Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis are complex disorders with undetermined etiology. Several hypotheses suggest that IBDs result from an abnormal immune response against endogenous flora and luminal antigens in genetically susceptible individuals. The dysfunction of the mucosal immune response is implicated in the pathogenesis of IBD. The balance between pro-inflammatory cytokines [tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-1\(b\), IL-8, and IL-17A], anti-inflammatory cytokines (IL-4 and IL-13), and immunoregulatory cytokines (IL-10 and transforming growth factors \(\beta\)) is disturbed. Moreover, evidence from animal and clinical studies demonstrate a positive correlation between an increased concentration of nitric oxide (NO) and the severity of the disease. Interestingly, proinflammatory cytokines are involved in the up-regulation of inducible oxide synthase (iNOS) expression in IBD. However, anti-inflammatory and immunoregulatory cytokines are responsible for the negative regulation of iNOS. A positive correlation between NO production and increased pro-inflammatory cytokine levels [tumor necrosis factor-\(\alpha\), IL-6, IL-17, IL-12, and interferon-\(\gamma\)] were reported in patients with IBD. This review focuses on the role of cytokines in intestinal inflammation and their relationship with NO in IBD.

**Key words:** Inflammatory bowel disease; Cytokines; Nitric oxide; Inducible nitric oxide synthase; Immuno-pathogenesis

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Soufli I, et al. Cytokines and nitric oxide in IBD

INTRODUCTION

Inflammatory bowel disease (IBD), represented primarily by ulcerative colitis (UC) and Crohn’s disease (CD) is a multifactorial condition characterized by the chronic inflammation of the gastrointestinal tract. It is widely accepted that IBD results from an uncontrolled mucosal immune response to intestinal microflora in genetically susceptible hosts[1,2]. The mechanisms underlying the deregulated immune response in IBD continue to be extensively investigated to understand the etiopathophysiology of this disease further and to identify new therapeutic strategies. The inflamed intestine of patients with IBD is massively infiltrated by inflammatory cells that release a large number of pro-inflammatory mediators, such as cytokines and nitric oxide (NO)[3].

NO is a free radical which has several physiological and pathological functions. It is generated from the oxidation of the amino acid L-arginine by a family of enzymes called the nitric oxide synthases (NOS). Three distinct isoforms of NOS are known: (1) two isoforms constitutively expressed in neuronal (nNOS); and (2) endothelial (eNOS) tissues; as well as an inducible isofrom (iNOS) expressed primarily by immune cells (e.g., macrophages)[4]. The constitutively expressed isoforms release low levels of NO that exert physiological functions, whereas iNOS releases a high output of NO production under immunogenic and inflammatory stimuli[5].

iNOS is highly expressed upon activation of the transcription factor nuclear factor-kappa B (NF-κB) in response to many stimuli including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-6, interleukin-1alpha (IL-1α), lipopolysaccharide (LPS), bacterial and viral components[4,5,6,7]. The protective actions of inducible NO have clearly been demonstrated. Its actions include protection against pathogens, reduction of leukocyte adherence, inhibition of macrophage activation, and the inhibition of Th1 type cytokines[8]. Substantial evidence suggests that INOS-induced NO exerts protective effects during acute experimental colitis[8,9]. However, in IBD, the high levels of NO released in the mucosa appear to be strongly implicated in the maintenance of the chronic inflammation. In this context, it has been shown that NO can cause tissue damage and an exacerbation of inflammation indirectly through the generation of peroxynitrite[6,12].

The dysregulated balance between pro- and anti-inflammatory cytokines, as well as the immuno-regulatory cytokines observed in IBD distinguish a distinct T cell profile in CD and UC. Classically, CD is described as Th1 type immune response characterized by the secretion of IFN-γ, IL-12, and TNF-α. In contrast, UC is viewed similar to an atypical Th2 type immune response which generates high levels of IL-5, IL-4, and IL-13[13,14]. In addition, several studies have shown the involvement of Th17 type cytokines (i.e., IL-17, IL-23, IL-22, and IL-6) in the pathogenic process of both CD and UC[15,16]. Interestingly, both Th1 and Th17 cytokines are involved in the up-regulation of NO expression in IBD. Indeed, a positive correlation between NO production and increased pro-inflammatory cytokine levels (e.g., TNF-α, IL-6, IL-17 IL-12 and IFN-γ) have been reported in IBD plasma[16,17].

Considerable research has been conducted over the past year to better understand the pathogenesis of IBD, and has led to the development of novel therapeutic strategies based on targeting cytokines, their receptors, as well as the modulation of NO. The assessment of NO production in IBD might be a useful inflammatory marker to predict the stage and the progression of disease[18]. Unfortunately, some of the current strategies have shown limited efficacy. Hence, a better understanding of the underlying mechanisms of the inflammation and the immune response in IBD may give rise to new alternative, complementary therapeutic strategies.

This review will address the cytokine involvement and relationship with NO in the immuno-pathogenesis of IBD.

NO AND IBD

NO is a lipophilic free radical which plays a key role in regulating the homeostasis of many biological systems. It is synthesized by NOS which catalyzes the oxidation of the terminal nitrogen of the amino acid L-arginine and produces L-citrulline and NO. Three NOS isoforms have been identified and characterized in humans and mice; their nomenclature respects the chronological order in which they were purified: (1) the neuronal form (nNOS or NOS1); (2) the inducible form (iNOS or NOS2); and (3) the endothelial form (eNOS or NOS3). nNOS and eNOS are termed constitutive NOS (cNOS) as they are calcium-dependent, and are respectively expressed constitutively in neuronal and endothelial tissues[18,19]. The effects of NO differ depending on the rate, duration, place of production, and the nature of the target molecules. Under physiological conditions, cNOS generate low levels of NO which have direct regulatory effects (e.g., neurotransmission and the regulation of blood vessels)[19]. In contrast, iNOS generates high levels of NO which mediates antimicrobial and antitumoral activities[19]. This isoform was first isolated in murine macrophages and was subsequently found in several other cell types, including epithelial cells, hepatocytes, endothelial cells, and fibroblasts. It is expressed after the...
induction by immunologic and inflammatory stimuli\cite{16,20-22}. However, when NO is produced in excess, it becomes noxious. It causes deleterious effects indirectly through the creation of reactive nitric oxide species (RNOS), such as peroxynitrite anion (OONO·−), the nitroxy anion (NO−) and dioxide nitrogen (NO2), responsible for the oxidative stress\cite{7,23}. Peroxynitrite, is a molecule with high oxidative potential that can trigger cytotoxic processes, such as lipid peroxidation and DNA damage leading to tissue damage and inflammation\cite{24}. NO has been implicated as a pathogenic mediator in a variety of conditions, such as Alzheimer’s disease, rheumatoid arthritis (RA), Behcet disease, multiple sclerosis (MS), Sjogren’s syndrome, and IBD\cite{25}.

The deleterious role of NO in IBD was proposed after clinical studies reported the presence of a high levels of nitrite/nitrate in the plasma, urine, and the lumen of the colon\cite{26-28}. Moreover, a correlation between the overexpression of iNOS, the increased concentration of NO, and the severity of diseases was shown\cite{29}. In fact, increased levels of NO were found in the serum, stool, and urine of patients in the active phase of UC and CD compared to those in the inactive phase\cite{26,29}. Our study\cite{16,17} showed significantly higher serum levels of NO in CD patients compared to UC patients. However, data from previous studies reported no significant differences between these two categories of disease, whereas higher systemic levels of NO in UC compared to CD was found\cite{16,17,26,29}. A significant difference was observed in the NO concentrations between the active and inactive phase of the disease. This observation suggests a possible use of serum NO levels for monitoring disease activity in both types of IBD\cite{16,26,29}.

While several studies conducted using animal models indicate the deleterious effect of NO, recent studies have shown that NO may also exert a protective effect against colitis\cite{29-32}. One study conducted using a DSS-induced colitis model found that nitrite administration exerts both preventive and therapeutic effects in colonic inflammation\cite{33}. More recently, iNOS deficiency enhanced the inflammation aggravation in an animal model of colitis through enhancing a Th17 differentiated subset\cite{34}.

**CYTOKINES IMPLICATED IN IBD**

The dysfunction of the mucosal immune response in IBD is characterized by abnormalities in both the innate and adaptive immune systems. The final common pathway of this dysregulated immune activation is an abundant infiltration of immune cells in the intestinal mucosa\cite{15,35-39}. These cells were found to release excessive proinflammatory mediators that amplify the inflammatory cascade through the activation of mitogen-activated protein kinases (MAPK) and NF-κB. Several studies have reported evidence of the contribution of cytokines, adhesion molecules, reactive oxygen metabolites (ROMs), and NO in mucosal inflammation and injury in triggering IBD\cite{30,41}. Cytokines are small soluble peptides which are produced by diverse immune and non-immune cells. They exert their biological functions through specific receptors activating the janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway that controls gene expression in target cells\cite{42}. In IBDs, the balance between pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-8, and IL-17), anti-inflammatory cytokines (e.g., IL-4 and IL-13), and immunoregulatory cytokines (e.g., IL-10 and TGF-β) is disrupted\cite{43}. According to the cytokine environment found in IBDs patients, CD and UC were conventionally associated with a different CD4+ helper T cell profile based on the Th2/Th1 paradigm. Thus, CD was described as Th1 type immune response promoted by the transcription factors STAT-4 and T-bet and characterized by the secretion of IFN-γ, IL-12, and TNF-α\cite{13,44}. Indeed, the studies conducted by our group and other teams produced high levels of IL-12 and IFN-γ in CD patients with active disease\cite{37,45}. IL-12 produced by macrophages/monocytes and dendritic cells plays a pivotal role in enhancing natural killer (NK) cell-mediated cytotoxicity. Moreover, it has been shown that both IL-12 and IL-18 induce a high levels of IFN-γ production leading to the reinforcement of the Th1 immune response\cite{14,45-47}.

In addition, TNF-α plays a pivotal role in the production of NO and enhances the production of metalloproteinases (MMP) leading to the loss of epithelial integrity\cite{48,49}. In contrast, UC is viewed as a Th2 type immune response promoted by the expression of the transcription factors STAT-6 and Gata-3, as well as the secretion of IL-5, IL-4, and IL-13. Furthermore, Fuss et al\cite{50} demonstrated that UC patients, unlike CD patients, have atypical natural killer T (NKT)-cells. These cells produce high levels of IL-13 and have cytotoxic activity toward epithelial cells. Similarly, studies using the experimental model of colitis induced by oxazolone have demonstrated that IL-13 produced by NKT cells is the driving cytokine of the disease. Indeed, IL-13 causes alterations of the epithelial barrier function by stimulating epithelial cell apoptosis and the downregulation of tight junction proteins.

Currently, the aforementioned classical concept of the pathogenesis of IBDs is reconsidered with the strong involvement of Th17 cells. This subset of CD4+ T helper cells is promoted by the activation of the transcription factors STAT-3 and retinoid-related orphan receptor gamma (ROR-γt) and is characterized by the production of IL-17A, IL-17F, IL-22, IL-21, IL-6, and IL-26, as well as the chemokine CCL20\cite{51,52}. Several pieces of evidence support the implication that Th17 cells in the intestinal mucosa provide protection against invading pathogens (e.g., Candida and Salmonella), through the chemotaxis of neutrophils and the stimulation of antimicrobial peptide production by epithelial cells\cite{53}. However, both in CD and UC, high levels of Th17 cytokines have been found in the serum and inflamed mucosa. Increased IL-17A production can drive and aggravate the chronic inflammatory response\cite{17,54,55}. More recently, another subset of Th17 cells, Th1/Th17 cells producing both IFN-γ and IL-17 has been identified in the ileal form of active CD and experimental models of colitis\cite{56-58}. In addition, it
has been reported that Th17 induces the production of a high levels of TNF-α, IL-1β, chemokines (IL-8), and matrix metalloproteinases (MMP) (e.g., MMP-9). Moreover, the expression of the cytokine IL-23 and chemokine CCL20, a chemoattractant for Th17 cells expressing the receptor CCR6, is highly up-regulated in CD lesions. Additionally, IL-23 is a crucial effector cytokine necessary for the stabilization and expansion of Th17 cells. It enhances the expression of the master transcription factor (RORγt) following IL-6 and tumor growth factor-beta (TGF-β) stimulation[46]. Moreover, it plays an important role in the development and propagation of the inflammatory response in the gut by inhibiting the expression of the transcription factor Forkhead box P3 (Foxp3) and the development of T regulatory cells (Treg)[15,46].

The Th17/Treg balance plays an essential role in maintaining intestinal homeostasis. The immunoregulatory cytokine, TGF-β orchestrates the differentiation of Th17 and Treg cells in a dose-dependent manner. In the presence of high levels of IL-6 and inflammatory mediators, TGF-β promotes the differentiation of Th17 cells. Conversely, high levels of TGF-β and low levels of IL-6 and inflammatory mediators promote the development of inducible Foxp3+Treg cells (iTreg)[50-61]. Regarding the pro-inflammatory role of IL-6, elevated levels of this cytokine and its soluble receptor, sIL-6R were found in the colonic mucosa and sera of patients with IBD. Compelling evidence in human and in animal models has shown that IL-6 plays an important role in maintaining a chronic response by promoting the accumulation of T cells resistant to apoptosis. In addition, IL-6 induces the production of IFN-γ, TNF-α, and IL-1β, and increases the expression of adhesion proteins, such as intercellular adhesion molecule-1 (ICAM-1) protein which participates in the migration and activation of inflammatory cells to the intestine[62,63].

It is well established that ongoing inflammation in CD and UC is mediated by uncontrolled T cell responses. Altered Treg regulatory mechanisms have been documented in IBD. However, it remains unclear whether this defect is due to a numerical lack of Treg or a defective TGF-β and IL-10 immunoregulatory activity[64,65]. Interestingly, it has been shown that in the inflamed colon of CD patients, there is a common CD4+ T cell population which co-expresses both Foxp3 and RORγt. This resident Treg population exhibits plasticity towards Th17 in an inflammatory environment. The Treg/Th17 balance is tightly regulated by intestinal factors, such as endogenous microflora as well as the presence of retinoic acid. Indeed, it has been reported that the vitamin A metabolite, retinoic acid promotes Treg differentiation while inhibiting the formation of Th17 cells[66]. Thus, these data support the involvement of an altered intestinal microenvironment in the development of IBD and the rupture of gut homeostasis.

Other studies conducted on IBD experimental models reported the implication of other cytokines with an immunomodulatory role [e.g., IL-25, thymic stromal lymphopoietin (TSLP), and IL-22], thereby paving the way for new therapeutic strategies in IBD[67-69].

**CYTOKINE REGULATION OF NO IN IBD**

The inflamed tissue of patients with active IBD is characterized by a massive infiltration of immune cells that release several pro-inflammatory mediators and produce high, de novo levels of NO. The expression of iNOS is highly regulated at both the transcriptional and post-transcriptional level by several pro-inflammatory cytokines and immunogenic stimuli (e.g., LPS)[60,70].

In both patients and animal models of IBD, a positive correlation between the overproduction of pro-inflammatory cytokines (e.g., IL-1β, TNF-α, IFN-γ) and an overexpression of iNOS was found. This expression was primarily detected in the lamina propria mononuclear cells and the colon epithelial cells of the inflamed mucosa[6,16,17,27,30,71,72]. Several studies conducted on a dextran sulfate sodium (DSS)-induced experimental model of colitis in BALB/c mice indicated that the neutralization of endogenous TNF-α and/or IFN-γ ameliorated the chronic colitis and concomitantly decreased the generation of NO. These data support the fact that IFN-γ and TNF-α are both involved in the exacerbation of DSS-induced colitis and may exert their detrimental role in the colonic mucosa partly through the induction of the high output of NO. These cytokines had an additive effect on the severity of histological damage and NO colonic levels. However, it seems that IFN-γ is the most potent inducer of iNOS in macrophages and epithelial cells than TNF-α, since its neutralization was more effective in attenuating the experimental colitis[30].

Moreover, our studies reported an up-regulation of iNOS expression in the inflamed colonic mucosa which correlates with high systemic levels of NO, IFN-γ, and IL-12. These observations suggest that IFN-γ and IL-12 may play a pivotal role in IBD pathogenesis through the NO pathway[16]. Human peripheral blood mononuclear cells (PBMC) from IBD patients were shown to produce elevated levels of NO compared to the controls. The proinflammatory cytokines: IFN-γ, IL-6, TNF-α, and IL-1β stimulate NO production in vitro in PBMCs from patients with CD and UC, suggesting that human PBMCs may constitute another cellular source of NO in IBD[16,17]. Interestingly, this work reported a positive correlation between Th17 cytokines including IL-6, IL-23, IL-17A, and NO production in the plasma of patients with IBD. Moreover, the mucosal alterations were strongly correlated with high NO2 and pSTAT3 expression in the colonic mucosa of patients with active IBD. These observations suggest that IL-17 may be a potent inducer of iNOS expression in the inflamed mucosa of IBD patients leading to the exacerbation of the tissue damage. The mechanism by which IL-17 induces NO production is likely dependent on the expression of NF-κB. In this context, in vitro studies using osteoclast cells showed that IL-17 induced the high expression of the mRNA of the NF-κB isoform RelA et p50[73].

The negative regulation of iNOS could be achieved by Th2 derived cytokines (e.g., IL-13, IL-4). The inhib-
Cytokines play a crucial role in the pathogenesis of CD and UC as they orchestrate many aspects of intestinal inflammation. A disturbance balance between proinflammatory and immunoregulatory cytokines has been reported in IBD. High levels of proinflammatory cytokines detected in the mucosa of patients with IBD induce a decrease in NO-derived iNOS production.

A decrease in NO and iNOS activity has been closely associated with the initiation and maintenance of inflammation in human and experimental IBD. Evidence suggests that immunoregulatory and anti-inflammatory cytokines (e.g., IL-10, IL-13, and TGF-β) modulate the pro-inflammatory cytokine-derived iNOS expression and activity in intestinal inflammation, thus contributing to the maintenance of homeostasis in gut inflammation. In this context, several studies suggest that pro-inflammatory cytokines might be an important target for the modulation of intestinal inflammation. Moreover, studies using experimental models of IBD have led to a better understanding of cytokine involvement in the pathogenesis of IBD and have opened new lines of research based on their therapeutic relevance. To date, anti-TNFα is one of the most effective cytokine-based therapies for IBD. Nevertheless, several data have shown that the existence of a network of cytokines with multi-layered responses are involved in the perpetuation of the diseases and tissue injury. Therefore, it becomes rational to consider the possibility of simultaneous neutralization of more than one cytokine to provide long-term control of inflammation.

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Souffi I et al. Cytokines and nitric oxide in IBD

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