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Review

New insights into Th9 cells in inflammatory bowel diseases

Markus F. Neurath [*]

Department of Medicine 1, Deutsches Zentrum Immuntherapie DZI, University of Erlangen-Nürnberg, Kussmaul Research Campus & Ludwig Demling Endoscopy Center of Excellence, Erlangen, Germany

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ABSTRACT

The involvement of T helper cells in the pathogenesis of inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, has been a subject of considerable research interest. The clinical picture of IBD is characterised by chronic intestinal inflammatory processes that may lead to complications such as stenoses, abscesses, fistulas and colorectal cancer. Recent findings have indicated that T helper 9 (Th9) cells, which secrete the cytokine IL-9, play a role in the pathogenesis of IBD. These cells have been observed to damage the intestinal epithelium by IL-9 production and to amplify the mucosal inflammatory immune response by activating other immune cells. Studies utilising murine models of chronic intestinal inflammation have demonstrated that targeting IL-9 or Th9 cells can alleviate inflammatory responses. In consideration of these findings, it will be of interest to delve into the potential of neutralizing IL-9 function as a therapeutic intervention for patients suffering from IBD.

1. Inflammatory bowel diseases: clinical and pathophysiological aspects

The mucosal immune system has been identified as being critical for the maintenance of gut homeostasis in healthy individuals. In this regard, the immune system is required to regulate potentially harmful antigens (e.g. food antigens, microbial antigens) from the lumen [1-3]. The functionality of this process is contingent upon the integrity of the intestinal epithelial barrier, which encompasses both physical (e.g. tight junctions) and chemical (e.g. antimicrobial peptides, mucins, secretory immunoglobulin A) components [4]. Alterations in barrier function have been demonstrated to result in uncontrolled activation of the mucosal immune system. In this context, mucosal immune cells are exposed to a multitude of antigens, which subsequently leads to immune cell activation and the production of cytokines [3,5-8]. This process may consequently result in chronic intestinal inflammation, as observed in patients with inflammatory bowel diseases (IBD).

The two major forms of inflammatory bowel diseases are Crohńs disease (CD) and ulcerative colitis (UC). It has been established that such diseases have the capacity to result in uncontrolled mucosal inflammation. Typical clinical symptoms include abdominal discomfort and persistent, occasionally bloody diarrhoea [3]. While UC is confined to the large intestine, CD has the potential to manifest in any section of the gastrointestinal tract. Inflammation in CD frequently exhibits a discontinuous and patchy pattern, while in UC, inflammation is typically continuous, with the highest disease activity observed in the rectum. Furthermore, there are also differences between both diseases with regard to the depth of the inflammatory process in the bowel wall [5,9]. In the context of UC, the inflammatory response is typically confined to the mucosa and submucosa. In contrast, CD is characterised by the propagation of inflammation across the entire bowel wall, a phenomenon referred to as transmural inflammation [10-12].

It is important to note that inflammation in IBD patients is not necessarily restricted to the intestine and may also occur in other organs. Consequently, IBD can be regarded as a systemic disease. Extraintestinal manifestations of the disease are typically characterised by the occurrence of inflammatory skin diseases, such as erythema nodosum and pyoderma gangraenosum, or ocular diseases, including conjunctivitis and episcleritis [13,14]. Additionally, primary sclerosing cholangitis, a biliary system disease, is also observed in a small subgroup of patients. The aetiology of these inflammatory diseases is probably driven by trafficking of immune cells from the inflamed gut into other tissues, translocation of bacterial vesicles, or systemic effects of circulating proinflammatory cytokines [4].

Abbreviations: CD, Crohńs disease; UC, ulcerative colitis; IBD, Inflammatory bowel disease; Th9, T helper type 9 cells.

[*] Correspondence to: Department of Medicine 1, Deutsches Zentrum Immuntherapie DZI, Kussmaul Campus for Medical Research, Ludwig Demling Endoscopy Center of Excellence University Erlangen-Nürnberg, Germany.

E-mail address: markus.neurath@uk-erlangen.de.

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It is important to note that IBD has the potential to result in a number of significant complications, including, but not limited to, tissue fibrosis, stenoses, abscess formation, fistulas, and colorectal cancer [3]. It is an established medical fact that chronic intestinal inflammation frequently leads to tissue fibrosis and possibly also stenoses in patients suffering from IBD [15,16]. In particular, a significant proportion of patients diagnosed with CD who exhibit ileal disease must undergo surgical intervention to treat fibrostenotic disease [17,18]. Furthermore, the formation of abscesses has been observed in IBD patients necessitating drainage procedures or surgical intervention. Many IBD patients also suffer from arthralgias or arthritis. In some patients with CD, fistulas may occur between different parts of the intestine or between the intestine and other organs, such as the bladder. Finally, the presence of a chronic inflammatory process in IBD patients has been demonstrated to be a significant risk factor for the development of colitis-associated colon cancer [19,20].

2. Insights into the pathophysiology of IBD

IBD are multifactorial diseases in which genetic predispositions in individual patients interact closely with environmental factors and the composition of the gut microbiota [21-24]. The existence of familial clusters, as well as the observation that first-degree relatives of individuals diagnosed with IBD demonstrate a markedly elevated risk of developing the disease themselves, provides evidence for a key role of genetic factors. Genome-wide association studies (GWAS) have identified specific pathways involved in the pathogenesis of IBD [23,24]. These studies have identified more than 200 genetic risk regions and genetic polymorphisms that have been associated with IBD. The impact of these genetic variants is primarily observed in processes such as the immune response to intestinal bacteria, the function of the gut barrier, and the mechanisms of cellular degradation of bacteria and cell organelles. In the context of CD, the NOD2 (CARD15) gene is of particular significance [25,26]. This gene is involved in the recognition of bacterial components and plays a central role in the activation of the immune system. It is important to note that other key genes in CD include the ATG16L1 and IRGM genes, which have been shown to regulate autophagy [27-30]. The role of cytokines in the pathophysiology of IBD is highlighted by the observation that IL23R gene polymorphisms are present in patients with CD and UC [30,31]. It has been established that these polymorphisms offer protection to the host, thereby enabling them to prevent an augmented response by IL-17-producing T cells (termed Th17 cells). These cells have the capacity to produce a plethora of pro-inflammatory cytokines, which in turn serve to amplify mucosal inflammation in cases of IBD [32,33]. Further polymorphisms were identified in the TNFSF15 gene, which is predominantly linked to CD and regulates T cell function [34]. Finally, polymorphisms in mucin genes have been detected in UC [35]. In summary, evidence indicates that genetic factors play a pivotal role in the initiation and progression of IBD. However, it should be noted that genetic factors generally exhibit a high degree of interaction with environmental factors, thus resulting in the manifestation of IBD.

It is evident that environmental factors exert a significant influence on the onset and progression of IBD [21,36]. It is evident that smoking constitutes a major risk factor for the development of CD, with a substantial increase in deterioration in the disease's progression. In addition, evidence suggests that it exerts a protective effect on the development of UC. Moreover, it has become clear that nutrition plays an important role in IBD development. A Western diet that is highly processed and low in fibre has been demonstrated to increase the risk of developing IBD, while a plant-rich diet with anti-inflammatory properties has been shown to have a protective effect [21]. This factor may play a key role in the increasing incidence and prevalence of IBD in Western countries. Furthermore, the utilisation of medications such as non-steroidal anti-inflammatory drugs, in conjunction with frequent or early childhood antibiotic use, has been demonstrated to promote the development of the disease. This occurs through the damaging of the intestinal mucosa (non-steroidal anti-inflammatory drugs) or the alteration of the microbiome (antibiotics), consequently leading to dysbiosis and potentially gut inflammation. A number of other recognised risk factors have been identified, including environmental pollution, appendectomy (in UC), exposure to pesticides (e.g. propyzamide), and early childhood influences such as caesarean delivery, lack of breastfeeding, or an overly sterile environment [37-39]. Importantly, the interplay between genetic predisposition and environmental exposures varies considerably between IBD patients, contributing to the heterogeneity observed in disease manifestation and progression.

The interaction between genetic and environmental factors has been demonstrated to result in barrier alterations in patients suffering from IBD. These alterations in intestinal barrier function play a pivotal role in the pathophysiology of IBD. Barrier alterations are typically observed in patients with active IBD [40-42]. Furthermore, recent research has identified the presence of alterations in the intestinal barrier in IBD patients who are clinically inactive as a risk factor for disease flares [40]. This finding highlights the significant role of intestinal barrier dysfunction in the pathogenesis of IBD. As demonstrated by a range of experimental studies, the concept that barrier dysfunction can lead to translocation of bacterial antigens and other luminal antigens, including food antigens, into the mucosa has been established. In the mucosa, antigen presentation occurs through the uptake of antigens by antigen-presenting cells, including dendritic cells and macrophages. This process subsequently results in the activation of both T and B cells. T cell activation has been demonstrated to induce the production of numerous pro-inflammatory cytokines, which are considered to be pivotal in the pathogenesis of disease [6,43-45]. Moreover, B cells can augment T cell-dependent mucosal inflammation and can produce autoantibodies in IBD patients, thereby contributing to IBD pathophysiology.

In consideration of the proposed relevance of T cells in the pathogenesis of IBD, the present review will concentrate on the role of cytokine production by activated T cells in this disease. The article will specifically focus on the role of IL-9-producing Th9 cells, which have recently been implicated in the development and perpetuation of disease.

3. The role of T cell subsets in IBD pathogenesis

A plethora of studies have analysed the presence and activation status of T lymphocytes in the lamina propria in IBD patients [5]. The results of these studies demonstrated unequivocally that there was an expansion and activation of lamina propria T cells in both CD and UC patients. Furthermore, additional studies analysed the cytokine profile and the presence of key transcription factors in these cells. It was found that lamina propria T cells in CD express the transcription factor T-bet and produce increased amounts of IFN-gamma upon stimulation, consistent with an increased presence of Th1 cells in this disease [46, 47]. Conversely, an elevated production of IL-5 and IL-13 cytokines, along with the presence of the Th2 T cell-associated transcription factor GATA-3, was observed in patients with UC [47]. Furthermore, a number of studies have reported an increase in mucosal Th17 cells expressing the transcription factor RORC in both CD and UC patients and Th17 cells can produce various pro-inflammatory cytokines including IL-6 and TNF [45,48]. These cells were reportedly activated by the cytokine IL-23, and several research groups have reported increased levels of this cytokine in the inflamed mucosa of IBD patients [49,50]. Despite the fact that more recent studies utilising single cell technologies have unequivocally demonstrated a significant degree of plasticity in T cell cytokine responses in IBD patients, the aforementioned studies have concomitantly suggested the presence of both similarities and dissimilarities in cytokine profiles between CD and UC patients.

Additional studies have also observed an increase in the number of anti-inflammatory regulatory T cells (Tregs) in inflamed mucosa in IBD

[51]. These cells produce the anti-inflammatory cytokine TGF-beta, which can ameliorate inflammatory processes. However, the increase in Treg cells in IBD is lower than the increase in effector T cell numbers. Furthermore, IL-10-producing Tr1 cells are present in the IBD mucosa, although several studies have reported a reduction in Tr1 cell numbers in IBD [52,53]. Taken together, these findings suggest an imbalance between pro- and anti-inflammatory T cell subsets in the inflamed mucosa of IBD patients.

The current treatment algorithms for IBD comprise molecules and antibodies that target homing receptors, immune cell trafficking, signalling molecules and cytokines [54-59]. Furthermore, cellular immunotherapies are currently being assessed for their therapeutic efficacy [60,61]. The functional relevance of the pro-inflammatory cytokines previously mentioned was analysed in controlled clinical trials on IBD patients by the use of neutralising antibodies. These clinical investigations revealed that the antibody fontolizumab, which neutralises the cytokine IFN-gamma, did not lead to effective suppression of mucosal inflammation in patients diagnosed with CD [62]. Furthermore, antibodies targeting IL-13, such as tralokinumab and anrukinzumab, demonstrated no clinical efficacy in patients diagnosed with UC [63,64]. However, the efficacy of antibodies targeting TNF and IL-23 in both CD and UC was remarkable. Consequently, antibodies directed against TNF, including adalimumab and infliximab, have been approved for the treatment of IBD [65-67]. In a similar fashion, antibodies directed against IL-23, including risankizumab, mirikizumab and guselkumab, have been approved for utilisation in both CD and UC [68-70]. These studies highlighted the significance of IL-23-driven Th17 cells in the pathogenesis of IBD.

In addition to the above T helper cell subsets, there is a growing body of literature describing the presence of a T helper cell subset that produces IL-9, known as Th9 subset [71-78]. These cells have been identified as a Th17 cell-independent T cell subset, which has been found to play a significant role in both inflammation and cancer [75,79-86]. Consequently, the investigation of the presence and function of these cells in IBD was deemed a subject of interest. It is noteworthy that recent studies have identified the presence of IL-9-producing T cells in the lamina propria of patients with IBD. It is noteworthy that a significant increase in Th9 cells was observed in the inflamed mucosa of patients with active UC [87,88]. The potential relevance of these cells in the pathogenesis of IBD will be discussed in the following section of this review article.

4. Th9 cells in IBD patients and experimental models of colitis

An increase in serum IL-9 levels was reported among IBD patients. Furthermore, a positive correlation was identified between serum IL-9 levels and IL-6 production, as well as between serum IL-9 levels and disease severity [89]. This finding is consistent with the hypothesis that IL-9 may possess a pro-inflammatory function in cases of IBD.

In addition to the aforementioned observations, the expression of IL-9 mRNA was studied in gut samples from patients suffering from IBD. Specifically, elevated IL-9 mRNA expression was observed in patients with UC, while unchanged or reduced IL-9 mRNA expression levels were evident in CD patients [87,88]. These studies suggested the potential presence of IL-9-producing cells, including innate lymphoid cells, mast cells, and Th9 cells, within the inflamed mucosa of patients with UC. Subsequent experimental analyses provided evidence for an increased presence of Th9 cells in this disease. Indeed, immunohistochemistry revealed the presence of IL-9-producing T cells and PU.1-expressing T cells in the UC mucosa, thus suggesting the presence of Th9 cells [87,88]. The majority of these cells were observed in the lamina propria, with only a small number located in the epithelium [90]. However, lower amounts of these IL-9-producing cells were noted in CD mucosa. The underlying reasons for the observed discrepancy in Th9 cell numbers between CD and UC remain to be fully elucidated. However, experimental findings suggested the presence of Th9 inducing cytokines in UC, such as TGF-beta, and IL-33. As IL-33 levels in UC appear to be elevated in comparison to those observed in CD [91,92], IL-33 could be a potential factor contributing to the increased presence of Th9 cells in UC. The presence of Th9 cells in UC was associated with an increased expression of transcription factors which are known to induce IL-9 producing T cells, namely IRF4 and GATA-3 [93-96].

In order to elucidate the role of IL-9 signaling in IBD, several studies have been conducted which examined the expression of IL-9R on intestinal cells [87,88,97]. These studies demonstrated marked expression of IL-9R on intestinal epithelial cells, thus suggesting that the gut barrier could be a target for IL-9 function. In order to address this issue, a series of cell culture experiments were conducted using intestinal epithelial cells and IL-9. These experiments demonstrated that IL-9 has the capacity to reduce STAT3-dependent proliferation and expansion of epithelial cells. In terms of functionality, IL-9 has been demonstrated to induce pSTAT5 in these cells, while also suppressing wound healing in the intestine.

In addition to the above studies in patients with IBD, various studies have explored the functional role of IL-9 and Th9 cells in murine models of chronic intestinal inflammation [78,98-100]. Despite the fact that none of these models fully replicate IBD in humans, they are nevertheless useful in deciphering the functional relevance of IL-9 signalling under in vivo conditions [101,102]. One experimental study examined the function of IL-9-expressing invariant natural killer T cells and determined that these cells could protect mice from colitis via IL-4 effects [103]. In experimental dextran sodium sulphate (DSS)-induced colitis, however, the administration of IL-9 specific neutralising antibodies over a period of two weeks resulted in a protective effect, suggesting that this cytokine exerts a pro-inflammatory function in vivo [90]. Furthermore, Fas signaling-mediated Th9 cell differentiation exacerbated experimental DSS colitis [104]. In an adoptive transfer model of colitis in recombination-activating gene 1 (RAG1)-deficient mice, IL-9 and IL-10-expressing FoxP3-effector T cells exhibited no suppressive function, but rather exacerbated the colitis activity induced by CD45Rbhigh effector T cells [105], This finding aligns with the hypothesis that IL-9-producing effector cells can promote tissue inflammation. Furthermore, constitutive IL-9 expression exacerbated inflammation upon transfer of CD4 + CD45RBhigh T cells from wild-type but not from Il9r-/- mice, indicating that IL-9 exerts direct effects on T cells to drive colitis activity [106]. Furthermore, it was established that the expression of the CD155 ligand CD96 was instrumental in regulating the pathogenic potential of Th9 cells in the context of transfer colitis. Transfer of CD96high Th9 cells resulted in a diminished colitis activity when compared to CD96low Th9 cells [107]. It was demonstrated that the consistent blocking of CD96 resulted in the restoration of the pro-inflammatory properties of CD96high Th9 cells in the context of transfer colitis. In addition to CD96, the cytokine IL-36 gamma has been identified as a potent regulator of Th9 cell activity in colitis. This finding is supported by the observation that mice deficient in IL-36-gamma were protected from intestinal inflammation, and this protective effect was associated with diminished Th9 cell numbers [108]. Concurrently, other researchers have documented the observation that the alleviation of experimental colitis symptoms is concomitant with diminished IL-9 levels. For instance, treatment with VEGF-C resulted in a reduction in DSS colitis activity, an effect which was associated with a significant decrease in IL-9 levels and Th9 responses [109].

The findings, obtained from murine models of colitis, collectively suggested that IL-9 and Th9 cells producing IL-9 exert pro-inflammatory functions. This suggests that they are potential targets for therapy. In accordance with this concept, IL-9 deficiency has been shown to protect mice from experimental TNBS-induced colitis [110]. Furthermore, in a murine model of colitis induced by the hapten reagent oxazolone, an increased number of IL-9-producing cells and Th9 cells were identified as target for therapy. As the Th9-cell–associated transcription factor PU.1 is encoded by the *Spi1* gene, Cd4Cre conditional *Spi1* knockout mice enabled the analysis of PU.1 function in T cells. These studies showed that mice deficient in Th9 cells (Spi1Cd4Cre) exhibited a diminished response to inflammation in the experimental oxazolone-induced colitis model [87]. Moreover, the presence of IL-9 neutralising antibodies has been demonstrated to have a beneficial effect on both acute and chronic oxazolone-induced colitis. This finding serves to emphasise the functional relevance of this cytokine in the development and chronicity of colitis.

Mechanistic studies have demonstrated that IL-9 has the capacity to bind to the IL-9R on intestinal epithelial cells, thereby exerting its influence on epithelial barrier integrity and wound healing. Specifically, studies in the TNBS-induced colitis model suggested that IL-9 deficiency induced tight junction proteins such as occludins, while the pore-forming protein claudin-2 was unchanged [110]. Furthermore, IL-9 has been demonstrated to compromise intestinal barrier function in oxazolone-induced colitis and to impede mucosal wound healing in vivo [87]. Recent studies have also demonstrated the importance of death receptor 3 (DR3) signalling in the pathogenicity of Th9 cells [111]. In these studies, wild-type and DR3-deficient Th9 cells from SAMP knockout mice were adoptively transferred into immunodeficient mice, following which analysis of colitis severity was conducted. It was determined that DR3-deficient Th9 cells exhibited a reduced capacity to induce experimental colitis in comparison to wild-type Th9 cells. This finding suggests that the TL1A/DR3/Th9 pathway may represent a promising target for the treatment of IBD in vivo [111]. In accordance with this concept, TL1A overexpressing mice exhibited heightened DSS colitis activity in comparison to wild-type controls, concurrently demonstrating impaired intestinal barrier function [112,113]. The potential relevance of these findings was emphasised by studies in humans, which demonstrated that patients with UC who exhibited elevated TL1A expression experienced more severe mucosal inflammation, accompanied by higher levels of IL-9, PU.1 and Th9 cells, in comparison to patients with lower TL1A expression [113].

Although Th9 cells are defined by their production of IL-9, they can also secrete other cytokines, including IL-10, IL-21, and in some situations IL-17 [75,78,86]. The pro-inflammatory role of Th9 cells in IBD appears paradoxical given production of the anti-inflammatory cytokine IL-10, but it is likely that the net proinflammatory effect of Th9 cells reflects the combined action of multiple Th9-derived cytokines and context-dependent interactions with other immune cells and intestinal epithelial cells (Fig. 1) [5,114,115]. For example, IL-21 produced by Th9 cells may contribute to T, B and NK cell activation, can stimulate Th1 and Th17 effector T cell pathways and augment intestinal inflammation, potentially amplifying the pathogenic effect of IL-9 [116-118]. Moreover, IL-6 produced by Th9 cells may augment colitis activity by activating immune cells such as neutrophils, macrophages and Th17 effector T cells [119-121]. Finally, IL-9 derived from Th9 cells can induce immune cell activation and direct damage of intestinal epithelial cells in colitis [87,88]. Thus, Th9-mediated pathology in IBD likely results from a coordinated cytokine milieu rather than a single effector molecule.

How can we target IL-9 or IL-9-producing Th9 cells in individuals with IBD? One obvious option would be to set up a clinical study using neutralising anti-IL-9 antibodies in patients with IBD. But this hasn’t been done yet. However, studies using an anti-IL-9 antibody (MEDI-528) have been conducting in adults with uncontrolled moderate-to-severe asthma [122], although this treatment did not lead to significant improvement of symptom control. Another way to stop IL-9 production could be to target important proteins that control gene activity, such as PU.1/SPI1, IRF-4, BATF, NFAT or GATA-3. In a study in oxazolone

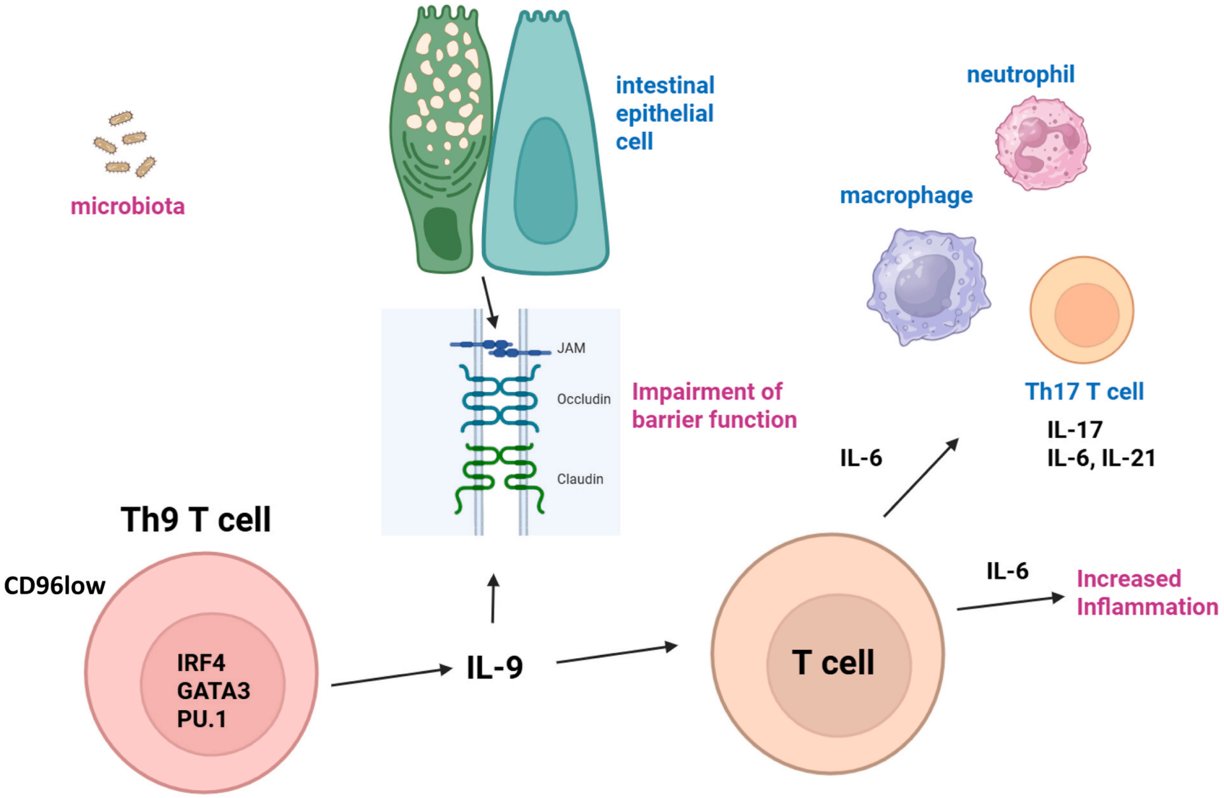

Fig. 1. Regulatory role of IL-9 in IBD patients and patients with colitis-associated colon cancer. In the inflamed mucosa of UC patients, IL-9 is predominantly produced by lamina propria Th9 cells that concurrently express the transcription factors IRF4 and GATA-3. In this context, CD96low Th9 cells play a critical role. IL-9 has been demonstrated to exert its effects on two distinct cell types: memory CD44 + T cells, where it has been shown to regulate IL-6 production, and intestinal epithelial cells that express the IL-9R. Previous studies highlighted the impact of IL-9R signalling in intestinal epithelial cells on STAT3-dependent proliferation and the alteration of barrier proteins. Thereby, IL-9-dependent processes lead to impaired barrier function and aggravated intestinal inflammation.

colitis, it was found that when the authors used a special DNAzyme to target GATA-3 expression, it stopped GATA-3 from being produced and reduced the production of pro-inflammatory cytokines, including IL-9. This led to a reduction in gut inflammation [95]. Moreover, chemical agents or herbal remedies might be used to modulate Th9 function. For instance, Neobavaisoflavone, the active constituent of the herb Psoralea corylifolial, was used to suppress PU.1-dependent IL-9 production by T cells and experimental colitis in vivo [123]. Finally, as discussed above, a new approach for IBD therapy could be to target the TL1A/DR3/Th9 pathway [111]. Hereby, various clinical trails targeting TL1A function have been conducted in IBD [124-126] suggesting that targeting TL1A could become a new clinical frontier in anti-cytokine therapies in IBD [127].

In short, these findings show that IL-9 and Th9 cells might play a regulatory role in the development of experimental colitis and IBD in humans. Future studies will have to work out what role IL-9 plays in IBD patients through controlled clinical trials. While experimental studies over the past decade have consistently implicated IL-9 in IBD pathogenesis, clinical testing of IL-9 blockade in IBD patients by pharmaceutical companies has not yet been reported. Possible reasons may include concerns about the redundancy of cytokine networks in human IBD, concerns about the negative outcome of anti-IL-9 trials in asthma and prioritization of multi-cytokine drugs with strong preclinical or clinical evidence [43,122,128-130]. Nevertheless, IL-9 remains an interesting candidate for future therapeutic evaluation, and clinical studies may be considered in the next years.

5. A potential role of Th9 cells in colitis-associated colon cancer

In patients with IBD-associated dysplasias and colorectal cancer, there were also a high number of lamina propria cells producing IL-9 and expressing PU.1 [131,132]. Actually, there was a general increase in PU.1-positive Th9 cells during the normal mucosa-UC mucosa-colitis-associated dysplasia sequence. These cells were very common in the lamina propria and less common in the epithelium [132]. Experiments with cell cultures were used to see what the role of IL-9 was. In colitis-associated colon cancer, IL-9 caused the growth of colonic epithelial cells by increasing the expression of c-Myc and cyclinD1 [133]. Other studies looked at what IL-9 does by looking at IL-9 knockout mice and mice with PU.1 deficiency in T cells in the AOM/DSS model of colitis-associated neoplasias. These studies showed that IL-9 deficiency protected from tumorigenesis, suggesting a pro-tumoral role of IL-9 and Th9 cells. Furthermore, it was observed that IL-9-producing Th9 cells regulate IL-6 production. The latter is a well-known pro-tumoral cytokine that controls proliferation and expansion of intestinal epithelial cells in colitis-associated cancer [134]. In summary, these findings suggested that IL-9 plays also an important role in colitis-associated colon cancer and future studies will have to address the function of IL-9 in patients with colorectal cancer.

6. Conclusion

The above experimental findings indicate that Th9 cells and their key cytokine IL-9 play a central pro-inflammatory role in IBD, particularly in ulcerative colitis, through a coordinated network of Th9-derived cytokines including IL-21, IL-6, and IL-9 itself. The function of these pro-inflammatory cytokines lies in their ability to regulate diverse immune cell subsets. Such cell types include, but are not limited to, T, B and NK cells, macrophages and neutrophils. Additionally, IL-9 has a direct regulatory effect upon intestinal epithelial cells, thus inducing epithelial cell death, impaired barrier function and impaired wound healing. Experimental colitis models and mechanistic studies have highlighted that targeting Th9 cells or IL-9 signalling via neutralising antibodies, transcription factor modulation, or the TL1A/DR3 pathway can suppress colitis severity. Notwithstanding this preclinical evidence, clinical trials specifically targeting IL-9 or IL-9R signalling in IBD have not yet been performed, a situation that may be due to concerns regarding redundancy in cytokine networks in IBD, prior negative results in asthma patients, and the prioritisation of broader therapeutic targets for IBD in early clinical trials. Beyond the context of IBD, experimental data suggest that Th9 cells and IL-9 contribute to colitis-associated colorectal cancer, where they drive epithelial proliferation of tumor cells and regulate pro-tumoral cytokines such as IL-6 that favour tumor growth. Collectively, these findings establish Th9 cells and IL-9 as both pathogenic mediators in intestinal inflammation and potential therapeutic targets. It is expected that future studies be conducted to provide greater clarity on the precise role of Th9 in human IBD. In addition, the efficacy of Th9- or IL-9-targeted therapies should be evaluated in controlled clinical trials.

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Data availability

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