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REVIEW

Study of tumor necrosis factor receptor in the inflammatory bowel disease

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Abstract

Ulcerative colitis (UC) and Crohn's disease (CD) are part of Inflammatory Bowel Diseases (IBD) and have pathophysiological processes such as bowel necrosis and enteric neurons and enteric glial cells. In addition, the main inflammatory mediator is related to the tumor necrosis factor-alpha (TNF-α). TNF-α is a mediator of the intestinal inflammatory processes, thus being one of the main cytokines involved in the pathogenesis of IBD, however, its levels, when measured, are present in the serum of patients with IBD. In addition, TNF-α plays an important role in promoting inflammation, such as the production of interleukins (IL), for instance IL-1β and IL-6. There are two receptors for TNF as following: The tumor necrosis factor 1 receptor (TNFR1); and the tumor necrosis factor 2 receptor (TNFR2). They are involved in the pathogenesis of IBD and their receptors have been detected in IBD and their expression is correlated with disease activity. The soluble TNF form binds to the TNFR1 receptor with, and its activation results in a signaling cascade effects such as apoptosis, cell proliferation and cytokine secretion. In contrast, the transmembrane TNF form can bind both to TNFR1 and TNFR2. Recent studies have suggested that TNF-α is one of the main pro-inflammatory cytokines involved in the pathogenesis of IBD, since TNF levels are present in the serum of both patients with UC and CD. Intravenous and subcutaneous biologics targeting TNF-α have revolutionized the treatment of IBD, thus becoming the best available agents to induce and maintain IBD remission. The application of antibodies aimed at neutralizing TNF-α in patients with IBD that induce a satisfactory clinical response in up to 60% of patients, and also induced long-term maintenance of disease remission in most patients. It has been suggested that anti-TNF-α agents inactivate the pro-inflammatory cytokine TNF-α

by direct neutralization, *i.e.*, resulting in suppression of inflammation. However, anti-TNF-α antibodies perform more complex functions than a simple blockade.

Key Words: Tumor necrosis factor 1 receptor; Tumor necrosis factor 2 receptor; Inflammatory bowel diseases; Enteric nervous system; tumor necrosis factor-alpha

Core Tip: This review summarizes the role of Tumor Necrosis Factor-alpha (TNF-α) in promoting inflammation. Studies have suggested that TNF-α is one of the main pro-inflammatory cytokines involved in the pathogenesis of Inflammatory Bowel Diseases (IBD). In addition, the enteric nervous system is affected by IBD. There are two receptors for TNF: The tumor necrosis factor 1 receptor; and the tumor necrosis factor 2 receptor. They are involved in the pathogenesis of IBD. The application of antibodies aimed at neutralizing TNF-α in patients with IBD induce a satisfactory clinical recovery. This review addresses the main aspects of TNF-α in IBD and anti-TNF therapies.

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INTRODUCTION

Inflammatory bowel diseases (IBD) comprise ulcerative colitis (UC) and Crohn's disease (CD), which are chronical and recurrent disorders that affect the gastrointestinal (GI) tract[1-4]. The etiology of IBD is not yet fully understood, but there are reports of a complex relationship between genetic[5,6], immunological and environmental factors[7-10], as well as gut microbiota[11-15]. There is an imbalance between anti- and pro-inflammatory cytokines that cause an exacerbated and inadequate immune response.

The enteric nervous system (ENS) is composed by intrinsic neurons, their axons and enteric glial cells, which constitute a complex of structures responsible for controlling motility of the GI tract, secretion of gastric acid, regulation of fluid movement through the epithelium, local blood flow control, and interactions with the endocrine and immune systems of the gut[16-18]. The ENS is affected by IBD which causes necrosis, apoptosis, degeneration of enteric ganglia and alterations on motility patterns [19-23].

Tumor necrosis factor-alpha (TNF-α) is a mediator in intestinal inflammatory processes, thus being one of the main cytokines involved in pathogenesis of IBD, with high levels in patients with IBD[24,25]. There are two receptors for TNF-α as following: The tumor necrosis factor receptor 1 (TNFR1); and the tumor necrosis factor receptor 2 (TNFR2). After TNF-α binding to these receptors, it activates signaling pathways for cell survival, death and differentiation[26]. An increase in TNF-α expression can lead to mucosal barrier defects in patients with IBD, which increases inflammation and worsens the prognosis [10].

Due to the TNF-α relation with IBD, biological drugs have been used to treat CD and UC with neutralizing monoclonal antibodies used for TNF-α target and blockade, which reduce the development of the inflammatory process and the activation of immune system cells[27]. Anti-TNF-α agents are indicated by various guidelines for the treatment of IBD[28,29] and the use of these agents induces a satisfactory clinical response, and long-term maintenance of disease remission in most patients[24,30]. This review aims to provide the main aspects of IBD and TNF-α relationship, elucidating the role of the TNF-α receptors, anti TNF-α therapy and some perspectives related to the involvement of the ENS.

THE ENS AND IBD

The ENS is a complex of structures responsible for controlling motility of the GI tract, secretion of gastric acid, regulation of fluid movement through the epithelium, changes in local blood flow, and interactions with the endocrine and immune systems of the gut[16-18]. The ENS is located in the intestinal wall and is organized into two ganglionated plexuses: The myenteric plexus; and the submucosal plexus[16-18].

The myenteric plexus (Auerbach's plexus) is situated between the longitudinal muscle layer and the circular muscle layer throughout the entire GI tract, from the esophagus to the rectum. It has three

components as following: A primary plexus; a secondary plexus; and a tertiary plexus. The myenteric plexus is involved with reflex regulation of the contractile activities of the muscle layer[16,17]. The submucosal plexus (Meissner's plexus) is predominantly found in the small and large intestines, with a smaller ganglion and finer interconnected fibers when compared to the myenteric plexus[16,17]. It has a direct role in controlling secretion and absorption through motor neurons that regulate the secretomotor and vasomotor activity of the mucosal layer[16,17].

Enteric neurons can be classified according to their function into motor neurons, interneurons, and Intrinsic Primary Afferent Neurons[16]. Motor neurons are further divided according to their chemical code into excitatory neurons (labeled by the enzyme choline acetyltransferase or by calretinin), inhibitory neurons (labeled by the enzyme neuronal nitric oxide synthase), and secretomotor/vasodilator neurons. Excitatory and inhibitory motor neurons are observed in the myenteric plexus and are involved in motility control, while secretomotor/vasodilator neurons are observed in the submucosal plexus and are responsible for innervating the mucosa and regulating secretion, absorption, and local blood flow[16,17].

Enteric glial cells are small, consisting of numerous processes that do not synthesize myelin, and are also essential for the organization and function of the ENS[31]. These cells have a star shape with numerous branches that surround the neurons. They also exhibit a series of voltage-dependent ion channels that are connected by gap junctions, giving the impression of an intimate and complex intertwining of neurons and glial cells. In addition to their role in supporting neurons, enteric glia cells regulate synaptic transmission, release cytokines, and mediate communication with the immune system [32-34].

Enteric glial cells are identified by immunohistochemical methods such as labeling of cells expressing glial fibrillary acidic protein (GFAP) and/or calcium-binding protein S100/S100β since mature enteric glial cells express these protein types[35,36]. GFAP expression is modulated by enteric glial cell proliferation, differentiation, and inflammation[22]. S100 is a calcium-binding protein that can be found in the nucleus or cytoplasm and acts to regulate the cytoskeleton structure and function as well as the calcium homeostasis in the cytoplasm[35,37,38]. Under inflammatory conditions, enteric glial cells can acquire new functional properties, and in patients with IBD there was an increase in GFAP expression in mucosal inflammation compared to non-inflamed areas[39].

The enteric plexuses are formation of cells that spread throughout the entire GI tract, however, differences in the density and size of enteric neurons and glial cells, as well as in ganglion morphology, may occur in the same segment of the GI tract in different species, or in different experimental models such as undernourishment protein and renutrition[40,41], obesity[42,43], ischemia and reperfusion[44-47], and intestinal inflammation[23,48-52].

About IBD specifically, they are classically classified into UC and CD, disorders that chronically and recurrently affect the GI tract[1-4]. Inflammatory reactions in the intestinal mucosa cause epithelial damage that compromises the intestinal barrier[53]. Although the etiology of IBD is not yet fully understood, they are usually triggered by a complex relationship between genetic[5,6], immunological and environmental factors[7-10], and gut microbiota itself[11-15]. There is, then, an imbalance between anti- and pro-inflammatory cytokines that cause an exacerbated and inadequate immune response. It is emphasized that, in colitis, there are alterations in the neuronal density such as imbalances of contractile and secretory functions associated with diarrhea due to intestinal inflammation[20,49,50,52].

CD is characterized by a segmental and transmural disorder that can affect the entire GI tract, and it could be noted there is also involvement of T-auxiliary cells (TCD4) in the pathogenesis of the disease [54,55]. In contrast, UC is characterized by continuous inflammation of the distal colon and a modification of the cytokine profile coming from Th2 cells, involved in humoral immune response patterns[2,56]. The main clinical manifestations of IBD are abdominal pain, diarrhea, vomiting, weight loss, and the presence of blood in the stool[2,50] and, worryingly, it has been demonstrated that this occurrence has increased worldwide over the years[57-60].

The literature has shown that the ENS may be affected by the IBD, thus presenting necrosis, apoptosis and degeneration of enteric ganglia[19-23]. Similarly, alterations in neurotransmitters and neuropeptides of enteric neurons have been noted in these pathologies[19,48]. Furthermore, injuries in the ENS result in activation of enteric glial cells[61,62], and the onset and/or progression of IBD can be attributed to an immune-mediated damage of enteric glial cells[32]. This activation is pointed to as a signaling mechanism that results in subsequent neuronal death[63].

The diversity of neurotransmitters and receptors found in the ENS makes the intestine one of the main tissue choices for studies of neurotransmitter receptors in pharmacological tests. In turn, several ENS-related treatment strategies have been explored to alter gut function in an effort to improve symptoms, which include drugs targeting opioid, serotoninergic, dopaminergic, and cholinergic receptors[64].

Induced colitis models in the laboratory has been widely used to study intestinal inflammation, especially through dextran sulfate sodium and 2,4,6-trinitrobenzene sulfonic acid[65-69]. Despite this, the cell signaling mechanisms underlying neuronal and tissue damage are poorly understood[49,70], and new therapeutic approaches for IBD are emerging[71-74].

As expected, experimental animal models of colitis, enteric neuronal hyperplasia and hypoplasia may be associated with increased and reduced levels of TNFα production, respectively[75,76]. In addition,

hypertrophy and hyperplasia of enteric neurons have been reported in IBD[77]. Although, the mechanism responsible for neuronal modulation of inflammation severity is still unclear, due to modulations of neuroimmune interactions, it is speculated that enteric neurons could produce and regulate cytokines involved in IBD[76].

TNFR

Specific markers have been identified in GI tract when tissues are affected by injury or disease such as IBD. They are responsible for mucosal injury and tissue damage and consequently may trigger autoimmune disease - specific immune responses in UC[10]. The TNF-α, inducible nitric oxide synthase, heme oxygenase 1, arginase-1 or CD206 in higher levels can lead to massive tissue damage in the intestine[25,54,78].

TNF-α is a mediator in intestinal inflammatory processes, being one of the main cytokines involved in pathogenesis of IBD, since their levels, are frequently high in patients with IBD[24,25]. TNF-α was first described in 1975 by a group in Sloan-Kettering who identified TNF as a promising serum soluble activity[79]. Thus, TNF-α plays roles in promoting inflammation such as the production of interleukins (IL) such as IL-1β and IL-6[10,80]. In the central nervous system (CNS), TNF-α plays homeostatic roles by regulating crucial physiological processes, such as synaptic plasticity, learning and memory, sleep and food and water intake[81]. However, some findings demonstrated that overexpression of TNF in the CNS has negative effects on cognitive functions and TNF deficiency is related to learning processes and poor memory[82]. In addition, it may be involved in gliosis and tissue remodeling and in various processes about mechanisms subserving cognition, such as synaptic scaling, change in neurotransmitter metabolism, and the process of neurodevelopment[82,83]. This observation may pave the way for understand mechanisms of innate immunity and the pathogenesis of infectious diseases which are driven by the same cascade of pro-inflammatory cytokines[79].

TNF-α is mainly generated by macrophages and monocytes. However, other cells such as some subsets of T cells, NK cells, dendritic cells, B cells, cardiomyocytes, fibroblasts, and astrocytes are also low-level producers of this cytokine[84]. In pathological conditions, astrocytes and microglia release large amounts of TNF-α, seeing that the production of this cytokine is an important component of the neuroinflammatory response that is associated with various neurological disorders such as Alzheimer's, Parkinson's, multiple sclerosis and amyotrophic lateral sclerosis[81].

TNF-α operates significantly in the apoptotic phase increasing the expression of the TNF receptor-associated factor 2 (TRAF2)[53]. Furthermore, TNF-α activates mitogen-activated protein kinase and nuclear factor which contribute to cell differentiation and proliferation and increased expression of pro-inflammatory cytokines[10]. Two distinct forms of TNF-α were identified: 26kDa homotrimeric transmembrane precursor form (mTNF), which is cleaved by the TNF-α-converting enzyme, and matrix metalloproteinase (TACE/Adam17) to its next 17kDa TNF soluble form (sTNF) of monomers[85,86]. Both forms of TNF are biologically active and are signaled through two distinct receptors discussed below.

There are two receptors for TNF being: The 75 kDa TNFR1, ubiquitously expressed and has a cellular death domain; and the 55 kDa TNFR2 has been found in lymphocytes and endothelial cells. Interactions of TNF-α with its receptor activate signaling pathways for cell survival, death and differentiation that control immune function and disease, and various receptors pairs of ligands within TNF family molecules expressed by immune cells that play important roles in T cell Immunity[26].

When TNF-α binds to TNFR1 and TNFR2, several intracellular pathways are activated, thus mediating cell death and/or survival response (Figure 1). When TNF-α binds to TNFR1, TNF receptor associated death domain protein (TRADD) is activated which, in turn, can induce the activation of three signaling pathways. In the first one, after TNFR1 activation, TRADD binds to FAS-associated death domain protein, which recruits caspase 8 proteins, culminating in the activation and cleavage of caspase 3, as well as leading to cell death by apoptosis[87]. The second TNFR1 pathway is related to the recruitment of TRAF2 and receptor-interacting protein (RIP) kinase *via* TRADD. TRAF2, in turn, recruits the IκB kinase (IKK) protein, which will be activated by RIP and will result in the phosphorylation of nuclear factor κB (NF-κB), which will mediate the transcription of proteins involved in the inflammation response and cell survival[87,88]. The third pathway resulting from TNFR1 activation is connected with activation of mitogen-activated protein kinase (MAPK) pathways *via* TRAF2, which activate MAPK kinase kinase 1/4 (MEKK1/4) and, upon phosphorylation, MEKK4/7 leads to activation of c-Jun N-terminal kinase, which is translocated to the nucleus and activate transcription factors such as activator protein 1 (AP-1), that can converge to activate the apoptotic and survival responses[89-91].

Although the pathways behind TNFR2 activation remains poorly understood, when the TNF-α binds to TNFR2, its activation is mediated by TRAF2, and TNFR2 has been widely known as a mediator of the activation of genes related to cell survival and proliferation[91-93]. After TNF-α binds to TNFR2, TRAF2 is activated which, through common signaling pathways to TNFR1 activation, can activate NF-κB through IKK, and AP-1 *via* MEKK, which can also be activated *via* apoptosis signal-regulating kinase 1 [94]. Furthermore, activation of TRAF2 *via* TNFR2 can lead to the recruitment of cellular inhibitor of

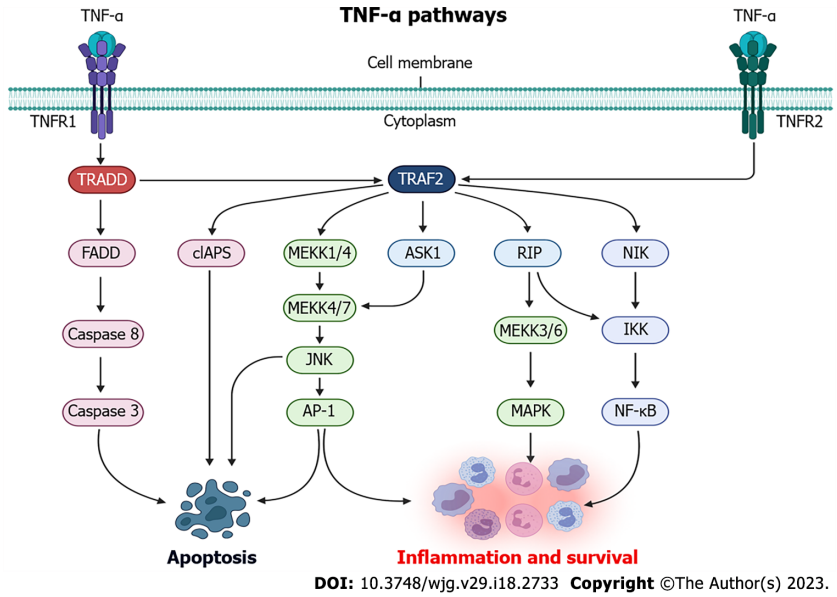

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Figure 1 Tumor necrosis factor-alpha signaling pathways. TNF-α: Tumor necrosis factor-alpha; TNFR1: Tumor necrosis factor receptor 1; TNFR2: Tumor necrosis factor receptor 2; TRADD: TNF receptor associated protein with death domain; FADD: FAS-associated death domain protein; cIAPS: Cellular inhibitor of apoptosis; MEKK: MAPK kinase kinas; JNK: N-terminal jun kinase; ASK1: Apoptosis signal-regulating kinase 1; IKK: IκB kinase; NF-κB: Nuclear factor κB; RIP: Receptor-interacting protein kinase. Created with BioRender.com.

apoptosis (cIAPS), which will partially inhibit caspase activation and, for this reason, reduce apoptosis response[95]. When both TNFR1 and TNFR2 are activated together, cIAPS recruitment is reduced and the caspase activity, mainly mediated by TNFR1, is activated[91].

These receptors are involved in the pathogenesis of IBD and their expression is correlated with disease activity[96]. The sTNf binds selectively to the TNFR1 receptor, and its activation results in a signaling cascade with effects such as apoptosis, cell proliferation and cytokine secretion[24,97]. In contrast, the mTNF can bind both to TNFR1 and TNFR2[91]. TNFR1 signaling pathways deserve attention, due to cytotoxic effects triggered by activation of TNFR1 *via* sTNF binding and it could be noted that some aspects regarding TNFR2 function are still unclear[91].

Some studies pointed to the presence of a functional cross-talk between TNFR1 and TNFR2, whichever TNFR2 would act as an complement-dependent cytotoxic effect of TNFR1, thus being responsible for the inhibition of anti-apoptotic pathways and for the increase in the cytotoxicity triggered by TNFR1 when both receptors are co-expressed and activated[91,98,99]. This finding could be seen as a distinct situation of the classic phenomenon in which the balance between apoptotic and anti-apoptotic signals triggered by TNF-α determines the accuracy in cell signaling[91].

The TNFR2 pathway does not contain death domains and its stimulation can result in proliferation, migration and production of cytokines such as IL-1 and IL-6. This receptor not only activate an intracellular signaling pathway, but can also induce reverse signaling within the cell expressing TNF-α [100].

TNFR2 is also involved in several autoimmune diseases, playing a protective role or being involved in its development. Thus, TNFR2 is known to be involved in rheumatoid arthritis, CD, erythematosus systemic lupus, UC, scleroderma, among other diseases[10]. It was recognized that the expression of TNFR2 is more limited than that in TNFR1, *i.e.*, this finding suggests that the sTNF-mediating signaling pathway *via* TNFR1 drives a predominantly pro-inflammatory program, whereas mTNF binding to TNFR2 primarily initiates immune modulation and tissue regeneration[84]. Thus, an increase in TNF-α expression can cause mucosal barrier defects in patients with IBD, exacerbating inflammation[10]. However, only a part of the role of TNF-α receptors in the pathogenesis of IBD is understood. It is known that it can be indicated the presence of TNFR2 in the CNS, *i.e.*, in neurons of the cerebral cortex [83], and no data in the literature could identify the presence of TNFR2 in enteric neurons.

ANTI-TNF-α TREATMENT

The immune response plays an important role in the initiation and maintenance of UC[101]. Cytokines play key roles in inflammatory processes, such as targeting cell signaling molecules during inflammation and UC pathogenesis through different roles, such as the production of inflammatory mediators and activation of inflammatory pathways[5,57,102,103]. They are also involved in several biological processes, such as cell activation, differentiation and central factors in the process of developing the

inflammatory and immune response. In addition, studies provide evidence of their involvement in epithelial injury, and consequently, intestinal barrier injury and tissue damage[5,104,105].

The treatment approach in the control of inflamed GI tissue in IBD, including clinical, laboratory conditions, endoscopic and histological remission for a prolonged period, play an important role in its evolution and possibly modifying the natural course of the disease[9,106]. Recent studies have suggested that TNF-α is one of the main pro-inflammatory cytokines involved in the pathogenesis of IBD, as higher TNF-α levels are present in the serum of both patients with UC and CD[25].

For the treatment of IBD, different classes of drugs can be used, respecting the particularities of CD and UC, with the aim of alleviating the symptomatic crisis of patients, as well as inducing and maintaining remission of the disease[107,108]. Generally, the first treatment option for mild to moderate cases of UC and CD involves aminosalicylates, or 5-ASAs, and other treatments include the use of corticosteroids, immunosuppressants, and biological drugs[109,110].

Biological drugs used to treat IBD are monoclonal antibodies that neutralize/block key targets in the development of intestinal[27]. There are biological drugs that target, for example, integrins, interleukins, and cytokines, such as TNF-α, which are related to the development of the inflammatory process and the activation of immune system cells (Figure 2)[111,112].

Currently, four anti-TNF-α agents are indicated by various guidelines for the treatment of IBD: Infliximab; adalimumab; certolizumab pegol; and golimumab[28,29]. Infliximab and adalimumab are indicated for the treatment of both UC and CD, while golimumab is indicated only for the treatment of UC and certolizumab pegol only for CD. American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) guidelines recommend the use of infliximab, adalimumab, and certolizumab pegol to induce and maintain CD remission in moderate to severe patients unresponsive to corticosteroid or methotrexate treatment, and regarding UC, it could be noted that AGA and ACG recommend the use of infliximab, adalimumab and golimumab in patients who have not responded to conventional therapy[28,29]. These anti-TNF-α antibodies bind to TNF-α, blocking its harmful effects, such as NF-κB activation and increase of pro-inflammatory cytokines, that mediate intestinal inflammation[113,114].

Intravenous and subcutaneous biologics targeting TNF-α have revolutionized the treatment of IBD, becoming the best available agents, when conventional therapy does not work, to induce and maintain IBD remission[115-117]. The application of this type of antibodies in patients with IBD induces a satisfactory clinical response in up to 60% of patients, and induced long-term maintenance of disease remission in most patients[24,30] and also reduces colorectal cancer risks[118]. Despite this, some patients do not improve after the use of these antibodies, some relapses within the first year of treatment and, one alternative used for the management of these cases has been to change the anti-TNF-α used for another one, or even to increase the dosage used[119]. Other alternative option for anti-TNF-α non responsiveness is the use other biological medicines like anti-integrin or anti-interleukin therapies.

Anti-integrin therapy, such as vedolizumab, which can be used for UC and CD treatment, block the integrin α4β7, which is expressed in B and T lymphocytes and interact with mucosal addressin-cell adhesion molecule-1 on intestinal vessels[120-122]. So, vedolizumab blocks lymphocyte trafficking only in the gut, preventing a systemic immunosuppression[123]. Otherwise, natalizumab blocks the integrin α4β7 and α1β7 and blocks lymphocyte trafficking in other organs, for example the brain, which can lead to infections such as progressive multifocal leukoencephalopathy[124]. For this reason, the use of natalizumab is very carefully, considering risk-benefits factors, and it is not available in some countries. Other biological medicine is ustekinumab, an anti-interleukin agent for subunit p40 of IL-12 and IL-23, used for CD and UC. This biological medicine attenuates the immune cell activation by these interleukins and consequently reduces inflammatory response and pro-inflammatory signaling[125-127].

Limitations of therapy with biological drugs include the high cost of adherence to therapy, differences in legislation and availability of these drugs in different countries, and the meticulous risk-benefit analysis related to the choice over treatment alternatives. However, new strategies and medicines have constantly been studied at pre-clinical and clinical instances for treatment of IBD.

ANTI-TNF-α TREATMENT AND APPROACH IN THE ENS

Although the involvement of TNF-α in the ENS is poorly described in the literature, it is reported that the ENS has TNF-α receptors and responds to the inflammatory stimulus, can lead to changes in motility patterns and fluid and electrolyte balance, a condition often found in patients with IBD[128]. When comparing the intestine, under normal conditions, and the intestine in IBD, some aspects must be considered (Figure 3). Under physiological conditions, large populations of microorganisms (bacteria, virus and fungi) inhabit the gut, which constitute the gut microbiota[129]. This microbiota establishes a symbiosis with the host[130]. The intestinal barrier, composed mainly by mucus layer and epithelial, is an intact and functional structure[131]. There is a balance between the levels of pro-inflammatory cytokines TNF-α, IL-12 and IL-23, and anti-inflammatory cytokines such as transforming growth factor-beta and IL-10 by innate immune cells, which leads to a balance between regulatory and effector T cells,

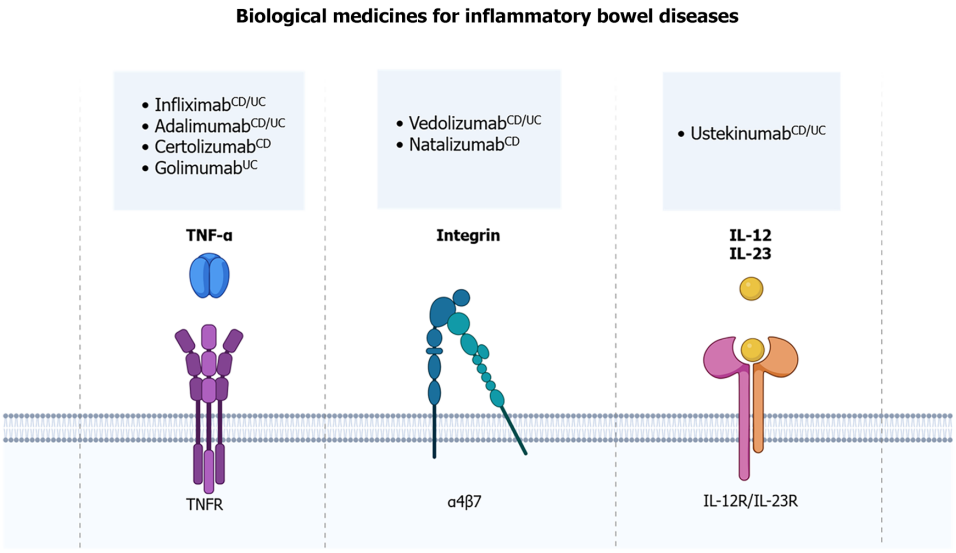

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Figure 2 Biological medicines for inflammatory bowel diseases. Biological medicines used for the treatment of inflammatory bowel diseases (IBD) can be classified into anti- Tumor necrosis factor (TNF)-α, anti-integrin and anti-interleukin therapies. Anti-TNF-α binds to TNF-α and inhibits TNF receptor activation. Infliximab, adalimumab, certolizumab pegol and golimumab are examples of anti-TNF-α used in the treatment of IBD. Vedolizumab and natalizumab are anti-integrin agents, which bind to the α4β7 integrin and prevent the migration of inflammatory cells into the intestinal tissue. Ustekinumab is an anti-interleukin that blocks interleukin (IL)-12 and IL-23, which cannot bind to IL-12 receptor and IL-23 receptor on T and B lymphocytes, thus reducing the inflammatory response in the gut. ^{CD}indication only for Crohn's Disease; ^{UC}indication only for Ulcerative Colitis; $^{CD/UC}$indication both for Crohn's Disease and Ulcerative Colitis. TNF-α: Tumor necrosis factor-alpha; IL: Interleukin. Created with BioRender.com.

inducing tolerance to microorganisms from the gut microbiota[130,132]. In physiological conditions, both submucosal plexus and myenteric plexus are functional and controls, respectively, fluid secretion and intestinal motility.

In IBD, there is an imbalance in the gut microbiota (dysbiosis), the intestinal barrier is compromised, with a reduction in the mucus layer, weakening of the intercellular junctions and consequently increased epithelial permeability and entry of microorganisms in the lamina propria[15,133]. Innate immune cells increase the secretion of pro-inflammatory cytokines such as TNF-α, IL-12 and IL-23, which leads to a dysregulation of the immune system, which increases the activity of effector T cells which, in turn, recruit cells for the inflammatory response[134]. Morphological findings include submucosal edema, as well as a reduction in the number of neurons in the SMP, causing changes in secretion patterns and loss of neurons in the myenteric plexus, thus changing the motility patterns[51,52,135].

Experimental UC has been shown to affect enteric neurons, causing changes in the number of enteric neurons and glia, as well as changes in intestinal motility and secretion patterns[50-52,136]. As the presence of TNFR1 and TNFR2 have been reported in the ENS, the use of anti-TNF-α agents can exert a series of beneficial effects on ENS levels, improving the inflammatory response, peristalsis and intestinal secretion patterns, relieving symptoms such as diarrhea, fecal bleeding and colic. However, despite the important approach to the ENS and its relationship with IBD, literature data on anti-TNF treatment with analysis focused on the ENS are scarce. Therefore, further studies on the role of mechanisms/signaling pathways of sTNF, mTNF, TNF-α and their receptors in enteric neurons in IBD are needed, since this approach can guide the choice of a more adequate, effective anti-TNF-α agent with lower chances of failure responsiveness.

CONCLUSION

This review provided main details about TNF-α relationship with IBD. The role of TNF receptors in the development of IBD is an issue that deserves attention and may be a key to the treatment of UC and CD. In addition, anti- TNF-α treatments have been very promising in the treatment of IBD unresponsive to conventional therapies. The relationship of the ENS with TNF-α and its response to anti- TNF-α treatment are important aspects to be addressed, as they may direct new therapies and reduce non-responsiveness to specific anti- TNF-α agents.

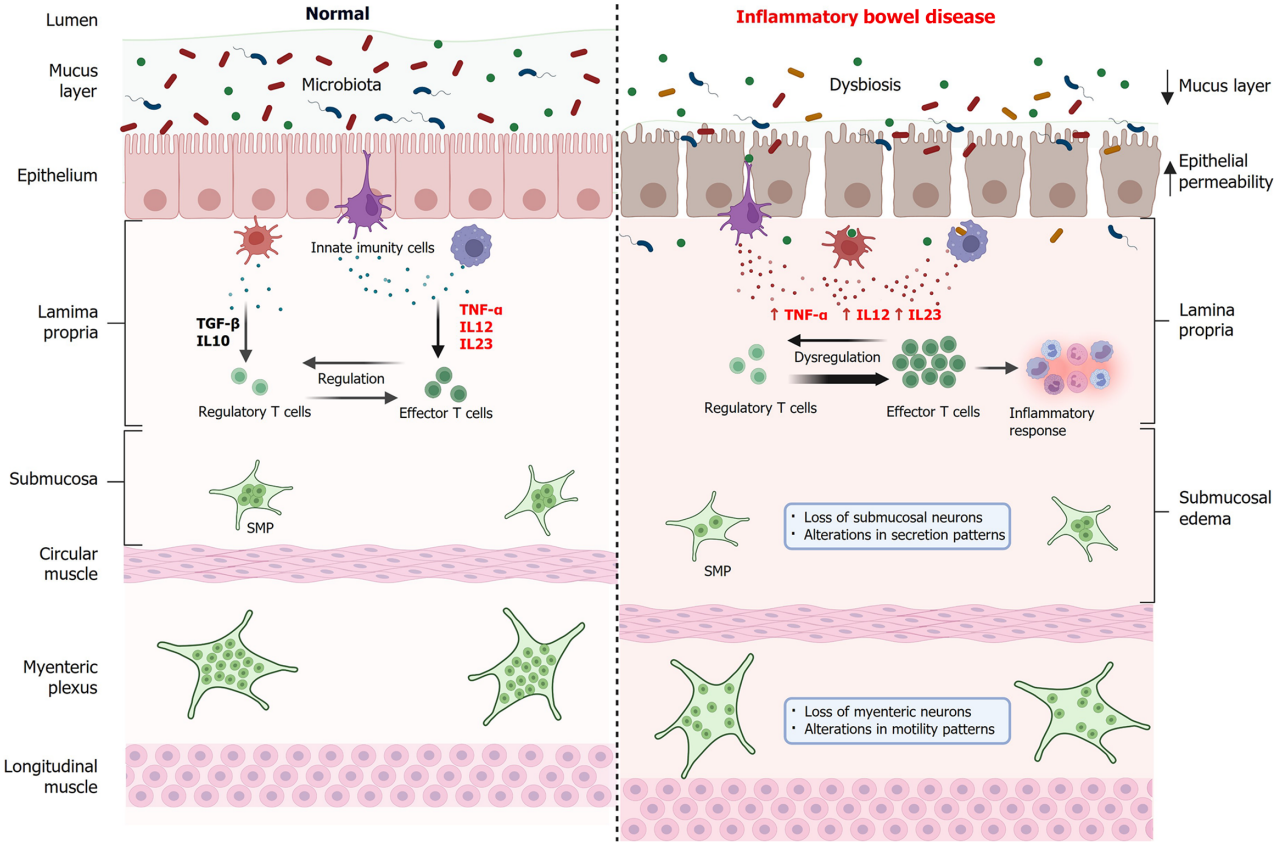

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Figure 3 Comparison of the intestine in normal conditions and in the bowel with inflammatory bowel disease. Under normal conditions (left), the intestinal microbiota establishes a symbiotic condition with the host, the intestinal barrier is intact and functional, and there is a balance between the levels of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-12 and IL-23 and anti-inflammatory cytokines such as transforming growth factor beta and IL-10 by innate immune cells. In this way, there is a regulation of the immune response through a balance between regulatory T cells and effector T cells. Submucosal plexus (SMP) and myenteric plexus neurons are functional and controlling, respectively, fluid secretion and intestinal motility. In inflammatory bowel diseases (IBD) (right), there is an imbalance in the intestinal microbiota, the intestinal barrier is compromised, with a reduction in the mucous layer, increased epithelial permeability and consequent passage of microorganisms to the lamina propria. Innate immune cells increase the secretion of pro-inflammatory cytokines such as TNF-α, IL-12 and IL-23, which leads to a dysregulation of the immune system mediated by T cells, increasing the activity of effector T cells which, in turn, recruit cells for the inflammatory response. In IBD, submucosal edema is observed, as well as a reduction in the number of neurons in the SMP, causing changes in secretion patterns and loss of neurons in the myenteric plexus, resulting in changes in motility patterns. TNF-α: Tumor necrosis factor-alpha; IL: Interleukin. Created with BioRender.com.

FOOTNOTES

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