HHS Public Access

Author manuscript

*Curr Opin Gastroenterol*. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

*Curr Opin Gastroenterol*. 2015 November ; 31(6): 471–476. doi:10.1097/MOG.0000000000000212.

# Role of Th2 immunity in intestinal inflammation

**Giorgos Bamias**[1] and **Fabio Cominelli**[2]

[1]Academic Department of Gastroenterology, Kapodistrian University of Athens, Laikon Hospital, Athens, 11527, Greece

[2]Division of Gastrointestinal and Liver Disease, Case Western Reserve University, School of Medicine, Cleveland, OH, 44106, USA

## Abstract

**Purpose of Review—**Type 2 (Th2) immune responses play important roles in intestinal immunity by contributing to the maintenance of mucosal homeostasis, conferring protection against helminthic inflection, but also participating in pro-inflammatory pathways in chronic intestinal inflammatory disorders, including inflammatory bowel disease (IBD). The current review focuses on recent developments regarding the role of type 2 responses in intestinal inflammation.

**Recent Findings—**Th2 gut mucosal responses are promoted by mediators that are released following injury to the epithelium and act as alarmin-type danger signals. IL-33 is prominent among such factors and demonstrates a dichotomous function exerting either protective or pro-inflammatory effects, depending on its cellular compartmentalization. The pool of type 2 effector cells has been enriched recently to include not only classical CD4+ Th2 lymphocytes but also a subset of innate lymphocytes (ILC2) that express the transcriptional factor GATA3 and secrete IL-4, IL-5, and IL-13. ILC2 play important roles during infection with helminthes and bi-directionally interact with Th2 CD4+ lymphocytes, thus, establishing a transition from innate to adaptive immunological pathways. Type 2 responses are also involved in pro-inflammatory pathways at the intestinal mucosa and neutralization of the pivotal cytokines IL-4 and IL-13 has been shown to regulate experimental intestinal inflammation. In striking contrast, however, neutralization of human IL-13 had no therapeutic effect in patients with ulcerative colitis.

**Summary—**Further studies will be required to delineate the specific mechanisms of type 2 mucosal immunity in IBD and examine the applicability of Th2-targeted therapies for intestinal inflammation.

### Keywords

Mucosal immunity; Th2 responses; ILC2; helminthes; inflammatory bowel disease

Correspondence to: Giorgos Bamias, Academic Department of Gastroenterology, Kapodistrian University of Athens, Laikon Hospital, 17 Agiou Thoma st., 11527, Athens, Greece Phone: +30210-7456504, Fax: +30210-7791839, gbamias@gmail.com and Fabio Cominelli, M.D., Ph.D., Case Western Reserve University School of Medicine, Division of Gastrointestinal and Liver Disease, 11100 20 Euclid Avenue, Cleveland, Ohio 44106-5066 Phone: (216) 844-7344, Fax:21 (216) 844-7371, fabio.cominelli@uhhospitals.org.

Conflicts of interest: None.

## Introduction

Type 2 (Th2) immune responses in the gastrointestinal tract have evolved as a protective mechanism against injury caused by multicellular metazoan parasites of mammals, also known as helminthes (1). Although the Th terminology was, initially, introduced in reference to CD4+, lymphocytic responses, it has now become evident that additional cell populations (of both the innate and adaptive immunity) critically participate in such responses, along with a variety of soluble mediators (2). The “core” signature of Th2 responses is the secretion of the cytokines IL-4, IL-15, and IL-13 by lymphocytes that express the transcription factor GATA3 (3). These type 2 cells and modules provide protection from helminthic infections through several additive functions, including smooth muscle hypercontractility, enhanced mucus secretion and induction of intestinal mastocytosis, all of which aim at worm killing and expulsion. In parallel, Th2 mediators are also involved in the process of wound healing (4). This combination of protection against infection and tissue repair render Th2 factors critical regulators of intestinal tissue homeostasis. However, when Th2 immunity becomes dysregulated and over-reactive, it may lead to deleterious consequences. On the one hand, the persistence of Th2 effector pathways may lead to unrelenting inflammation, whereas overzealous tissue repair processes may end up in excessive collagen deposition, fibrosis, and stricturing complications. The first pathway is probably involved in the pathogenesis of chronic intestinal inflammation that takes place in ulcerative colitis, whereas Th2-induced fibrogenesis may underlie the augmented mucosal and transmural fibrotic process that occurs in both forms of inflammatory bowel disease (Crohn’s disease and ulcerative colitis). In the current review, we will present new evidence on the role of Th2 immunity in protective and inflammatory immunological pathways at the intestine.

## Upstream regulators of Th2 immunity

The initial development of Th2 responses is affected by signals provided by IL-4 itself but is also regulated by other cytokines. Although the cellular source of the initial burst of IL-4 is not clearly defined, epithelial-derived, Th2-promoting factors have been increasingly delineated. The latter include thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, which are all released after injury to the epithelium and alert the immune system for the breach in epithelial integrity. Among those Th2-promoting factors, IL-33 has been the most thoroughly investigated.

IL-33 is a member of the IL-1 family of cytokines which binds to receptor ST2 (5). IL-33 localizes to intestinal epithelial cells, and its full-length form is released upon epithelial damage, acting as an “alarmin” and triggering wound healing at the mucosa (6). Nevertheless, IL-33 is also capable of inducing inflammation. A recent publication raised the possibility that the final outcome (protection vs. inflammation) may be related to cellular compartmentalization of IL-33 expression. In particular, pro-inflammatory effects were dependent upon loss of nuclear sequestration of IL-33. These pathways were tested in a mouse strain with abolished signal for nuclear localization of IL-33 (IL-$33^{tm1/+}$ mice); thus, produced IL-33 was localized to the cytoplasm only (7). This was associated with constant release of IL-33 into the systemic circulation which led to significant increase in serum

IL-33 levels. Interestingly, IL-33$^{tm1/+}$ mice developed multiorgan inflammation, including enterocolitis, which bore the characteristics of Th2 type inflammation, such as eosinophilic infiltration of target tissues and elevated IL-5 expression. When IL-33$^{tm1/+}$ were crossed to ST2 null mice, inflammation was abrogated, despite high systemic levels of IL-33. These results imply that IL-33 is sequestrated in the nucleus and this prohibits its systemic release and deleterious pro-inflammatory function. On the other hand, when nuclear sequestration in aborted, IL-33 is released from the cell and induces pro-inflammatory responses, leading to local and systemic inflammation. Whether such a mechanism actually takes place during acute or chronic inflammatory intestinal disorders remains to be elucidated. Irrespectively of the specific mechanism, pro-inflammatory effects of IL-33 were previously shown in experimental models of colitis (8, 9). In particular, ST2 KO mice were protected from acute DSS-colitis and administration of anti-ST2 neutralizing antibodies ameliorated the severity of colitis (9). In a different approach, exogenous IL-33 administration resulted in exaggerated inflammation after DSS administration via the induction of Th2 immunity, with elevations of IL-4 and IL-13 (8). IL-33 treatment significantly impaired the epithelial barrier integrity and increased intestinal permeability. Furthermore ST2-deficient mice demonstrated accelerated wound healing after biopsy-inflicted colon injury. Taken together, these studies suggest that IL-33/ST2 signaling may be associated with tissue repair defects which, at the event of acute trauma, lead to delayed healing and increased leakiness of the gut epithelium, resulting in more severe and prolonged colitis. It should be kept in mind, however, that IL-33 is a Janus-like cytokine that demonstrates dichotomous functions being either protective or pro-inflammatory, depending on the specific experimental or clinical conditions (10). Important recent studies have shown that, besides its Th2-polarizing effects, IL-33/ST2 signaling plays crucial roles in the development and function of regulatory cell populations at the gut mucosa (11, 12). Regulatory T cells (Tregs) highly express ST2 and respond to alarmin-like IL-33 to restrain intestinal inflammation. Treg responsiveness to IL-33 was enhanced by APC-derived IL-2 and limited by IL-23 (12). These results raise the possibility that interactions between pro-inflammatory (IL-23-dependent) and regulatory (IL-33-dependent) elements dictate the fate of intestinal immune responses (12). Furthermore, a population of IL-33-induced, IL-10-producing B lymphocytes was recently identified at the intestinal mucosa, which displays the characteristics of a regulatory population with anti-inflammatory properties; hence it was designated as Breg$^{IL-33}$ cells (13).

How IL-33 affects the development of Th2 responses in the intestine is not clear. A recent study showed that IL-33 treatment of mucosal lymphocytes led to significant upregulation of the master Th2 transcription factor GATA3, whereas, expression of the Th1 regulator T-bet was not affected (14). In addition, the mucosal expression of IL-33 was significantly elevated and positively correlated with disease severity in two animal models of experimental colitis (piroxicam-accelerated colitis in IL-10$^{-/-}$ mice and DSS colitis) but also in patients with UC. Expression of IL-33 highly correlated with that of GATA3, thus, providing indirect evidence for the biological importance of this cytokine as a stimulator of Th2 responses.

Other factors that influence the initial development of Th2 responses were also recently reported in variable systems, with APCs being central to this process. These included

negative roles of APC-derived IL-6 and of IL-21 on the regulation of Th2 immune responses (15, 16) and a positive role for the subset of CD141+ dendritic cells that preferentially induce the secretion of IL-4– and IL-13 by CD4+ lymphocytes via engagement of the OX40 ligand (17). Of great importance for intestinal immunity is the recent report that indigenous eosinophils that inhabit the small intestine are capable of inducing Th2 polarizing properties to DCs (18). It was shown that eosinophil-deficient mice were protected from Th2-mediated peanut food allergy and anaphylaxis. When the eosinophilic pool was reconstituted, protection was aborted. It was subsequently shown that eosinophils critically affected both the activation of CD103+ DCS and their migration to the draining lymph nodes. These were essential steps for Th2 priming of lymphocytes. Control of DC function was mediated through degranulated eosinophil peroxidase.

## Downstream effectors of Th2 immunity

Th2-promoting signals converge to the activation of GATA3 which, in turn, induces transactivation of the IL-4 promoter and upregulation of IL-5 and IL-13 genes. The importance of GATA3-induced, Th2-cytokine-mediated pathways for the development of intestinal inflammation was clearly shown in a recent study, which examined the severity of DSS-colitis in mice transgenic for T-bet (Th1 dominant), GATA-3 (Th2 dominant), and RORγt (Th17 dominant) (19). Interestingly, GATA-3 Tg mice developed the most severe colitis and this was associated with significant mucosal upregulation of IL-13.

Nowadays, the pool of cells that share the aforementioned properties and fulfill the definition of type 2 effectors has been expanded to include cells other than the CD4+ Th2 subset, with particular attention on type 2 innate lymphoid cells (ILC2) (20). These are lineage negative lymphocytes, lack antigen specificity, and express markers of Th2 polarized cells (21). They reside at mucosal sites, including the gut and mesenteric adipose tissue; and are important elements of the defensive response against helminthes. Recently, it was shown that during type 2 responses a crosstalk takes place between ILC2 and CD4+Th2 cells which is important for optimal anti-helminthic responses. In one study, depletion of ILC2 in mice led to impairment of Th2 responses (22). In this study ILCs were shown to express MHCII and bi-directionally interact with Th2 lymphocytes. On the one hand, CD4+ activation by dendritic cells was augmented; on the other hand, T-cells secreted IL-2 that subsequently promoted the proliferation of and IL-13 secretion by ILC2s. This was critical for the biological activity of ILCs as deletion of MHCII led to defective expulsion of the helminth *Nippostrongylus brasiliensis*. These findings were confirmed in another study, which demonstrated that ILC2 and CD4+ T cells positively affect each other's functionality (23). Similarly to the previous study, CD4+ T cells stimulated ILC2 function by providing IL-2, whereas, ILC2 were capable to express MHCII and present antigens to naive T cells via cell contact both *in vitro* and *in vivo*. This interaction favored the development of Th2 immunity at the same time suppressing Th1 differentiation.

Factors that influence the development and function of ILC2 during protective mucosal immunity are also increasingly recognized. One such factor may be the endogenous danger signal adenosine. It was shown that blockade of adenosine receptor A2BAR negatively affected the development of Th2 responses against the intestinal nematode

*Heligmosomoides polygyrus* and inhibited worm expulsion (24). In the absence of A2BAR several parameters of type 2 responses were decreased, including eosinophil recruitment, M2 macrophage infiltration, defective IL-4 and IL-13 production, and compromised IL-33 upregulation in response to infection. Exogenous IL-33 administration restored effective type 2 immunity. These results showed that when the epithelium is damaged by helminth invasion, several danger-associated molecular patterns (DAMP) such as IL-33 and adenosine are released and initiate protective immunity at the intestinal mucosa. In a different study, the transcription factor Nfi3 was shown to de required for the development of ILC2 (and ILC3) (25). This was of significant biological importance as mice defective for Nfi3 failed to exert effective mucosal responses to *C. rodentium* infection. ILC2s were also shown to express the TNF-receptor superfamily member TNFRSF25/DR3 (26). When DR3 bound to its cognate ligand TNFSF15/TL1A, augmentation of ILCs development and function was observed. Interestingly, this occurred independently of the presence of IL-25 or IL-33, indicating the presence of redundant pathways for ILCs function. Accordingly, mice deficient for DR3 expression failed to clear gut infection by helminthes. These studies demonstrate the significance of TL1A/DR3 interactions for mucosal immunity.

The identity of the critical cell population that produces the effector cytokines during pathogenic type 2 immune responses remains undefined. Previous studies showed that, in UC, which is considered a paradigm of Th2 type response, the pathogenetic population is a non-invariant NKT cell that demonstrates elevated IL-13 production upon stimulation (27). An important recent study further characterized this population and shed light into the stimulatory triggers for IL-13 production (28). In particular, cells that are isolated from the lamina propria of UC patients are enriched for type-II NKT cells which are absent in the healthy intestine. These cells are signified by their ability to bind lyso-sulfatide glycol lipid-loaded CD1d tetramer. Upon stimulation these cells secrete large quantities of IL-13, which denotes a dominance of Th2 type responses. They are also capable of inducing epithelial cell cytotoxicity; hence they may contribute to UC pathogenesis via impairment of the epithelial barrier. Interestingly, lyso-sulfatide glycolipid stimulation also led to upregulation of the receptor IL-13Rα2. Using multicolour quantum dot-staining technology, it was demonstrated that this population is affluent in the lamina propria of UC patients and defined by the concomitant expression of IL-13Rα2 and CD161 and the capability of IL-13 secretion. In all, these findings confirm the predominance of Th2-pathways in UC.

Oxazolone-induced colitis is considered an experimental analogue of UC, as both depend on type 2 mucosal immunity. Recently, a novel treatment was tested in oxazolone treated mice, utilizing a bifunctional IL-4/IL-13 antagonist, in the hopes that such combinatorial blockade would overcome the redundant effects of these cytokines (29). Binding of IL-13 was accomplished via a derivative of the murine IL-13Ra2 extracellular sequence and of IL-4 via a derivative of rat anti-mouse IL-4 mAb 11B11. Administration of this agent to oxazolone-treated mice was associated with significant amelioration of disease severity. These results are in line with the absence of oxazolone-induced colitis in mice lacking IL-4Ra or STAT6, thus been unable to develop IL-4 or IL-13-mediated immunity (30, 31).

The aforementioned studies clearly show that Th2 responses may exert pro-inflammatory roles and point out the therapeutic potential of their neutralization. On the other hand,

induction of Th2 responses may also be of benefit when mucosal inflammation is mediated through Th1 or Th17 pathways. One such example is the ameliorating effect of IL-4 gene therapy on the severity of TNBS- colitis, which is Th1-mediated (32). Intraperitoneal injection of plasmid pcDNA3.0-mIL-4 resulted in significant decreases in tissue injury by TNBS. This was associated with decreases in the mucosal expression of the IFN-γ and TNF-α, indicating a suppression of Th1 pro-inflammatory responses. Applying a different approach, Heylen et al. administered soluble worm proteins from Schistosoma mansoni in mice that developed colitis after adoptive transfer of T cells (33). This model of colitis is Th1/IFN-γ-dependent and the pathogenetic hypothesis of worm protein administration was that they would induce an anti-inflammatory Th2 response. Curative (given after the establishment of colitis) and, to lesser degree, preventive (before colitis establishment) administration of worm proteins resulted in a significant improvement of the clinical and histological parameters of colitis. The immunological effect of such treatment was signified by a decrease in IFN-γ and IL-17A mucosal mRNA expression and concomitant elevation of IL-4 expression. Therefore, this potentially Th2-inducing factor modified the mucosal milieu in favor of anti-inflammatory responses. These data are complimentary to the current case for administration of helminthes as a therapeutic option in IBD (34, 35) and demonstrate that Th2 responses may be homeostatic or pro-inflammatory at the intestinal mucosa, depending on the specific situation.

## Therapeutic implications

Despite the accumulated evidence pointing to a pivotal role for Th2 immunity during chronic inflammatory pathways at the intestinal mucosa, therapeutic application of anti-IL-13 blockade was associated with highly disappointing results. In the last year, results of large clinical trials reported failure of two anti-IL-13 monoclonal antibodies to induce clinical benefit it patients with moderate to severe ulcerative colitis. In the first study, anrukinzumab, a humanised IgG1, anti-IL-13 antibody was administered to patients with mild and moderate active UC. Anrukinzumab inhibits attachment of IL-13 to IL-4Rα, without affecting binding to IL-13α1 or IL-13α2 (36). Treatment with anrukinzumab failed to reach the primary endpoint which was the fold change from baseline in faecal calprotectin at Week 14. Secondary outcomes such as change in total Mayo score, clinical response, clinical remission, and mucosal healing also were not met. Similar negative results were reported with tralokinumab (CAT-354) an IL-13-neutralizing human immunoglobulin G4 monoclonal antibody (37). It was administered in patients with moderate-to-severe UC. Treatment did not reach statistical significance regarding clinical response, which was the primary endpoint, although there were significant differences in improvements in clinical remission and mean partial Mayo scores between and placebo. The reasons for this quite “absolute” failure of anti-IL-13 treatment are not easily understood (38). Accelerated clearance of anrukinzumab was reported in UC patients in comparison to healthy volunteers or patients with asthma (39). This implies that a suboptimal dose may have been used in the UC trials. Nonetheless, the answer most probably lies in the complexity of immunological pathways that underlie IBD, the wide-spectrum of IL-13-mediated effects on mucosal immunity and the immunophenotype variation within the patient population. Indeed, the high rates of failure of biological therapies should indicate that the model of “one treatment

cures all" must be abandoned and replaced by targeted therapies after careful genetic and immunological phenotyping of patients (40).

## CONCLUSION

In conclusion, type 2 responses are implicated in several aspects of gut homeostasis but also in chronic intestinal inflammation. The latter may be protective as in the case of helminthic infection or deleterious as in IBD. The pathways that mediate these scenarios are constantly enriched with new cellular and molecular components. Better delineation of these mechanisms and understanding of their opposite effects will define the applicability of Th2-targeted therapies for intestinal inflammation.

## Acknowledgments

None

Financial support or sponsorship: Supported by grants from the National Institutes of Health: DK091222, DK055812, DK097948 and DK042191.

## REFERENCES AND RECOMMENDED READING

1. Allen JE, Sutherland TE. Host protective roles of type 2 immunity: parasite killing and tissue repair, flip sides of the same coin. Semin Immunol. 2014; 26:329–340. [PubMed: 25028340]
2. Paul WE, Zhu J. How are T(H)2-type immune responses initiated and amplified? Nat Rev Immunol. 2010; 10:225–235. [PubMed: 20336151]
3. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. 2015; 135:626–635. [PubMed: 25528359]
4. Gause WC, Wynn TA, Allen JE. Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. Nat Rev Immunol. 2013; 13:607–614. [PubMed: 23827958]
5. Pastorelli L, De Salvo C, Vecchi M, et al. The role of IL-33 in gut mucosal inflammation. Mediators Inflamm. 2013; 2013:608187. [PubMed: 23766561]
6. Lopetuso LR, Scaldaferri F, Pizarro TT. Emerging role of the interleukin (IL)-33/ST2 axis in gut mucosal wound healing and fibrosis. Fibrogenesis Tissue Repair. 2012; 5:18. [PubMed: 23062310]
7•. Bessa J, Meyer CA, de Vera Mudry MC, et al. Altered subcellular localization of IL-33 leads to non-resolving lethal inflammation. J Autoimmun. 2014; 55:33–41. This study describes the development of a novel murine strain which allows for the discrimination between different subcellular localizations of IL-33 and dissects the functional implications of such diverse topography. [PubMed: 24786898]
8. Sedhom MA, Pichery M, Murdoch JR, et al. Neutralisation of the interleukin-33/ST2 pathway ameliorates experimental colitis through enhancement of mucosal healing in mice. Gut. 2013; 62:1714–1723. [PubMed: 23172891]
9. Pushparaj PN, Li D, Komai-Koma M, et al. Interleukin-33 exacerbates acute colitis via interleukin-4 in mice. Immunology. 2013; 140:70–77. [PubMed: 23582173]
10. Bamias G, Corridoni D, Pizarro TT, et al. New insights into the dichotomous role of innate cytokines in gut homeostasis and inflammation. Cytokine. 2012; 59:451–459. [PubMed: 22795953]
11. Schiering C, Krausgruber T, Chomka A, et al. The alarmin IL-33 promotes regulatory T-cell function in the intestine. Nature. 2014; 513:564–568. [PubMed: 25043027]
12•. Matta BM, Lott JM, Mathews LR, et al. IL-33 is an unconventional Alarmin that stimulates IL-2 secretion by dendritic cells to selectively expand IL-33R/ST2+ regulatory T cells. J Immunol. 2014; 193:4010–4020. This study describes for the first time an involvement of IL-33 mediated pathways in the survival and function of regulatory T cells and raise the possibility of dissociated pro-inflammatory and regulatory pathways. [PubMed: 25217167]

13. Sattler S, Ling GS, Xu D, et al. IL-10-producing regulatory B cells induced by IL-33 (Breg(IL-33)) effectively attenuate mucosal inflammatory responses in the gut. J Autoimmun. 2014; 50:107–122. [PubMed: 24491821]

14. Seidelin JB, Coskun M, Kvist PH, et al. IL-33 promotes GATA-3 polarization of gut-derived T cells in experimental and ulcerative colitis. J Gastroenterol. 2015; 50:180–190. [PubMed: 25112700]

15. Mayer A, Debuisson D, Denanglaire S, et al. Antigen presenting cell-derived IL-6 restricts Th2-cell differentiation. Eur J Immunol. 2014; 44:3252–3262. [PubMed: 25092208]

16. Lin PY, Jen HY, Chiang BL, et al. Interleukin-21 suppresses the differentiation and functions of T helper 2 cells. Immunology. 2015; 144:668–676. [PubMed: 25351608]

17. Yu CI, Becker C, Metang P, et al. Human CD141+ dendritic cells induce CD4+ T cells to produce type 2 cytokines. J Immunol. 2014; 193:4335–4343. [PubMed: 25246496]

18•. Chu DK, Jimenez-Saiz R, Verschoor CP, et al. Indigenous enteric eosinophils control DCs to initiate a primary Th2 immune response in vivo. J Exp Med. 2014; 211:1657–1672. This study shows that indigenous, small intestinal eosinophils induce the acquisition of Th2 polarizing properties to resident DCs. [PubMed: 25071163]

19. Okamura M, Yoh K, Ojima M, et al. Overexpression of GATA-3 in T cells accelerates dextran sulfate sodium-induced colitis. Exp Anim. 2014; 63:133–140. [PubMed: 24770638]

20. Walker JA, McKenzie AN. Development and function of group 2 innate lymphoid cells. Curr Opin Immunol. 2013; 25:148–155. [PubMed: 23562755]

21. Spits H, Artis D, Colonna M, et al. Innate lymphoid cells--a proposal for uniform nomenclature. Nat Rev Immunol. 2013; 13:145–149. [PubMed: 23348417]

22••. Oliphant CJ, Hwang YY, Walker JA, et al. MHCII-mediated dialog between group 2 innate lymphoid cells and CD4(+) T cells potentiates type 2 immunity and promotes parasitic helminth expulsion. Immunity. 2014; 41:283–295. This is the first report of a potential crosstalk between ILC2s and Th2 CD4+ cells which is critical for the development of Th2 responses and immunity against helmithic infection. [PubMed: 25088770]

23. Mirchandani AS, Besnard AG, Yip E, et al. Type 2 innate lymphoid cells drive CD4+ Th2 cell responses. J Immunol. 2014; 192:2442–2448. [PubMed: 24470502]

24. Patel N, Wu W, Mishra PK, et al. A2B adenosine receptor induces protective antihelminth type 2 immune responses. Cell Host Microbe. 2014; 15:339–350. [PubMed: 24629340]

25. Seillet C, Rankin LC, Groom JR, et al. Nfil3 is required for the development of all innate lymphoid cell subsets. J Exp Med. 2014; 211:1733–1740. [PubMed: 25092873]

26•. Yu X, Pappu R, Ramirez-Carrozzi V, et al. TNF superfamily member TL1A elicits type 2 innate lymphoid cells at mucosal barriers. Mucosal Immunol. 2014; 7:730–740. This study implicates the TL1A/DR3 system of TNF/TNFR-like cytokines in the function of mucosa-associated ILC2s and indicates the participation of this system in innate immunity pathways. [PubMed: 24220298]

27. Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. J Clin Invest. 2004; 113:1490–1497. [PubMed: 15146247]

28••. Fuss IJ, Joshi B, Yang Z, et al. IL-13Ralpha2-bearing, type II NKT cells reactive to sulfatide self-antigen populate the mucosa of ulcerative colitis. Gut. 2014; 63:1728–1736. In this study, the authors present a pivotal, UC-specific, Th2-polarizing, pathogenic population of type-II NKT cells that bind lyso-sulfatide glycol lipid-loaded CD1d tetramers and secrete IL-13. [PubMed: 24515806]

29. Kasaian MT, Page KM, Fish S, et al. Therapeutic activity of an interleukin-4/interleukin-13 dual antagonist on oxazolone-induced colitis in mice. Immunology. 2014; 143:416–427. [PubMed: 24831554]

30. Rosen MJ, Chaturvedi R, Washington MK, et al. STAT6 deficiency ameliorates severity of oxazolone colitis by decreasing expression of claudin-2 and Th2-inducing cytokines. J Immunol. 2013; 190:1849–1858. [PubMed: 23303670]

31. Hoving JC, Kirstein F, Nieuwenhuizen NE, et al. B cells that produce immunoglobulin E mediate colitis in BALB/c mice. Gastroenterology. 2012; 142:96–108. [PubMed: 21983080]

32. Xiong J, Lin YH, Bi LH, et al. Effects of interleukin-4 or interleukin-10 gene therapy on trinitrobenzenesulfonic acid-induced murine colitis. BMC Gastroenterol. 2013; 13:165. [PubMed: 24314293]

33. Heylen M, Ruyssers NE, De Man JG, et al. Worm proteins of Schistosoma mansoni reduce the severity of experimental chronic colitis in mice by suppressing colonic proinflammatory immune responses. PLoS One. 2014; 9:e110002. [PubMed: 25313594]

34. Elliott DE, Weinstock JV. Where are we on worms? Curr Opin Gastroenterol. 2012; 28:551–556. [PubMed: 23079675]

35. Elliott DE, Weinstock JV. Helminthic therapy: using worms to treat immune-mediated disease. Adv Exp Med Biol. 2009; 666:157–166. [PubMed: 20054982]

36•. Reinisch W, Panes J, Khurana S, et al. Anrukinzumab, an anti-interleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study. Gut. 2015 This study reports the results of a clinical trial on the administration of a monoclonal antibody against IL-13 that failed to induce clinical response to patients with active UC.

37•. Danese S, Rudzinski J, Brandt W, et al. Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study. Gut. 2015; 64:243–249. This study is complimentary to the previous clinical trial, as the use of a different monoclonal antibody was also ineffective as treatment of active UC. [PubMed: 25304132]

38. Tilg H, Kaser A. Failure of interleukin 13 blockade in ulcerative colitis. Gut. 2015

39. Hua F, Ribbing J, Reinisch W, et al. A pharmacokinetic comparison of Anrukinzumab, an anti-IL-13 monoclonal antibody, among healthy volunteers, asthma and ulcerative colitis patients. Br J Clin Pharmacol. 2015

40. Bamias G, Cominelli F. Immunopathogenesis of inflammatory bowel disease: current concepts. Curr Opin Gastroenterol. 2007; 23:365–369. [PubMed: 17545770]

## KEY POINTS

Mucosal Th2 immunity may be initiated via the release of alarmin-type molecules, such as adenosine or IL-33, from injured epithelial cells.

Type-II NKT cells that bind lyso-sulfatide glycol lipid-loaded CD1d tetramers and secrete IL-13 are a pivotal pathogenic population in ulcerative colitis.

Type 2 innate lymphoid cells (ILC2) are important mediators of mucosal, Th2-type immunity against infection with helminthes.

Th2 cytokines are implicated in both pro-inflammatory and homeostatic pathways at the intestinal mucosa.

Neutralization of IL-13 via monoclonal antibodies was ineffective as a therapeutic strategy in patients with ulcerative colitis.