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Review

The role of interleukin-13 in chronic inflammatory intestinal disorders

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ABSTRACT

Interleukin (IL)-13 is a cytokine playing a pivotal role in T helper (Th)2 immune response supposed to be implicated in some intestinal disorders. IL-13 is produced by Th2 cells, natural killer T cell, innate lymphoid cells and innate immune cells, which contribute to trigger and maintain a chronic idiopathic intestinal inflammation. In murine models IL-13 exerts pleiotropic functions, playing either pathogenic or protective roles according to the different experimental conditions. As regards celiac disease, IL-13 is considered to be involved mostly in the refractory phase rather than at uncomplicated stage. Discrepancies have been observed in the role of IL-13 upon the inflammation and fibrosis in ulcerative colitis (UC) and in Crohn's disease, respectively. Failure of the anti-IL-13 monoclonal antibodies tralokinumab and anrukinzumab in UC patients in clinical trials support the absence of a role for IL-13 in UC.

This review deals with IL-13 in several experimental colitis models -such as oxazolone-, trinitrobenzene sulfonic acid- or dextran sodium sulphate-induced colitis- and chronic intestinal inflammatory disorders -including celiac disease, UC and Crohn's disease-, and it also highlights the attempts to modulate IL-13 as therapeutic tool.

1. Introduction

Interleukin (IL)-13 belongs to Th helper (Th)2 family cytokines together with IL-4 and IL-5. Its gene is located in human chromosome 5q31 within a cluster of cytokine genes, such as IL-3, IL-4, IL-5 and granulocyte–macrophage colony stimulating factor [1]. The Th2 transcription factor GATA3 modulates the transcription of IL-13, which binds to two cell surface receptors but largely signals through only one [2,3]. In particular, upon dimerising with IL-4Rα, the IL-13 receptor (IL-13R)α1 receptor forms the type 1 IL-13R, which increases its affinity for IL-13 and transduces intracellular signals by phosphorylating the signal transducer and activator of transcription (STAT) 6 through Janus kinases. The type 1 IL-13Rα1/IL-4Rα receptor binds not only IL-13, but also IL-4 via IL-4Rα. Besides STAT6, the activation of other signaling molecules in the type 1 IL-13R pathway, such as phosphatidylinositol 3-kinase (PI3K), STAT3 and mitogen activated protein kinase (MAPK), has been detected in different *in vitro* cell models [4–7]. On the other hand, the type 2 IL-13R, i.e. IL-13Rα2, exists mostly as a monomer and binds IL-13 with higher affinity in comparison to the dimeric type 1 IL-13R. This different binding affinity is noteworthy, as upon interacting with the type 1 IL-13R, IL-13 first binds to IL-13Rα1 monomer with the low affinity prior to dimerising with the IL-4Rα receptor, thus favoring the capture of IL-13 from IL-13Rα2 [8]. The type 2 IL-13R works mostly as a decoy receptor for IL-13, binding the cytokine and making it unavailable for activating the type 1 IL-13R, without inducing its own intracellular signal. IL-13Rα2-expressing cells have been considered as scavengers for IL-13 due to their capacity to eliminate it from culture medium and, thus, limit activity of IL-13 [9]. As this regards, when a cell co-expresses both receptors, IL-13-mediated STAT6 phosphorylation is generally inhibited because of the preferential binding of IL-13 to type 2 IL-13R [10]. On the other hand, IL-13Rα2 can inhibit IL-4-induced STAT6 phosphorylation and interact with IL-4Rα in the absence of IL-13, although IL-13Rα2 does not bind IL-4 [11,12]. Accordingly, it seems that the IL-13Rα2 is able to mediate inhibition of type 1 IL-13Rα1/IL-4Rα receptor signaling by further mechanisms in addition to scavenging IL-13. Although the IL-13Rα2

Abbreviations: CD, celiac disease; CrD, Crohn's disease; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; IL-13R, IL-13 receptor; ILC, innate lymphoid cell; MAPK, mitogen activated protein kinase; MMP, matrix metalloproteinase; NK, natural killer; PI3K, phosphatidylinositol 3-kinase; STAT, signal transducer and activator of transcription; Th, Th helper; TNBS, trinitrobenzene sulfonic acid; TNF, tumor necrosis factor; UC, ulcerative colitis

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does have a short intracellular portion, which should not recognise binding sites for signaling molecules, type 2 IL-13 has been reported to bind to intracellular signals, such as STAT3, MAPK and PI3K [13–15]. However, it is unknown whether this happens through a direct mechanism or by binding of additional proteins to the intracellular portion of IL-13Rα2. Furthermore, in mice IL-13Rα2 also exists as a soluble protein, which is able to bind IL-13 with a lower affinity, due to its cleavage from matrix metalloproteinase (MMP)-8 or alternative splicing of the *IL-13Rα2* gene [16,17]. Conversely, a soluble form of IL-13Rα2 does not seem to be present in humans. The expression and pathway of IL-13 are regulated at different levels. Its transcription and production are positively regulated by both GATA3 and the hedgehog pathway, whereas they are negatively regulated by interferon (IFN)-α [18]. Additionally, the IL-13Rα2 receptor can be considered as a negative regulator of IL-13 pathway, as its transcription is induced by IL-13 itself or IFN-γ, thus leading the receptor from intracellular locations to cell surface [10,19,20].

After reviewing the role of IL-13 in the healthy and diseased gut, in the last section of this review we will discuss the therapeutic strategies aimed at modulating IL-13 in chronic intestinal diseases.

2. The physiological role of IL-13 in the gut

Different immune cell types secrete IL-13 both in mice and humans (Table 1, Fig. 1). Being a Th2 cytokine together with IL-4 and IL-5, IL-13 is produced by activated $CD4^+$ T cells in Th2-associated disorders, including human and experimental allergic reactions and in parasitic infections. In addition, innate immune cells, including eosinophils, basophils, mast cells, natural killer (NK) cells and NKT cells, are also able to produce IL-13 in humans [21–24].

In ulcerative colitis (UC) patients a population of non-invariant NKT cell demonstrated elevated IL-13 production upon stimulation and manifested pathogenic capabilities [21]. More recently, a study form the same group investigated the stimulatory triggers for IL-13 production, including the recognition of the glycolipid lyso-sulfatide [25]. This antigen-specific activation led to IL-13 production by Type 2 NKT cells and induction of pathogenic functions directed towards the epithelial integrity. Interestingly, lyso-sulfatide stimulation up-regulated the IL-13Rα2 receptor, thus inducing a positive feedback loop [25]. Factors influencing the initial development of IL-13-mediated Th2 responses include the interaction with other immune cell populations. A subset of $CD141^+$ dendritic cells, for instance, preferentially induce the secretion of IL-13 and IL-4 by $CD4^+$ lymphocytes via engagement of the OX40 ligand [26].

Several novel IL-5- and IL-13-secreting and Th2 trascription factor GATA3-expressing cells with innate immune function and negative for both B and T cell markers, called innate lymphoid cells (ILCs) were found in the murine small bowel [27]. IL-13-secreting ILC2 cells express MHCII molecules and can interact with Th2 Cells [28], influencing their functional status. Moreover, $CD4^+$ T cells activation by dendritic cells stimulated their capability to secrete IL-2 that subsequently promoted the proliferation of and IL-13 secretion by ILC2s. This was critical for the biological activity of ILCs. A potentially important link between IL-13-producing ILCs and the gut is that IL-13 release can be stimulated by gut epithelium-derived cytokines, such as IL-33, IL-25 -also known as IL-17E-, and thymic stromal lymphopoietin, which are themselves produced in reaction to inflammation and infection [29–32]. Mechanistically, these ILCs may also be a source of IL-13 in response to signals not requiring the presence of B or T cells [33,34]. Interestingly, these ILCs have a human equivalent that can be isolated from peripheral blood but their function has yet to be established in the gut [35]. Therefore, while IL-13 is assumed to be produced mostly from Th2 type $CD4^+$ cells in the human gut in response to helminth infection, other IL-13-expressing cells, including NKT cell or ILCs, may contribute to trigger and maintain a chronic idiopathic intestinal inflammation.

3. Role of IL-13 in experimental colitis

Several spontaneous or chemically induced murine models can be valuable tools to define the role of IL-13 during intestinal inflammation. These experimental models showed that IL-13 demonstrates pleiotropic functions, playing either pathogenic or protective roles according to the different experimental conditions.

Longitudinal observation over 35 weeks of the disease development in IL-10-deficient mice, spontaneously developing colitis, indicated that IL-4 and IL-13 production increased progressively from pre- to early to late disease, contributing to pathogenesis [36]. Conversely, in BLIMP-1 knockout mice, who develop a spontaneous Th17-mediated colitis, targeting the soluble pre-ligand assembly domain of tumor necrosis factor receptor 1 conferred protection against colitis through a re-balance of the cytokine milieu towards protective IL-13/IL-4 production [37].

Among the chemically-induced models, oxazolone-induced colitis mostly resemble human UC, as they both depend on the pathogenic activation of Th2 immune cells and on the presence of IL-13. In the seminal paper of Fuss et al. [38] IL-13 production by unconventional Type 2 NKT cells demonstrated to be critical for colitis development, since its neutralization by IL-13Rα2-Fc administration prevented colitis. Recently, a bifunctional IL-4/IL-13 antagonist was tested in oxazolone-treated mice, showing significant amelioration of the disease, similarly to what observed in mice lacking IL-4Rα or STAT6, being these mice unable to develop IL-4 or IL-13-mediated immunity upon oxazolone administration [39]. Therapeutic inhibition of IL-13 pathogenic function in oxazolone-induced colitis was also achieved by administration of the sphingosine-1-phosphate modulator FTY720 [40]. The therapeutic effects of FTY720 were associated with a prominent reduction of IL-13, IL-4 and IL-5 production. Strikingly, FTY720 inhibited GATA3 and T1/ST2 expression which represent highly relevant markers for Th2 differentiation and Th2 effector function, respectively.

Trinitrobenzene sulfonic acid (TNBS) is instead the experimental system most closely resembling human Crohn's disease (CrD). Albeit in this model a Th1/Th17 response is elicited, production of the Th2-

Table 1
The main cell types involved as source and/or target of interleukin (IL)-13.

Cell type	Source	Target	Main effects of IL-13	References
Epithelial cells	No	Yes	IL-13 exposure decreases transepithelial resistance and increases epithelial paracellular permeability	[83]
Muscle cells	?	No	Conflicting data on the pro-fibrogenic role of IL-13	[70,75]
Basophils	Yes	No	IL-13 production is enhanced by IL-33	[22]
Mast cells	Yes	No	IL-13 expression is induced by cross-linking of the high-affinity IgE receptor	[23]
Eosinophils	Yes	No	Upon CD28 ligation, IL-13 is released by eosinophils	[24]
Dendritic cells	No	No	A subset of $CD141^+$ dendritic cells preferentially induce the secretion of IL-13 by $CD4^+$ lymphocytes via engagement of the OX40 ligand	[26]
Non-invariant NKT cells	Yes	Yes	IL-13 production is triggered by the glycolipid lyso-sulfatide, which in turn up-regulates the IL-13Rα2 receptor	[25]
ILCs2	Yes	No	IL-13-expressing ILC2 need MHCII to promote parasitic helminth expulsion	[28]
Th2 cells	Yes	No	IL-13 production is enhanced by IL-33	[22]

Ig, immunoglobulin; ILC, innate lymphoid cell; IL-13R, IL-13 receptor; MHC, major histocompatibility complex; NKT, natural killer T; Th, T helper.

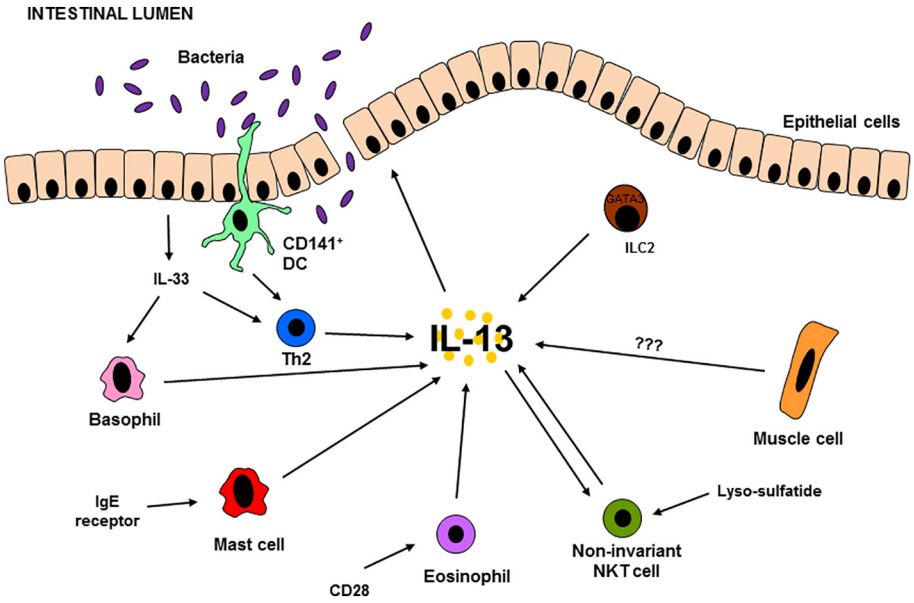

Fig. 1. The role of interleukin (IL)-13 in the gut. IL-13 is produced mainly by T helper (Th)2 cells, basophils, mast cells, eosinophils, non-invariant natural killer (NK)T cells and innate lymphoid cells (ILCs)2. Epithelium-derived IL-33 induces the production of IL-13 by Th2 cells and basophils. In addition, $CD141^+$ dendritic cells (DCs) also promote IL-13 release by Th2 cells. High-affinity IgE receptor, CD28 and the glycolipid lyso-sulfatide trigger IL-13 expression by mast cells, eosinophils and non-invariant NKT cells, respectively. Conversely, there are contrasting data on the production of IL-13 by muscle cells. In parallel, IL-13 increases epithelial paracellular permeability.

associated IL-13 has been detected in TNBS-treated mice, especially upon its chronic administration. Chronic TNBS model has been widely used to study the peculiar function of IL-13 in the promotion of fibrotic processes, particularly observed in CrD patients. In mice chronically treated with TNBS, late onset fibrosis is driven by IL-13 signaling via IL-13Rα2 and the production of transforming growth factor-β1 [41], the most pivotal cytokine involved in intestinal fibrogenesis [42]. As a consequence, blockade of IL-13 signaling in these mice via IL-13Rα2 and transforming growth factor-β1 signaling by small interfering RNA or decoy oligonucleotides resulted in the inhibition of fibrosis development [43]. In this model, though, IL-13 has been shown to act also as a molecular switch in those processes leading to the resolution of inflammation. Spontaneous amelioration of chronic inflammation has been shown to be critically dependent on IL-13 activation of STAT6, followed by phosphorylation (inactivation) of glycogen synthase kinase-3b, leading ultimately to a switch from IL-17 to IL-10 production by immune cells [44].

Dextran sodium sulphate-induced colitis has been also shown to promote IL-13 secretion by T cells, possibly as a direct consequence of recognition of bacterial antigens and products upon bacterial translocation [45]. Indeed, GATA3 dominant transgenic mice developed a colitis that was more severe compared to that induced in T-bet or RORγt dominant transgenic mice, and this observation was associated with significant mucosal up-regulation of IL-13 [46].

4. Role of IL-13 in chronic intestinal inflammatory disorders

In this section we review the role of IL-13 in the main chronic intestinal immune-mediated disorders, such as celiac disease (CD), UC and CrD (Table 2).

4.1. Celiac disease

CD is an immune-mediated enteropathy induced in genetically susceptible individuals by the ingestion of gluten [47]. It is well-known that both Th1 and Th17 cells trigger and sustain lesions in the small bowel mucosa of celiac patients [48,49].

Although *COELIAC2*, which is located in chromosome 5q 31-33 and also encompass IL-13, has been suggested as genetic risk factor for CD [50], no different genetic variation was reported at *IL-13* gene between celiac patients and controls [51]. The production of IL-13 as well as that of other Th2 cytokines, such as IL-4, IL-5, and IL-10, by duodenal biopsies is similarly low in patients with untreated CD, treated CD and controls [52]. Plasma levels of IL-13 do not differ between CD at diagnosis and after gluten-free diet, and controls [53]. On the other hand, serum amount of IL-13 has been shown to be increased in celiac children in comparison to controls [54,55]. Peripheral blood mononuclear cells isolated from celiac patients under gluten-free diet and stimulated by gliadin produce higher concentration of IL-13, though at low amounts, than those from control subjects [56]. However, peripheral NKT cells are reduced in celiac patients to 30% of those in normal subjects, whereas IL-13-positive NKT cells increase to 41% in normal subjects, but do not change in celiac patients after 4 h of anti-CD3/anti-CD28 antibody stimulation [57].

Lastly, IL-13 secretion by lamina propria lymphocytes is higher in patients with refractory CD than in those with uncomplicated untreated

Table 2
Experimental studies investigating the role of interleukin (IL)-13 in human chronic intestinal inflammatory disorders.

Disease	Observation	Functional interpretation	References
CD	The production of IL-13 and other Th2 cytokines IL-4, IL-5, and IL-10 by duodenal biopsies is low in patients with untreated CD	Th2 immune response is not implicated in CD	[52]
CD	IL-13 secretion by LPMCs is higher in refractory CD than in those with uncomplicated untreated CD	The cytokine milieu is distinct between refractory CD and uncomplicated untreated CD	[58]
UC	Mucosal amounts of IL-13 is low in UC	Active UC is associated with low mucosal IL-13	[67–70]
UC	*Ex vivo* stimulated LPMCs from UC produce increased IL-13	IL-13 is increased in UC	[21,71]
CrD	IL-13 transcripts are increased in fibrotic CrD muscle layer explants	IL-13 is increased in fibrotic CrD muscle layer	[75]
CrD	There are no differences in IL-13 transcripts in muscle layer explants between fibrostenosing CrD and healthy controls	IL-13 is not increased in fibrotic CrD muscle layer	[70]

CD, celiac disease; CrD, Crohn's disease; LPMC, lamina propria mononuclear cell; Th, T helper; UC, ulcerative colitis.

CD [58]. The whole mucosal cytokine profile looks to be distinct between refractory CD and uncomplicated untreated CD, as suggested by the up-regulation of IL-6 and tumor necrosis factor (TNF)-α only in the former and by the increase in IFN-γ and IL-21 only in latter one [59].

4.2. Inflammatory bowel disease

CrD and UC, collectively known as inflammatory bowel diseases (IBD), are chronic/relapsing immune-mediated diseases of the small and the large intestine [60,61]. Specifically, while UC affects exclusively the colonic mucosa [61], CrD may involve both the ileum and the colon, and a transmural extension of the inflammatory process is frequently observed, leading to the development of complications, such as stenosis and fistulae [60]. IBD is a complex and heterogeneous disorder, which may also have extraintestinal manifestations, such as giant cell arteritis [62]. Current theories postulate that IBD-related intestinal inflammation originates from a dysregulated immune response against gut luminal antigens, including those deriving from the intestinal bacterial flora [63,64]. Even if both innate and adaptive immune cells have been shown to play a role in IBD pathogenesis, studies involving human samples and murine models have identified in $CD4^+$ T helper cells the main orchestrators of both UC- and CrD-related mucosal inflammation [65]. This hypothesis is further substantiated by the efficacy of T-cell directed therapies in the control of IBD clinical activity [66]. As known, $CD4^+$ T cells mostly exert their biological actions by the coordinated secretion of a wide range of soluble mediators, known as cytokines. Pioneer studies of the T cell cytokine profile in inflamed mucosal specimens of CrD and UC patients have revealed that these two conditions are indeed rather dissimilar from an immunological perspective. Specifically, while CrD patients are characterized by increased production of Th1 cytokines, such as IFN-γ and TNF-α, UC patients display increased levels of IL-4, a cytokine classically associated with Th2 response. On the basis of these data, a 'Th1/Th2' paradigm was created for CrD and UC, respectively, which dominated the IBD immunological scene for over a decade, since the discovery of the novel class of Th17 cells as being associated with both CrD and UC mucosal inflammation [67,68]. Moreover, further cytokines, such as IL-9 and IL-37, are involved mostly in UC rather than in CrD pathogenesis [65,69].

After the initial report of UC as being associated with increased levels of Th2-related cytokines, since the early 2000s several laboratories began to evaluate the expression of IL-13 in inflamed mucosa of UC patients, yielding somewhat conflicting results. An early report by Vainer et al. [70] found protein concentrations of IL-13 to be reduced in UC inflamed mucosa with respect to mucosa obtained from active CrD and healthy controls. In the same study, negligible levels of IL-13 transcripts were found in gut specimens from active UC patients [70]. These findings were later confirmed by Kadivar et al. [71], who showed reduced IL-13 concentrations in organ culture supernatants obtained from endoscopic biopsies or surgical specimens of pediatric UC patients with respect to CrD or normal controls. Importantly, in most studies UC disease activity seemed to be negatively correlated with IL-13 expression, as levels of this cytokine were found to be lower in patients with active vs inactive disease, and no correlation was found between mucosal IL-13 concentration and histologic disease severity [70–72]. More recently, our group provided additional evidence to these negative data [73]. In particular, by using a combination of endoscopic biopsies and surgical specimens from IBD patients and controls, we confirmed similar mucosal IL-13 mRNA levels and IL-13 protein production in active UC, inactive UC and controls [73]. Additionally, no differences were found in IL-13 secretion from *ex vivo* stimulated lamina propria mononuclear cells between UC and CrD patients, and controls [73]. Consistently, UC lamina propria T lymphocytes were not characterized by increased surface levels of chemoattractant receptor-homologous molecule expressed on Th2 cells [73], a marker for Th2 cells in humans, and predominantly expressed by $IL\text{-}4^+/IL\text{-}13^+$ T cells.

In sharp contrast with the above-mentioned data, in 2004 and 2005 two papers published by the same group reported that *ex vivo* stimulated lamina propria T cells extracted from resected specimens of UC patients produced increased protein levels of IL-13 with respect to CrD and healthy individuals [21,74]. These Authors went on in identifying a subset of non-invariant NKT cells as the main cell population implicated in IL-13 production, on the basis of the requirement of intact CD1d-mediated signaling for IL-13 secretion and surface expression of CD161. It should be underlined, however, that increased infiltration of UC mucosa by $CD161^+$ T cells has not been confirmed across all the studies, including our own [73,75]; more importantly, this marker has recently been reported to be expressed on a wide range of lamina propria inflammatory cells, including Th17 lymphocytes. The reason for such huge discrepancies in observed IL-13 production in UC mucosa are at present unclear, and could possibly include both technical and patient-related variables (e.g. disease severity, disease duration and current treatment), although very similar experimental conditions were observed across the studies.

In the last few years, extramucosal IL-13 expression in the gut of IBD patients has gained interest from a therapeutic standpoint, as this cytokine has been implicated in the development of fibrosis [76], a frequent complication of CrD, and frequently leading to the development of bowel strictures [77]. In this regard, Bailey et al. [78] documented increased levels of mRNA transcripts in fibrotic CrD muscle with respect to patients with healthy mucosa. A trend towards increased IL-13 transcripts between fibrotic CrD and uninflamed CrD samples was also observed, albeit not statistically significant [78]. These findings, however, have been challenged by our own data, failing to document differences in IL-13 mRNA levels in muscle layer explants from fibrostenosing CrD and healthy controls [73].

In contrast to studies ascertaining IL-13 production in IBD mucosa, few reports have been published regarding the expression of IL-13 receptor subunits in healthy or inflamed intestine. With respect to this, we recently observed that $CD3^+$ and $CD68^+$ LPMCs isolated from inflamed CrD mucosa express significantly higher intracellular levels of IL-13Rα1 with respect to HC and UC, even if surface expression of IL-4Rα, IL-13Rα1 and IL-13Rα2 subunits, as evaluated by flow cytometry, is very low or absent [73]. More promising results have been obtained in studies evaluating IL-13 subunits expression in non-immune cells of IBD patients. Heller et al. [74] detected the presence of IL-13Rα1 and IL-4Rα on colonic enterocytes of non-inflammatory controls and patients with UC, confirming earlier results obtained on colonic epithelial cell lines [79]. A quantitative analysis on *ex vivo* isolated human intestinal epithelial cells led to the observation that they express increased levels of IL-13Rα1 and IL-13Rα2 subunits in UC, with respect to CrD and healthy intestine, and similarly to those extracted from colorectal cancer [80]. This is in line with a reported increased expression of phosphorylated STAT6 in the colonic epithelial layer during active UC, thus confirming the functional activity of IL-13-mediated signaling in the epithelium [81]. Consistently with a putative role of IL-13 in CD-related fibrogenesis, a trend towards increased transcription of IL-13Rα2 was observed in muscular layer of fibrotic CrD as compared with UC [78]. In line with these results, we recently described increased intracellular levels of IL-4Rα, IL-13Rα1 and IL-13Rα2 in myofibroblasts isolated from uninflamed areas of strictured CrD ileum, with respect to healthy individuals [73].

Studies regarding functional activities of IL-13 in IBD have demonstrated that this cytokine exerts a range of pleiotropic effects over both immune and non-immune cells. Consistently with a regulatory effect of IL-13 on innate immune responses, initially suggested in patients with inflammatory arthritis [82], in the late 90s a series of studies reported an additive effect of this cytokine in IL-10-mediated inhibition of lipopolysaccharide-mediated inflammatory cytokine release and lysosomal enzymes by IBD peripheral blood and lamina propria monocytes and mature macrophages [83–85]. Our recent report of a negative effect of recombinant human IL-13 on inflammatory cytokine production by UC LPMCs added on these observations, and contributed to

exclude an adjuvant role for this cytokine on mucosal immune responses in UC [73].

In contrast with the above-mentioned regulatory activities of IL-13 on immune responses, a relevant role for this cytokine in altering epithelial cell homeostasis aimed at inducing mucosal inflammation has been proposed. In an early report, Fuss et al. [21] demonstrated a synergistic effect of IL-13 on NKT cell-mediated epithelial cell cytotoxicity. Importantly, a similar effect was observed by using purified UC-derived $CD4^+CD161^+$ cells. By a combination of *in vitro* experiments, the same group proposed that IL-13 may act independently in modulating epithelial homeostasis, showing that exposure to this cytokine caused a significant decrease in transepithelial resistance and an increase in paracellular permeability in monolayers of colorectal cancer cells [86]. This, in turn, was associated with a significant increase of epithelial cell apoptosis and an increased expression of the pore-forming tight junction protein claudin-2, while expression of zonula occludens-1 and occludin remained unchanged [74]. In a recent report, Rosen et al. [81] documented that IL-13 effects on epithelial cell apoptosis and claudin-2 expression are STAT6-dependent, as they can be completely prevented by transfecting epithelial cells with a STAT6-specific small interfering RNA.

In contrast to what observed in circulating fibrocytes isolated from asthmatic patients, in which IL-13 exerts a direct effect on collagen production [87], an indirect role for this cytokine in CrD-related fibrogenesis has been advocated. Indeed, submucosal and muscle-derived fibroblasts extracted from the intestine of CrD patients did not upregulate collagen production following exposure to recombinant IL-13 [73,78]. On the contrary, IL-13 stimulation of CrD-derived fibroblasts led to a significant downregulation of MMP-2, and to reduced TNF-α-induced synthesis of MMP-1 and MMP-9 [78], proteases involved in the breakdown of extracellular matrix components in several physiological processes, including tissue remodeling [88].

5. Modulating IL-13 as therapeutic tool

The evidence of increased IL-13 production in active UC, together with the reported role of IL-13 in sustaining UC-related mucosal damage, have led to the hypothesis that blockade of this cytokine could represent a promising therapeutic strategy in UC. To this end, two phase II randomised clinical trials have been conducted, evaluating the safety and efficacy of tralokinumab and anrukinzumab, two neutralizing IL-13 monoclonal antibodies, in patients with active UC (Table 3).

Tralokinumab (formerly CAT-354) is a human IgG4 monoclonal antibody, which binds to and neutralises IL-13. This antibody has demonstrated clinical efficacy and an acceptable safety and tolerability profile in patients with asthma [89]. In a phase IIa, randomised, double-blind, placebo-controlled, multicenter trial, 111 patients with moderately-to-severely active UC were randomised in a 1:1 ratio to receive either tralokinumab 300 mg or placebo subcutaneously every 2 weeks for a total of 12 weeks [90]. The study failed to meet its primary endpoint, as reported clinical response rates at week 8 were 38% and 33% for tralokinumab and plabebo, respectively ($p = .406$) [90]. Additionally, no differences were observed between treatment groups in terms of mucosal healing ($p = .104$) [90]. Interestingly, a significantly higher proportion of patients receiving tralokinumab were in clinical remission at week 8 with respect to those receiving placebo (18% vs 6%, $p = .033$) [90]. Overall, tralokinumab was well tolerated, even if a larger number of adverse events was reported in the tralokinumab group than the placebo group, mostly represented by worsening of UC and headache [90]. No treatment-related serious adverse event was observed throughout the trial [90].

Anrukinzumab (formerly IMA-638) is a humanised IgG1 antibody that binds to IL-13 and inhibits attachment of IL-13 to IL-4Rα, thus interrupting IL-13 signaling [91]. Importantly, anrukinzumab does not block IL-13 binding to IL-13Rα1 and IL-13Rα2. In a phase IIa, randomised, double-blind, placebo-controlled, multicenter trial, 84 patients with active UC were randomised to receive anrukinzumab 200, 400 or 600 mg or placebo as five intravenous administrations at baseline and at weeks 2, 4, 8 and 12 [92]. Primary endpoint of the trial was fold change from baseline in fecal calprotectin at week 14, while changes in total Mayo score and Mayo subscores, clinical response rate at week 14 and clinical remission rate at week 14 were evaluated as additional predefined exploratory endpoints. The study failed to meet its primary endpoint, as no differences in fecal calprotectin levels at week 14 were observed with any drug dose with respect to placebo [92]. On the opposite, a paradoxical significant increase in fecal calprotectin was observed with the highest drug dose [92]. As for the clinical endpoints, no statistically significant ($p < .2$) differences were observed between any of the anrukinzumab groups and the placebo group for clinical response or remission rates, and for mucosal healing [92]. Overall, anrukinzumab was well tolerated, even if three treatment-related severe adverse events were observed, including abdominal pain and worsening of UC, which was mostly observed in the 600 mg group [92].

Although tralokinumab and anrukinzumab were demonstrated to be ineffective in UC, recently additional molecules, such as bispecific antibodies, have been hypothesizing as new therapeutic tools in IBD in addition to the approved antibodies targeting TNF-α, α4β7 integrin and IL-12/IL-23 [93].

6. Concluding remarks

While it is well-established that IL-13 is involved in intestinal Th2 disorder, such as parasitic infections, constrasting results have been reported on this cytokine in UC and CrD-related intestinal fibrosis. However, the negative results from clinical trials aimed at assessing the efficacy of anti-IL-13 monoclonal antibodies in UC patients support the absence of a role for IL-13 in UC. Its involvement in CrD complications, such as intestinal strictures and fistulae, is still the subject of further extensive investigation.

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Table 3
Clinical trials investigating the therapeutic potential of targeting interleukin (IL)-13.

Drug	Target	Drug type	Disease	Clinical trial	Findings	Reference
Tralokinumab	IL-13	Human mAb	UC	NCT01482884	Tralokinumab did not significantly improve clinical response	[87]
Anrukinzumab	IL-13	Humanised mAb	UC	NCT01284062	No therapeutic effect of anrukinzumab	[89]

mAb, monoclonal antibody; UC, ulcerative colitis.

Statement of author contributions

All authors participated in the drafting of the manuscript and provided approval of the final submitted version.

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