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REVIEW

Resolution of Crohn's disease

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Abstract

Crohn's disease (CD) is characterized by chronic inflammation of the gastrointestinal tract and represents one of the main inflammatory bowel disease (IBD) forms. The infiltration of immune cells into the mucosa and uncontrolled production of pro-inflammatory cytokines and other mediators trigger the chronic inflammatory reaction in the intestine [1]. The inflammatory setting consists of subsequent events that comprise an induction phase, the peak of inflammation which is subsequently followed by the resolution phase. The induction phase, which represents the first phase of inflammation, is important for the rapid and efficient activation of the immune system for sufficient host defense. The permanent sensing of exogenous or endogenous danger signals enables the fast initiation of the inflammatory reaction. The immune cell infiltrate initiates an inflammatory cascade where released lipid and protein mediators play an indispensable role [2, 3]. The last decades of research strongly suggest that resolution of inflammation is similarly a tightly coordinated and active process. The basic concept that resolution of inflammation has to be regarded as an active process has been thoroughly described by others [4–6]. The following review focuses on mechanisms, pathways, and specific mediators that are actively involved in the resolution of inflammation in CD.

Keywords Resolution of inflammation · Crohn's disease · Intestine · IL23 · Anti-TNF therapy · Apoptosis

Crohn's disease

The precise etiology of CD has not yet been fully elucidated, but current immunopathogenic concepts strongly indicate that mucosal inflammation is caused by an altered immune response in individuals with a genetic predisposition. This inflammatory reaction is believed to be a consequence of a multifaceted interaction among environmental factors, luminal antigens, and the respective mucosal immune system [7–9]. CD is characterized by segmental and transmural inflammation that can principally occur in all parts of the gastrointestinal tract, with the terminal ileum and colon representing the most often affected segments. Clinical symptoms are defined by disease location and behavior as wells as severity of inflammation. They frequently comprise abdominal cramping, persistent diarrhea, severe fecal urgency, fatigue, anemia, and weight loss [10]. Up to 50% of patients are affected by skin, joint, or eye extra-intestinal manifestations that often occur before the diagnosis of CD is made. Extra-intestinal manifestation can moreover also occur at other parts of the body (e.g., lung) [11]. Bowel damage and disability are also attendant symptoms in CD and reflect the progressive and debilitating course of disease in this IBD entity. The inflamed intestine may cause various complications such as formation of abscesses, stenoses, fistulae, and heightened incidence of colitis-associated neoplasias [10]. Therefore, CD patients often have a limited quality of life and a pronounced morbidity is furthermore linked with CD. Recently, it has been shown that CD is characterized by a rapidly increasing incidence worldwide, which is especially evident in newly industrialized countries, making CD a global disease. Europe (322 per 100,000 in Germany) and North America (319 per 100,000 in Canada) have shown the highest prevalence, but the steady increase in areas with previously low incidence is best reflected in Africa, South America, and Asia, where rising annual percentage changes have been recently recorded [12].

In CD, there is a dire need for rational and optimized anti-inflammatory therapy to prevent progression and subsequent complications of disease [13]. Earlier treatment goals mainly focused on the alleviation of clinical symptoms alone, but in the course of time and development of novel targeted therapies, clinical remission, steroid-free remission, and finally

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mucosal healing have become an integral part in the successful therapeutic management of CD. Transmural healing assessed in cross-sectional imaging and the inclusion of a validated histological scoring instrument into the definition of mucosal healing could determine future therapeutic goals [14]. The most widely used therapies in CD consisted of corticosteroids and immunosuppressants (thiopurines and methotrexate). A major breakthrough was achieved by the development of biological therapies that are directed against specific mediators of the inflammatory process. The first substance class to be approved for therapy of CD were anti-TNF antibodies (infliximab, adalimumab, and certolizumab pegol). Antibodies against the integrin alpha4beta7 (vedolizumab) and interleukin 12 and interleukin 23 through their common p40 subunit (ustekinumab) have been approved for CD therapy in the following years [15, 16]. Despite the large clinical success of the mentioned targeted therapies, it was found that only subgroups of CD patients will benefit from these treatments, while a substantial proportion of patients do not show signs of clinical response. Furthermore, there are currently no clinically compatible predictive biomarkers for an individual guidance of drug therapy. It is therefore of utmost clinical importance to gain a deeper understanding of the respective mode of action of the respective therapies to guarantee the most efficient and suitable therapy for each single patient [17].

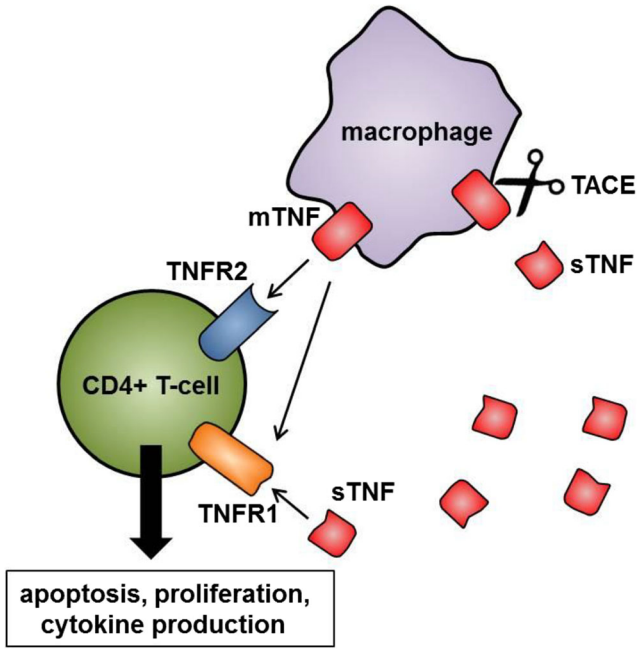

Fig. 1 TNF signaling mechanism. TNF is initially expressed as a membrane bound form (mTNF) by immune cells like macrophages. mTNF can be processed by the TNF alpha converting enzyme (TACE) into a soluble form (sTNF) which is able to activate both TNFR1 and TNFR2, whereas sTNF mainly activates TNFR1 on immune cells like $CD4^+$ T cells. The binding of mTNF or sTNF to TNFR1 or TNFR2 can lead to apoptosis, proliferation, and different cytokine production

The impact of anti-TNF therapy in the resolution of inflammation

IL-23 and TNF are among the main mediators produced by $CD14^+$ intestinal macrophages which infiltrate into the inflamed intestine of CD patients [18, 19]. In particular, mucosal immune cells like macrophages and T cells have been linked with being actively involved in the maintenance of intestinal inflammation in CD. The involved T cells are characterized by enhanced proliferation, resistance against apoptosis, and excessive pro-inflammatory cytokine production [8, 20, 21]. Resistance against apoptosis leads to the accumulation of pro-inflammatory cells that are thus involved in the initiation and perpetuation of the inflammatory reaction. Caspases are a protease family that are strongly involved in the induction of apoptosis [22, 23]. TNF is on the one hand able to induce survival and proliferation of cells via the NF-kB signaling pathway, but on the other hand is also able to initiate the induction of apoptosis via regulation of caspases [24] (Fig. 1).

Anti-TNF agents are commonly used as a highly efficient therapy in CD, underlining the pivotal importance of cytokines like TNF in the immunopathogenesis of the disease [25–27]. Although they are often effective in the resolution of CD, leading to endoscopic remission (Fig. 2a), they however fail in a relevant subgroup of patients, resulting in ongoing inflammation with signs of endoscopic disease activity (Fig. 2b). About one third of CD patients do not demonstrate therapeutic efficacy upon initiated anti-TNF therapy (primary non-response); moreover, 30%–50% lose response to therapy in the course of treatment (secondary non-response) [28, 29].

Secondary non-response to anti-TNF therapy has so far primarily been associated with immunogenicity. Interestingly, the application of another anti-TNF antibody in these patients often also fails to show therapeutic efficacy [30, 31]. Besides neutralizing antibodies against the anti-TNF agents, insufficient levels of the drug in the serum has also been considered to explain inefficient therapeutic response [30]. In contrast, a recently published study demonstrated that a large cohort of patients who lose response to anti-TNF therapy exhibit sufficient levels of anti-TNF antibody in the serum and do not develop relevant levels of neutralizing antibodies against TNF [32]. These results strongly suggest that in addition to pharmacodynamic factors, existence of TNF-independent forms of CD that circumvent resolution of inflammation might similarly be involved in failure of anti-TNF agent therapy. Although some reasons for therapeutic non-response have been characterized in the last years, the concept of immune-related mechanisms that drive resistance to biologic therapy in IBD and thus blocking the resolution of inflammation in CD is still poorly understood. Here, studies in recent years have demonstrated that expression of the target molecule in the inflamed tissue may have a pivotal influence on the response to anti-TNF therapy in IBD. It could

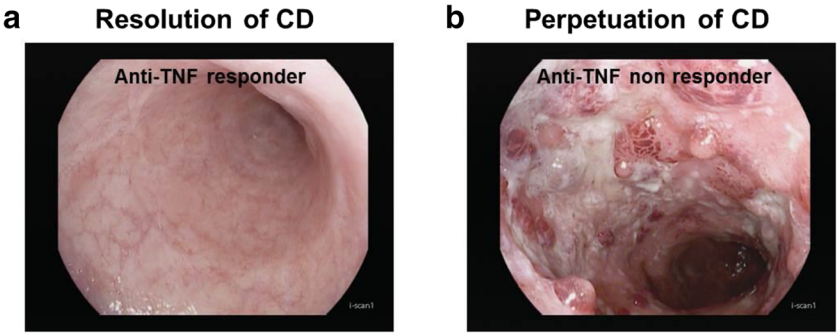

Fig. 2 Endoscopic resolution and perpetuation of mucosal inflammation in CD patients treated with an anti-TNF agent. (A) Patient with Crohn's colitis demonstrating resolution of inflammation after initiated anti-TNF therapy. (B) Anti-TNF antibody treated patient with Crohn's colitis demonstrating signs of severe mucosal inflammation during ongoing anti-TNF therapy

be shown that anti-TNF antibodies are able to bind to membrane-bound TNF (mTNF) expressing macrophages, which leads to the induction of apoptosis in TNFR2 expressing mucosal T cells that lack the mTNF-dependent co-stimulation [33]. The interplay between mTNF (macrophages) and TNFR2 (T cells) therefore represents a potential component in the development of resistance to apoptosis in mucosal T cells in CD, which critically contributes to disease pathogenesis in CD. The importance of this mechanism is supported by the finding of an in vivo molecular endoscopy study in 25 CD patients, where high mucosal expression of mTNF before initiation of anti-TNF therapy was linked to higher clinical and endoscopic response rates to following anti-TNF therapy [34, 35]. Furthermore, other findings have similarly implicated that immune signaling pathways may predict and control responsiveness to anti-TNF therapy in IBD [17]. The release of cytokines and resulting different cytokine levels in the inflamed mucosa of CD patients has thus been moved into the focus as a possible reason for insufficient response rates to anti-TNF therapy. Besides elevated levels of IL1B, IL17A, and S100A8 in CD patients who do not respond to anti-TNF therapy, altered levels of IL-6 and IL-23p19 have similarly been found in CD non-responders [36]. Another study elegantly demonstrated that elevated pretreatment expression of intestinal oncostatin-M and mucosal plasma cells, as well as inflammatory macrophages were also linked to lack of efficient anti-TNF therapy [37, 38]. These findings indicate that immune cells and the interplay of cytokines in the inflamed mucosa of CD patients have to be regarded as critical components for the resolution of inflammation process.

Regulatory T cells as mediators for the resolution of CD

Regulatory T cells are mainly divided into classically activated regulatory T cells (Tregs) and type 1 regulatory T cells (Tr1). Tregs can be identified via the transcription factor FoxP3, while Tr1 cells are characterized by the production of high levels of IL-10 [39, 40]. The last years of research have focused on the role of Tregs and Tr1 cells in tolerance and immune balance, but little is known about the role of these cells in the resolution of inflammation process [41]. Elevated levels of IL-10 and diminished IL-17A and RORγt levels can influence the differentiation of pro-inflammatory Th17 into anti-inflammatory Tr1 cells and therefore have an impact on the resolution of inflammation cascade [42, 43]. Alternative immunotherapeutic approaches represent a novel part of therapeutic research in CD. In a pilot study, antigen specific T cells, which were generated ex vivo, were administered intravenously and could reach a dose-dependent therapeutic effect in CD patients, which was accompanied by a favorable safety profile [44]. These findings suggest that changes in T-cell plasticity play a central role in the resolution of inflammation and might be an interesting target for future CD therapy.

Regulatory innate lymphoid cells (ILCreg) are important for intestinal barrier function

Different types of immune cells contribute to the resolution of inflammation process in CD. Activated ILCreg cells are characterized by the secretion of IL-10 and TGF beta while non-activated ILCregs are normally found as resting cells in the lamina propria of the murine and human intestine. The secretion of anti-inflammatory cytokines by ILCregs influences the release of IFN-γ and IL-17 but does not alter the production of IL22, a cytokine which together with IL-10 was shown to be an integral part in the resolution of inflammation conveyed by T cells. The role of IL-10 in CD is controversially discussed. Early-onset CD is linked to genetic variants in the IL-10 receptor, whereas therapeutic administration of IL-10 was not able to induce clinical efficacy [45–47]. The cytokine IL-22 is involved in the induction of proliferative and anti-apoptotic signals and thereby contributes to the restoration of the barrier function in the adaptive and innate immune system [48, 49]. Further cytokines that show similar effects are IL-28 and IL-36 and together with IL-22, they are able to foster resolution of inflammation [50, 51].

Monocytes/macrophages and neutrophils are key players in the innate immune response

T cells as well as monocytes/macrophages are centrally involved in the pathogenesis of CD, but especially tissue macrophages also influence resolution of inflammation [52–54]. M2-like macrophages produce anti-inflammatory cytokines like IL-10 and TGF-beta and are therefore important for the homeostasis in the healthy mucosa. Regarding the inflamed mucosa of IBD patients, elevated cytokine levels of IL-23, IL-6, TNF-α, or IL-1β are found, which are mainly produced by pro-inflammatory M1 like macrophages [55, 56]. These macrophages are responsible for the phagocytosis of apoptotic cells like neutrophils which accumulate in the inflamed tissue and trigger, if not properly cleared, the perpetuation of inflammation and tissue damage [57]. Phosphatidylserine (PS) is normally located in the inner layer of the membrane of immune cells, but in apoptotic cells, PS can be found outside the cell, where it interacts with different receptors to mediate efferocytosis [58, 59]. A study where mucosal barrier function was mechanically broken revealed a diminished infiltration of neutrophils in CD patients [60]. Missing sensor signals and diminished migration of neutrophils might have an impact on the recruitment of phagocytic cells and therefore contribute to the perpetuation of inflammation in CD.

IL-23 causes perpetuation of inflammation in CD

Different studies revealed that besides TNF, other cytokines are also important players in the development of CD. It has been demonstrated that especially IL-23 is centrally involved in the pathogenesis of CD [1, 61–63]. Polymorphisms in genes encoding the IL-23R have been analyzed in genome-wide association studies (GWAS) and were linked to IBD pathogenesis, indicating a central role of IL-23 in mucosal inflammation [64, 65]. Moreover, elevated levels of IL-23 in the mucosa of CD patients further emphasize its critical role in IBD pathogenesis [66]. Recently, published data demonstrate that treatment with the selective IL-23p19 inhibitors risankizumab or brazikumab result in high response rates in the cohort of CD patients that did not respond to previous anti-TNF therapy [67, 68]. These findings strongly indicate involvement of IL-23 in anti-TNF-resistant gut inflammation. This is supported by a recently published study, where mucosal TNFR2-expressing $CD4^+$ T cells circumvent anti-TNF induced apoptosis through co-expression of the IL-23R, which is activated by upregulated IL-23 production of mucosal $CD14^+$ macrophages. Here, IL-23 caused activation of pSTAT3 in mucosal $CD4^+$ T cells which results in resistance to apoptotic signals. The activated T cells are characterized by the release of high amounts of Th1 and Th17 cytokines. These $TNFR2^+IL\text{-}23R^+$ T cells expand and accumulate in the mucosa of anti-TNF refractory CD patients where they perpetuate chronic intestinal inflammation (Fig. 3) [69].

However, the mechanisms by which the IL-23R may influence effector functions and pathways contributing to resolution of inflammation in CD are currently not fully understood.

Pro-resolving lipid molecules (PLMs)

In contrast to the initiation of inflammation, which has been meticulously investigated during the past four decades, resolution of inflammation is far less well understood [53, 70]. Although concepts describing resolution of inflammation as a passive process have been largely banished, the characterization of pathways that are activated during the resolution of inflammation process, and thereby orchestrate programs which terminate inflammation, has remained incomplete [71]. Resolution of inflammation includes several active processes rather than a stepwise disappearance of pro-inflammatory factors and mediators or dilution of chemokine gradients [72–74]. Serhan and others have highlighted the importance of "pro-resolving" factors in the context of resolution of inflammation [6, 75]. Pro-resolving lipid mediators are produced by a concerted action of arachidonate lipoxygenases (ALOX), mediating the production of pro-resolving lipid mediators. These are mainly found in alternatively activated macrophages and eosinophils [76, 77]. Among these pro-resolving molecules, those derived from essential polyunsaturated fatty acids (PUFAs) have been shown to induce favorable effects on a plethora of human inflammatory disorders, including CD. Although numerous pre-clinical and clinical studies tried to establish the therapeutic application of PUFAs in intestinal inflammation, either as fatty acid precursors or single metabolites, contradictory results have so far precluded final assessment of this treatment approach in the IBD field [78–80].

Microbiota

The gut microbiota represents another key component in the pathogenesis of IBD [81]. It comprises bacteria, fungi, viruses, and other microorganisms. The composition of the microbiota can be influenced by environmental factors, diet, and hygiene during childhood, whereas in adult persons a more stable and defined composition is evident [82, 83]. In healthy conditions, there is a homeostasis between the intestinal microbiome, mucosal barrier function, and the gut immune system. In CD, this homeostasis is altered, reflected by microbial imbalance, disrupted barrier function, and immune system activation [81]. The concept of a perturbed gut microbiota composition is

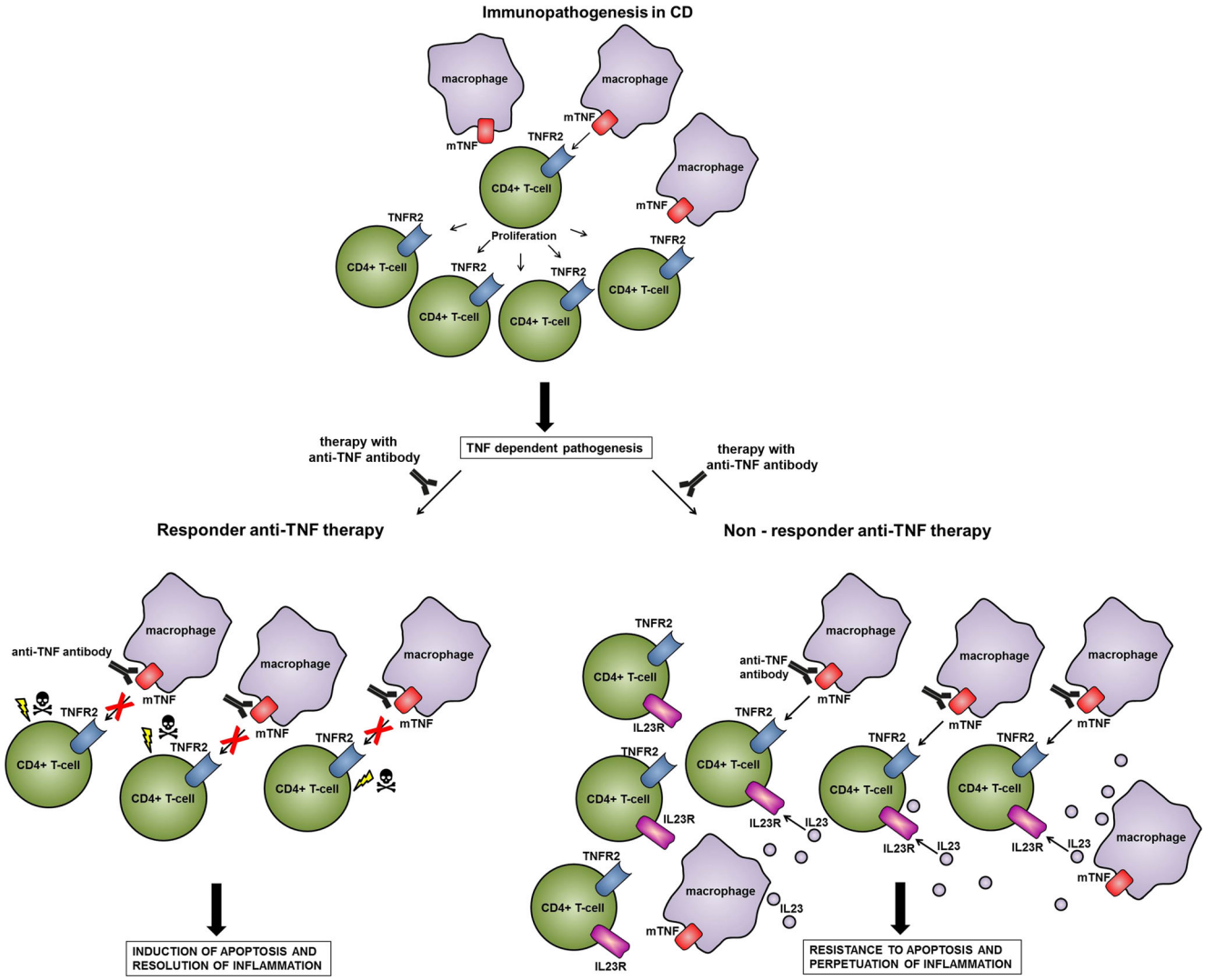

Fig. 3 IL-23 mediates resistance to apoptosis in CD. Model of IL-23-mediated resistance to apoptosis of mucosal $CD4^+$ T cells in anti-TNF refractory CD patients. In CD, tissue-infiltrating $CD14^+$ intestinal macrophages have been suggested to dominate the inflamed mucosa. Here, mTNF expressing $CD14^+$ macrophages activate $CD4^+$ T cells via the TNFR2, leading to mucosal inflammation in CD (upper image). In responders to initiated anti-TNF therapy, anti-TNF antibodies bind to mTNF-expressing $CD14^+$ macrophages, thereby inhibiting activation of the TNFR2 on mucosal $CD4^+$ T cells. The resulting blockade of TNFR2-dependent signaling pathways finally leads to the indirect induction of apoptosis in intestinal $CD4^+$ T cells in CD and resolution of inflammation (lower left image). In anti-TNF refractory patients, TNFR2 bearing gut $CD4^+$ T cells additionally express the IL-23R. Heightened production of IL-23 from $CD14^+$ macrophages leads to binding to the IL-23R on $CD4^+TNFR2^+$ T cells and induction of STAT3 activation. This activation leads to the expansion of $CD4^+IL\text{-}23R^+TNFR2^+$ T cells that are resistant to apoptosis induction by anti-TNF antibodies, resulting in the perpetuation of mucosal inflammation (lower right image). Adapted from Schmitt et al. 2019 [69]

one of the striking findings in recent IBD research. Some changes of the microbiota seem to be characteristic for either CD or UC, while others appear to be attributed more generally to IBD. The most consistent changes can here be found regarding biodiversity [84–86]. In contrast to healthy controls, a reduced diversity in the fecal microbiome can be found in CD patients [87]. Even within the same patient, a reduction of diversity and a diminished bacterial load can be found in the inflamed tissue compared to unaffected tissue [88]. A multicenter study with samples collected from multiple concurrent gastrointestinal locations revealed that changes in the bacterial composition (increased findings of Veillonellaceae, Pasteurellacaea, Enterobacteriaceae, and Fusobacteriaceae and decreased findings of Bacteroidales, Erysipelotrichales, and Clostridiales) strongly correlated with the level of mucosal inflammation of the disease. This study also revealed that rectal mucosa-associated microbiome profiling offered a reliable biomarker for the diagnosis of CD at the early stage of disease [89]. Antibiotics, probiotics, and prebiotics have been developed for the treatment of IBD with different results.

Whereas antibiotics at least achieved low effects in CD for a short time-span, studies for probiotics and prebiotics are generally disappointing and did not result in clinically relevant efficacy [90]. The use of single antibiotics can show a short-lived and modest therapeutic effect in CD at best, but has not been shown to be effective at all in patients with UC. Combinations of different antibiotics might slightly improve outcomes, but the long-term use of antibiotics may also lead to the development of antibiotic resistance in gut microbes [91, 92] and can altogether not be recommended for CD therapy. Studies have demonstrated that prognostic biomarkers from microbial profiling might be instrumental for personalized therapy. For example, microbial structure data in combination with apolipoprotein A1 levels can be used to predict steroid-free remission in children newly diagnosed with CD [93]. It was shown that ileal levels of *F. prausnitzii* increase the risk for postoperative recurrence of CD [94]. Furthermore, there is a correlation between microbial signatures and responsiveness to therapy and microbial imbalance is linked with relapse in patients after cessation of infliximab [95, 96]. The effect of an immunomodulatory therapy on the microbiota and its role in response to therapy is currently insufficiently studied and several studies showed controversial results. Sensing for pathogens which enter the gut due to a disrupted intestinal barrier is one important function of the mucosal immune system. A permanent influx of bacteria and bacterial antigens may contribute to the lack of resolution of inflammation and chronification of CD [97, 98].

Genetic risk factors and environmental influence on the resolution of CD

Although the pathophysiology of CD has not been fully clarified yet, it is currently assumed that a complex interaction between environmental, genetic, and intestinal microbial factors leads to a pathological auto-inflammatory response directed toward the intestine [99]. GWAS has become an integral part in the research field of multifactorial diseases like CD. Analysis of polymorphism or disease-susceptible genes with GWAS offers new possibilities to treat CD and to avoid the side effect of medications. There are several risk haplotypes which contribute to loss of efficacy. The HLA-DRB1*03 allele for example has also been associated with a sevenfold higher risk for the development of antibodies against infliximab [100]. Certain genes of the IL-23 pathway are IBD susceptibility genes, suggesting a critical role for this pathway in maintaining intestinal immune homeostasis [101]. Another important cytokine is IL-10 which germ-line variants have been linked to UC and CD [102, 103]. The composition of intestinal bacteria and its critical role in the pathogenesis of IBD has come to the fore in the last years of research. CD-specific genes like NOD2, ATG16L1, and IRGM have focused attention on innate immunity in general and more specifically on microbial recognition and autophagy [60, 104, 105]. Important links have been elicited between NOD2 and autophagy, a natural regulated mechanism of the cell that disassembles dysfunctional components. NOD2 initiates autophagy by recruiting ATG16L1 to the cell membrane at the site of bacterial entry. Dendritic cells from CD patients, with NOD2 or ATG16L1 mutation, are defective in autophagy, bacterial handling, and antigen presentation [106, 107]. Environmental factors are also key components in the development of CD and can influence the disease outcome [108]. Higher social and hygiene status (with most likely less acute intestinal infections and subsequent acute inflammatory responses) is associated with a higher risk to suffer from IBD [109]. Environmental factors such as titanium dioxide, aluminum, or dietary emulsifiers may directly or indirectly activate pro-inflammatory pathways and thereby disturb the natural balance of the immune system which is an important part in the resolution of CD [110–112].

Conclusions

Resolution of inflammation is a strictly regulated process depending on cells, lipid, and protein mediators that maintain tissue homeostasis and prevent the development of chronic inflammatory diseases. In addition to universal mechanisms, specific mechanisms and cell interactions have been identified that control the resolution of inflammation in CD. Molecular mechanisms like resistance to apoptosis during inefficient anti-TNF therapy, altered cytokine secretion, or microbial imbalance in the gut of CD patients trigger the perpetuation of inflammation. Several pathways have to be considered as therapeutically relevant in this setting as their induction may provide new insights to control inflammation in CD without affecting the overall inflammatory response. First examples like antibodies targeting IL-23 in anti-TNF resistant patients give hope for therapeutic approaches that might be based on insights to the molecular phenotype of CD in specific situations. These approaches are therapeutically needed to enable sought-after resolution of inflammation based on a sound immunopathogenic basis.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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