Introduction

The etiology of Inflammatory Bowel Diseases [(IBDs: Crohn’s disease (CD) and Ulcerative Colitis (UC)] is still largely unknown. Their pathogenesis seems to be the result of a combination of environmental, genetic and immunological factors which lead to inflammation of the gut mucosa in genetically predisposed individuals. IBDs are widely believed to originate from a dysregulated immune response to enteric bacteria. IBDs can often produce extraintestinal manifestations such as arthritis, iritis, skin disease (e.g., erythema nodosum), vasculitis and haemolytic anaemia. These manifestations seem to be more frequent when the colon is involved rather than when the inflammation is limited to the small bowel. Furthermore, the observation that extraintestinal symptoms generally improve or disappear when the gastrointestinal disease is effectively treated suggests that there is a causal association between gut inflammation and extraintestinal phenomena. The underlying mechanisms by which this occurs are not fully understood and this will be the topic of this paper. We will focus mainly on the relationship between gut inflammation and joint involvement in order to clarify the immune linkages between IBDs disease and spondyloarthropathies.

IBDs Pathophysiology

IBDs develop in a complex environment such as intestinal mucosa: this latter in fact constitutes an immunologic system in which both immune tolerance and defense against harmful organisms usually occur. This mucosal immune system is crucial for host defense and it is continuously exposed to large amounts of exogenous and en-
dogenous antigens. This phenomenon is responsible for the activation of the immune response in the intestinal mucosa and it is often able to act as a trigger for cytokine production and eventually for the occurrence of inflammation and tissue damage.

Several mechanisms have been identified as possible explanations of the pathologic processes involved in IBD. Dysfunctions of the intestinal immune system and cross-reactivity against host epithelial cells play a major role as mechanisms by which inflammation takes place. In addition to immune cells, there are many mediators involved in inflammation and tissue damage: eicosanoids, biological amines, cytokines and platelet-activating factor have been shown to influence the inflammatory process. It is currently accepted that dysregulation of the mucosal immune system is a major factor contributing to the IBD pathogenesis, which is the outcome of a process involving three essential and interactive factors such as host susceptibility, enteric microflora and mucosal immunity. This means that IBD is determined by genetic alterations that in turn affect the function of the mucosal immune system, leading it to overreact to normal intestinal microflora.

The role of cytokines in IBD pathophysiology is not completely understood. However, it seems clear that the nature of the immune response and the cytokine profile generated are under genetic control and determine the features of the inflammatory process. There is general agreement that CD is associated with type 1 helper T cell cytokines such as TNF-α, IFN-γ, IL-12. The cytokine profile of UC is less clear: there is preferentially a Th2 response associated with cytokines such as IL-15 and IL-10. IL-10 seems to play a crucial role in the balance of the mucosal immune system, promoting physiological activation and preventing the pathological inflammation typical of IBDs.

The pathophysiological concept for IBD is now changing as a result of research with the description of a new immunological pathway, the IL-23/IL-17 axis. IL-23 is produced by antigen-presenting cells and is capable of promoting a subset population of Th cells to produce IL-17 (Th17 cells). Other studies show that the IL-23/IL-17 axis may play a pivotal role in intestinal inflammation. Moreover, elevated levels of expression of IL-23 and IL-17 have been demonstrated in CD. Furthermore, Duerr et al. reported a significant association between CD and a gene on chromosome 1p31 that encodes for a receptor for IL-23 highly expressed on memory T cells.

**Joint Manifestations in IBDs: Clinical and Epidemiologic Evidence**

IBDs are associated with both peripheral and axial arthropathies. They are usually classified in the large group of spondyloarthopathies (SpA) that includes several entities such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), undifferentiated spondyloarthropathy (USpA) and reactive arthritis (ReA). The association between IBDs and arthropathy has been known for many years. Early work demonstrated that 10 to 18% of patients with classic IBDs develop sacroilitis. The occurrence of arthritis among IBD patients has been reported in different percentages depending on the case series examined.

An interesting study by de Vlam et al. examined 103 patients with IBD in order to assess the prevalence of joint involvement among these patients. All patients were questioned and examined for SpA symptoms and underwent X-rays of the sacroileal joints, and HLA genotyping was performed. Patients previously diagnosed with SpA were excluded. The Authors found that 39% of these patients had clinically evident articular manifestations, 30% complained of inflammatory low back pain, 10% had synovitis and 7% had peripheral enthesopathy. Of these patients, 90% fulfilled the diagnostic criteria for SpA, while the remaining 10% fulfilled the criteria for AS. A most interesting result of the study is that 18% of the patients had asymptomatic sacroilitis that seemed to be related to disease duration. In this series, HLA-B27 conferred an additional risk for inflammatory low back pain in patients with IBD.

It had already been observed that IBD-associated sacroilitis differs from idiopathic AS only in that the prevalence of HLA-B27, while still high in IBD-associated sacroilitis, is significantly lower than in idiopathic AS. However, the association with HLA-B27 in IBD-associated sacroilitis seems to be relevant. In a study by Russel et al., it has been shown that more than 50% of subjects who have B-27 and Crohn’s disease will develop AS, while only 1 to 2% of normal subjects and 20% of first-degree relatives of a proband with AS will develop the disease. The relationship between arthritis in IBDs and genetic factors related to their pathogenesis is the topic of several studies. We will focus on this aspect below when discussing the immunological basis of arthritic involvement.
The clinical classification currently adopted to describe IBD-related arthritis was provided by Orchard et al in 1998. In their paper joint involvement in IBDs was subdivided into three patterns as follows:

**Type I arthritis:** peripheral, pauciarticular arthritis that involves less than five joints. This pattern usually precedes the onset of IBD and, once established, it often parallels the activity of gut inflammation. It usually is self-limiting and does not determine joint deformities, involving first the knee and affecting 5% of the patients with IBD.

**Type II:** peripheral non-symmetric polyarthritis with five or more joints involved. Often the arthritis affects the metacarpophalangeal joints. About 3 to 4% of IBD patients have this form of articular disease.

**Type III:** an SpA, sometimes with peripheral joint involvement. Spondylitis occurs in 1 to 26% of patients with IBD.

Type II and III usually do not reflect the activity of the underlying intestinal disease and rarely precede the onset of IBD.

**Immune Linkages Between Gut and Joint Inflammation: the Immunological Basis of Joint Involvement in IBDs**

Gut involvement is a prominent feature of all SpA subgroups. In IBD the existence of a close relationship between gut inflammation and joint inflammation constitutes an intriguing issue. This linkage can be examined from at least three different angles. First, it is possible to assess the prevalence of intestinal inflammation in patients diagnosed with an SpA, or to assess the prevalence of joint disease in patients already diagnosed with an IBD. Second, we can look for the genetic factors underlying both diseases. Third, we can focus on immunological aspects characteristic of the disease process in the joint and gut environments, respectively. The aim of this speculation is the answer to this question: how do the joints talk with the gut?

The first level of evidence about the existence of a gut-joint axis is the observation that, in patients with SpA, gut inflammation is a common feature. This was widely demonstrated by ileocolonoscopic studies that found a prevalence of gut involvement in 25 to 75% of SpA patients, with differences depending on the subtype. Also, it was shown that, during the follow-up, 6% of these patients developed manifest Crohn’s disease. This finding was confirmed recently using abdominal scintigraphy with labeled leucocytes: the examination revealed intestinal signs of inflammation in 50% of patients.

In order to explain the close relationship between gut and joint inflammation (Figure 1), two major hypotheses have been proposed: (i) the homing hypothesis, based on the possible aberrant localization of T cells (particularly CD8+ T cells) in the synovium after priming in the gut, and (ii) the altered trafficking of a particular subset of macrophages, namely CD163+ cells, which are able to present antigens and to activate lymphocytes, and have a particular functional profile, as showed in vitro by the production of large amounts of TNF-α and low levels of IL-10 after stimulation with LPS.

Earlier research attempted to demonstrate a causative role of certain bacterial species in gut infections, such as Salmonella and Yersinia, and related joint diseases. Some Authors hypothesized that, after an initial gut infection, viable bacterial organisms were able to reach the joint compartment and here trigger synovial inflammation. Ultimately this theory was excluded, because little evidence supports the hypothesis of a causal connection, although genetic materials such as RNA or DNA have been isolated in the synovial fluid in different rheumatic diseases, including ReA and even rheumatoid arthritis. Many studies highlight the difficulties in clinical and aetiological interpretation of detection of bacterial DNA or other microbial materials in the joint. Two other considerations argue against the possibility that viable bacteria could have a direct role in inducing joint inflammation: first, the lack of evidence of living bacteria in the joints, and second, the failure of prolonged antibiotic therapy even in ReA. By contrast, there is a large body of evidence that bacterial antigens are detectable in peripheral blood and in the synovial fluid in patients with SpA. Therefore, it is crucial to understand how bacterial products reach the joint. This is the starting point of the first of the two major hypotheses mentioned above.

It is conceivable that T cells, reactive to bacterial antigens, home into the synovium and, after reactivation, induce joint inflammation. Several observations support this hypothesis. First, evidence in studies comparing the histological features of different joint diseases demonstrates that the inflammatory infiltrate in the synovium and the enthesis of SpA patients is rich in CD8+ T cells.
Second, the functional analysis of T cells infiltrating the gut, circulating in the peripheral blood and infiltrating the synovium shows an identical cytokine profile with an impaired production of Th1 cytokines such as IFN-γ, IL-2 and TNF-α, as seen in gut mucosa of CD and SpA patients. This finding was demonstrated in an interesting study by Van Damme et al. in which a functional analysis of gut lymphocytes of SpA patients was performed. The impaired Th1 profile was also seen in non-inflamed gut mucosa, suggesting the possibility of pre-histological immune alterations in the gut. A convincing argument is that this aberrant cytokine profile could be modified by means of biological drugs targeting TNF-α as shown in vitro by Baeten et al. and by the efficacy these drugs demonstrated in the treatment of SpA.

The third observation has to do with the ability of gut-derived lymphocytes to home into the synovium using multiple homing receptors. Among these cell adhesion molecules, β7 integrins are important for T cell homing both in CD and in SpA. It has been illustrated that T cells derived from the gut express abnormal levels of αEβ7 integrin and its ligand E-cadherin is expressed by gut mucosa both in CD and SpA, confirming the presence of similar immune alterations in these two diseases.

It remains to be explained how these cells create an inflammation-prone environment after homing into the synovium. A possible mechanism is that T cells reactivate in the synovium because of antigen presentation via the class I MHC molecules. Indeed, it has been proposed that HLA-B27 is involved in both priming and reactivation of cytotoxic CD8+ T lymphocytes by presenting either specific bacterial peptides or arthritogenic self-peptides cross reacting with bacterial antigens. CD4+ T cells are also involved in this process; it is not clear, however, which mechanisms activate these cells. CD4+ T cell reactivity

Figure 1. An overview of the pathogenesis of IBD-related arthritis.
appears to be not only directed at bacterial antigens but also at HLA-B27 itself, particularly if factors such as infections influence the expression of abnormal forms of the molecule.\textsuperscript{38}

An important observation derives from histology studies in human SpA that show that professional antigen-presenting cells expressing Class II MHC and co-stimulatory molecules are detectable in gut mucosa but not in the synovium.\textsuperscript{25,39} According to this observation, it is conceivable that the priming of naïve CD4+ T cells occurs in SpA at a distant site like gut mucosa or lymph nodes and not in joint tissue. The question remains, however, as to which trigger is responsible for T cell activation in the synovium. Perhaps, the development of arthritis requires a local stimulus provided by bacterial antigens present in the synovial fluid, or host antigens cross-reacting with bacterial ones, or by HLA-B27 itself. The reactivation of memory T cells in the synovial membrane appears to be related to the presence in the synovium of a particular population of macrophages, carrying the scavenger receptor CD163. These cells, which express high levels of HLA-DR molecules, work as antigen-presenting cells first; yet they have a particular cytokine profile and are able to produce large amounts of TNF-\(\alpha\) and low levels of IL-10 when stimulated with LPS.\textsuperscript{25} This finding is very convincing because it fits in to the concept that alterations in the innate immune system are crucial in determining susceptibility to an uncontrolled inflammation, such as occurs in IBDs and SpA. The concept that the innate immune system is crucial in maintaining the homeostasis of the gut environment is strongly suggested by experimental models such as IL-10 deficient mice.\textsuperscript{40} These animals are highly prone to developing colitis and, more interestingly, demonstrate significant alterations in the species and levels of bacteria colonizing the colon. They also show an impaired cellular immune response to bacteria.\textsuperscript{40}

The Link Between Genetic Factors and Joint Inflammation

The discovery of CARD15 led to the first association between CD and a susceptibility gene. This gene encodes for an intracellular protein which acts as a receptor for bacterial cell wall components, such as muramylpeptides derived from peptidoglycan and lipopolysaccharide, resulting in the activation of nuclear factor \(\kappa\)-B.\textsuperscript{41-43} Three independent single nucleotide polymorphisms (SNPs) have been associated with CD. These polymorphisms increase the risk of CD three-fold for eterozygotes and 40-fold for homozygotes or compound-eterozygotes, and are associated with the disease in 30 to 46% of patients.\textsuperscript{41} There is no consensus on the association with phenotypic characteristics of CD but several independent studies have suggested the association of CARD15 variants with four factors: ileal disease, fibrostenosing disease, familial predisposition to CD and early age at onset.\textsuperscript{44-46} In 2004, Peeters et al. demonstrated a connection between CARD15 and CD and sacroiliitis.\textsuperscript{47} Prior to this study, no associations had been proved between CARD15 variants and extraintestinal manifestations of CD. Previous research by Van der Paardt et al.\textsuperscript{48} had found no association between CARD15 and idiopathic AS and concluded that future work should focus on determining whether there is an association between CARD15 and the subgroup of patients with CD and AS, which Peeters et al.\textsuperscript{47} took up in their cross-sectional clinical and radiological study into the possible association between CARD15 and the presence of radiological sacroiliitis, a main characteristic of spondylitis and the most frequent rheumatic manifestation of CD. They studied 102 consecutive CD patients over 13 months, with a control group of 54 patients without CD. They took radiographs of the sacroiliac joints, scoring using the New York grading system, and they genotyped all the patients for CARD15 variants. Radiological sacroiliitis was found in 23 CD patients; 9 of these patients fulfilled the criteria for AS, of the remaining 14 patients, 11 were clinically asymptomatic. CARD 15 polymorphisms were significantly higher in CD patients than in the control group (54.9% vs 15%, \(p<0.001\)). 68% of the patients with radiological sacroiliitis carried at least one CARD15 variant, whereas the frequency in CD patients without radiological sacroiliitis was 48%. Seven of nine patients with AS carried a CARD15 variant. The study found no significant association between the presence of CARD15 and peripheral arthritis or enthesopathy. In relation to HLA-B27 status, the overall frequency of this haplotype in CD patients was 6%, but it rose to 13% in patients with sacroiliitis. CARD15 variants were found to be the only significant predictor of sacroiliitis (\(p=0.039\)), independent of HLA-B27, ileal involvement, need for resective small bowel surgery, familial CD or age of onset. The authors concluded that CARD15 variants could be considered a possible genetic predictor of sacroiliitis in CD.
In 2005, the same group\textsuperscript{49} studied whether polymorphisms in the CARD15 gene could be associated with the presence of preclinical intestinal inflammation in spondyloarthropathies. Three groups were examined: 104 patients with SpA (subdivided into two groups, AS and Un-SpA), 156 patients with CD and a control group of 140 patients. All the patients with SpA underwent ileocolonoscopy with multiple biopsies. The histological findings were subdivided into three types of involvement: normal, acute or chronic, according to previous studies. Chronic inflammation was found in 40 patients (38%). The prevalence of CARD15 in the total SpA population was 20%, with no statistically significant difference versus the control group (17%); whereas, in the CD group, the incidence of CARD15 variants was 49%, which was statistically significant with respect to the control group. Among the SpA patients with chronic gut inflammation, the carrier frequency of CARD15 variants was 38% (15 out of 40 patients). This frequency was significantly higher than that of the control group population ($p=0.006$), but not statistically different from that of the CD group. The study concluded that CARD15 is correlated with the presence of chronic gut inflammation in patients with SpA, and in fact identifies a subgroup of these patients. Chronic gut inflammation in most patients with spondyloarthropathy remains asymptomatic, and the Authors suggested that the presence of CARD15 variants could be linked to the development of this alteration rather than to CD itself.

Recently Peeters et al published new results\textsuperscript{50} which do not confirm an association of CARD15 variants with the presence of sacroiliitis. The study included 251 patients with CD, all of whom underwent radiographs of the sacroiliac joints, and 233 of whom were genotyped for CARD15 variants. The prevalence of radiographic sacroiliitis was 27%. The Authors measured the association of sacroiliitis with CARD15 genotype and clinical features, but found no association between sacroiliitis and CARD15 genotype, age, age at onset of CD, gender, smoking history, disease duration, familial history, ileal or colonic involvement, upper-GI involvement, history of ileal resection or history of fistulas. They did find a significantly high prevalence of peripheral arthritis and uveitis among patients with sacroiliitis. This finding was confirmed by multivariate analyses. The Authors commented that these results conflict with their own previous observations and suggest that this may reflect the poor reproducibility in genetic association studies of complex multigenic diseases\textsuperscript{51,52}.

Another genetic association that has been studied is that of polymorphisms of IL-23R and CD. As described by Duerr et al\textsuperscript{15}, IL-23R polymorphisms have been implicated in conferring protection to ileal CD. Rahman et al\textsuperscript{53} examined 796 AS patients (with a control group of 742 patients) and established a connection between IL-23R polymorphisms and AS. The report suggested that the IL-23 pathway could be a possible target for treatment of AS. There are no data concerning a possible association between IL-23R polymorphisms and extraintestinal manifestations of CD.

**Conclusions**

Arthritis is the most common extraintestinal manifestation of IBD and its pathogenesis is immunologically mediated. CD and UC are chronic inflammatory diseases occurring in the gut of genetically susceptible individuals independently of a specific pathogen. The interaction between antigen-presenting cells and the local bacterial flora contributes to an uncontrolled activation of mucosal CD4+ T lymphocytes with the following release of pro-inflammatory cytokines. Anti-TNF-\textalpha therapy has profoundly changed the management of refractory SpA and of refractory luminal and fistulizing CD as TNF-\textalpha plays a central role in the pathogenesis of both SpA and mucosal inflammation in CD, driving enhanced production of cytokines, chemokines and proteolytic enzymes.

The efficacy in CD provided the rationale for the use of anti-TNF\textalpha drugs in patients with UC, a disorder in which TNF-\textalpha is expressed at high levels in the colonic mucosa, is produced by colonic lamina propria mononuclear cells and is found in elevated concentrations in stools, rectal dialysates, and urine\textsuperscript{54,55}.

However, a subset of SpA and IBD patients does not respond to anti-TNF-\textalpha therapy. Therefore, cytokines or factors other than TNF-\textalpha may also participate in the pro-inflammatory cytokine cascade. Recent findings\textsuperscript{56} show that the IL-23/IL-17 axis may play a pivotal role in intestinal inflammation and IL-23 is suggested to have a key role in the pathogenesis of chronic arthritis, dependent on the promotion and
proliferation of IL-17-producing Th17 cells. Other strategies aimed to block the immune-mediated inflammatory processes in patients with IBD and arthritis must be developed according to the identification of other cytokines and intracellular signaling pathways involved in pro-inflammatory responses. In this setting, future possible target for IBD’s therapy could be the IL-23/IL-17 axis.

However, further investigations are necessary to assess the possibility of categorizing patients for an individualized therapeutic approach. It is clear that there is a subgroup of SpA patients who do not respond to the standard anti-TNF-α therapy. Future work has to answer the question whether these patients could have benefit from a therapy targeting other inflammatory mediators such as IL-23.

References


