Int J Colorectal Dis (2003) 18:181–187
DOI 10.1007/s00384-002-0444-1

REVIEW

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The gut as an organ of immunology

Accepted: 20 September 2002
Published online: 5 November 2002

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Abstract *Background:* In normal conditions human gut mucosa is infiltrated with a large number of mononuclear cells due to continuous stimulation by luminal antigens. This state of "physiological" inflammation is tightly controlled, as several mucosal cells interact to maintain an appropriate local immune response. Moreover, gut-associated lymphoid tissue must constantly distinguish harmless antigens that are present in food and on commensal bacteria from pathogenic microbes. *Interventions and research:* The oral administration of soluble protein antigens induces a state of systemic immunological unresponsiveness specific to the fed protein, termed oral tolerance. The two major mechanisms to explain oral tolerance are anergy/deletion of autoreactive lymphocytes and active suppression. Changes in the pathways of immune activation are detected in chronic intestinal inflammation, such as inflammatory bowel disease or celiac disease. *Conclusion:* An appreciation of the current knowledge of the gut immune system is of importance for understanding and development of new treatment modalities in chronic intestinal inflammation.

Keywords Gut-associated immune system · Oral tolerance · Chronic inflammatory bowel disease

Introduction

The intestinal mucosa contains a highly specialized immune system which differs in many aspects from other compartments of the immune system. The gut mucosal immune system is exposed to a wide variety of antigens derived from foods, resident bacteria, and invading micro-organisms. These need to be limited by a barrier that allows absorption of nutrients but also provides immune defense from harmful antigens. For better understanding of the mucosal immune response it is useful to divide the gut-associated lymphoid tissue into inductive and effector sites, although recent data indicate that these distinctions are not absolute.

The inductive site for the mucosal immune response

The primary inductive sites are organized lymphoid aggregates placed in the wall of the small and large intestine. In the small bowel these aggregates are called Peyer's patches, first described by Johannes Conrad Peyer (1653–1712), a Swiss anatomist and naturalist, and consist of multiple lymphoid follicles [1, 2]. They are found on the antimesenteric side of the bowel and are composed of specialized follicle-associated epithelium, a subepithelial dome overlying B cell follicles that contain germinal centers, and interfollicular regions with high endothelial venules and efferent lymphatic vessels [3]. Peyer's patches are unique among lymphoid tissues in that they contain no afferent lymphoid vessels; all lymphoid cells traffic into the Peyer's patches via migration from the bloodstream across the high endothelial venules, mediated by mucosa-specific adhesion molecules.

Isolated lymphoid follicles are also present in high numbers in the wall of the large bowel and the appendix. Since they have structural similarities to the Peyer's patches, they are assumed to have similar functions, although this remains to be proven. Following ingestion, antigens and micro-organisms are transported from the gut lumen via specialized M cells, which are scattered among conventional epithelial cells overlying the dome of Peyer's patch follicles. Compared with epithelial cells, with which they share a common progenitor cell, they have a pronounced capacity to transport a wide variety of substances and microbes to the subepithelial dome region. Here dendritic cells are the main antigen-presenting cells that bind bacterial products with their Toll-like receptors. The latter are a part of the innate immune defense, recognizing conserved patterns on micro-organisms. Signals initiated by the interaction of Toll-like receptors with specific microbial patterns direct the subsequent inflammatory response [4]. In the mouse model it has been shown that dendritic cells in different states of maturation exist at different sites of the Peyer's patches. Dendritic cells in the subepithelial dome process antigen as relative immature cells and then migrate to the T cell region and present antigen to naive T cells. Here they have the properties of mature dendritic cells, with high surface expression of costimulatory molecules such as CD40, CD80, and CD86 and adhesion molecules such as CD44 and intercellular adhesion molecule 1 [5]. It is suggestive that the intestinal T cells with distinct regulatory abilities, such as those producing transforming growth factor (TGF) β and interleukin (IL) 10, are stimulated by interaction with less differentiated dendritic cells in the Peyer's patches [5]. In the follicle such T cells provide help for the B cell switch to IgA, a process that is completed in the germinal center. IgA is the major mucosal immunoglobulin and can help to dispose of antigens without provoking the complement cascade. Following IgA switch and affinity maturation B cells migrate from the Peyer's patches to the mesenteric lymph node via efferent lymphatic vessels and finally to the lamina propria where they undergo terminal differentiation into plasma cells.

The effector site for the mucosal immune response

The main effector site of intestinal immune responses is the lamina propria, where mature T and B cells migrate following induction in the Peyer's patches. The lamina propria contains a large and heterogeneous group of lymphoid and myeloid cells; in addition to lymphocytes, there are macrophages, dendritic cells, neutrophils, and mast cells. Effector mechanisms that protect mucosal surfaces include cytotoxic T cells and effector $CD4^+$ T cells for cytokine production and IgA response. Lamina propria T cells are mainly $CD4^+$ T cells (60–70%), the majority of which express the αβ T cell receptor (TCR; 95%) just as in peripheral blood [6]. However, lamina propria T cells differ from peripheral blood lymphocytes in that they are in a more highly activated state and express CD25 and HLA-DR antigen, presumably as a result of continuous exposure to luminale antigens, but have a decreased proliferation rate when stimulated by mitogen or specific antigens [7]. Another characteristic of lamina propria T cells is that they produce high levels of cytokines when stimulated with mitogen or via CD2 [8, 9, 10]. Lamina propria T cells have a mature or memory phenotype, indicated by the surface markers $CD44^{high}$, $CD62^{low}$, $CD45RB^{low}$ (mice)/$CD45RO^+$ (human) and high levels of the integrin $\alpha_4\beta_7$ [11, 12, 13]. Taken together, lamina propria $CD4^+$ T cells are highly differentiated effector cells with a raised threshold of activation that prevents immune responses to harmless intraluminale antigens. $CD8^+$ T cells account for about 30–40% of T cells in the lamina propria. This cell population contains cytolytic effector cells, which seem to control the level of viral infection and other micro-organisms that share an intracellular stage in their life cycle in the lamina propria [14]. A more restricted T cell population develops independently of the Peyer's patches and is integrated in the epithelial layer. These intraepithelial lymphocytes (IEL) are predominantly $CD8^+$ T cells. In humans 5–30% of small intestinal IELs bear a γδ TCR and lack CD4 and CD8 or are $CD8^+$ [15, 16]. Predominant CD8 expression implies that IELs react in a MHC I restricted manner to antigens. However, the composition of IEL is different according to the anatomical sites. While most human jejunal IEL are $CD8^+$, there are much more $CD4^-$ $CD8^-$ IEL in the ileum and large bowel, most probably due to the different intraluminale content of microflora and food [16]. The CD8 molecule on IEL is expressed predominantly as a homodimer of the CD8 α-chain. The phenotypic complexity of IEL therefore suggests that they have different functions. It has been demonstrated that $CD4^+/CD8^-$ and the CD4/CD8 double-positive IEL subset support the differentiation of Peyer's patch B cells into immunoglobulin producing cells. Furthermore, surface expression of $\alpha E\beta_7$ integrin, the ligand of which is E-cadherin on epithelial cells [17], and the production of keratinocyte growth factor by IEL [18] suggest that some IEL populations play a role in maintenance of epithelial barrier integrity. In addition, TCRγδ T cells may be involved in regulating the intestinal immune response [19]. In the lamina propria IgA antibodies secreted by plasma cells keep the homeostasis of the epithelium by interacting with antigen within the gut lumen after epithelial transcytosis or inside infected epithelial cells or by formation of immune complexes with antigen in the lamina propria. However, it is clear that the antibody response is highly dependent on T cell help [20]. This cell network in the mucosal immune system is highly integrated by

Table 1 Cytokine help for the regulation of mucosal immunoglobulin response

Th subset	Cytokine production	Effect on IgA response
Th1	IL-2	Synergizes with IL-5 and TGF-β for enhanced IgA synthesis
	IFN-γ	Immunoglobulin switch to IgG2a
	Lymphotoxin β	Development of Peyer's patches
Th2	IL-4, IL-5	Induce differentiation of secretory IgA^+ B cells in plasma cells
	IL-6	Induces IgA synthesis
	IL-10	Downregulates Th1 response, induces IgA synthesis
Th3	TGF-β	Induces IgA isotype switching

the expression of specific costimulatory and adhesion molecules and the production of effector molecules such as cytokines.

Mechanisms of oral tolerance

Oral tolerance is defined as the induction of a state of systemic immune nonresponsiveness to orally administered antigen upon subsequent antigen challenge. This mechanism presumably prevents the development of an immune reaction or allergy against intestinal intraluminale antigens. However, the site of induction of oral tolerance and the type of antigen-presenting cell generating the tolerogenic immune response is not clear. Most of data on oral tolerance have so far been obtained in the animal model of ovalbumin-TCR transgenic mice. T cells appear to be the major target of tolerance, and the reduction in antibody responses after antigen feeding are due to the reductions in helper activity rather than to a tolerization of B cells directly. The major mechanisms of tolerance induction are clonal deletion, clonal anergy, and the induction of suppressor cells [21]. IL-12, a Th1-directing cytokine, may be a key regulatory cytokine for these various pathways in the mucosal immune response. Factors that suppress IL-12 production by antigen-presenting cells result in suppressor or regulating T cells producing TGF-β and possibly IL-4 and IL-10, while factors that induce IL-12 production result in T cells producing the proinflammatory cytokine interferon (IFN) γ [22, 23, 24]. The nature and localization of the antigen-presenting cells responsible for tolerogenic presentation of fed antigens are unclear. T cell activation and/or deletion can be rapidly observed in the Peyer's patches of antigen fed mice [25].

As mentioned above, dendritic cells are the main antigen-presenting cells in the Peyer's patches and re usually considered to have a high ability to activate T cells constitutively. However, there is increasing evidence that targeting antigen to resting dendritic cells, which lack costimulatory molecules, favors the induction of tolerance rather than immunity [26, 27]. In addition, enterocytes, which express MHC class II molecules constitutively but lack costimulatory molecules such as B7.1 and ICAM-1 [28, 29], could also account for tolerogenic antigen presentation. Recent data indicate that Peyer's patches alone are not important for the induction of oral tolerance. In a mouse model with targeted mutation in the gene of the tumor necrosis factor (TNF) α family the inhibition of the development of Peyer's patches and mesenteric lymph nodes is associated with a loss of orally but not intraperitoneally induced peripheral immune tolerance [30]. Although it is clear that oral antigen can suppress autoimmunity in animals, further studies are necessary to characterize the pathways of tolerating antigen presentation in humans.

Cytokine regulation of the gut mucosal immune response

The differentiation into different T helper cell and T regulatory (Tr) cell cytokine response is a reasonable framework for describing the immune reactivity of systemic lymphoid tissues. Th1 cells secrete proinflammatory cytokines such as IFN-γ and TNF-α; Th2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13, and promote IgA expression and other immunoglobulin isotypes (Table 1). Th3 cells secrete TGF-β, and Tr cells produce predominantly IL-10. Many of the functions of T cells in the gastrointestinal immune system are mediated by secreted cytokines. Recently it has been shown that lamina propria T cells are high producers of IL-10 compared to peripheral blood T cells [31, 32]. It seems likely that IL-10 secreting regulatory T cells inhibit Th1 cell activation, and that IL-10 produced locally in the intestine acts on macrophages to prevent their activation and the induction of proinflammatory cytokines, thus inhibiting T cell recruitment into the intestine. In line with this, it has been shown that regulatory T cells, induced by oral antigen uptake, have the characteristics of Th2 or Th3 cells [21, 33] (Fig. 1). On the other hand, it has also been demonstrated that continuous feeding of low-dose antigen induces a Th1 cytokine response in the ovalbumin-TCR transgenic mouse model [34]. In accord with this, human lamina propria cells spontaneously secrete high levels of IFN-γ, with a further increase upon stimulation via CD2 [35, 36]. It has been shown that antigen-specific stimulation of human Peyer's patch T cells in vitro re-

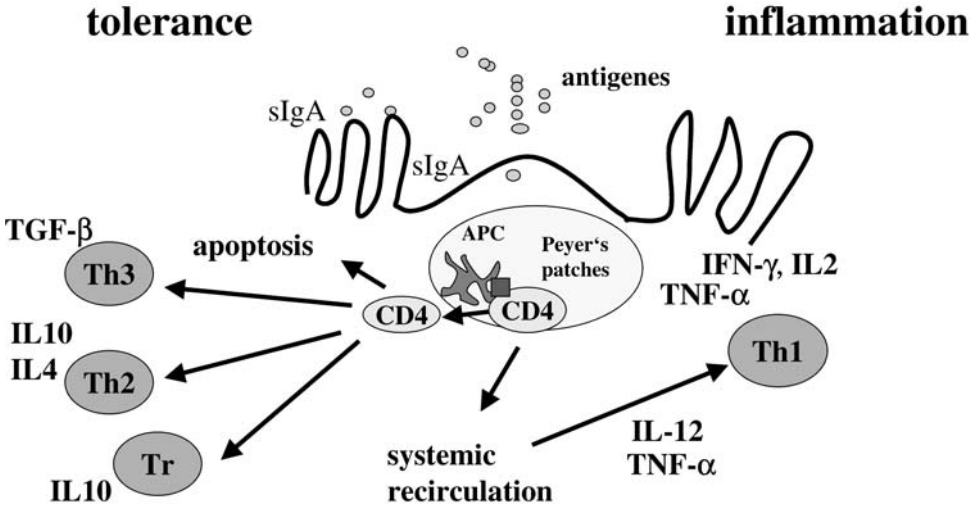

Fig. 1 Tolerance versus inflammation in the gut immune system. Antigens in the gut lumen are neutralized by secretory IgA (*sIgA*) and presented in the Peyer's patches by subepithelial antigen-presenting cells (*APC*) to CD4-positive T cells. In the normal situation tolerance is induced by apoptosis of activated T cells or cytokine (IL-10, TGF-β) induced suppression of the immune response in the gut mucosa. In chronic intestinal inflammation, such as Crohn's disease, IL-12 production by antigen-presenting cells boosts IFN-γ and T helper (*Th*) 1 cell differentiation. Th1 cells leave the Peyer's patches, enter the systemic circulation, and return to the lamina propria where they mediate a chronic inflammatory cytokine response

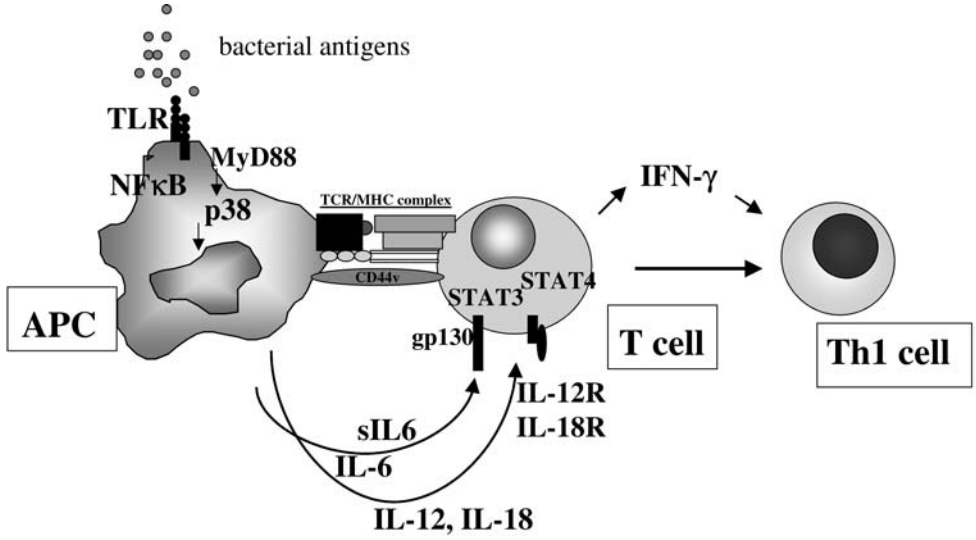

Fig. 2 Interaction of antigen-presenting cells (*APC*) and T cells in the gut mucosa. Mature APC regulate the T cell response to local antigen challenge. T cell activation, which is initiated by adherence of T cells to APC following recognition of the T cell receptor and MHC/peptide complex, is dependent on ligation of costimulatory molecules, for example, CD40 and CD44 variants, which regulates production of T cell activating cytokines. In the Peyer's patches engagement of Toll-like receptors (*TLR*) by products of the gut flora activates nuclear transcription factor κB (NF-κB) and the mitogen-activated protein kinase p38 via the receptor MyD88 thus increasing IL-12 production of APC (macrophages/mature dendritic cells) and directing a Th1-cytokine response

sults in secretion of IFN-γ [37]. Furthermore recent data indicate that Th1 cytokine production is not only proinflammatory but can be protective in the immune regulation of certain infectious or autoimmune diseases [38] (Fig. 2). Therefore, except for rodents studies, there seems to be no absolute clear bias towards Th1 or Th2 in the human intestinal immune response [39].

In addition to TCR engagement, T cells require a second signal in the form of costimulation to be fully activated. In the lymphoid system, dendritic cells express high levels of the major costimulatory molecules, and these are up-regulated upon maturation. In the normal mucosa, however, lamina propria antigen-presenting cells provide only low levels of costimulatory

signals [40], but this second signal is up-regulated in inflammatory bowel disease [41]. Several reports suggest that the level and type of costimulation a naive T cell receives influences whether Th1 or Th2 cells develop. Further, different types of antigen-presenting cells may selectively trigger either Th1 or Th2 responses; however, the same antigen-presenting cell can function equally well for inducing a Th1 or Th2 response (reviewed in [42]). The costimulatory molecule CD40 has been shown to induce a Th1 cytokine response by the production of IL-12 in macrophages and dendritic cells. In addition, CD40 ligand is a key molecule that delivers T cell help to B cells for immunoglobulin switching in the mucosa [43]. CD44v7 is a recently described costimulatory molecule that is up regulated in T cells and macrophages following ligation of CD40 in Th-1 mediated intestinal inflammation in animal models and human disease [44, 45, 46]. Recent studies have also presented evidence that the ligands B7.1 (CD80) and B7.2 (CD86) on activated B cells play distinct roles in differentiation of Th1 or Th2 type cells [47, 48]. It will be important to determine whether differences in the expression of costimulatory molecules in mucosal inductive sites regulate the intestinal immune response to mucosal antigens.

The gut mucosal immune system in diseases

Inasmuch as oral tolerance controls the immune response to foreign antigens, a breakdown of oral tolerance might result in intestinal immunization that leads to diseases. Nonallergic food hypersensitivity and chronic inflammatory bowel disease are two general types of intestinal inflammation. The most common form of food hypersensitivity is gluten-sensitive enteropathy (celiac disease), associated with the expression of the HLA antigen DQ2, or hypersensitivity caused by overexposure of the immature mucosal immune system to another food protein, mainly milk protein [49]. Celiac disease is clearly associated with an abnormal immune response to the inducing antigen gliadin or to autoantigens that cross-react with gliadin or form neoantigens. This response is a B cell reaction characterized by production of IgA antibodies to gliadin or tissue transglutaminase [50]. In addition, T cells with specificity to gliadin reencounter gliadin in the upper gastrointestinal tract and thus produce inflammatory cytokines and activate tissue metalloproteinases, which in consequence causes villous atrophy.

Other studies suggest that similar processes underlie inflammatory bowel disease. In the pathogenesis of chronic intestinal inflammation, such as Crohn's disease and ulcerative colitis, dysregulated $CD4^+$ T cell activation and proliferation in the intestinal mucosa is a key component [51]. Crohn's disease is characterized as a Th1-directed immune response with increased CD4 cell production of IFN-γ and activated macrophages that secret TNF-α and IL-12 [35, 52] (Fig. 1). Data obtained in animal models of experimental colitis and humans suggest that Crohn's disease can result from a defect in counterregulating the immune response, for example, by TGF-β, to normal mucosal antigens which initiates and/or sustains chronic inflammation [53, 54]. Furthermore, it has been shown that mice and humans normally are tolerant to their own gut flora, and that a breakdown of tolerance is associated with the development of chronic intestinal inflammation [55, 56]. As discussed above, it is likely that in the normal individual harmless intraluminal antigens fail to induce costimulatory activity in antigen-presenting cells. Therefore one cause of food-sensitive enteropathy and inflammatory bowel disease might be a factor that induces aberrant costimulation and thus causes breakdown of oral tolerance (Fig. 2). Of further importance it should be mentioned that recent progress in the epidemiology and genetics of inflammatory bowel disease has clearly demonstrated both environmental and genetic factors to play a role in the development of the diseases [57].

Modulation of the immune system as therapeutic strategy

Modulation of the immune response has become a new therapeutic strategy of intestinal inflammation within the past few years. Common immunosuppressive drugs usually act by inhibiting T cell proliferation and cytokine production. However, they are unspecific in their immunomodulatory effect and thus may interact with both proinflammatory and regulatory cytokines. Targeted therapy with specific inhibitors of proinflammatory cytokines or administration of regulatory or anti-inflammatory cytokines is currently under clinical investigation. Antagonism of TNF-α by monoclonal antibodies or fusion proteins is the only anticytokine treatment approved for clinical use in acute severe Crohn's disease. However, clinicians should precisely determine the indications and risks for each patient because of the severe adverse events of this therapy. Administration of several other cytokines, such as IL-10 and IFN-β, might have therapeutic potential in inflammatory bowel disease. Nuclear factor κB is a transcription factor that controls a variety of proinflammatory cytokines and has a central pathogenic role in chronic intestinal inflammation and might therefore define a new molecular target of anti-inflammatory therapy [58]. Recently the blockade of the adhesion molecule α_4-integrin has demonstrated an anti-inflammatory effect in patients with Crohn's disease. However, further studies should delineate which subgroup of patients profits from these therapies [59].

Conclusion

The mucosal surface of the gastrointestinal tract is constantly exposed to pathogens and harmless antigens from the bacterial flora and food. In addition to the physical barrier presented by mucosal epithelial cells, a local immune system plays a fundamental role in defense and self-tolerance. The mucosal immune system comprises several compartments: Peyer's patches and lymphoid follicles in the colonic mucosa, and lymphocytes in the lamina propria and intraepithelial lymphocytes. Peyer's patches mediate antigen uptake via specialized epithelial cells (M cells) and are rich in B cells for class switching into IgA-secreting cells. IgA secretion is one of the primary defenses against pathogens at mucosal surfaces. The lamina propria contains a high proportion of activated and memory T cells that allows rapid immune response against pathogens. In the physiological situation, mucosally encountered antigens induce tolerance of lamina propria and intraepithelial lymphocytes by modified antigen presentation, antigen-induced anergy, or deletion of T cells, or regulation of effector T cells by regulatory or suppressor T cells. Costimulatory molecules mediate cellular interaction and induce regulatory cytokines. Dysregulation of this complex immune response can result in a breakdown of oral tolerance and chronic intestinal inflammation. Insight into the homeostatic regulation of the intestinal immune system gives the pathophysiological rationale for new immunomodulatory drugs in the therapy of chronic inflammatory bowel disease.

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