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# Neuroimmune interaction between multiple sclerosis and inflammatory bowel disease

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## ABSTRACT

**Inflammatory bowel disease is represented by two well-known diseases: ulcerative colitis and Crohn's disease. These two entities have been found on multiple sclerosis patients. Although the location and clinical manifestations of these diseases are very different, their immune response patterns present many similarities. This article examines the immune pathology of inflammatory bowel disease and its relationship to the immunological behavior of multiple sclerosis.**

**Keywords:** MS; IBD; Immunological Relationship; HLA

## 1. INTRODUCTION

Inflammatory Bowel Diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) are characterized by chronic evolution affecting the gastrointestinal tract, with diverse patterns as well as extra-intestinal manifesttations [1].

UC affects exclusively the Colon and the rectum. Its main symptoms are rectorrhagia diarrhea and abdominal pain. In severe cases dehydration, fever, anemia and weight loss are also found. It usually comes with abdominal distention on the colic zone and associated tenderness to palpation [2,3].

In case of CD almost any part of the gastrointestinal tract may be affected. Thus its clinical manifestations depend on the place of the lesion. The most frequent symptoms are fever, diarrhea, abdominal pain, fatigue, and weight loss. Rectal bleeding is less frequent than in case of ulcerative colitis [4]. Fistulas and their connection to diverse organs of the abdominal and thoracic cavities as well as bacterial overgrowth with formation of abscesses when these fistulas occlude are very common [5].

Multiple sclerosis patients have been reported both for UC and CD [6-8]. Multiple sclerosis (MS) is a chronic, inflammatory and degenerative disease of the white matter of the central nervous system [9,10]. Its clinical manifestations depend on the location of the lesions, and its way of expression varies in relation to diverse immune conditions [11]. This article describes some IBD and MS immunologic mechanisms as well as its possible immunologic associations.

## 2. ULCERATIVE COLITIS AND CROHN'S DISEASE IMMUNOPATHOLOGY

The immunologic mechanism of the disease is still unknown, but for IBD, the more prevalent theory so far for IBD the prevailing theory is genetic susceptibility to the host and exposure to some environmental factor unleashing the inflammatory reaction against the intestine [12]. According to the theory, asides from intestinal microbial antigens and some environmental unleashing activator, genetic susceptibility, and immunologic behavior are key factors to the behavior of these pathologies [13].

## 3. GENETIC SUSCEPTIBILITY TO INFLAMMATORY BOWEL DISEASE

Six among the genes studied were identified as possibly related to the susceptibility to the host. The ones identified for CD are: *CARD*15, *SLC*22*A*4, *SLC*22*A*5, *DLG*5, *PPARG*, and for UC is *MDR*1.

### 3.1. Member 15 of the Family with Caspases Recruitment Domain

**(*CARD*15)** o ***NOD*2**: Some mutations of this *gen may have a Leucine rich repeat width recognizes bacteria*

*peptidoglycan*, this recognition complex acknowledges the k$\beta$ nuclear (NFk$\beta$), which unleashes the transcription of inflammatory molecules which take part on the defense of counter pathogens [14].

### 3.2. Solute Transporting Proteins (SLC22A4ySLC22A5)

These proteins with mutations in their promoter and in their transcribing region affect carnitine transportation at the intestinal epithelium [15].

### 3.3. Gen Homologous to Discs on Drosophila (DLG5)

Structural protein protecting the integrity of the epithetlium, altered on CD [16].

### 3.4. Peroxisome Proliferator Activated Receptor Gamma (PPARG)

Nuclear receptor which inhibits NFkB, reduced UC expression [17].

### 3.5. Multidrug Resistance Gen (*MDR*1)

Protein in charge of transporting cellular xenobiotics, variant 1 has been related to UC and CD [18].

## 4. INFLAMMATORY BEHAVIOR ON INFLAMMATORY BOWEL DISEASES (ULCERATIVE COLITIS AND CROHN'S DISEASE)

The IBDs present similar innate immunity. The response is characterized by the presence of activated macrophages and neutrophils, as well as T and B cells. Although expression of proinflammatory interleukins riseson both IBD sub-types, it is higher with Crohn's Disease. Interleukins rising expression on both pathologies are: IL-1$\beta$, TNF, IL-6, IL-8a and IL-18. The ones rising exclusively with CD through TH1 and TH17 cells are: IL-12, IL-23, IL-27, IFN$\gamma$, IL-17 and IL-21; and specifically expressed with UC are: IL-5 and IL-13 [13].

On both subtypes of pathologies a marked increase with respect to adhesion molecules is evident, the expression of molecular adhesion cell 1(ICAM1) rises on these immunologic cascades as it acts in fastening and transferring immune cells to the epithelium [19].

Initial recognition and bonding of epithelial cells and bacteria takes place through TLR receptors, which are normally found in low concentrations in the epithelium cells, and increase their expression in the presence of any immunogenic reaction against antigens. NFkB transcriptiontion is activated when the TLR receptor connects to its corresponding adjuvant. The NFkB factoris the main activator of the immunologic cascade on IBD, since after its initial expression, molecules such as: IL-1$\beta$, TNF, IL-6, IL-8, ICAM1 and adhesion molecules like CD40, CD80, CD 86 and ICOS (inducible T cells co-stimulator). Additionally it has been seen on trials with mice that NFkB attenuation, decreases experimental colitis [20].

Unlike innate immunity, acquired immunity on Crohn's Disease and on Ulcerative Colitis shows different patterns. On Crohn's Disease TH1 cells dominate the cascade. In this response, cells presenting antigens produce IL-12, which induces IFN-$\gamma$ into activating TH1. Production of TH17 in Crohn's Disease is regulated by the production of IL-17, which in turn is stimulated by IL-6, TGFB and by IL-23 [21].

In ulcerative colitis, the immunological pattern is characterized mainly by TH2 cells mediated by natural killer cells (NK) which produce IL-13. Natural killer cells in this immunologic pattern are produced by presentation of lipids and not by antigenic proteins. Activation of T cells takes place normally at the lymph nodes and is characterized by the secretion of IL-6, IL-12, IL-23, IL-10 or TGF$\beta$.

## 5. DEGENERATIVE AND INFLAMMATORY BEHAVIOR OF MULTIPLE SCLEROSIS

As experimental autoimmune encephalomyelitis (EAE) studies have shown Multiple Sclerosis is a TH1 CD4+ cells mediated disease, the immunologic cascade starts with the activation of the innate immune regulatory response to T cells; the presentation of the antigen between T cells and antigen presenter cells (APC) allows clonal expansion. T cell recognizes the antigens which join its receptor (TCR); this mediated by the intervention of the major histocompatibility complex (MHC), which is expressed on the surface of the antigens presenting cells APC).

TCR bonding by the MHC-antigen complex, with help from co-stimulating cells, unleashes a T cells stimulating signal [22].

The characteristics of the antigen that is presented and the co-stimulating production of cytokines within the node polarize the cellular differentiation to CD4+ T helper 1 (TH1), TH2, TH17or regulating T cells (TReg) andcytotoxic CD8+. After their clonal expansion these cells travel through leptomeningeal arteries crossing the hematoencephalic barrier (HEB), intervene a complex of cellular adhesion molecules, intercellular adhesion molecules I (ICAM-1) and vascular cellular adherence molecules 1 (VCAM1).

Metallo proteinases like MMP-9 and MMP-2 which digest the fibronectin and the collagen of the basal membrane also take part on HEB disruption [23]. When T cells (Th1, Th17, CD8+ cytotoxic and B cells) cross the HEB and arrive at the central nervous system (CNS),

 

they are reactivated, clonally expanded and differentiated by an autoantigen presented by the dendritic cells [24].

Together, astrocytes and activated microglia increase inflammatory cytokines, oxygen reactive species, glutamate excitotoxicity and production of antibodies against themyelin protein [25].

## 6. IMMUNOLOGICAL RELATIONSHIP BETWEEN INFLAMMATORY BOWEL DISEASE AND MULTIPLE SCLEROSIS

The association between these two entities has been reported in multiple instances. It was first described in 1982 [26-28]. With prevalence of 0.5% - 1.0% between MS and IBD, reason why its relationship is not considered a random phenomenon [29]. Additionally they share common epidemiologic elements such as age of appearance, clinical course, and geographic distribution [30].

The common patho physiological mechanism between these two entities is still unknown, but it seems to implicate genetic, immunologic, and environmental factors; among the genetic factors, diverse HLA alleles relate to the development of autoimmune diseases [31]. A non-HLA haplotype, IBD5 is currently considered an interacttion risk [32].

Two factors may be considered of great interest in the immune context: the first one is the phenomenon of antigenic mimicry with polyclonal lymphocytes activation. For MS there are several related entities; among them the human herpesvirus 6 (HHV-6) and the Epstein-Barr virus (EBV) [33,34] present a strong relationship to the development of MS, as well as the human herpesvirus type 1 (HSV-1) the varicella zoster virus (VZV or HSV-3), or the influenza virus. One related entity among bacteriais *Chlamydia pneumoniae* (Cpn) [35,36]. Molecular mimicry implies reactivity of T and B cells, whether with peptides or with antigenic determinants shared by infections and by autoantigens [37].

Specific myelin proteins autoreactivelymphocytes, IFN-$\gamma$ secretion by T helper 1 cells ("Th1"), production of IL-17, and Th17 cells activation are developed peripherally with subsequent migration to the central nervous system [38,39]. There are multiple proteins related to the immune mimicry phenomenon, and most significant among them:

- Proteolipid Protein (PLP) [40]
- Myelin Associated Glycoprotein (MAG) [41]
- S100$\beta$ Protein [42]
- Myelin Oligodendrocyte Glycoprotein (MOG) [43]
- Associated Oligodendrocyte Basic Protein (MOBP) [44]
- Oligodendrocyte Specific Glycoprotein (OSP) [45]
- Myelin Base Protein (MBP) [46]

The second relevant factor is immunomodulation mediated by parasites by their interaction with B and T cells, inducing a response modified by Th2, with a phenomenon of dendritic cells tolerance to antigens [47]. ES-62 is an *Acanthonema vitae* glycoprotein, with an immunomodulating effect, which inhibits IL-12 and IFN $\gamma$ secretion, IL10 proliferation and production, and inhibits dendritic cells maturation [48]. Helminthes infections may alter TLR4 expression on T cells, and in turn Schistosome-derive dlysophosphatidic serine may affect TLR2 activity, promoting dendritic cells differentiation which induce regulating T cells with IL10 anti inflammatory-interlokins secretion [49,50]. Other example are *Schistosomamansoni* eggs soluble fractions altering the TLR ligand, inducing dendritic cells activation, and enzymatic activity of helminthes derived products, whose function to maintain the infectious process is capable of modulating the innate system response [51].

Other interesting and common element reported for both pathologies is vitamin D deficiency [52].

## 7. CONCLUSION

The incidence of patients with cases of inflammatory bowel disease whether Crohn's disease or ulcerative colitis and multiple sclerosis has been increased during the past 50 years. Both pathologies share epidemiologic characteristics such as age of occurrence, the clinical course and geographic dependent prevalence and incidence. Shared cellular factors are IBD5 protein, antigenic mimicry with diverse human proteins and with some bacteria, as well as parasite mediated immunomodulation.

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