J Immunol. 2010 Jun 15;184(12):6799-806. Epub 2010 May 19.

# Downregulation of Th17 cells in the small intestine by disruption of gut flora in the absence of retinoic acid.

Cha HR, Chang SY, Chang JH, Kim JO, Yang JY, Kim CH, Kweon MN.

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## Abstract

Retinoic acid (RA), a well-known vitamin A metabolite, mediates inhibition of the IL-6-driven induction of proinflammatory Th17 cells and promotes anti-inflammatory regulatory T cell generation in the presence of TGF-beta, which is mainly regulated by dendritic cells. To directly address the role of RA in Th17/regulatory T cell generation in vivo, we generated vitamin A-deficient (VAD) mice by continuous feeding of a VAD diet beginning in gestation. We found that a VAD diet resulted in significant inhibition of Th17 cell differentiation in the small intestine lamina propria by as early as age 5 wk. Furthermore, this diet resulted in low mRNA expression levels of IL-17, IFN regulatory factor 4, IL-21, IL-22, and IL-23 without alteration of other genes, such as RORgammat, TGF-beta, IL-6, IL-25, and IL-27 in the small intestine ileum. In vitro results of enhanced Th17 induction by VAD dendritic cells did not mirror in vivo results, suggesting the existence of other regulation factors. Interestingly, the VAD diet elicited high levels of mucin MUC2 by goblet cell hyperplasia and subsequently reduced gut microbiome, including segmented filamentous bacteria. Much like wild-type mice, the VAD diet-fed MyD88-/-TRIF-/- mice had significantly fewer IL-17-secreting CD4+ T cells than the control diet-fed MyD88-/-TRIF-/- mice. The results strongly suggest that RA deficiency altered gut microbiome, which in turn inhibited Th17 differentiation in the small intestine lamina propria.

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## Supplemental Content


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# Characterization of IL-17A-producing cells in celiac disease mucosa.

Monteleone I, Sarra M, Del Vecchio Blanco G, Paoluzi OA, Franzè E, Fina D, Fabrizi A, MacDonald TT, Pallone F, Monteleone G.

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### Abstract

Celiac disease (CD) is a gluten-sensitive enteropathy associated with a marked infiltration of the mucosa with IFN-gamma-secreting Th1 cells. Recent studies have shown that a novel subset of T cells characterized by expression of high levels of IL-17A, termed Th17 cells, may be responsible for pathogenic effects previously attributed to Th1 cells. In this study, we characterized the expression of IL-17A-producing cells in CD. By real-time PCR and ELISA, it was shown that expression of IL-17A RNA and protein is more pronounced in active CD biopsy specimens in comparison with inactive CD and normal mucosal biopsy specimens. Flow cytometry confirmed that IL-17A is overproduced in CD mucosa and that CD4(+) and CD4(+)CD8(+) cells were major sources. The majority of IL-17A-producing CD4(+) and CD4(+)CD8(+) cells coexpressed IFN-gamma but not CD161. The addition of a peptic-tryptic digest of gliadin to ex vivo organ cultures of duodenal biopsy specimens taken from inactive CD patients enhanced IL-17A production by both CD4(+) and CD4(+)CD8(+) cells. Because we previously showed that IL-21, a T cell-derived cytokine involved in the control of Th17 cell responses, is overproduced in CD, we next assessed whether IL-17A expression is regulated by IL-21. Blockade of IL-21 activity by a neutralizing IL-21 Ab reduced IL-17A expression in cultures of active CD and peptic-tryptic digest of gliadin-treated CD biopsy specimens. In conclusion, our data show that IL-17A is increased in CD and is produced by cells that also make IFN-gamma.

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## Supplemental Content


Mediators Inflamm. 2009;2009:517052. Epub 2009 Nov 18.

# Th17: a new participant in gut dysfunction in mice infected with Trichinella spiralis.

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### Abstract

Trichinella spiralis infection in rodents is a well-known model of intestinal inflammation associated with hypermotility. Our aim was to elucidate if Th17 cells were involved in the development of gastrointestinal hypermotility in this experimental model. Intestinal inflammation was observed by hematoxylin-eosin (HE) staining. Jejunal smooth muscle contractility was investigated in response to acetylcholine (Ach). The effects of IL-17 on jejunum smooth muscle contractility were explored. Flow cytometry was used to analyze the

proportion of Th17 cells in jejunum. The levels of IL-17, IL-23, and TGF-beta1 in jejunum were measured by Western blot. Our results showed that the inflammation in jejunum was severe at 2 weeks postinfection (PI), which was not discernible at 8 weeks PI. Jejunal smooth muscle contractility was increased at 2 weeks PI and kept higher at 12 weeks PI. The proportion of Th17 cells and the expression of IL-17 were upregulated in jejunum at 2 weeks PI and normalized at 8 weeks PI. When jejunual smooth muscle strips were cultured with IL-17, contractions elicited by Ach were enhanced in a concentration-dependent manner. Our data suggest that Th17 cells are increased during acute infection with Trichinella spiralis and IL-17 may contribute to jejunal muscle contractility in mice.

PMID: 20016839 [PubMed - indexed for MEDLINE]PMCID: PMC2786920Free PMC Article

## Supplemental Content



World J Gastroenterol. 2009 Dec 14;15(46):5784-8.

# Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease.

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### Abstract

The etiopathology of inflammatory bowel disease (IBD) remains elusive. Accumulating evidence suggests that the abnormality of innate and adaptive immunity responses plays an important role in intestinal inflammation. IBD including Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract, which is implicated in an inappropriate and overactive mucosal immune response to luminal flora. Traditionally, CD is regarded as a Th1-mediated inflammatory disorder while UC is regarded as a Th2-like disease. Recently, Th17 cells were identified as a new subset of T helper cells unrelated to Th1 or Th2 cells, and several cytokines [e.g. interleukin (IL)-21, IL-23] are involved in regulating their activation and differentiation. They not only play an important role in host defense against extracellular pathogens, but are also associated with the development of autoimmunity and inflammatory response such as IBD. The identification of Th17 cells helps us to explain some of the anomalies seen in the Th1/Th2 axis and has broadened our understanding of the immunopathological effects of Th17 cells in the development of IBD.

PMID: 19998498 [PubMed - indexed for MEDLINE]PMCID: PMC2791270Free PMC Article

## Supplemental Content


Cell. 2009 Oct 30;139(3):485-98.

# Induction of intestinal Th17 cells by segmented filamentous bacteria.

Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, Tanoue T, Imaoka A, Itoh K, Takeda K, Umesaki Y, Honda K, Littman DR.

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### Abstract

The gastrointestinal tract of mammals is inhabited by hundreds of distinct species of commensal microorganisms that exist in a mutualistic relationship with the host. How commensal microbiota influence the host immune system is poorly understood. We show here that colonization of the small intestine of mice with a single commensal microbe, segmented filamentous bacterium (SFB), is sufficient to induce the appearance of CD4(+) T helper cells that produce IL-17 and IL-22 (Th17 cells) in the lamina propria. SFB adhere tightly to the surface of epithelial cells in the terminal ileum of mice with Th17 cells but are absent from mice that have few Th17 cells. Colonization with SFB was correlated with increased expression of genes associated with inflammation and antimicrobial defenses and resulted in enhanced resistance to the intestinal pathogen Citrobacter rodentium. Thus, manipulation of this commensal-regulated pathway may provide new opportunities for enhancing mucosal immunity and treating autoimmune disease.

PMID: 19836068 [PubMed - indexed for MEDLINE]PMCID: PMC2796826Free PMC Article

## Supplemental Content


J Allergy Clin Immunol. 2009 May;123(5):997-1003. Epub 2009 Apr 11.

# Regulation of TH17 cells in the mucosal surfaces.

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## Abstract

The mucosal surfaces represent the main intersection between jawed vertebrates and the environment. The mucosal surface of the intestine alone forms the largest surface that is exposed to exogenous antigens as well as the largest collection of lymphoid tissue in the body. Therefore, a protective immune activity must coexist with efficient regulatory mechanisms to maintain a health status of these organisms. The discovery of a new lineage of T(H) cells that produce IL-17 has provided valuable new insight into host defense and the pathogenesis of inflammatory diseases at the mucosal surfaces. Of particular interest for these surfaces, it has been reported that peripherally-induced regulatory T cells and T(H)17 effector cells arise in a mutually exclusive fashion, depending on whether they are activated in the presence of TGF-beta or TGF-beta plus inflammatory cytokines such as IL-6. This review addresses the protective and pathogenic roles of T(H)17 cells in the mucosal surfaces and potential regulatory mechanisms that control their development.

PMID: 19362732 [PubMed - indexed for MEDLINE]PMCID: PMC2679861Free PMC Article

## Supplemental Content



Cell Host Microbe. 2008 Oct 16;4(4):337-49.

# Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine.

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## Abstract

The requirements for in vivo steady state differentiation of IL-17-producing T-helper (Th17) cells, which are potent inflammation effectors, remain obscure. We report that Th17 cell differentiation in the lamina propria (LP) of the small intestine requires specific commensal microbiota and is inhibited by treating mice with selective antibiotics. Mice from different sources had marked differences in their Th17 cell numbers and animals lacking Th17 cells

acquired them after introduction of bacteria from Th17 cell-sufficient mice. Differentiation of Th17 cells correlated with the presence of cytophaga-flavobacter-bacteroidetes (CFB) bacteria in the intestine and was independent of toll-like receptor, IL-21 or IL-23 signaling, but required appropriate TGF-beta activation. Absence of Th17 cell-inducing bacteria was accompanied by increase in Foxp3+ regulatory T cells (Treg) in the LP. Our results suggest that composition of intestinal microbiota regulates the Th17:Treg balance in the LP and may thus influence intestinal immunity, tolerance, and susceptibility to inflammatory bowel diseases.

PMID: 18854238 [PubMed - indexed for MEDLINE]PMCID: PMC2597589Free PMC Article

## Supplemental Content



J Exp Med. 2008 Sep 29;205(10):2191-8. Epub 2008 Sep 1.

# Commensal-dependent expression of IL-25 regulates the IL-23-IL-17 axis in the intestine.

Zaph C, Du Y, Saenz SA, Nair MG, Perrigoue JG, Taylor BC, Troy AE, Kobuley DE, Kastelein RA, Cua DJ, Yu Y, Artis D.

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### Abstract

Alterations in the composition of intestinal commensal bacteria are associated with enhanced susceptibility to multiple inflammatory diseases, including those conditions associated with interleukin (IL)-17-producing CD4(+) T helper (Th17) cells. However, the relationship between commensal bacteria and the expression of proinflammatory cytokines remains unclear. Using germ-free mice, we show that the frequency of Th17 cells in the large intestine is significantly elevated in the absence of commensal bacteria. Commensal-dependent expression of the IL-17 family member IL-25 (IL-17E) by intestinal epithelial cells limits the expansion of Th17 cells in the intestine by inhibiting expression of macrophage-derived IL-23. We propose that acquisition of, or alterations in, commensal bacteria influences intestinal immune homeostasis via direct regulation of the IL-25-IL-23-IL-17 axis.

PMID: 18762568 [PubMed - indexed for MEDLINE]PMCID: PMC2556798Free PMC Article

## Supplemental Content

Immunol Cell Biol. 2007 Feb-Mar;85(2):155-9. Epub 2007 Jan 16.

# Cytokine regulation of immunopathology in toxoplasmosis.

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## Abstract

Toxoplasma gondii infection is an important cause of central nervous system and ocular disease, both in immunocompromised and in certain immunocompetent populations. Although parasite-mediated host cell lysis is probably the principal cause of tissue destruction in immunodeficiency states, hypersensitivity and inflammatory responses may underlie severe disease in otherwise immuno-sufficient individuals. In this review, we have critically evaluated the body of experimental evidence indicating a role of CD4 T cells in systemic and local immunopathology associated with T. gondii infection. We also discuss the pathogenic roles of cytokines produced by T helper (Th) 1 and Th17 cells and the protective and homeostatic roles of interleukin (IL)-10, transforming growth factor-beta and IL-27 in modulating hypersensitivity responses induced by T. gondii.

PMID: 17228318 [PubMed - indexed for MEDLINE]

## Supplemental Content



J Immunol. 2008 Jan 1;180(1):559-68.

# Commensal gut flora drives the expansion of proinflammatory CD4 T cells in the colonic lamina propria under normal and inflammatory conditions.

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## Abstract

We tested in B6 mice whether the local expansion of CD4 T cells producing proinflammatory cytokines including IL-17 (Th17 cells) in the colonic lamina propria (cLP) depends on the commensal microflora. High numbers of CD4 Th17 cells were found in the lamina propria of the ileum and colon but not the duodenum, jejunum, mesenteric lymph nodes, spleen, or liver of specific pathogen-free (SPF) mice. The microflora is required for the accumulation of cytokine (IL-17, IFN-gamma, TNF-alpha, IL-10)-producing CD4 T cells in the cLP because only low numbers of cytokine-producing cLP CD4 T cells were found in syngeneic (age- and sex-matched) germfree mice. The fraction of cLP Th17 cells was higher in (type I and type II) IFN- but not IL-4- or IL-12p40-deficient SPF congenics. cLP CD4 Th17 cells produce IL-17 but not IFN-gamma, TNF-alpha, IL-4, or IL-10. cLP CD4 Th17 cells accumulate locally in colitis induced by adoptive transfer of IFN-gamma+/+ or IFN-gamma-/- CD4 T cells into congenic SPF (but not germfree) RAG-/- hosts. In this colitis model, cLP CD4 T cells that "spontaneously" produce IL-17 progressively increase in number in the inflamed cLP, and increasing serum IL-17 levels appear as the disease progresses. Commensal bacteria-driven, local expansion of cLP CD4 Th17 cells may contribute to the pathogenesis of this inflammatory bowel disease.

PMID: 18097058 [PubMed - indexed for MEDLINE]Free Article

# Supplemental Content



# The Role of Th17 in Neuroimmune Disorders: Target for CAM Therapy. Part I.

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CD4(+) effector cells, based on cytokine production, nuclear receptors and signaling pathways, have been categorized into four subsets. T-helper-1 cells produce IFN-gamma, TNF-beta, lymphotoxin and IL-10; T-helper-2 cells produce IL-4, IL-5, IL-10, IL-13, IL-21 and IL-31; T-helper-3, or regulatory T-cells, produce IL-10, TGF-beta and IL-35; and the recently discovered T-helper-17 cell produces IL-17, IL-17A, IL-17F, IL-21, IL-26 and CCL20. By producing IL-17 and other signaling molecules, Th17 contributes to the pathogenesis of multiple autoimmune diseases including allergic inflammation, rheumatoid arthritis, autoimmune gastritis, inflammatory bowel disease, psoriasis and multiple sclerosis. In this article, we review the differential regulation of inflammation in different tissues with a major emphasis on enhancement of neuroinflammation by local production of IL-17 in the brain. By understanding the role of pathogenic factors in the induction of autoimmune diseases by Th17

cells, CAM practitioners will be able to design CAM therapies targeting Th17 and associated cytokine activities and signaling pathways to repair the intestinal and blood-brain barriers for their patients with autoimmunities, in particular, those with neuroinflammation and neurodegeneration.

Evid Based Complement Alternat Med. 2009 Jul 21. [Epub ahead of print]



Links

# The Role of Th17 in Neuroimmune Disorders: Target for CAM Therapy. Part II.

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Decades of research went into understanding the role that Th1 autoreactive T-cells play in neuroinflammation. Here we describe another effector population, the IL-17-producing T-helper lineage (Th17), which drives the inflammatory process. Through the recruitment of inflammatory infiltration neutrophils and the activation of matrix metalloproteinases, IL-17, a cytokine secreted by Th17 cells, contributes to blood-brain barrier breakdown and the subsequent attraction of macrophages and monocytes into the nervous system. The entry of cells along with the local production of inflammatory cytokines leads to myelin and axonal damage. This activation of the inflammatory response system is induced by different pathogenic factors, such as gut bacterial endotoxins resulting in progressive neurodegeneration by Th17 cells. Through the understanding of the role of bacterial endotoxins and other pathogenic factors in the induction of autoimmune diseases by Th17 cells, CAM practitioners will be able to design CAM therapies targeting IL-17 activity. Targeted therapy can restore the integrity of the intestinal and blood-brain barriers using probiotics, N-acetyl-cysteine, alpha-lipoic acid, resveratrol and others for their patients with autoimmunities, in particular those with neuroinflammation and neurodegeneration.

**1:** Evid Based Complement Alternat Med. 2009 Jul 21. [Epub ahead of print]



Links

# The Role of Th17 in Neuroimmune Disorders: A Target for CAM Therapy. Part III.

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Abundant research has mapped the inflammatory pathways leading to autoimmunity and neuroinflammatory disorders. The latest T helper to be identified, Th17, through its proinflammatory cytokine IL-17, plays a pathogenic role in many inflammatory conditions. Today, healthcare providers have a wealth of anti-inflammatory agents from which to choose. On one hand, pharmaceutical companies market brand-name drugs direct to the public and physicians. Medical botanical knowledge, on the other hand, has been passed down from generation to generation. The demands for natural

healing therapies have brought corresponding clinical and laboratory research studies to elucidate the medicinal properties of alternative practices. With a variety of options, it can be difficult to pinpoint the proper anti-inflammatory agent for each case presented. In this review, the authors highlight a vast array of anti-inflammatory medicaments ranging from drugs to vitamins and from botanicals to innate molecules. This compilation may serve as a guide for complimentary and alternative healthcare providers who need to target neuroinflammation driven by Th17 and its inflammatory cytokine IL-17. By understanding the mechanisms of anti-inflammatory agents, CAM practitioners can tailor therapeutic interventions to fit the needs of the patient, thereby providing faster relief from inflammatory complaints.