Review Article

Immunopathogenesis of Ulcerative Colitis and Crohn's Disease

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I N F O

A B S T R A C T

Crohn's disease and ulcerative colitis are two forms of inflammatory bowel disease, caused by an altered mucosal immune response, and characterized by chronic inflammation of the gastrointestinal tract, augmentation of pro-inflammatory mediator production, and reduction of those with anti-inflammatory effects, as well as by upregulation of the expression of chemokines and adhesion molecules, thus promoting cell infiltration into the inflamed tissue, which finally leads to epithelial cell apoptosis and mucosal damage.

Keywords: Ulcerative Colitis, Crohn's Disease, Microbiota

Introduction

The ability of the gastrointestinal tract to act as a barrier against potentially harmful molecules and to defend against pathogenic bacteria is essential for the maintenance of intestinal immune homeostasis as it is regularly exposed to an enormous load of foreign antigens, various microorganisms and toxic molecules.[1] Gut-associated lymphoid tissue protects the intestinal mucosa from the intestinal antigens by producing secretory IgA, Transforming Growth Factor (TGF)-β, and Interleukin (IL)-10, which are immuno-suppressive cytokines.[2] The epithelial layer is covered in a mucus layer packed with antimicrobial peptides preventing most microbes from ever getting close to the epithelial lining.[3]

Ulcerative Colitis (UC) and Crohn Disease (CD) are chronic nonspecific Inflammatory Bowel Diseases (IBD). The number of patients suffering from these diseases has been increasing all over the world, especially in West Europe and North America.[4] The highest incidence rates and prevalence of IBD have been reported from North America, northern Europe, and the UK, where the rates are beginning to stabilise. Rates continue to rise in low-incidence areas such as southern Europe and Asia.[5] Ulcerative colitis is a disease mainly involving the rectum and the colon. However CD is a disease mainly involving the colon and/or the terminal ileum. Pathogenesis of IBD is not fully clarified, but the combined association of environmental factors, disease susceptibility genes, and dysregulated immune reaction is very important for the pathogenesis of IBD.[4]

Aetiology of IBD

There are a many divergent suppositions about the possible causes of IBD.[6] The exact cause of IBD is still unknown, but is thought to be due to a combination of a patient's genetics, immune response, microbiome, and the environment that result in an uncontrolled and excessive immune response against commensal flora in genetically susceptible individuals.[7] There is an agreement that none of these components can by itself triggers or maintain intestinal

Bribi N et al.
Int. J. Adv. Res. MicroBiol. Immunol. 2019; 1(1)

46

inflammation but it is their integration and reciprocal influence what determines whether IBD will emerge and with which clinical phenotype. The etiology of IBD is the results of a combination of many immunological factors in which an uncontrolled immune response within the intestinal lumen leads to inflammation in genetically predisposed individuals. Damage to the epithelial gut mucosa in IBD has been linked to elevated levels of effector immune cells such as activated CD4^{+} and CD8^{+} cytotoxic T cells, perforin, and cytolytic intraepithelial lymphocytes (IELs).[8,9,10] Environmental factors are essential components of the pathogenesis of IBD. Epidemiological, clinical and experimental evidence support an association between IBD and a large number of seemingly unrelated environmental factors, which include smoking, diet, drugs, geographical and social status, stress, microbial agents, intestinal permeability and appendectomy.[8-1]

Microbiota Factors

The gut is exposed continuously to a diversity of food components, antigens, commensal microflora, and pathogens.[12] The major environmental factors implicated in the pathogenesis of IBD are commensal bacterial flora. [13] The gut microbiota is dominated by members of the phylum *Firmicutes* and *Bacteroidetes* and, to a lesser extent, members of the *Actinobacteria* phylum. Also, the *Actinobacteria*, *Bifidobacterium* and *Collinsella* are the more abundant ones. They modulate the expression of genes involved in several important intestinal functions, including nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, angiogenesis, and postnatal intestinal maturation. This symbiotic relation is established during the first 2-3 years of life. Primary colonisation is orderly, with aerobic species predominating first, followed by anaerobic species, with the timing and composition of these microbial successions being influenced both by the mother and the environment.[5-14] The interaction of the host with its abundant microbiota is complex. Altered barrier function subsequently induces the translocation of microbial products and commensal bacteria from the gut lumen into the bowel wall, which leads to immune cell activation and cytokine production. If acute mucosal inflammation cannot be resolved by anti-inflammatory mechanisms and the suppression of pro-inflammatory immune responses, chronic intestinal inflammation develops. In turn, chronic inflammation may cause complications of the disease and also tissue destruction, which are both driven by mucosal cytokine responses.[7-15]

Crohn's disease is generally characterized by increased permeability of the intestinal barrier that can promote translocation of bacteria across the intestinal mucosa. It is also associated with an increase in Gram-negative bacteria in the intestinal mucosa and a decrease in potentially beneficial bacterial species (dysbiosis). Most of the genes currently recognized as implicated in CD pathogenesis are related to interactions between bacteria and the immune system leading to a leaky epithelial barrier and altered mechanisms of phagocytosis and autophagy.[16]

Immune response in IBD

The innate immune response plays a critical role in IBD. Macrophages and activated Dendritic Cells (DC) release several mediators and cytokines that actively regulate the inflammatory response in CD and UC. Once secreted by these Antigen Presenting Cells (APC), these cytokines trigger and differentiate many T cells activating the adaptive immune response. IBD has also a T cell dysregulation where clearance of overreactive and autoreactive cells is disturbed, in addition to an imbalance of Treg/Th1, Th2 and newly described Th17 cells populations in the activated state. CD and UC patients have increased levels of several pro-inflammatory cytokines such as TNF-α and IL-6 involved in adaptive and innate immune responses, additionally, the altered mucosal immune response, is characterized by augmentation in the expression of adhesion molecules and chemokines.[4-17-18]

The studies of the inflamed mucosa from patients with UC and CD also revealed the increased expression of some pro-inflammatory cytokines. In addition, various lipid mediators of inflammation and chemokines are also produced. Recruitment of blood-borne effector cells is mediated from the activated endothelium through adhesion molecules and chemokines, which are both upregulated by IFN-γ, TNF-α, and IL-1. This activity leads to amplification of the inflammatory cascade and secretion of more inflammatory mediators, destructive enzymes, and free radicals that cause tissue injury and are implicated in the pathogenesis of fibrosis, mucosal permeability, and diarrhea. Intestinal inflammation in CD is oriented to a T helper Th1 and Th17 immune response, characterized by an enhanced expression of IL-12/IL-23 and IFNγ/IL-17. However, UC shows a continuous mucosa-limited inflammation, primarily affecting the colon, oriented to a Th2 response and an excess of IL-5 and IL-13 production. The immunological response in UC has been described as Th2-atypical because of the absence of IL-4, detected in colonic biopsies of patients with UC. Furthermore, recent findings indicate that mature human CD4^{+} T cells are not inflexible lineages and may modulate the expression of different cytokines with respect to a particular inflammatory environment.[9-19]

In IBD, the loss of immune tolerance toward the enteric flora it is mediated by different molecules.[17] Currently, the pathogenesis of UC and CD is not completely understood, although the chronic relapsing inflammation is thought to be result from a dysregulated, aberrant immune response to intestinal flora in a context of genetic predisposition. Th1

47

Bribi N et al.
Int. J. Adv. Res. MicroBiol. Immunol. 2019; 1(1)

lymphocytes coordinate the inflammation in IBD mainly via production of TNF-α, which increased production of IL-1β and IL-6, proliferation of fibroblasts and pro-coagulant factors, and initiation of cytotoxic, and apoptotic. TNF-α is an agonist of the p38 and c-Jun N-terminal Kinase (JNK) cascades, two important Mitogen-Activated Protein Kinase (MAPK) pathways of inflammatory responses. IL-1α and IL-1β are produced and secreted by monocytes, macrophages, neutrophiles, and endothelial cells.[9-19] The overproduction of effector T cells participates in the development and exacerbation of IBD. Altogether, APCs, Th1, Th2, Th17, T regulatory cells, and their cytokine products play a complex role in IBD. These cellular interactions are modulated by both traditionally studied cytokines (TNF-α, INF-γ, IL-1, IL-6, IL-4, IL-5, IL10, and TGF-β) and others recently characterized (like IL-13, IL-12, IL-18, IL-23), considered to be either pro or anti-inflammatory.[17]

In patients with IBD, anti-inflammatory and pro-inflammatory cytokines have been shown to be produced by various cells of the mucosal immune system in response to environmental triggers, such as commensal microorganisms. In particular, Dendritic Cells (DCs), neutrophils, macrophages, Natural Killer (NK) cells, Intestinal Epithelial Cells (IECs), Innate Lymphoid Cells (ILCs), and mucosal effector T cells produce cytokines in the inflamed mucosa. The balance between pro-inflammatory and anti-inflammatory cytokines in the mucosa regulates the development and potential perpetuation of mucosal inflammation in patients with IBD.[15-17] A significant decrease in the ratio of IL1 receptor antagonist to IL1 was found in the intestinal mucosa of patients with Crohn's disease and patients with ulcerative colitis when compared with control subjects, which indicates increased activation of the IL1 system in IBD. IL1β promoted innate immune pathology in *Helicobacter hepaticus*-triggered intestinal inflammation by augmenting the recruitment of granulocytes and the activation of ILCs.[15] Also, IL-6 has been reported to play an important role in the development of CD. Increased levels of serum IL-6 were detected in serum of patients with Crohn's and cultures of colonic mucosal specimens. Blocking the IL-6 pathway with an anti-IL-6R antibody was shown to prevent the development of colitis in a T cell transfer mouse model of CD by inhibiting ICAM-1 and VCAM-1 expressions, T cell proliferation, and pro-inflammatory cytokine production, such as IFN-γ, TNF-α, IL1α and IL1β. On the basis of these promising results, initial studies were carried out using an IL6R specific antibody (Tocilizumab) to block IL6 signalling in patients with IBD.[15-20-21] In addition to IL-1 and IL-6, TNF-α exerts its pro-inflammatory effects through increased expression of adhesion molecules, proliferation of fibroblasts and pro-coagulant factors, as well as initiation of cytotoxic, apoptotic, acute-phase responses, and inhibition of apoptosis. TNF-α expression in human macrophages was discovered in the colonic tissue and macrophages in both patients with CD and UC and serum levels of TNF-α correlate with clinical and laboratory indices of intestinal disease activity.[17] TNF-α may exert various pro-inflammatory functions in colitis by binding to its receptors TNFR1 and TNFR2 followed by the intracellular activation of the transcription factor nuclear factorκB (NFκB). TNF-α signalling in colitis drives pleiotropic pro-inflammatory effects, including augmented angiogenesis, the induction of Paneth cell death via necroptosis, the production of matrix metalloproteinases by myofibroblasts, the activation of macrophages and effector T cells, and the direct damage of IECs via myosin light chain kinase (MLCK) activation.[15]

Conclusion

In conclusion, the pharmacological therapy of inflammatory bowel diseases includes immunomodulators, aminosalicylates and biologics. They show intestinal anti-inflammatory properties, and they have been reported to downregulate the increased production of pro-inflammatory mediators by stimulated immune and epithelial cells, including IL-1β, IL-6, TNF-α, NO, enzymzes, and eicosanoids. Future research directed toward understanding genetic, environmental, and immune-pathogenesis of IBD will identify new therapeutic targets for the treatment of these physiological disorders.

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Conflict of Interest: None

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Bribi N et al.
Int. J. Adv. Res. MicroBiol. Immunol. 2019; 1(1)

48

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