 11–22.
[39] K. Fujihashi, T. Dohi, P.D. Rennert, M. Yamamoto, T. Koga, H. Kiyono, J.R. McGhee, Peyer's patches are required for oral tolerance to proteins, Proc. Natl. Acad. Sci. U. S. A. 98 (6) (2001) 3310–3315.
[40] T.W. Spahn, A. Fontana, A.M. Faria, A.J. Slavin, H.P. Eugster, X. Zhang, P.A. Koni, N.H. Ruddle, R.A. Flavell, P.D. Rennert, H.L. Weiner, Induction of oral tolerance to cellular immune responses in the absence of Peyer's patches, Eur. J. Immunol. 31 (4) (2001) 1278–1287.
[41] T.W. Spahn, H.L. Weiner, P.D. Rennert, N. Lugering, A. Fontana, W. Domschke, T. Kucharzik, Mesenteric lymph nodes are critical for the induction of high-dose oral tolerance in the absence of Peyer's patches, Eur. J. Immunol. 32 (4) (2002) 1109–1113.
[42] T.A. Kraus, J. Brimnes, C. Muong, J.H. Liu, T.M. Moran, K.A. Tappenden, P. Boros, L. Mayer, Induction of mucosal tolerance in Peyer's patch-deficient, ligated small bowel loops, J. Clin. Invest. 115 (8) (2005) 2234–2243.
[43] F.G. Chirdo, O.R. Millington, H. Beacock-Sharp, A.M. Mowat, Immunomodulatory dendritic cells in intestinal lamina propria, Eur. J. Immunol. 35 (6) (2005) 1831–1840.
[44] E. Jaensson, H. Uronen-Hansson, O. Pabst, B. Eksteen, J. Tian, J.L. Coombes, P.L. Berg, T. Davidsson, F. Powrie, B. Johansson-Lindbom, W.W. Agace, Small intestinal CD103+ dendritic cells display unique functional properties that are conserved between mice and humans, J. Exp. Med. 205 (9) (2008) 2139–2149.
[45] C.M. Sun, J.A. Hall, R.B. Blank, N. Bouladoux, M. Oukka, J.R. Mora, Y. Belkaid, Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid, J. Exp. Med. 204 (8) (2007) 1775–1785.
[46] J.L. Coombes, K.R. Siddiqui, C.V. Arancibia-Carcamo, J. Hall, C.M. Sun, Y. Belkaid, F. Powrie, A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism, J. Exp. Med. 204 (8) (2007) 1757–1764.
[47] M. Iwata, A. Hirakiyama, Y. Eshima, H. Kagechika, C. Kato, S.Y. Song, Retinoic acid imprints gut-homing specificity on T cells, Immunity 21 (4) (2004) 527–538.
[48] R. Forster, A.C. Davalos-Misslitz, A. Rot, CCR7 and its ligands: balancing immunity and tolerance, Nat. Rev. Immunol. 8 (5) (2008) 362–371.
[49] T. Worbs, U. Bode, S. Yan, M.W. Hoffmann, G. Hintzen, G. Bernhardt, R. Forster, O. Pabst, Oral tolerance originates in the intestinal immune system and relies on antigen carriage by dendritic cells, J. Exp. Med. 203 (3) (2006) 519–527.
[50] T.W. Spahn, H. Herbst, P.D. Rennert, N. Lugering, C. Maaser, M. Kraft, A. Fontana, H.L. Weiner, W. Domschke, T. Kucharzik, Induction of colitis in mice deficient of Peyer's patches and mesenteric lymph nodes is associated with increased disease severity and formation of colonic lymphoid patches, Am. J. Pathol. 161 (6) (2002) 2273–2282.
[51] W.A. Walker, K.J. Isselbacher, Uptake and transport of macromolecules by the intestine. Possible role in clinical disorders, Gastroenterology 67 (3) (1974) 531–550.
[52] S. Husby, J.C. Jensenius, S.E. Svehag, Passage of undegraded dietary antigen into the blood of healthy adults. Quantification, estimation of size distribution, and relation of uptake to levels of specific antibodies, Scand. J. Immunol. 22 (1) (1985) 83–92.
[53] K.M. Smith, J.M. Davidson, P. Garside, T-cell activation occurs simultaneously in local and peripheral lymphoid tissue following oral administration of a range of doses of immunogenic or tolerogenic antigen although tolerized T cells display a defect in cell division, Immunology 106 (2) (2002) 144–158.
[54] B.H. Zinselmeyer, J. Dempster, A.M. Gurney, D. Wokosin, M. Miller, H. Ho, O.R. Millington, K.M. Smith, C.M. Rush, I. Parker, M. Cahalan, J.M. Brewer, P. Garside, In situ characterization of CD4+ T cell behavior in mucosal and systemic lymphoid tissues during the induction of oral priming and tolerance, J. Exp. Med. 201 (11) (2005) 1815–1823.
[55] H.J. Peng, M.W. Turner, S. Strobel, The generation of a 'tolerogen' after the ingestion of ovalbumin is time-dependent and unrelated to serum levels of immunoreactive antigen, Clin. Exp. Immunol. 81 (3) (1990) 510–515.
[56] A.W. Thomson, P.A. Knolle, Antigen-presenting cell function in the tolerogenic liver environment, Nat. Rev. Immunol. 10 (11) (2010) 753–766.
[57] R.Y. Peng, D.W. Wang, Z.H. Xu, Y.B. Gao, R.B. Yang, P. Liu, Z.P. Wang, Y.P. Li, The changes and significance of mast cells in irradiated rat liver, J. Environ. Pathol. Toxicol. Oncol. 13 (2) (1994) 111–116.
[58] M.P. Callery, T. Kamei, M.W. Flye, The effect of portacaval shunt on delayed-hypersensitivity responses following antigen feeding, J. Surg. Res. 46 (4) (1989) 391–394.
[59] A. Goubier, B. Dubois, H. Gheit, G. Joubert, F. Villard-Truc, C. Asselin-Paturel, G. Trinchieri, D. Kaiserlian, Plasmacytoid dendritic cells mediate oral tolerance, Immunity 29 (3) (2008) 464–475.
[60] A.M.C. Faria, R. Maron, S.M. Ficker, A.J. Slavin, T. Spahn, H.L. Weiner, Oral tolerance induced by continuous feeding: enhanced up-regulation of transforming growth factor-β/interleukin-10 and suppression of experimental autoimmune encephalomyelitis, J. Autoimmun. 20 (2) (2003) 135–145.
[61] H.L. Weiner, A. Friedman, A. Miller, S.J. Khoury, A. al-Sabbagh, L. Santos, M. Sayegh, R.B. Nussenblatt, D.E. Trentham, D.A. Hafler, Oral tolerance: immunologic mechanisms and treatment of animal and human organ-specific autoimmune diseases by oral administration of autoantigens, Annu. Rev. Immunol. 12 (1994) 809–837.
[62] J. Ngan, L.S. Kind, Suppressor T cells for IgE and IgG in Peyer's patches of mice made tolerant by the oral administration of ovalbumin, J. Immunol. 120 (3) (1978) 861–865.
[63] A.O. Afuwape, M.W. Turner, S. Strobel, Oral administration of bovine whey proteins to mice elicits opposing immunoregulatory responses and is adjuvant dependent, Clin. Exp. Immunol. 136 (1) (2004) 40–48.
[64] K. Nakamura, A. Kitani, W. Strober, Cell contact-dependent immunosuppression by CD4(+)CD25(+) regulatory T cells is mediated by cell surface-bound transforming growth factor beta, J. Exp. Med. 194 (5) (2001) 629–644.
[65] T. Oida, X. Zhang, M. Goto, S. Hachimura, M. Totsuka, S. Kaminogawa, H.L. Weiner, CD4+CD25- T cells that express latency-associated peptide on the surface suppress CD4+CD45RBhigh-induced colitis by a TGF-beta-dependent mechanism, J. Immunol. 170 (5) (2003) 2516–2522.
[66] M.L. Chen, B.S. Yan, Y. Bando, V.K. Kuchroo, H.L. Weiner, Latency-associated peptide identifies a novel CD4+CD25+ regulatory T cell subset with TGFbeta-mediated function and enhanced suppression of experimental autoimmune encephalomyelitis, J. Immunol. 180 (11) (2008) 7327–7337.
[67] Y. Chen, J. Inobe, R. Marks, P. Gonnella, V.K. Kuchroo, H.L. Weiner, Peripheral deletion of antigen-reactive T cells in oral tolerance, Nature 376 (6536) (1995) 177–180.
[68] T. Marth, W. Strober, B.L. Kelsall, High dose oral tolerance in ovalbumin TCR-transgenic mice: systemic neutralization of IL-12 augments TGF-beta secretion and T cell apoptosis, J. Immunol. 157 (6) (1996) 2348–2357.
[69] T. Marth, M. Zeitz, B.R. Ludviksson, W. Strober, B.L. Kelsall, Extinction of IL-12 signaling promotes Fas-mediated apoptosis of antigen-specific T cells, J. Immunol. 162 (12) (1999) 7233–7240.
[70] A.L. Meyer, J. Benson, F. Song, N. Javed, I.E. Gienapp, J. Goverman, T.A. Brabb, L. Hood, C.C. Whitacre, Rapid depletion of peripheral antigen-specific T cells in TCR-transgenic mice after oral administration of myelin basic protein, J. Immunol. 166 (9) (2001) 5773–5781.
[71] P. Garside, M. Steel, E.A. Worthey, P.J. Kewin, S.E. Howie, D.J. Harrison, D. Bishop, A.M. Mowat, Lymphocytes from orally tolerized mice display enhanced susceptibility to death by apoptosis when cultured in the absence of antigen in vitro, Am. J. Pathol. 149 (6) (1996) 1971–1979.
[72] T. Kaji, S. Hachimura, W. Ise, S. Kaminogawa, Proteome analysis reveals caspase activation in hyporesponsive CD4 T lymphocytes induced in vivo by the oral administration of antigen, J. Biol. Chem. 278 (30) (2003) 27836–27843.
[73] E.R. Kearney, K.A. Pape, D.Y. Loh, M.K. Jenkins, Visualization of peptide-specific T cell immunity and peripheral tolerance induction in vivo, Immunity 1 (4) (1994) 327–339.
[74] Y. Chen, J. Inobe, H.L. Weiner, Inductive events in oral tolerance in the TCR transgenic adoptive transfer model, Cell. Immunol. 178 (1) (1997) 62–68.
[75] I. Gutgemann, A.M. Fahrer, J.D. Altman, M.M. Davis, Y.H. Chien, Induction of rapid T cell activation and tolerance by systemic presentation of an orally administered antigen, Immunity 8 (6) (1998) 667–673.
[76] N. Van Houten, S.F. Blake, Direct measurement of anergy of antigen-specific T cells following oral tolerance induction, J. Immunol. 157 (4) (1996) 1337–1341.
[77] M.F. Neurath, S. Finotto, I. Fuss, M. Boirivant, P.R. Galle, W. Strober, Regulation of T-cell apoptosis in inflammatory bowel disease: to die or not to die, that is the mucosal question, Trends Immunol. 22 (1) (2001) 21–26.
[78] M.L. Miller, J.S. Cowdery, C.A. Laskin, M.F. Curtin Jr., A.D. Steinberg, Heterogeneity of oral tolerance defects in autoimmune mice, Clin. Immunol. Immunopathol. 31 (2) (1984) 231–240.
[79] C.G. Freire-de-Lima, D.O. Nascimento, M.B. Soares, P.T. Bozza, H.C. Castro-Faria-Neto, F.G. de Mello, G.A. DosReis, M.F. Lopes, Uptake of apoptotic cells drives the growth of a pathogenic trypanosome in macrophages, Nature 403 (6766) (2000) 199–203.
[80] W. Chen, W. Jin, H. Tian, P. Sicurello, M. Frank, J.M. Orenstein, S.M. Wahl, Requirement for transforming growth factor beta1 in controlling T cell apoptosis, J. Exp. Med. 194 (4) (2001) 439–453.
[81] A. Ramachandran, M. Madesh, K.A. Balasubramanian, Apoptosis in the intestinal epithelium: its relevance in normal and pathophysiological conditions, J. Gastroenterol. Hepatol. 15 (2) (2000) 109–120.
[82] M. Boirivant, R. Pica, R. DeMaria, R. Testi, F. Pallone, W. Strober, Stimulated human lamina propria T cells manifest enhanced Fas-mediated apoptosis, J. Clin. Invest. 98 (11) (1996) 2616–2622.
[83] F.P. Huang, N. Platt, M. Wykes, J.R. Major, T.J. Powell, C.D. Jenkins, G.G. MacPherson, A discrete subpopulation of dendritic cells transports apoptotic intestinal epithelial cells to T cell areas of mesenteric lymph nodes, J. Exp. Med. 191 (3) (2000) 435–444.
[84] V.A. Fadok, D.L. Bratton, A. Konowal, P.W. Freed, J.Y. Westcott, P.M. Henson, Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF, J. Clin. Invest. 101 (4) (1998) 890–898.
[85] W.E. Paul, R.A. Seder, Lymphocyte responses and cytokines, Cell 76 (2) (1994) 241–251.
[86] H.L. Weiner, The mucosal milieu creates tolerogenic dendritic cells and T(R)1 and T(H)3 regulatory cells, Nat. Immunol. 2 (8) (2001) 671–672.
[87] D.A. Horwitz, S.G. Zheng, J.D. Gray, The role of the combination of IL-2 and TGF-beta or IL-10 in the generation and function of CD4+ CD25+ and CD8+

regulatory T cell subsets, J. Leukoc. Biol. 74 (4) (2003) 471–478.
[88] W. Chen, W. Jin, N. Hardegen, K.J. Lei, L. Li, N. Marinos, G. McGrady, S.M. Wahl, Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3, J. Exp. Med. 198 (12) (2003) 1875–1886.
[89] F. Macian, F. Garcia-Cozar, S.H. Im, H.F. Horton, M.C. Byrne, A. Rao, Transcriptional mechanisms underlying lymphocyte tolerance, Cell 109 (6) (2002) 719–731.
[90] M.A. Kriegel, C. Rathinam, R.A. Flavell, E3 ubiquitin ligase GRAIL controls primary T cell activation and oral tolerance, Proc. Natl. Acad. Sci. U. S. A. 106 (39) (2009) 16770–16775.
[91] W. Ise, K. Nakamura, N. Shimizu, H. Goto, K. Fujimoto, S. Kaminogawa, S. Hachimura, Orally tolerized T cells can form conjugates with APCs but are defective in immunological synapse formation, J. Immunol. 175 (2) (2005) 829–838.
[92] C.C. Whitacre, I.E. Gienapp, C.G. Orosz, D.M. Bitar, Oral tolerance in experimental autoimmune encephalomyelitis. III. Evidence for clonal anergy, J. Immunol. 147 (7) (1991) 2155–2163.
[93] D. Melamed, A. Friedman, Direct evidence for anergy in T lymphocytes tolerized by oral administration of ovalbumin, Eur. J. Immunol. 23 (4) (1993) 935–942.
[94] A. Friedman, H.L. Weiner, Induction of anergy or active suppression following oral tolerance is determined by antigen dosage, Proc. Natl. Acad. Sci. U. S. A. 91 (14) (1994) 6688–6692.
[95] D. Melamed, A. Friedman, In vivo tolerization of Th1 lymphocytes following a single feeding with ovalbumin: anergy in the absence of suppression, Eur. J. Immunol. 24 (9) (1994) 1974–1981.
[96] K. Hirahara, T. Hisatsune, K. Nishijima, H. Kato, O. Shiho, S. Kaminogawa, CD4+ T cells anergized by high dose feeding establish oral tolerance to antibody responses when transferred in SCID and nude mice, J. Immunol. 154 (12) (1995) 6238–6245.
[97] S. Inada, S. Yoshino, M.A. Haque, Y. Ogata, O. Kohashi, Clonal anergy is a potent mechanism of oral tolerance in the suppression of acute antigen-induced arthritis in rats by oral administration of the inducing antigen, Cell. Immunol. 175 (1) (1997) 67–75.
[98] T. Takahashi, Y. Kuniyasu, M. Toda, N. Sakaguchi, M. Itoh, M. Iwata, J. Shimizu, S. Sakaguchi, Immunologic self-tolerance maintained by CD25+CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state, Int. Immunol. 10 (12) (1998) 1969–1980.
[99] M.A. Gavin, S.R. Clarke, E. Negrou, A. Gallegos, A. Rudensky, Homeostasis and anergy of CD4(+)CD25(+) suppressor T cells in vivo, Nat. Immunol. 3 (1) (2002) 33–41.
[100] N.M. Tsuji, K. Mizumachi, J. Kurisaki, CD4+CD25+ regulatory T cell clones induced in Peyer's patches, Int. Immunol. 15 (4) (2003) 525–534.
[101] M.D. Mannie, S.K. Rendall, P.Y. Arnold, J.P. Nardella, G.A. White, Anergy-associated T cell antigen presentation. A mechanism of infectious tolerance in experimental autoimmune encephalomyelitis, J. Immunol. 157 (3) (1996) 1062–1070.
[102] L.S. Taams, A.J. van Rensen, M.C. Poelen, C.A. van Els, A.C. Besseling, J.P. Wagenaar, W. van Eden, M.H. Wauben, Anergic T cells actively suppress T cell responses via the antigen-presenting cell, Eur. J. Immunol. 28 (9) (1998) 2902–2912.
[103] A. Lanoue, C. Bona, H. von Boehmer, A. Sarukhan, Conditions that induce tolerance in mature CD4+ T cells, J. Exp. Med. 185 (3) (1997) 405–414.
[104] K.R. Ryan, B.D. Evavold, Persistence of peptide-induced CD4+ T cell anergy in vitro, J. Exp. Med. 187 (1) (1998) 89–96.
[105] G. Lombardi, K. Arnold, J. Uren, F. Marelli-Berg, R. Hargreaves, N. Imami, A. Weetman, R. Lechler, Antigen presentation by interferon-gamma-treated thyroid follicular cells inhibits interleukin-2 (IL-2) and supports IL-4 production by B7-dependent human T cells, Eur. J. Immunol. 27 (1) (1997) 62–71.
[106] L.S. Cauley, K.A. Cauley, F. Shub, G. Huston, S.L. Swain, Transferable anergy: superantigen treatment induces CD4+ T cell tolerance that is reversible and requires CD4-CD8- cells and interferon gamma, J. Exp. Med. 186 (1) (1997) 71–81.
[107] A.M. Thornton, E.M. Shevach, CD4+CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production, J. Exp. Med. 188 (2) (1998) 287–296.
[108] G.F. Hoyne, J.R. Lamb, Regulation of T cell function in mucosal tolerance, Immunol. Cell Biol. 75 (2) (1997) 197–201.
[109] Y. Nishizuka, T. Sakakura, Thymus and reproduction: sex-linked dysgenesia of the gonad after neonatal thymectomy in mice, Science 166 (3906) (1969) 753–755.
[110] A. Kojima, Y. Tanaka-Kojima, T. Sakakura, Y. Nishizuka, Spontaneous development of autoimmune thyroiditis in neonatally thymectomized mice, Lab. Invest. 34 (6) (1976) 550–557.
[111] K. Fukuma, S. Sakaguchi, K. Kuribayashi, W.L. Chen, R. Morishita, K. Sekita, H. Uchino, T. Masuda, Immunologic and clinical studies on murine experimental autoimmune gastritis induced by neonatal thymectomy, Gastroenterology 94 (2) (1988) 274–283.
[112] S. Sakaguchi, T. Takahashi, Y. Nishizuka, Study on cellular events in post-thymectomy autoimmune oophoritis in mice. I. Requirement of Lyt-1 effector cells for oocytes damage after adoptive transfer, J. Exp. Med. 156 (6) (1982) 1565–1576.
[113] S. Sakaguchi, T. Takahashi, Y. Nishizuka, Study on cellular events in post-thymectomy autoimmune oophoritis in mice. II. Requirement of Lyt-1 cells in normal female mice for the prevention of oophoritis, J. Exp. Med. 156 (6) (1982) 1577–1586.
[114] S. Sakaguchi, N. Sakaguchi, M. Asano, M. Itoh, M. Toda, Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases, J. Immunol. 155 (3) (1995) 1151–1164.
[115] F. Ramsdell, Foxp3 and natural regulatory T cells: key to a cell lineage? Immunity 19 (2) (2003) 165–168.
[116] S. Sakaguchi, F. Powrie, Emerging challenges in regulatory T cell function and biology, Science 317 (5838) (2007) 627–629.
[117] C.E. Tadokoro, G. Shakhar, S. Shen, Y. Ding, A.C. Lino, A. Maraver, J.J. Lafaille, M.L. Dustin, Regulatory T cells inhibit stable contacts between CD4+ T cells and dendritic cells in vivo, J. Exp. Med. 203 (3) (2006) 505–511.
[118] D. Mucida, N. Kutchukhidze, A. Erazo, M. Russo, J.J. Lafaille, M.A. Curotto de Lafaille, Oral tolerance in the absence of naturally occurring Tregs, J. Clin. Invest. 115 (7) (2005) 1923–1933.
[119] K.S. Kim, S.W. Hong, D. Han, J. Yi, J. Jung, B.G. Yang, J.Y. Lee, M. Lee, C.D. Surh, Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine, Science 351 (6275) (2016) 858–863.
[120] D. Mucida, Y. Park, G. Kim, O. Turovskaya, I. Scott, M. Kronenberg, H. Cheroutre, Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid, Science 317 (5835) (2007) 256–260.
[121] T. Hirano, Interleukin 6 and its receptor: ten years later, Int. Rev. Immunol. 16 (3–4) (1998) 249–284.
[122] E. Bettelli, Y. Carrier, W. Gao, T. Korn, T.B. Strom, M. Oukka, H.L. Weiner, V.K. Kuchroo, Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells, Nature 441 (7090) (2006) 235–238.
[123] H.L. Weiner, Oral tolerance: immune mechanisms and the generation of Th3-type TGF-beta-secreting regulatory cells, Microbes Infect. 3 (11) (2001) 947–954.
[124] H. Ochi, M. Abraham, H. Ishikawa, D. Frenkel, K. Yang, A.S. Basso, H. Wu, M.-L. Chen, R. Gandhi, A. Miller, R. Maron, H.L. Weiner, Oral CD3-specific antibody suppresses autoimmune encephalomyelitis by inducing CD4+CD25-LAP+ T cells, Nat. Med. 12 (6) (2006) 627–635.
[125] A.P. da Cunha, H.Y. Wu, R.M. Rezende, T. Vandeventer, H.L. Weiner, In vivo anti-LAP mAb enhances IL-17/IFN-gamma responses and abrogates anti-CD3-induced oral tolerance, Int. Immunol. 27 (2) (2015) 73–82.
[126] H. Ishikawa, H. Ochi, M.L. Chen, D. Frenkel, R. Maron, H.L. Weiner, Inhibition of autoimmune diabetes by oral administration of anti-CD3 monoclonal antibody, Diabetes 56 (8) (2007) 2103–2109.
[127] W.C. Bevier, A.L. Trujillo, G.B. Primbs, M.K. Bradley, L. Jovanovic, Oral anti-CD3 monoclonal antibody delays diabetes in non-obese diabetic (NOD) mice: effects on pregnancy and offspring—a preliminary report, Diabetes Metab. Res. Rev. 27 (5) (2011) 480–487.
[128] C. Hu, H. Ding, X. Zhang, F.S. Wong, L. Wen, Combination treatment with anti-CD20 and oral anti-CD3 prevents and reverses autoimmune diabetes, Diabetes 62 (8) (2013) 2849–2858.
[129] Y. Ilan, R. Maron, A.M. Tukpah, T.U. Maioli, G. Murugaiyan, K. Yang, H.Y. Wu, H.L. Weiner, Induction of regulatory T cells decreases adipose inflammation and alleviates insulin resistance in ob/ob mice, Proc. Natl. Acad. Sci. U. S. A. 107 (21) (2010) 9765–9770.
[130] H.Y. Wu, E.M. Center, G.C. Tsokos, H.L. Weiner, Suppression of murine SLE by oral anti-CD3: inducible CD4+CD25-LAP+ regulatory T cells control the expansion of IL-17+ follicular helper T cells, Lupus 18 (7) (2009) 586–596.
[131] N. Sasaki, T. Yamashita, M. Takeda, M. Shinohara, K. Nakajima, H. Tawa, T. Usui, K. Hirata, Oral anti-CD3 antibody treatment induces regulatory T cells and inhibits the development of atherosclerosis in mice, Circulation 120 (20) (2009) 1996–2005.
[132] H.L. Weiner, A.P. da Cunha, F. Quintana, H. Wu, Oral tolerance, Immunol. Rev. 241 (1) (2011) 241–259.
[133] S. Gregori, K.S. Goudy, M.G. Roncarolo, The cellular and molecular mechanisms of immuno-suppression by human type 1 regulatory T cells, Front. Immunol. 3 (2012) 30.
[134] S. Gregori, L. Passerini, M.G. Roncarolo, Clinical outlook for type-1 and FOXP3(+) T regulatory cell-based therapy, Front. Immunol. 6 (2015) 593.
[135] H.Y. Wu, F.J. Quintana, A.P. da Cunha, B.T. Dake, T. Koeglsperger, S.C. Starossom, H.L. Weiner, In vivo induction of Tr1 cells via mucosal dendritic cells and AHR signaling, PLoS One 6 (8) (2011) e23618.
[136] L. Mayo, A.P. Cunha, A. Madi, V. Beynon, Z. Yang, J.I. Alvarez, A. Prat, R.A. Sobel, L. Kobzik, H. Lassmann, F.J. Quintana, H.L. Weiner, IL-10-dependent Tr1 cells attenuate astrocyte activation and ameliorate chronic central nervous system inflammation, Brain 139 (Pt 7) (2016) 1939–1957.
[137] M. Girardi, Immunosurveillance and immunoregulation by gammadelta T cells, J. Invest. Dermatol. 126 (1) (2006) 25–31.
[138] P. Vantourout, A. Hayday, Six-of-the-best: unique contributions of gammadelta T cells to immunology, Nat. Rev. Immunol. 13 (2) (2013) 88–100.
[139] D. Wesch, C. Peters, H.H. Oberg, K. Pietschmann, D. Kabelitz, Modulation of gammadelta T cell responses by TLR ligands, Cell. Mol. Life Sci. 68 (14) (2011) 2357–2370.
[140] K. Inagaki-Ohara, T. Chinen, G. Matsuzaki, A. Sasaki, Y. Sakamoto, K. Hiromatsu, F. Nakamura-Uchiyama, Y. Nawa, A. Yoshimura, Mucosal T cells bearing TCRgammadelta play a protective role in intestinal inflammation, J. Immunol. 173 (2) (2004) 1390–1398.
[141] Y. Chen, K. Chou, E. Fuchs, W.L. Havran, R. Boismenu, Protection of the intestinal mucosa by intraepithelial gamma delta T cells, Proc. Natl. Acad. Sci. U. S. A. 99 (22) (2002) 14338–14343.
[142] L.A. Mielke, S.A. Jones, M. Raverdeau, R. Higgs, A. Stefanska, J.R. Groom, A. Misiak, L.S. Dungan, C.E. Sutton, G. Streubel, A.P. Bracken, K.H. Mills, Retinoic acid expression associates with enhanced IL-22 production by gammadelta T cells and innate lymphoid cells and attenuation of intestinal inflammation, J. Exp. Med. 210 (6) (2013) 1117–1124.

[143] S.P. Jeong, J.A. Kang, S.G. Park, Intestinal intraepithelial TCRgammadelta(+) T cells are activated by normal commensal bacteria, J. Microbiol. 50 (5) (2012) 837–841.
[144] R.M. Rezende, A.P. da Cunha, C. Kuhn, S. Rubino, H. M'Hamdi, G. Gabriely, T. Vandeventer, S. Liu, R. Cialic, N. Pinheiro-Rosa, R.P. Oliveira, J.T. Gaublomme, N. Obholzer, J. Kozubek, N. Pochet, A.M. Faria, H.L. Weiner, Identification and characterization of latency-associated peptide-expressing gammadelta T cells, Nat. Commun. 6 (2015) 8726.
[145] J. Mengel, F. Cardillo, L.S. Aroeira, O. Williams, M. Russo, N.M. Vaz, Anti-gamma delta T cell antibody blocks the induction and maintenance of oral tolerance to ovalbumin in mice, Immunol. Lett. 48 (2) (1995) 97–102.
[146] K. Fujihashi, T. Dohi, M.N. Kweon, J.R. McGhee, T. Koga, M.D. Cooper, S. Tonegawa, H. Kiyono, gammadelta T cells regulate mucosally induced tolerance in a dose-dependent fashion, Int. Immunol. 11 (12) (1999) 1907–1916.
[147] M.F. Kagnoff, Effects of antigen-feeding on intestinal and systemic immune responses. III. Antigen-specific serum-mediated suppression of humoral antibody responses after antigen feeding, Cell. Immunol. 40 (1) (1978) 186–203.
[148] M.P. Chalon, R.W. Milne, J.P. Vaerman, In vitro immunosuppressive effect of serum from orally immunized mice, Eur. J. Immunol. 9 (10) (1979) 747–751.
[149] B.S. Bhogal, Y.D. Karkhanis, M.K. Bell, P. Sanchez, B. Zemcik, G.W. Siskind, G.J. Thorbecke, Production of auto-anti-idiotypic antibody during the normal immune response. XII. Enhanced auto-anti-idiotypic antibody production as a mechanism for apparent B-cell tolerance in rabbits after feeding antigen, Cell. Immunol. 101 (1) (1986) 93–104.
[150] S. Sato, J.H. Qian, S. Kokudo, R. Ikegami, T. Suda, T. Hamaoka, H. Fujiwara, Studies on the induction of tolerance to alloantigens. III. Induction of antibodies directed against alloantigen-specific delayed-type hypersensitivity T cells by a single injection of allogeneic lymphocytes via portal venous route, J. Immunol. 140 (3) (1988) 717–722.
[151] D.G. Hanson, N.M. Vaz, L.C. Maia, J.M. Lynch, Inhibition of specific immune responses by feeding protein antigens. III. Evidence against maintenance of tolerance to ovalbumin by orally induced antibodies, J. Immunol. 123 (5) (1979) 2337–2343.
[152] E.E. Jarrett, E. Hall, The development of IgE-suppressive immunocompetence in young animals: influence of exposure to antigen in the presence or absence of maternal immunity, Immunology 53 (2) (1984) 365–373.
[153] N. de Weerd, P.L. Bhalla, M.B. Singh, Oral immunization with a recombinant major grass pollen allergen induces blocking antibodies in mice, Int. Arch. Allergy Immunol. 130 (2) (2003) 119–124.
[154] A.T. Clark, S. Islam, Y. King, J. Deighton, K. Anagnostou, P.W. Ewan, Successful oral tolerance induction in severe peanut allergy, Allergy 64 (8) (2009) 1218–1220.
[155] P. Varshney, S.M. Jones, A.M. Scurlock, T.T. Perry, A. Kemper, P. Steele, A. Hiegel, J. Kamilaris, S. Carlisle, X. Yue, M. Kulis, L. Pons, B. Vickery, A.W. Burks, A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response, J. Allergy Clin. Immunol. 127 (3) (2011) 654–660.
[156] W. Halota, P. Ferenci, D. Kozielewicz, D. Dybowska, N. Lisovoder, S. Samira, I. Shalit, R. Ellis, Y. Ilan, Oral anti-CD3 immunotherapy for HCV-nonresponders is safe, promotes regulatory T cells and decreases viral load and liver enzyme levels: results of a phase-2a placebo-controlled trial, J. Viral Hepat. 22 (8) (2015) 651–657.
[157] G. Lalazar, M. Mizrahi, I. Turgeman, T. Adar, A. Ben Ya'acov, Y. Shabat, A. Nimer, N. Hemed, L. Zolotarovya, Y. Lichtenstein, N. Lisovoder, S. Samira, I. Shalit, R. Ellis, Y. Ilan, Oral administration of OKT3 MAb to patients with NASH, promotes regulatory T-cell induction, and alleviates insulin resistance: results of a phase IIa blinded placebo-controlled trial, J. Clin. Immunol. 35 (4) (2015) 399–407.
[158] A. Sherman, J. Su, S. Lin, X. Wang, R.W. Herzog, H. Daniell, Suppression of inhibitor formation against FVIII in a murine model of hemophilia A by oral delivery of antigens bioencapsulated in plant cells, Blood 124 (10) (2014) 1659–1668.