Published in final edited form as:
Curr Opin Gastroenterol. 2014 November ; 30(6): 547–552. doi:10.1097/MOG.0000000000000118.

Cytokines and Mucosal Immunity

Giorgos Bamias[1], **Kristen O. Arseneau**[2], 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.

Summary

Elucidating the complexity of cytokine signaling within the normal mucosa and during acute and chronic inflammation will be a pivotal step towards understanding the pathogenesis of immune-mediated gut diseases, and developing effective therapies to treat them.

Keywords

Mucosal homeostasis; inflammation; cytokines; innate lymphoid cells

Introduction

The intestinal mucosa faces the constant challenge of maintaining a peaceful co-existence between commensal microbiota and the gut-associated immune system [1]. At steady-state, homeostasis signifies a tightly regulated communication between the two parts via successive but interrelated mucosal barriers. During acute injuries, barriers are temporarily compromised, allowing an influx of microorganisms into the lamina propria. In healthy mucosa, this is followed by complete architectural and functional recovery without permanent defects. Nevertheless, when, under genetic and/or environmental pressure, barrier dysfunction becomes permanent, the ability to handle everyday encounters with microbiota or repair acute traumas is lost and chronic inflammation is established [2]. This is best exemplified in Crohn's disease (CD) and ulcerative colitis (UC), collectively termed inflammatory bowel disease (IBD) [3].

Cytokines regulate the function of the mucosal barrier(s) at multiple levels [4]. Innate cytokines exert dichotomous roles during homeostatic and inflammatory pathways, as revealed by murine models of acute injury and repair [5]. Unexpectedly, deletion of several

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.

Purpose of Review

Cytokines are integral mediators for maintaining intestinal mucosal homeostasis, as well as prominent effector molecules during chronic gut inflammatory diseases. This review focuses on recent studies of the role of specific cytokines in mucosal immunity.

The authors declare no conflict of interest.

"pro-inflammatory" factors was associated with more severe active inflammation and delayed mucosal healing [6]. The cellular sources and temporal pattern of expression of a specific cytokine appear to dictate its ultimate function; transient epithelial expression maintains homeostatic control, whereas persistent production by monocytes leads to inflammation [7]. Adaptive immune responses are also complex at the intestinal mucosa, as chronic inflammation develops through sequential steps, each of which is mediated by distinct sets of cytokines [4, 8, 9]. In experimental models as well as in patients with IBD, initiation of ileitis or colitis is dominated by Th1-type responses, whereas Th2 and Th17 pathways prevail in later stages [10-13]. Furthermore, effector lymphocytes may convert to other phenotypes (effector-or even regulatory) [14]. Adding more to the complexity, cells with mixed innate/adaptive characteristics have been recently described. These innate lymphoid cells (ILCs) consist of several subpopulations of mucosal residents that regulate local immunity through the secretion of cytokines [15, 16]. Such variability not only creates difficulty to provide a uniform pathogenetic model for chronic inflammatory diseases, but will also critically affect the selection of future therapeutic targets.

The present review will focus on recent publications, presenting important new information for the role of specific cytokines in mucosal homeostasis and inflammation.

CYTOKINES OF THE IL-1 FAMILY

The concept of dichotomous cytokine function has been mostly based on observations regarding the role of members of the IL-1 family in intestinal inflammation, given that IL-1, IL-18 and IL-33 have demonstrated both pro-inflammatory and protective properties, depending on the type of receptor-bearing cells [6].

In keeping with this concept, Bersudsky et al. recently reported opposing roles for IL-1α and IL-1β during acute injury and repair by studying the natural course of acute dextran sulfate sodium (DSS)-induced colitis in mice deficient for the respective cytokines [17]. IL-1α has a pro-inflammatory role in this model, as IL-1α KO mice demonstrated no mortality and milder histological damage, compared to wild-type mice. They also displayed accelerated epithelial restitution and preserved barrier function. Mice carrying epithelial-specific deletion of the *il-1a* gene were similarly protected, pointing to the epithelium as the primary cellular source of pro-inflammatory IL-1α, which acts as an alarmin when its precursor is released from necrotic cells. On the other hand, IL-1β deficiency led to more severe colitis with failure of repair mechanisms, findings indicative of a protective role of IL-1β, which was mainly derived from lamina propria monocytes. In fact, when IL-1β-deficient mice received hematopoietic cells capable of producing IL-1β, restoration of repair mechanisms occurred. A protective role for IL-1β was previously proposed in rabbit formalin-immune complex colitis [18]. Therefore, deficient mucosal upregulation of "protective" IL-1β may impair homeostasis after transient injury and lead to chronic inflammation. Such impaired secretion of IL-1β from monocytes has also been described in IBD patients bearing NOD2 double mutant genotypes or mutations to a regulatory region downstream of the inflammasome component NLRP3 [19, 20]. Dichotomy of function between IL-1α and IL-1β had therapeutic implications as well, as neutralization of IL-1α via an anti-IL-1α-specific monoclonal antibodies (but not administration of the IL-1-receptor antagonist

[IL-1Ra], which blocks both IL-1α and IL-1β), led to decreased severity of DSS colitis in wild-type mice [17]. The ability to act as a pro-inflammatory alarmin was recently shown for IL-33, another member of the IL-1 family [21]. Bessa and co-investigators developed a novel mouse strain that lacks the signal for nuclear localization of IL-33 (IL-33^{tm1} mice). Constitutive detection of IL-33 in the systemic circulation was observed in this strain, indicating that when IL-33 is not localized to the nucleus, it gets released from the cell and may act as an alarmin. Accordingly, IL-$33^{tm1/+}$ mice develop severe multi-organ inflammation with prominent eosinophilic infiltration, leading to early death. Small and large intestines showed severe inflammatory lesions, indicative of loss of mucosal homeostasis. These effects were aborted when IL-$33^{tm1/+}$mice were crossed with mice deficient for the IL-33 receptor, ST2 ($ST2^{-/-}$/IL-$33^{tm1/+}$ mice), although a high concentration of IL-33 in the serum was still detected. Taken together, the studies by Bersudsky [17] and Bessa [21] imply that nuclear localization of the IL-1α precursor or IL-33 acts as an internal protective mechanism, preventing their extracellular movement [22, 23]. Nevertheless, upon DSS-induced cell necrosis or by the genetic blockade of nuclear localization of IL-33 in IL-$33^{tm1/+}$mice, these cytokines are released and mediate inflammatory responses due to their function as alarmins.

Further supporting a role for IL-33 in mucosal homeostasis/inflammation, two recent studies reported diminished severity of colitis and enhancement of mucosal healing in animal models of acute injury/repair in the presence of a deficient IL-33/ST2 pathway [24, 25]. In the first study [25], it was shown that ST2 KO mice had significantly less severe acute DSS colitis compared to wild-type controls, whereas administration of exogenous IL-33 exacerbated acute intestinal inflammation in DSS-treated wild-type mice. The latter was dependent upon intact IL-4-signaling as the same effects were not seen in IL-4 KO mice. The second study [24] confirmed the dependence of DSS, but also TNBS, colitis upon ST2 signaling as both were significantly milder in ST2 KO mice or in mice treated with anti-ST2 neutralizing antibodies. Compatible with the previous findings, IL-33 was localized to the nucleus of enterocytes and myofibroblasts, while strictly epithelial localization of ST2 was shown. Accordingly, absence of ST2 in non-hematopoietic cells was sufficient to protect against colitis via a mechanism that included enhanced wound healing and elevated expression or the cytoprotective factor connexin-43. Hence, IL-33/ST2 appear to be critically involved in the process of acute injury/mucosal healing in the gut. This is further supported by the recent identification of genetic polymorphisms in the *il-33* and *il-1r1* genes that modify the susceptibility for developing IBD [26]. It should be noted, however, that cytokines within the IL-1 family may occasionally exert opposite functional roles depending on the clinical or experimental conditions [6]. For example, in a recent study IL-33 acted in an anti-inflammatory mode by augmenting the development of a population of B lymphocytes with regulatory properties (Bregs) [27]. Accordingly, peritoneal injection of IL-33 exacerbated colitis in IL-10-deficient mice, whereas IL-33-treated wild type mice were protected from disease.

CYTOKINES OF THE TNF/TNFR SUPERFAMILIES

Several members of the TNF/TNFR superfamily act as co-stimulatory molecules, regulating the interactions between antigen-presenting cells (APCs) and lymphocytes [28]. This is of

particular importance for the mucosal environment due to the local abundance of bacterial antigens. Moreover, APC-lymphocyte binding is critical for the fate of immune responses and the shaping of ensuing adaptive immunity.

Interaction between APC-derived TL1A (TNFSF15) and its functional receptor DR3 (TNFRSF25) in lymphocytes contributes to both gut homeostasis and inflammation [29, 30]. A recently published study reported that type-2 innate lymphoid cells (ILC2s) abundantly express DR3 [31]. TL1A provides critical signals upon association with its cognate receptor, DR3, that promote the survival and augment the function of ILC2s, such as the secretion of IL-5 and IL-13. Accordingly, effective immunity against helminthic infection is compromised in DR3-deficient mice due to impaired innate ILC2 responses. Finally, TL1A functions independently but also synergistically with IL-25 or IL-33 to activate ILC2s. Similar defects were observed in the lungs of DR3-deficient mice, indicating that TL1A/DR3 are important mediators of mucosal immunity at various sites, and a possible mode of action is the activation of ILC2-mediated pathways [32] . It is also important to note that, so far, the only known ligand for DR3 is TL1A. Nevertheless, a recent publication reported that atsttrin is also capable to bind DR3 with high affinity [33]. Attstrin is an engineered molecule, which is derived from progranulin, a growth-factor with multiple biological functions, including the ability to bind to TNFR [34]. In this study, attstrin not only showed *in vitro* affinity for DR3 binding, but also significantly ameliorated the severity of DSS colitis, indicating that administration of attstrin may also be of clinical importance in the future. Another co-stimulatory molecule of the TNF family, LIGHT (TNFSF14) was recently shown to be a critical factor for the resolution of intestinal inflammation in mice [35]. Krausse et al. reported accelerated colonic inflammation when CD4/CD45RB^{hi} T cells were adoptively transferred into *tnfsf14/Rag1* double KO, compared to *Rag1* KO recipients alone. Furthermore, *tnfsf14* KO mice developed more severe DSS colitis than wild-type controls, both clinically and histologicaly. In addition, in the absence of intact LIGHT signaling, immune responses were enhanced within the inflamed mucosa, including elevated number of immunocytes and augmented production of cytokines. LIGHT was mainly produced by myeloid cells and interacted with the lymphotoxin β receptor to exert its protective effect [35].

An important characteristic of TNFSF/TNFRSF cytokines is that they are functionally implicated in common inflammatory pathways, either by regulating the initiation of responses through modification of APC-lymphocyte interactions or by acting as final effector molecules produced by innate immune cells. In this sense they offer unique therapeutic opportunities for chronic inflammatory diseases, irrespectively of the predominant immunophenotype. In the case of intestinal inflammation, this is emphasized by the significant therapeutic benefit for patients with CD or UC with the use of anti-TNF monoclonal antibodies. Recent studies have provided new evidence for the pathogenic mechanism through which blockade of TNF-α leads to anti-inflammatory effects. In a seminal study by Atreya et al., response to anti-TNF therapy directly correlated to the number of mucosal immunocytes expressing membrane TNF-α (mTNF) before treatment commencement [36]. The investigators administered fluorescent, specific, anti-TNF antibodies locally (i.e. via an endoscope) and were able to enumerate intestinal cells positive

for mTNF staining by use of confocal laser endomicroscopy. Response to anti-TNF treatment was critically dependent upon the number of TNF-expressing immunocytes, as patients with high numbers of mTNF almost universally responded to treatment (92%). In sharp contrast, patients with low numbers of mTNF expressing cells did not respond to the treatment (15%). In a different study, the relative contribution of neutralization of soluble vs. transmembrane TNF-α to the therapeutic effect was examined [37]. To accomplish this, the investigators utilized the model of colitis that follows adoptive transfer of $CD45RB^{hi}CD25^{neg}$T-cells to immunodeficient mice. As expected, administration of anti-TNF mAbs (that block both membrane and soluble TNF-α) suppressed colitis in recipient mice. Alternatively, mice treated with a dominant negative mutant of TNF-α (XENP1595) that selectively inhibits soluble TNF-α did not show amelioration in colitis. XENP1595 acts by exchanging subunits with native soluble TNF homotrimers and forming inactive heterotrimers which are unable to signal through TNFR1 or 2 [38]; membrane TNF-α signaling is not modified. Hence, it appears that neutralization of membrane TNF-α is the critical event for the amelioration of T-cell-mediated colitis. In the past, it was proposed that lymphocytes expressing membrane TNF-α are eliminated through apoptosis as an explanation for the differences in the therapeutic response between the various anti-TNF-α agents. However, a recent study reported that TNF-α produced exclusively by epithelial cells is sufficient to induce chronic enterocolitis in mice [39]. In this study, the investigators created an intestinal-specific $TNF^{\Delta ARE}$ mouse ($TNF^{i\Delta ARE}$) that expressed murine TNF-α under the promoter of the intestinal fatty acid binding protein (I-FABP) gene, which is only expressed on small intestinal epithelial cells with minimal spillover to colonocytes. The study showed that $TNF^{i\Delta ARE/i\Delta ARE}$ mice had elevated mucosal and systemic TNF-α levels and developed severe chronic ileitis but not extraintestinal manifestations. $TNF^{i\Delta ARE/i\Delta ARE}$ mice demonstrated dense infiltration of the lamina propria and mesenteric lymph nodes with activated lymphocytes, which produced both Th1 (IFNγ) and Th2 (IL-5, IL-13) cytokines and were able to adoptively transfer ileitis to immunologically naïve severe combined immunodeficient recipients. These results confirm the notion that the final immunological effect is dictated not only by the cellular origin, but also by the transient or constitutive pattern of TNF-α secretion.

CYTOKINES OF THE IL-23/TH17 AXIS

The IL-23/Th17 pathway is unique in several ways among the major effector pathways of adaptive immunity [40, 41]. First, IL-17 is detectable in healthy mucosa, where it contributes to preservation of homeostasis and effective immunity against specific microorganisms. Second, Th17 cells show considerable functional plasticity and may revert to Th1 or Th1/Th17 cells when exposed to specific mucosal microenvironments. Furthermore, the development of Th17 cells is interconnected with that of Tregs, as they both require the presence of TGF-β1. Finally, instead of producing only one or few effector molecules, Th17 cells are capable of producing several cytokines that often demonstrate diverse (or even opposing) functions, among which is interleukin-22 (IL-22). Several recent publications have provided important evidence of a central role for the IL-22 in mucosal immunity.

Traditionally, a protective role has been reserved for IL-22 in the regulation of gut homeostasis [42]. A recent study supports this concept by demonstrating depletion of IL-22-producing CD4+ cells in patients with active UC, but not in normal mucosa or healthy controls [43]. The proportion of Th22 cells (IL-22+, IL-17-) was decreased whereas that of Th17 (either IL-22- or IL-22+) increased among lamina propria mononuclear cell populations from UC patients. Interestingly, when multiple cytokines were analyzed at the single-cell level with flow cytometry it was found that the expression of IL-22 correlated more with that of IFN-γ and T-bet (Th1 markers) than with expression of the Th17 marker IL-17A, similar to previous studies [44]. This association may be related to the induction of Th1 and Th22 by identical microbiota constituents as shown in this study. Depletion of Th22 cells in UC was attributed to a negative regulatory effect of TGF-β1 on IL-22 production. This suppressive effect on "protective" IL-22 may offer an explanation as to why elevated mucosal TGF-β1 expression is inadequate to limit intestinal inflammation in UC. Another study linked the anti-inflammatory role of IL-22 to its secretion by γδ T cells and ILC3s, under the control of retinoic acid (RA) [45]. RA promoted binding of RA receptor to the IL-22 promoter in γδ T cells and upregulated *in vitro* the expression of IL-22 in both cell types. *In vivo* administration of RA attenuated acute DSS- or infectious colitis. Protection was aborted by an anti-IL-22 neutralizing antibody. RA-induced IL-22 upregulation resulted in enhancement of mucosal defenses via production of the antimicrobial peptides Reg3β and Reg3γ.

This protective mucosal function of IL-22, however, was recently shown not be uniform; rather, it appears to depend on the specific experimental setting and pathogenetic model. Indeed, neutralization of IL-22 protected mice deficient in IL-23R from anti-CD40 antibody-induced acute innate colitis in Rag1 KO mice [46]. In contrast, when IL-22 was added to IL-23R-deficient mice, disease developed. Taken together, this study implies that IL-23R+ ILCs may induce colitis via interleukin-22-dependent mechanism(s) and further add to the complexity of IL-22 function at the intestinal mucosa.

CONCLUSIONS

The role of cytokines in mucosal immunity continuous to evolve as new information is accumulated through the study of experimental models, the recognition of genetic polymorphisms associated with particular clinical entities, and the detailed identification of disease-specific mucosal and systemic immunophenotypes. Most cytokines appear to be surprisingly plastic in their function and the final outcome is not affected only by the specific molecules but also by the mucosal environment on the whole. The cellular sources and tissue specificities, the transient or permanent pattern of expression, the predominance of homeostatic or inflammatory pathways, and the occurrence of early or late phases of chronic inflammation, all influence the particular role that each cytokine plays in a specific situation. Understanding these aspects of cytokine function will be pivotal in elucidating the pathogenesis of intestinal inflammatory diseases and designing therapeutic strategies for their treatment.

Acknowledgments

This work was supported by NIH grants DK042191, DK055812 and DK09122 to Fabio Cominelli

Recent Findings

Dichotomous, or even opposing, functions have been described for several cytokines involved in intestinal innate immunity (most notably for members of the IL-1 family), which depend on the specific inflammatory conditions within the intestinal mucosa. For example, both IL-1α and IL-33 exhibit “alarmin”-type properties that can signal tissue or cell damage, which further add to their well-described pro-inflammatory roles. Co-stimulatory molecules of the TNF/TNFR superfamily, such as TL1A and LIGHT, are actively involved in mucosal proinflammatory pathways, but also may exert protection against infectious agents to facilitate recovery from acute inflammation. Finally, innate lymphoid cells are increasingly recognized as important cellular sources of pivotal mucosal cytokines, including the IL-23/Th17 cytokine, IL-23.

REFERENCES

1. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature. 2011; 474(7351):298–306. [PubMed: 21677746]
2. Cader MZ, Kaser A. Recent advances in inflammatory bowel disease: mucosal immune cells in intestinal inflammation. Gut. 2013; 62(11):1653–64. [PubMed: 24104886]
3. Neurath MF, Finotto S. Translating inflammatory bowel disease research into clinical medicine. Immunity. 2009; 31(3):357–61. [PubMed: 19766078]
4. Neurath MF. Cytokines in inflammatory bowel disease. Nat Rev Immunol. 2014; 14(5):329–42. [PubMed: 24751956]
5. Bamias G, et al. New insights into the dichotomous role of innate cytokines in gut homeostasis and inflammation. Cytokine. 2012; 59(3):451–9. [PubMed: 22795953]
6. Lopetuso LR, Chowdhry S, Pizarro TT. Opposing Functions of Classic and Novel IL-1 Family Members in Gut Health and Disease. Front Immunol. 2013; 4:181. [PubMed: 23847622]
7. Abraham C, Medzhitov R. Interactions between the host innate immune system and microbes in inflammatory bowel disease. Gastroenterology. 2011; 140(6):1729–37. [PubMed: 21530739]
8. Fiocchi C. Early and late inflammatory bowel disease: why and how are they different? Curr Opin Gastroenterol. 2011; 27(4):317–20. [PubMed: 21654382]
9. Bamias G, Cominelli F. Immunopathogenesis of inflammatory bowel disease: current concepts. Curr Opin Gastroenterol. 2007; 23(4):365–9. [PubMed: 17545770]
10. Bamias G, et al. Proinflammatory effects of TH2 cytokines in a murine model of chronic small intestinal inflammation. Gastroenterology. 2005; 128(3):654–66. [PubMed: 15765401]
11. Spencer DM, et al. Distinct inflammatory mechanisms mediate early versus late colitis in mice. Gastroenterology. 2002; 122(1):94–105. [PubMed: 11781285]
12. Fichtner-Feigl S, et al. Induction of IL-13 triggers TGF-beta1-dependent tissue fibrosis in chronic 2,4,6-trinitrobenzene sulfonic acid colitis. J Immunol. 2007; 178(9):5859–70. [PubMed: 17442970]
13. Kugathasan S, et al. Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease. Gut. 2007; 56(12):1696–705. [PubMed: 17682002]
14. Bluestone JA, et al. The functional plasticity of T cell subsets. Nat Rev Immunol. 2009; 9(11):811–6. [PubMed: 19809471]
15. Fuchs A, Colonna M. Innate lymphoid cells in homeostasis, infection, chronic inflammation and tumors of the gastrointestinal tract. Curr Opin Gastroenterol. 2013; 29(6):581–7. [PubMed: 24100718]
16. Walker JA, Barlow JL, McKenzie AN. Innate lymphoid cells--how did we miss them? Nat Rev Immunol. 2013; 13(2):75–87. [PubMed: 23292121]
17*. Bersudsky M, et al. Non-redundant properties of IL-1alpha and IL-1beta during acute colon inflammation in mice. Gut. 2014; 63(4):598–609. [PubMed: 23793223] [This study dissects the roles of IL-1α and IL-1β in the setting of acute intestinal mucosal inflammation and repair.]
18. Cominelli F, et al. Interleukin 1 suppresses inflammation in rabbit colitis. Mediation by endogenous prostaglandins. J Clin Invest. 1990; 85(2):582–6. [PubMed: 2298922]
19. van Heel DA, et al. Muramyl dipeptide and toll-like receptor sensitivity in NOD2-associated Crohn's disease. Lancet. 2005; 365(9473):1794–6. [PubMed: 15910952]

20. Villani AC, et al. Common variants in the NLRP3 region contribute to Crohn's disease susceptibility. Nat Genet. 2009; 41(1):71–6. [PubMed: 19098911]

21*. Bessa J, et al. Altered subcellular localization of IL-33 leads to non-resolving lethal inflammation. J Autoimmun. 2014 [This study demonstrates the importance of subcellular localization of IL-33 for its release into the systemic circulation and its function as a pro-inflammatory alarmin.]

22. Cohen I, et al. Differential release of chromatin-bound IL-1alpha discriminates between necrotic and apoptotic cell death by the ability to induce sterile inflammation. Proc Natl Acad Sci U S A. 2010; 107(6):2574–9. [PubMed: 20133797]

23. Afonina IS, et al. Granzyme B-dependent proteolysis acts as a switch to enhance the proinflammatory activity of IL-1alpha. Mol Cell. 2011; 44(2):265–78. [PubMed: 22017873]

24. Sedhom MA, et al. Neutralisation of the interleukin-33/ST2 pathway ameliorates experimental colitis through enhancement of mucosal healing in mice. Gut. 2013; 62(12):1714–23. [PubMed: 23172891]

25. Pushparaj PN, et al. Interleukin-33 exacerbates acute colitis via interleukin-4 in mice. Immunology. 2013; 140(1):70–7. [PubMed: 23582173]

26. Latiano A, et al. Associations between genetic polymorphisms in IL-33, IL1R1 and risk for inflammatory bowel disease. PLoS One. 2013; 8(4):e62144. [PubMed: 23634226]

27. Sattler S, 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; 50:107–22. [PubMed: 24491821]

28. Croft M. Co-stimulatory members of the TNFR family: keys to effective T-cell immunity? Nat Rev Immunol. 2003; 3(8):609–20. [PubMed: 12974476]

29. Bamias G, Jia LG, Cominelli F. The tumor necrosis factor-like cytokine 1A/death receptor 3 cytokine system in intestinal inflammation. Curr Opin Gastroenterol. 2013; 29(6):597–602. [PubMed: 24100723]

30. Bamias G, et al. Differential expression of the TL1A/DcR3 system of TNF/TNFR-like proteins in large vs. small intestinal Crohn's disease. Dig Liver Dis. 2012; 44(1):30–6. [PubMed: 21978578]

31*. Yu X, et al. TNF superfamily member TL1A elicits type 2 innate lymphoid cells at mucosal barriers. Mucosal Immunol. 2014; 7(3):730–40. [PubMed: 24220298] [This is the first demonstration that the TL1A/DR3 system of TNF-like factors is involved in the function of innate lymphoid cells.]

32. Meylan F, et al. The TNF-family cytokine TL1A promotes allergic immunopathology through group 2 innate lymphoid cells. Mucosal Immunol. 2014; 7(4):958–68. [PubMed: 24368564]

33*. Liu C, et al. Progranulin-derived Atsttrin directly binds to TNFRSF25 (DR3) and inhibits TNF-like ligand 1A (TL1A) activity. PLoS One. 2014; 9(3):e92743. [PubMed: 24651300] [This study provides evidence for a novel ligand for the receptor DR3 (TNFRSF25) that may also have therapeutic implications.]

34. Jian J, Konopka J, Liu C. Insights into the role of progranulin in immunity, infection, and inflammation. J Leukoc Biol. 2013; 93(2):199–208. [PubMed: 23089745]

35. Krause P, et al. The Tumor Necrosis Factor Family Member TNFSF14 (LIGHT) Is Required for Resolution of Intestinal Inflammation in Mice. Gastroenterology. 2014; 146(7):1752–1762. e4. [PubMed: 24560868]

36**. Atreya R, et al. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. Nat Med. 2014; 20(3):313–8. [PubMed: 24562382] [An important study demonstrating in vivo for the first time that the efficacy of anti-TNF treatment in patients with IBD depends on the number of mucosal immunocytes expressing membrane TNF-α.]

37. Perrier C, et al. Neutralization of membrane TNF, but not soluble TNF, is crucial for the treatment of experimental colitis. Inflamm Bowel Dis. 2013; 19(2):246–53. [PubMed: 22649027]

38. Zalevsky J, et al. Dominant-negative inhibitors of soluble TNF attenuate experimental arthritis without suppressing innate immunity to infection. J Immunol. 2007; 179(3):1872–83. [PubMed: 17641054]

39*. Bamias G, et al. Intestinal-specific TNFalpha overexpression induces Crohn's-like ileitis in mice. PLoS One. 2013; 8(8):e72594. [PubMed: 23977323] [This study shows that production of TNF-α by epithelial cells exclusively is sufficient to generate mucosal inflammation in mice.]

40. Siakavellas SI, Bamias G. Role of the IL-23/IL-17 axis in Crohn's disease. Discov Med. 2012; 14(77):253–62. [PubMed: 23114581]

41. Basu R, Hatton RD, Weaver CT. The Th17 family: flexibility follows function. Immunol Rev. 2013; 252(1):89–103. [PubMed: 23405897]

42. Sonnenberg GF, Fouser LA, Artis D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. Nat Immunol. 2011; 12(5):383–90. [PubMed: 21502992]

43**. Leung JM, et al. IL-22-producing CD4+ cells are depleted in actively inflamed colitis tissue. Mucosal Immunol. 2014; 7(1):124–33. [PubMed: 23695510] [This study provides direct proof for an important protective role of IL-22-producing CD4+ cells in the pathogenesis of acute mucosal inflammation.]

44. Volpe E, et al. Multiparametric analysis of cytokine-driven human Th17 differentiation reveals a differential regulation of IL-17 and IL-22 production. Blood. 2009; 114(17):3610–4. [PubMed: 19704117]

45**. Mielke LA, et al. 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. 2013; 210(6):1117–24. [PubMed: 23690441] [An important study that links retinoic acid with the production of IL-22 by gammadelta T cells and innate lymphoid cells at the intestine.]

46. Eken A, et al. IL-23R+ innate lymphoid cells induce colitis via interleukin-22-dependent mechanism. Mucosal Immunol. 2014; 7(1):143–54. [PubMed: 23715173]

KEY POINTS

IL-1-α and IL-33 act as pro-inflammatory alarmins when released from injured epithelial cells

IL-1-α and IL-1-β play opposite roles during acute mucosal inflammation/repair

ILCs are critical sources of mucosal cytokines including DR3 (ILC2s) and IL-22 (ILC3s)

The number of TNF-bearing mucosal cells predicts the therapeutic response to anti-TNF agents