

*Critical Review***Interleukin-19 Is a Negative Regulator of Innate Immunity and Critical for Colonic Protection**

Yasu-Taka Azuma^{1,*}, Yukiko Matsuo¹, Hidemitsu Nakajima¹, George D. Yancopoulos², David M. Valenzuela², Andrew J. Murphy², Margaret Karow², and Tadayoshi Takeuchi¹

¹Laboratory of Veterinary Pharmacology, Division of Veterinary Science,
Osaka Prefecture University Graduate School of Life and Environmental Science, Izumisano, Osaka 598-8531, Japan

²Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591, USA

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Abstract. The cytokine, interleukin (IL)-19, is a member of the IL-10 family that includes IL-20, IL-22, IL-24, and IL-26. Recent studies have shown that IL-19 is produced by keratinocytes, epithelial cells, macrophages, and B-cells. Little is known about the exact biological role of IL-19 in immunological regulation, although there is an increasing body of data demonstrating that IL-19 is associated with the development of Th2 responses and the pathogenesis of psoriasis. In this review, I shall attempt to discuss current knowledge about the role of IL-19 on macrophages and the potential role in inflammatory bowel disease.

Keywords: interleukin-19, inflammatory bowel disease (IBD), colonic inflammation, macrophages, cytokine

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are two of the most important types of inflammatory bowel diseases (IBD), and they are characterized by dysregulated intestinal inflammation and mucosal tissue damage in parts of the gastrointestinal tract (1, 2). The maintenance of intestinal homeostasis is complex and involves interactions among the intestinal microflora, the epithelium, and the host immune system. Although the etiology of UC and CD remains unclear, it is widely suggested that genetic susceptibility, enteric environmental factors, and immunological responses contribute to the pathogenesis of IBD. The pathogenesis of IBD is characterized by an imbalanced activation of T helper (Th)1- and Th2-dependent immune responses. UC and CD appear to be distinct pathways of inflammation, although UC and CD represent some clinical characteristics in common. UC primarily affects the colon and rectum in a superficial manner. Increased productions of interleukin (IL)-5, IL-

6, IL-10, and IL-13 have been observed in UC. CD affects the distal small intestine and colon in a transmural manner. CD appears to be an early increase in interferon (IFN)- γ , IL-2, IL-12, and subsequent increase in tumor necrosis factor (TNF)- α , IL-18, IL-10, and transforming growth factor (TGF)- β . Current therapy of IBD has developed as a result of understanding of the mucosal immunology processes in intestinal inflammation. IL-10 is a well-known anti-inflammatory and immunosuppressive cytokine and has shown promise in clinical trials for the treatment of IBD. Biologically based therapies, such as recombinant IL-10, can ameliorate the disorder (3, 4). New therapies targeting different levels of the inflammatory processes are being tested in clinical practice, including monoclonal antibodies (TNF- α , IL-6, IL-12), gene therapy (IL-10), selective adhesion blockade (integrin), and nucleic acid based therapies (NF- κ B, ICAM) (5).

Animal models of UC and CD are indispensable for both the identification of immune responses involved in the pathogenesis of IBD and the evaluation and development of innovative therapeutics for IBD (2, 6). As shown in Fig. 1, several of the knockout mice develop spontaneously mucosal inflammation (7). In 1993, it was first reported that IL-2- deficient (IL-2^{-/-}) mice (8) and IL-10^{-/-} (9) mice spontaneously develop colitis, indicating

*Corresponding author. azuma@vet.osakafu-u.ac.jp
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that IL-2 and IL-10 are each critical for colonic protection. These findings provided two new insights into the pathogenesis of IBD at that time: the first one is that a genetic factor lead to mucosal inflammation that resembles IBD and the second one is that altered immune responses contribute to the initiation and chronification of IBD. The most widely used IBD animal models are colitis chemically induced by 2,4,6-trinitrobenzene sul-



Fig. 1. IL-19 belongs to the IL-10 family. IL-19 is similar in sequence and structure to IL-10, but much more to IL-20 and IL-24, leading to these three cytokines being described as the “IL-19” subfamily. In contrast, IL-10, IL-22, and IL-26 are described as the “IL-10” subfamily.

Table 1. Animal models of IBD

Administration of exogenous agents	
Oral	Dextran sodium sulfate
Enema	TNBS
	Oxazolone
Gene-deficient animals	
IL-2 ^{-/-}	
IL-10 ^{-/-}	
TCRα ^{-/-}	
TCRβ ^{-/-}	
Transfer of cells into immunodeficient animals	
CD4 ⁺ CD44RB ^{high} into scid or Rag ^{-/-} mice	

fonic acid (TNBS) (10), oxazolone (11), and dextran sodium sulfate (DSS) (12, 13) (Table 1). Importantly, transfer of a T cell population (CD4⁺CD45RB^{high} T cells) that lacks regulatory T cells into *scid* or *Rag*^{-/-} animals induced colonic inflammation (14) (Table 1).

In experimental colitis models in rats and mice, as well as human IBD, infiltrated and activated macrophages play an important role in the initiation of colitis (15). Macrophages and dendritic cells are at the vanguard of an innate immune response, and much research on the pathogenesis of IBD has emphasized their crucial role in orchestrating the initial host reaction to infection. It has long been appreciated that an innate immune response must be tightly regulated to avoid the fatal consequences of an overwhelming or inappropriate inflammation. For example, exposure to lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria (for example, *Escherichia coli*, *Salmonella*, *Pseudomonas*, and *Klebsiella*) triggers the host release of acute phase and pro-inflammatory mediators that can promote life-threatening tissue damage in IBD.

The cytokine IL-19 is a member of the IL-10 family that includes IL-20, IL-22 (IL-TIF), IL-24 (MDA-7), and IL-26 (AK155) (16). Among the members of the IL-10 family, IL-19 is highly homologous to IL-20 and IL-24 (Fig. 1), sharing a receptor that is formed by a heterodimer of IL-20 receptor α (IL-20Rα) and β subunit (IL-20Rβ) (Fig. 2) (17 – 19). However, this is the only known receptor for IL-19, whereas IL-20 and IL-24 can also signal through a second pair of receptor chains — IL-22R / IL-20Rβ (17 – 19). Binding of IL-19 to its receptor complex activates the signal transducers and activators of transcription (STAT) pathways, notably, STAT1 and STAT3 (19). Recent studies have shown that IL-19 is produced by keratinocytes, epithelial cells, macrophages, and B-cells. Little is known about the exact biological role of IL-19 in immunological regulation; however, although there is an increasing body of data demonstrating

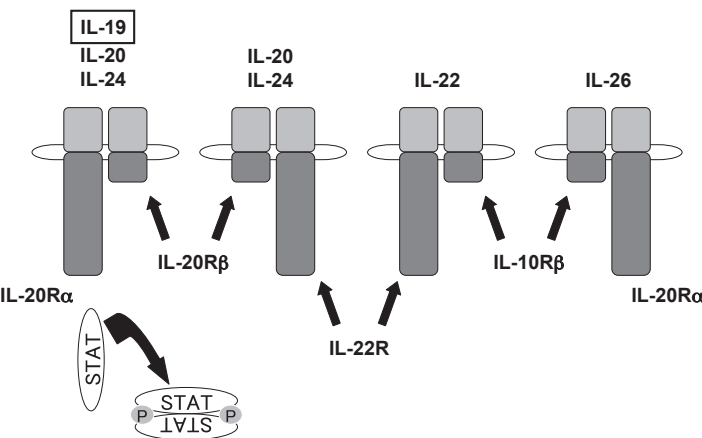


Fig. 2. The receptors of IL-10 family cytokines. IL-19, IL-20, and IL-24 can all bind to a heterodimer of IL-20Rα and IL-20Rβ. IL-20 and IL-24 also can bind to a heterodimer of IL-22R and IL-20Rβ. IL-22 and IL-26 can utilize a heterodimer of IL-22R / IL-10Rβ and IL-20Rα / IL-10Rβ, respectively.

that IL-19 is associated with the development of Th2 responses (20) including asthma (21, 22) and the pathogenesis of psoriasis (23 – 30). On the other hand, in vitro studies have shown that LPS can stimulate human monocytes to upregulate the mRNA expression of *IL-19* (16, 31, 32) and that recombinant IL-19 can induce mouse monocytes to produce pro-inflammatory cytokines, such as IL-6 and TNF- α (33), and anti-inflammatory cytokine IL-10 (34). Importantly, *IL-10*^{-/-} mice spontaneously develop colitis, and IL-19 is a member of the IL-10 family. In 2003, Valenzuela et al. generated *IL-19*^{-/-} mice using the VelociGene approach (35). In this review, we will discuss the current knowledge about the immunological role IL-19 on in vitro macrophage function and an in vivo experimental IBD model using *IL-19*^{-/-} mice.

2. Enhanced response in IL-19-deficient macrophage upon TLR stimulation

Table 2 shows the lymphoid and myeloid cellular composition of the deficient mice. *IL-19*^{-/-} mice were outwardly healthy and displayed normal lymphoid and myeloid cellular composition in the thymus, spleen, and lymph node, although it was reported that IL-19 has been associated with supporting Th2 responses. Bone marrow-derived macrophages (BMDM) were generated and stimulated with LPS, a well characterized bacterial stimulus of macrophage responses and a major cause of death in septic shock (36). After being stimulated with LPS for 18 h (37) or 24 h, macrophages from *IL-19*^{-/-} mice produced significantly more TNF- α and IL-12 than did wild-type (WT) cells. The effect on IL-6 production was not statistically significant. Similarly, when *IL-19*^{-/-} macrophages were stimulated with other toll-like receptor (TLR) ligands (38, 39), the production of these pro-inflammatory cytokines was enhanced. These results were surprising in light of an early study in which recombinant IL-19 was reported to induce TNF- α and IL-6 production in splenic macrophages (33). Yet this study and another recent study (34) using recombinant IL-19 did not detect such TNF- α , IL-12, and IL-6 induction.

Unlike *IL-19*^{-/-} macrophages, *IL-19*^{-/-} dendritic cells responded to stimulation with LPS (37) or other TLR ligands in a manner similar to the WT controls. The expression level of MHC class II and the costimulatory molecule CD86, both of which are normally upregulated after TLR stimulation, were equivalent on both WT and *IL-19*^{-/-} dendritic cells (37), as well as on WT and *IL-19*^{-/-} macrophages. The comparable LPS response between WT and *IL-19*^{-/-} dendritic cells is further supported by the absence of *IL-19* induction in WT dendritic cells (37). Taken together, these results indicate that IL-19 is a negative regulator of TLR signaling, particularly con-

Table 2. Normal development of T cell and myeloid lineage cells in thymus, spleen, and lymph nodes in *IL-19*^{-/-} mice, as analyzed by flow cytometry

	IL-19 ^{+/+}	IL-19 ^{-/-}
Thymus		
CD4 ⁺ CD8 ⁻	15.2	11.7
CD4 ⁻ CD8 ⁺	2.8	2.8
CD4 ⁺ CD8 ⁺	79.9	84.0
CD4 ⁺ CD69 ⁺ TCR $\alpha\beta$ ⁻	2.4	2.2
CD4 ⁺ CD69 ⁺ TCR $\alpha\beta$ ⁺	6.6	5.9
CD4 ⁺ CD69 ⁺ TCR $\alpha\beta$ ⁺	10.9	9.8
Spleen		
CD4 ⁺ CD8 ⁻	14.9	15.6
CD4 ⁻ CD8 ⁺	13.4	13.8
CD4 ⁺ CD8 ⁺	1.3	1.0
CD4 ⁺ CD69 ⁺ CD25 ⁻	4.4	4.0
CD4 ⁺ CD69 ⁺ CD25 ⁺	10.7	10.0
CD4 ⁺ CD69 ⁺ CD25 ⁺	4.0	3.1
CD4 ⁺ CD62L ⁺	5.6	6.6
CD11b ⁺	8.7	10.7
CD19 ⁺	62.9	56.6
NK1.1 ⁺	5.6	4.0
Lymph node		
CD4 ⁺ CD25 ⁻	34.4	38.2
CD4 ⁻ CD25 ⁺	1.6	1.1
CD4 ⁺ CD25 ⁺	5.8	5.1
CD4 ⁺ CD62L ⁺	59.2	46.6
CD8 ⁺ CD62L ⁻	16.4	16.9
CD8 ⁺ CD62L ⁺	39.5	37.4
CD8 ⁺ CD62L ⁺	17.0	15.9
NK1.1 ⁺	0.8	0.9
CD19 ⁺	25.2	20.0

Each number represents percentages.

trolling cytokine production in macrophages.

3. IL-19 is required for endotoxin tolerance

Negative regulation of TLR signaling has been implicated in the induction of endotoxin tolerance that “reprograms” activated macrophages (40, 41). This prevents them from massive release of pro-inflammatory mediators, such as TNF- α and IL-12, which characterizes an excessive inflammatory response to infectious agents, leading to septic shock and death (42, 43). To test the role of IL-19 in endotoxin tolerance, we first primed *IL-*

$IL-19^{-/-}$ macrophages with LPS and then challenged them 5–18 h later with LPS. Priming $IL-19^{-/-}$ macrophages with LPS for 5 or 18 h sustained a level of IL-12 production higher than that of WT macrophages (Fig. 3, right panel). In contrast, priming $IL-19^{-/-}$ macrophages with LPS for 18 h resulted in decreased IL-6 and TNF- α production of LPS upon further challenge (Fig. 3). The data suggest that IL-19 may play a function in endotoxin tolerance.

4. Induction of IL-19 via MyD88-dependent TLR signaling

Protein adaptors, such as MyD88 and TRIF (TIR domain-containing adaptor-inducing IFN β), modulate the TLR4 signaling pathway after LPS activates TLR4 (39, 44). MyD88 recruits members of the IL-1 receptor-associated kinase (IRAK) family of serine-threonine kinases, leading to the activation of mitogen-activated protein kinases and NF- κ B. These molecules are key in the induction of pro-inflammatory cytokines in macrophages, including TNF- α , IL-6, and IL-12. TRIF, which might contribute to MyD88 signals, can activate additional signaling pathways, such as those leading to IFN β production. LPS-induced $IL-19$ gene expression was examined using mice deficient in either *MyD88* (45) or *Lps2* (46) (also known as TRIF). When stimulated with LPS, macrophages from *MyD88^{-/-}* mice were unable to induce $IL-19$ mRNA expression, whereas *Lps2^{-/-}* macrophages exhibited normal $IL-19$ induction. Since most TLRs employ the MyD88 pathway and only some recruit TRIF, the $IL-19$ gene expression is likely to be induced by most or all TLRs (Fig. 4). Thus, IL-19 acts as a feedback regulator of TLR4 for LPS and other TLRs for various pathogenic microbial stimuli.

5. IL-19 signaling in macrophages

By RT-PCR analysis, there was the constitutive expression of *IL-20R α* and *IL-20R β* on WT macrophages. Further stimulation with LPS did not change receptor expression levels. Stimulation of WT macrophages with LPS induced the activation of STAT1 and STAT3, as evidenced by tyrosine phosphorylation. $IL-19^{-/-}$ macrophages, however, showed a reduced level of phosphorylation of both STAT1 and STAT3. These results are consistent with a reduced IL-19 response, despite the normal expression of its receptor complex on $IL-19^{-/-}$ macrophages.

6. Possible interaction of IL-10 with IL-19

There is a possibility that an immunoregulatory role for IL-19 is reminiscent of the widely accepted regulation

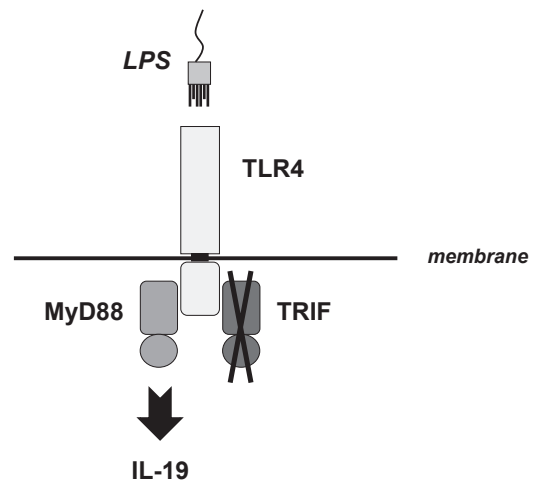


Fig. 4. LPS induced IL-19 expression through MyD88, but not TRIF.

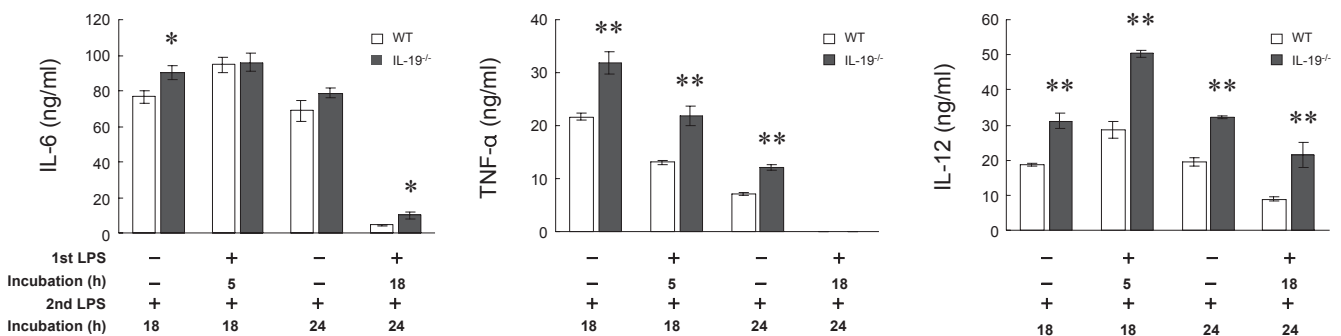


Fig. 3. Endotoxin tolerance was induced in BMDM from WT and $IL-19^{-/-}$ mice by pre-activation with 10 ng/ml of LPS. After 5 or 18 h, cells were washed and restimulated with 10 ng/ml of LPS. After 18 or 24 h, TNF- α , IL-12, and IL-6 were determined by ELISA. Each bar is a mean \pm S.E.M. ($n = 3 - 6$). * $P < 0.05$, ** $P < 0.01$ vs. corresponding WT (Student's unpaired two-tailed t -test).

of IL-10 on TLR signaling (47). The enhanced production of pro-inflammatory cytokines in *IL-19*^{-/-} macrophages was investigated due to the downregulation of IL-10. Both WT and *IL-19*^{-/-} macrophages secreted equivalent amounts of IL-10 after stimulation with LPS or other TLR ligands for 18 h (37) or 24 h, suggesting that IL-10 is not likely to mediate the suppressive effect of IL-19. Nevertheless, we cannot exclude the possibility that *IL-19*^{-/-} macrophages might not respond properly to IL-10 because the STAT3 signaling pathway, which is also known to transduce signals from the IL-10 receptor, was impaired.

Conversely, *IL-10* was reported to be produced earlier than the *IL-19* in response to LPS (16) and might therefore regulate the expression of *IL-19*. IL-10 inhibited LPS-induced expression of *IL-19* mRNA in human monocytes (33). Moreover, LPS-stimulated macrophages from *IL-10*^{-/-} mice expressed markedly more *IL-19* mRNA than stimulated WT macrophages (unpublished data). It seems that the transcription of the *IL-19* gene is regulated differently from the transcription of the *IL-10* gene. Th2 but not Th1 cytokines appear to promote the expression of *IL-19* (20), suggesting an implication of IL-19 in type-2 innate immunity (48).

7. Increased susceptibility of IL-19-deficient mice administrated with DSS to induce experimental colitis

IL-19^{-/-} mice displayed no overt symptoms of spontaneous colitis or intestinal inflammation up to 6 months of age, unlike *IL-10*^{-/-} mice (49). The susceptibility to the development of experimental colitis was investigated using *IL-19*^{-/-} mice. DSS is a sulfated polysaccharide that can disrupt the mucosal epithelial barrier, thereby exposing local macrophages to stimuli from the intestinal microflora. This DSS-induced colitis model shares histopathological features with human IBD. Colitis was exacerbated in *IL-19*^{-/-} mice. These mutant mice were extremely susceptible to DSS-induced colitis, resulting in severe weight loss as well as death (37). DSS administration revealed that the expression of *IL-19* mRNA was induced in the distal colon on day 5 (Fig. 5). Extremely high levels of IFN γ , IL-1 β , IL-6, IL-12, TNF- α , and KC were shown in the distal colon of *IL-19*^{-/-} mice on day 5 after DSS administration (37). Further histological analysis of distal colons revealed that alterations of crypt damage and infiltration in were much more severe compared with WT distal colon on day 5 after DSS administration (37). IL-19 may therefore play an important role in the protection of mucosal epithelial cells and the elimination of inflammation in the colon by limiting resident macrophage reactivity.

8. Conclusion

These observations show here that IL-19, an IL-10 homologue, has a crucial negative regulatory role. Consistent with this function, macrophages from *IL-19*^{-/-} mice showed enhanced proinflammatory cytokine production upon TLRs ligands (Fig. 6). These studies point to a key role for IL-19 in the innate myeloid cell response to pathogenic microbial stimuli. This role appears as a direct effect on macrophage pro-inflammatory cytokine production rather than as an indirect effect of IL-10 induction. Indeed, IL-10 appears insufficient in the induction of endotoxin tolerance to prevent lethality from septic shock (50). These observations now propose that IL-19 is crucial for the development or the maintenance of endotoxin tolerance in activated macrophages. The regulation of IL-19 and other closely related cytokine genes in the IL-10 family cluster warrants further investigation, as these cytokines are undoubtedly involved in shaping the outcome of an innate immune response.

Furthermore, *IL-19*^{-/-} mice had greatly exacerbated DSS-induced colitis. Compared to WT mice, the distal colon from *IL-19*^{-/-} mice revealed enhanced proinflam-

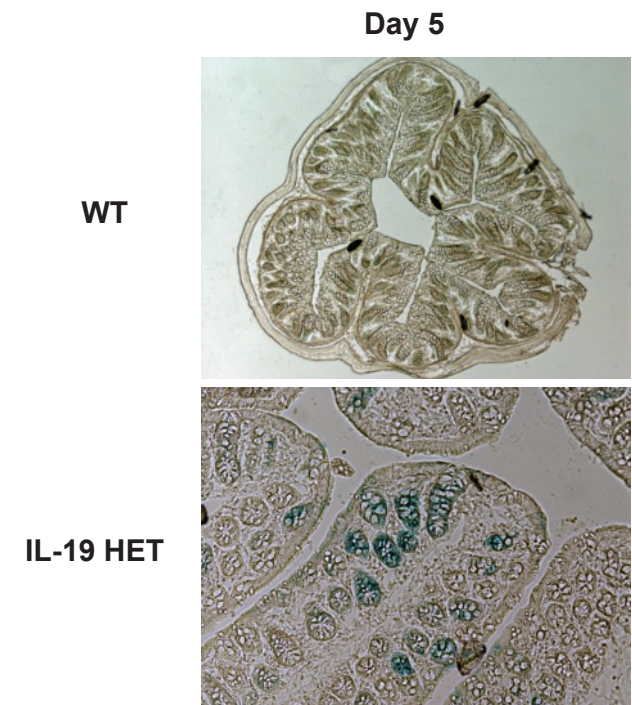


Fig. 5. IL-19 is induced as an expression of LacZ in IL-19 heterozygous mice at 5 days after DSS administration. IL-19 heterozygous mice and *IL-19*^{-/-} mice have a pZEN6 cassette containing a reporter LacZ gene in tandem with a neomycin resistance gene flanked by loxP sites (37). To visualize IL-19 expression induced by DSS in the distal colon, a LacZ detection kit, which is a staining kit to determine β -galactosidase activity (InvivoGen, San Diego, CA, USA), was used.

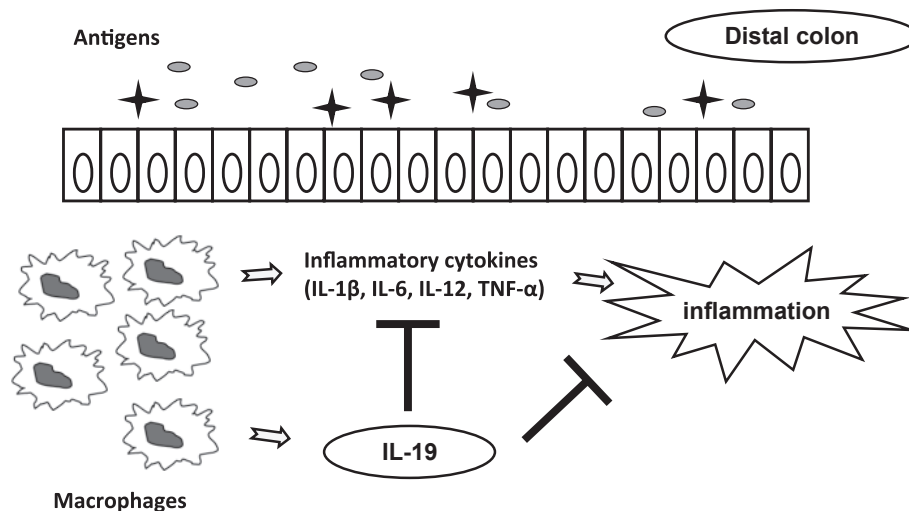


Fig. 6. Schema of possible role of IL-19 in the pathogenesis of experimental colitis.

matory cytokine production. The steady-state levels of cytokines and chemokines in the distal colon organ culture from *IL-19*^{-/-} mice are similar to that in WT mice. Consistent with this function, *IL-19*^{-/-} mice displayed no overt symptoms of spontaneous colitis or intestinal inflammation up to 6 months. DSS is a sulphated polymer that causes colitis by interfering with intestinal epithelial cell barrier function. More specifically, IL-19 is critical in controlling the production of inflammatory cytokines following injured intestinal epithelial cells.

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