# Pathophysiology and Pathogenesis of Immune-Mediated Inflammatory Diseases: Commonalities and Differences

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***ABSTRACT***. Immune-mediated inflammatory diseases (IMID) represent a diverse group of chronic conditions that share common pathways. Although the etiology of IMID has yet to be identified, it is well known that both genetic and environmental factors play an important role in the development of these disorders. Genome-wide association (GWA) studies and GW nonsynonymous single-nucleotide polymorphism (nsSNP) scans have recently led to identification of genes commonly found in several different IMID as well as those that are disease-specific. Current epidemiological, clinical, and experimental evidence has also confirmed an association between IMID and a large number of seemingly unrelated environmental factors, which include smoking, diet, drugs, geographical and social status, stress, and microbial agents. Data supporting the involvement of each of these factors in predisposing to, triggering, or modulating the course or outcome of IMID vary from strong to tenuous. The notion of shared genetic pathways creates new and powerful approaches for discovering the full spectrum and potential of susceptible genes in these potentially disabling chronic conditions. Insights relating to a specific immune pathway could provide targets for therapeutic interventions. (J Rheumatol 2010;37 Suppl 85:11–26; doi:10.3899/jrheum.091462)

*Key Indexing Terms:*

IMMUNE MEDIATED INFLAMMATORY DISEASES

PATHOPHYSIOLOGY PATHOGENESIS

Immune-mediated inflammatory disease (IMID) is a concept used to describe a group of chronic and potentially disabling conditions that share common inflammatory pathways. It is currently recognized that both genetic and environmental factors play an important role in the development of these disorders[1]. The influence of genetic predisposition on susceptibility to IMID was first identified by disease concordance rates in monozygotic twins and increased familial clustering[2]. Further, the dramatic decrease in the concordance rate of siblings compared with that of monozygotic twins supports the presence of multiple contributing genes. On the other hand, the lack of complete or even substantive concordance for these diseases among monozygotic twins underscores the importance of some environmental factors and indicates that these are not purely genetic diseases.

The relatively high heritability of IMID has prompted research to identify underlying disease-specific genes. Nonetheless, it has been established that each population holds a specific mutational pool[1]. In such pools, most mutations have mild effects individually, but in combination with other alleles may promote or protect from IMID[3]. This is why IMID are not inherited in a simple, classical Mendelian way, but instead have a complex or still unknown mode of inheritance. This interplay between genetic variants makes it difficult to measure and predict the risk of developing an IMID phenotype.

Genome-wide association (GWA) studies and GW nonsynonymous single-nucleotide polymorphism (nsSNP) scans have recently led to the identification of several loci in the human genome that are associated with disease susceptibility. These studies also indicate that certain loci and genes seem to predispose to multiple immune-related disorders. This further confirms the suggestion that shared molecular mechanisms that are due to common genetic variants contribute to a spectrum of conditions.

This article focuses on the common and different pathogenetic aspects of IMID and discusses how genetic analyses

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might advance our understanding of the pathology of these highly prevalent chronic conditions. The emphasis is on new genetic findings from recent GWA studies and the fact that the majority of newly identified genes can be mapped to a few shared immunological molecular pathways. The common pathways underlying IMID are highlighted.

## PATHOGENESIS OF IMID

Autoimmune diseases, including IMID, are the consequence of an inappropriate immune response directed to self-antigens. The susceptibility of certain individuals to develop autoimmune disease is associated with multiple genes, plus other risk factors including environmental triggers. Based on their function in IMID, pathogenesis-associated genetic loci can be grouped into 2 main categories. While the first category consists of intracellular signaling molecules and receptors (i.e., intracellular pattern-recognition receptors, intracellular tyrosine phosphatases, transcription factors, etc.), the second category includes cytokines and cytokine receptors.

## ROLE OF MAJOR HISTOCOMPATIBILITY COMPLEX AND HLA

The major histocompatibility complex (MHC) is the most gene-dense region of the human genome, containing ~250 genes, of which ~60% have immune-related functions. The region extends over 3.6 megabases (Mb) and is divided into 3 subregions: classes I, II, and III. The classical MHC molecules (also referred to as HLA molecules in humans) have a vital role in the complex immunological dialogue that occurs between T cells and other cells of the body. Indeed, before the advent of GWA studies, the main genetic region linked to immune disorders was the HLA region. Table 1 provides an overview of the strength of association between HLA and specific IMID[4].

*Table 1*. Strength of association between immune mediated-inflammatory diseases and HLA. From Zhernakova A, *et al,* Nat Rev Genet 2009; 10:43–55[4]; adapted with permission from Macmillan Publishers Ltd.

| Disease | Association* to HLA** | PAR† |
|---|---|---|
| Ankylosing spondylitis | Strong | 0.43 |
| Crohn's disease | Weak | 0.03 |
| Psoriasis | Moderate-strong | 0.21 |
| Rheumatoid arthritis | Strong | 0.5 |
| Ulcerative colitis | Weak-moderate | 0.16 |

* Only human leukocyte antigen (HLA) association in Caucasians has been reported. ** HLA association: strong if the odds ratio for reported alleles is above 4; moderate if the odds ratio is between 2 and 4; and weak if the odds ratio is below 2. † Population attributable risk (PAR) was calculated based on the HLA single-nucleotide polymorphisms that showed the strongest association to the disease in genome-wide association studies.

## HLA-B27 and Spondyloarthropathies

The discovery of the strong genetic association between ankylosing spondylitis (AS) and HLA-B27 was an important milestone in spondyloarthropathy (SpA) research[5,6]. HLA-B27 is present in over 90% of individuals with AS and in 50%–75% of patients with other forms of SpA, including reactive arthritis, psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-associated SpA, and isolated acute anterior uveitis, compared with only 7%–8% of the general population. Although the overall contribution of HLA-B27 to AS susceptibility is substantial at 20%–40%[7,8], it is also important to keep in mind that genetic susceptibility to AS is complex. For example, fewer than 5% of HLA-B27-positive individuals develop SpA in the absence of a family history[9].

The development of PsA involves alleles at the HLA-B and HLA-C loci (Figure 1)[10]. These include the HLA-C allele Cw*0602, which is the major determinant of susceptibility to psoriasis. HLA-B allele B*27 is associated with PsA, particularly the axial variant of PsA. Another consistent finding is the association between PsA and HLA-B38 and/or HLA-B39[11]. Further, it has been shown that HLA-Cw*06 and HLA-DRB1*07 are associated with patients with PsA of type I (onset before age 40 yrs) but not type II psoriasis (onset after age 40 yrs). Thus, it has been suggested that patients with PsA who have type I psoriasis have a genetic background different from those with type II psoriasis.

*HLA-B27 subtypes and the pathogenesis of AS*. HLA-B27 designates a family of about 28 closely related alleles. These subtypes differ by anywhere from 1 to close to 12 residues. Over 90% of patients with AS express the HLA-B27 gene, but only 2% of B27-positive individuals in the general population develop AS[12]. Although these epidemiological data strongly support the concept that B27 has a primary role in the pathogenesis of the disease, they do not explain why the vast majority of individuals with the HLA-B27 gene remain healthy. Different hypotheses have been formulated in an attempt to explain this association, including the higher expression of HLA-B27 molecules[13], HLA-B27 misfolding and the cellular stress response[14], the presentation of exogenous or self-peptides to B27+ CD8+ T cells[15], molecular mimicry of HLA-B27 with bacteria, and antigen presentation by B27 free heavy-chain homodimers[16].

The most dominant subtype is B*2705[17]. Although most of the common subtypes are associated with AS and other SpA, subtypes B*2706 and B*2709 present exceptions. Several hypotheses have been proposed to explain this, including differences in peptide-binding specificity[18,19], diminished misfolding capacity[20,21], and expression differences[13]. B*2705 has been reported to be expressed more highly on peripheral blood mononuclear cells (PBMC) from AS patients than healthy controls. This did not appear to be due to cell activation, as expression of other MHC class I

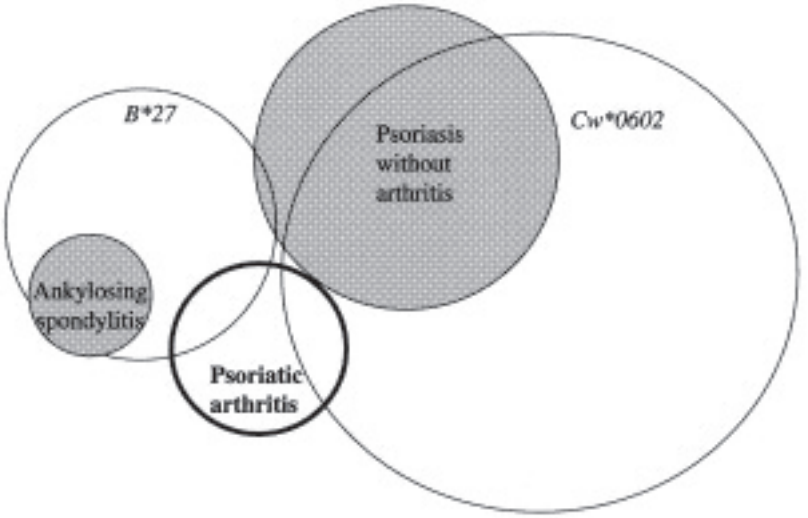


*Figure 1*. Representation of the complex relationship between HLA susceptibility and psoriatic arthritis (PsA). Areas on the diagram are not to scale. The right side represents the presence of the Cw*0602 allele in healthy individuals, its strong association with psoriasis susceptibility, and the fact that about 40% of those with psoriasis lack Cw*0602. The left side illustrates the almost complete association of B*27 with ankylosing spondylitis. Both Cw*0602 and B*27 alleles contribute independently to PsA susceptibility. From FitzGerald O and Winchester R, Arthritis Res Ther 2009;11:214[10]; with permission from BioMed Central.

molecules and additional markers was not increased. Thus, it was suggested that increased HLA-B27 expression in AS patients was an additional risk factor for disease[22]. Individuals with B*2709 were also found to have lower HLA-B27 expression than AS patients with B*2705, and similar to healthy B*2705 controls[23]. These findings imply that there may be differences in basal expression of HLA-B27 heavy chains that could be important in disease predisposition.

Preliminary data also indicate that HLA-B27 misfolding may be a stimulus for activating the interleukin 23 (IL-23)/IL-17 axis, which leads to inflammation (Figure 2)[21].

**HLA-DRB1 and Development of Rheumatoid Arthritis**

The HLA region contributes to one-third of the genetic risk for developing rheumatoid arthritis (RA). RA is associated with specific alleles of the class II gene, HLA-DRB1, collectively referred to as the shared epitope (SE)[24]. The fre-

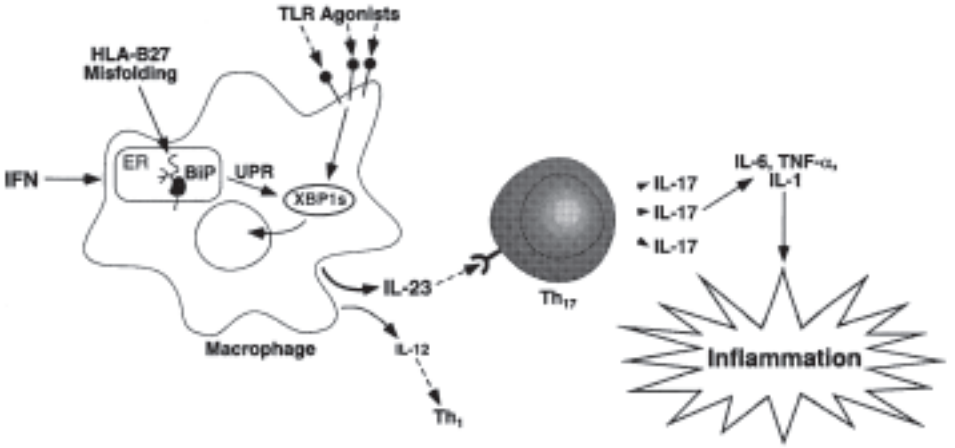


*Figure 2*. Proposed paradigm linking HLA-B27 misfolding to innate immune activation. HLA-B27 misfolding is hypothesized to result in activation of an intracellular stress response pathway known as the unfolded protein response (UPR), which leads to production of IL-23. Enhanced upregulation of interleukin 23 (IL-23) promotes IL-17 production from CD4 T cells of the Th17 lineage. Th17 cells can produce tumor necrosis factor-α (TNF-α) and IL-6, and IL-17 is also a potent proinflammatory cytokine that acts on many tissue cell types and further induces TNF-α, IL-6, and IL-1, as well as chemokines and metalloproteinases. From Colbert, *et al*, Prion 2009;3:15-26[21]; with permission from Landes Bioscience.

quency of RA-associated SE alleles has been found to vary considerably between ethnic groups. For example, the alleles *0401 and *0404 are predominantly associated with RA in Caucasian populations, *0405 allele in Asian populations, and *0101 allele in Israeli Jews. In addition, certain combinations of SE alleles can carry a higher risk than homozygosity for those alleles. The heterozygous combination of DRB1*0401/*0404 is strongly associated with early onset and a more severe form of disease than homozygosity for either allele[25].

New data support the hypothesis that the presence of HLA-DRB1 SE alleles can activate immune reactions such as the production of anticyclic citrullinated peptide antibodies (anti-CCP)[26]. Patients with RA who harbor these antibodies in the early stages of the disease could develop more severe erosive damage than those who lack them[27]. Although anti-CCP have been associated with structural damage in RA, it has not been determined whether this is independent of rheumatoid factor[28].

It is still unclear whether HLA-DRB1-SE association is the only genetic contribution to RA susceptibility arising from the HLA locus or whether other HLA loci are involved.

## T CELL DIFFERENTIATION AND SIGNALING

T cell differentiation requires the formation of a contact interface between an antigen-presenting cell (APC) and a T cell (Figure 3). The key event in T cell stimulation is the activation of the T cell receptor (TCR) by antigenic peptides presented by MHC molecules on the APC. The type of antigen that elicits the immune response and the type of cytokines secreted by APC determine whether T helper (Th) 0 cells differentiate into effector Th1, Th2, Th17, or regulatory T (Treg) cells (Figure 3)[4]. Effector Th cells determine the type of immune response by the production of specific cytokines, which can also downregulate other types of effector Th cells. Th1 cells produce IL-2, interferon-γ (IFN-γ), and lymphotoxin-α, and elicit cell-mediated immunity against intracellular pathogens. Th2 cells produce IL-4, IL-5, and IL-13, and are thought to have antiinflammatory or protective functions. Th17 cells represent the new lineage of effector T cells. The significant role of Th17 cells in the pathogenesis of autoimmunity was established with the discovery of IL-23 and its function in several IMID, such as psoriasis, AS, and Crohn's disease (CD) (see below).

Treg cells are a specialized subpopulation of T cells that act to suppress activation of the immune system and thereby maintain immune-system homeostasis and tolerance to self-antigens. In addition to the well established role of natural CD4+ CD25+ Treg cells in the maintenance of tolerance to self-antigens, there is accumulating evidence for distinct populations of Treg cells induced in the periphery after encounter with pathogens and foreign antigens. These antigen-specific T cells, termed Tr1 or Th3 cells, secrete IL-10 and/or transforming growth factor-ß (TGF-ß), but no IL-4 and little or no IFN-γ, and are induced by semimature dendritic cells under the influence of regulatory cytokines, including IL-10, TGF-ß, and IL-4. The demonstration that Treg cells can suppress the cytokine secretion and proliferation of both Th1 and Th2 cells[29,30] has raised the possibility that certain pathogens may promote the induction of Treg cells in order to subvert protective immune responses.

Other factors required for the proper activation of T cells include the activation of costimulatory molecules, such as cytotoxic T lymphocyte-associated protein 4 and costimulation by various cytokines via cytokine receptors.

### Membrane Receptors and Intracellular Signaling Molecules

*Intracellular tyrosine phosphatase*. Protein tyrosine phosphatases (PTP) play an essential role in signal transduction and are integral in the TCR signaling pathway. The PTPN22 620W allele confers a nearly 2-fold risk for RA, with odds ratios (OR) in the range of 3–4 for homozygous individuals. In fact, this variant confers the second largest genetic risk to the development of RA (Figure 4)[31]. On the other hand, there is no consistent evidence of association with psoriasis or PsA. For example, Nistor, *et al*[32] and Hinks, *et al*[33] noted no association in psoriasis and PsA, respectively. However, Li, *et al*[34] documented an association between PTP and psoriasis, and Butt, *et al*[35] an association between PTP and PsA.

The 620W allele appears to be protective for CD[36]. These contrasting patterns of association are likely to reflect fundamental similarities and differences in the mechanisms underlying the pathogenesis of IMID. The importance of the 620W allele is further supported by the fact that there is no association with PTPN22 in the Asian populations, and indeed Asian populations rarely carry the 620W variant. Attempts to identify additional PTPN22 variants that may associate with RA in Asian populations have not been successful[37,38].

Recent data also suggest that dysfunctioning in lymphoid PTP lyp signaling is implicated in 4 autoimmune diseases: type I diabetes, RA, systemic lupus erythematosus (SLE), and Graves' disease[39].

A second intracellular tyrosine phosphatase, PTPN2, encoded on chromosome 18p11, has been associated with CD[36] with OR of 1.3[40].

*Intracellular pattern-recognition receptors*. The nucleotide-binding oligomerization domain protein 2 (NOD2; also known as CARD15) on chromosome 16q12 was the first susceptibility gene for CD to be successfully identified. It is a cytoplasmic recognition protein involved in bacterial peptidoglycan signaling through detection of the muropeptide N acetylmuramic-L-Ala-D-isoGln[41-43] (Figure 5). NOD2 is expressed in intestinal epithelial cells, as well as in endothelial cells, neutrophils, and monocyte-derived cells such as macrophages and dendritic cells (DC). Thus, there are potentially both local intestinal and systemic effects of NOD2 genetic variants.

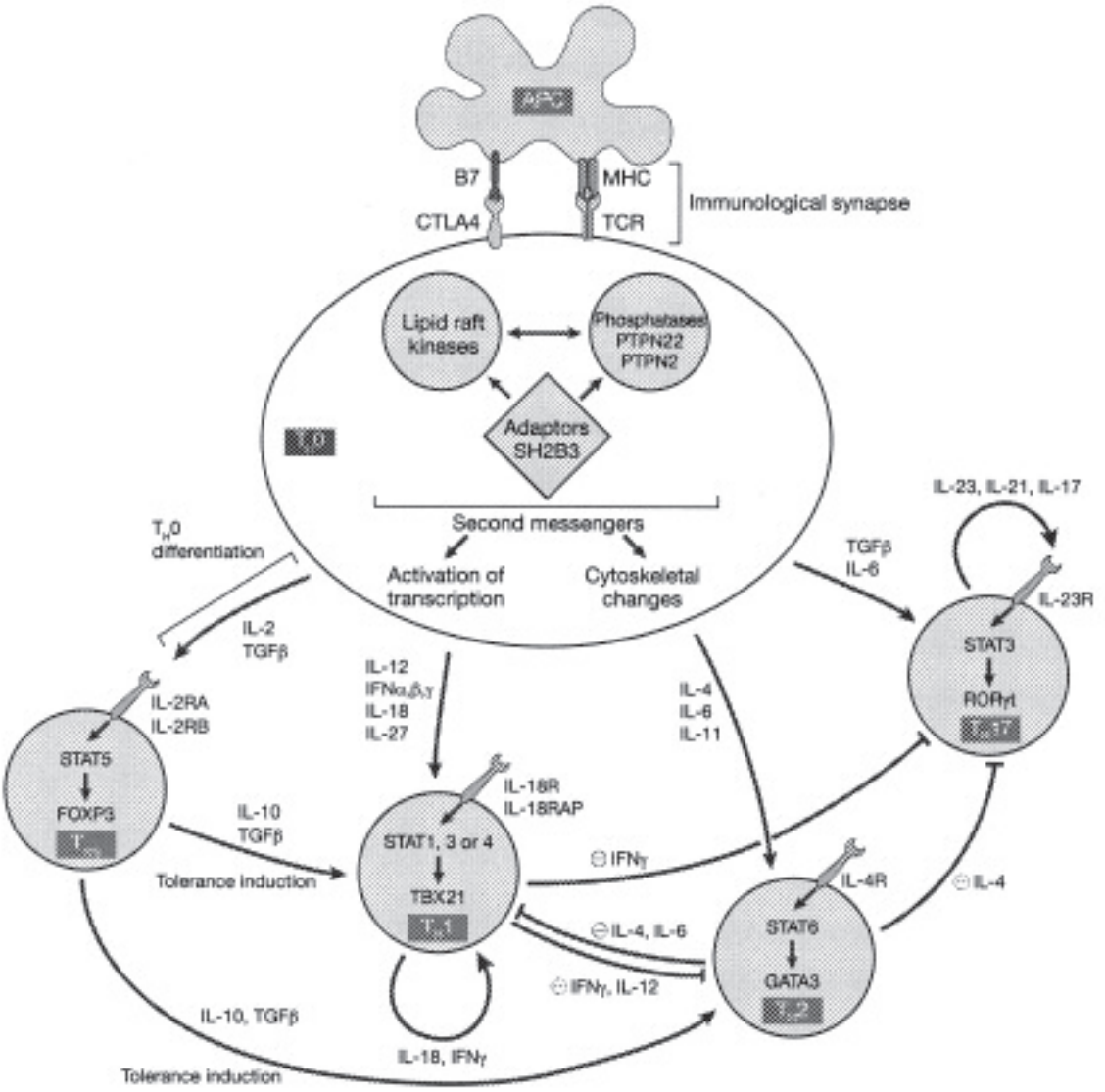


*Figure 3*. Model for T helper (Th) or T regulatory (Treg) differentiation from naive CD4+ T cells. T cell signaling requires formation of a contact [interface between an antigen-presenting cell (APC) and a T cell]. The key event in T cell stimulation is the activation of the T cell receptor (TCR) by antigenic peptides presented by MHC molecules on the APC. Other factors required for T cell differentiation and signaling include: activation of costimulatory molecules and costimulation by various cytokines via cytokine receptors. Th1 cells differentiate in the presence of IL-12, interferon-α/-ß/-γ, IL-18, and IL-27. Th2 cells depend on the presence of IL-4, IL-6, and IL-11. Th17 cells require a combination of transforming growth factor-ß1 and proinflammatory cytokines (such as IL-6). Upregulation of the IL-23 receptor makes these cells responsive to IL-23. Human Th17 cells produce IL-23, IL-21, and IL-17. From Zhernakova, *et al*, Nat Rev Genet 2009;10:43-55[4]; with permission from Macmillan Publishers Ltd.

Disease-associated mutations in the NOD2 gene alter the response to peptidoglycan stimulation in terms of cytokine production and gene expression patterns[44]. NOD2 alleles also appear to influence intestinal location of disease[45]. However, the exact mechanism(s) that explain the NOD2-mediated susceptibility to CD are still unclear.

NOD2 risk alleles are relatively uncommon in the normal population (1%–7%)[46], and the risk ratios for CD in heterozygotes are in the range of 2–3, with much higher risk ratios (approaching 20) for homozygotes[40]. The low frequency of these alleles suggests that these risk variants arose fairly recently in the European population. Further, they are extremely rare in other major ethnic groups.

**Transcription Factors and Pathogenesis of IMID**

Signal transducer and activator of transcription 4 (STAT4) is a member of a family of transcription factors that have distinct roles in cytokine receptor signaling[47]. STAT4 is highly

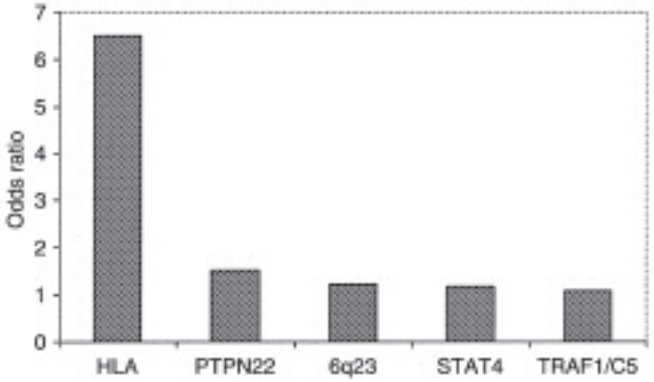


*Figure 4*. Contribution of known genetic risk factors for RA. HLA: human leukocyte antigen; PTPN2: protein tyrosine phosphatase, non-receptor type 2; STAT 3: signal transducer and activator of transcription 3; TRAF1/C5: tumor necrosis factor receptor-associated factor 1/complement component 5. From Bowes and Barton, Rheumatology 2008;47:399-402[31]; with permission of Oxford University Press.

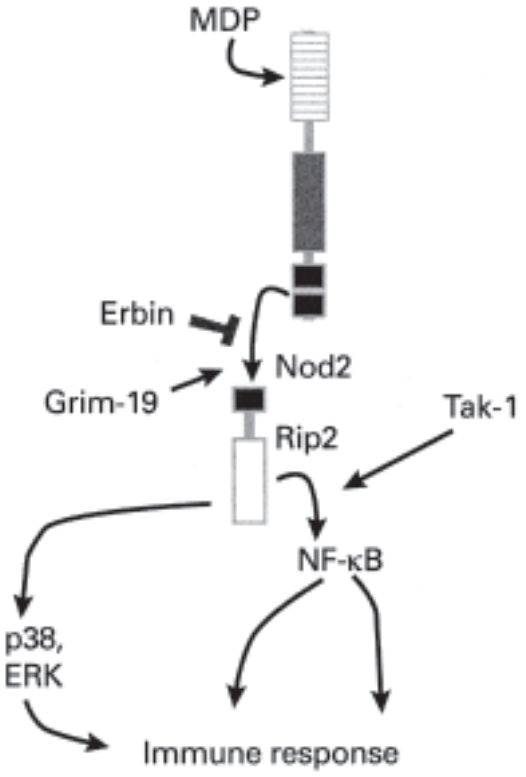


*Figure 5*. Overview of normal NOD2-signaling pathway. Upon recognition of MDP, NOD2 recruits through homophilic interactions the adaptor RIP2. Once recruited, RIP2 activates NF-κB, p38, and ERK, which elicit immune response. NOD2-signaling has been shown to be essential for healthy conditions by modulating cytokines, chemokines, and defensin production. NOD2: nucleotide-binding oligomerization domain protein 2; Rip2: serine-threonine kinase (also known as RICK or CARDIAK); ERK: extracellular signal regulated kinases; MDP: muramyl dipeptide; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; Tak-1: transforming growth factor-ß-activated kinase 1. From Vignal, *et al*, Microbes Infect 2007;9:658-63[43]; with permission from Elsevier.

associated with SLE, but modestly associated with RA (OR 1.25; Figure 4)[31]. STAT4 associations with RA are observed in both Caucasian and Asian populations[48,49].

STAT4 is a key molecule for IL-12 signaling in T and natural killer (NK) cells, leading to the production of IFN-γ and differentiation of CD4 T cells into a Th1 phenotype[50]. Upon IL-12R binding, STAT4 is phosphorylated and forms homodimers. These homodimers are translocated to the nucleus, where they initiate transcription of STAT4 target genes, including IFN-γ[51].

Inhibiting STAT4 by oligodeoxynucleotides or antisense oligonucleotides results in suppression of the disease in arthritis models[52]. Further, STAT4-knockout mice are highly resistant to the induction of proteoglycan-induced arthritis. In RA patients, the high expression of STAT4 in DC in the synovium disappears after treatment with disease-modifying antirheumatic drugs[53,54]. This suggests that STAT4 might be a potential therapeutic target.

GWA studies revealed other transcription factors as important susceptibility genes for autoimmunity. For example, the association of NKX2-3, a member of a family of homeodomain-containing transcription factors, with CD has been confirmed[36]. STAT3 and Janus kinase 2 (JAK2) are also associated with CD. The JAK-STAT pathway is a focal point in signal transmission downstream of cytokine and growth factor signals from cell-surface receptors to the nucleus to modify transcription of various genes. The present findings are particularly significant, given the role of both genes in IL23R signaling[55], and the central role of STAT3 in Th17 differentiation[56]. However, JAK2 or STAT3 are also downstream of several other cytokines implicated in CD pathogenesis (Table 2) in addition to IL-23, highlighting the pathophysiologic complexity of these new associations[36].

Spleen tyrosine kinase (Syk) is another important mediator of immunoreceptor signaling in a host of inflammatory cells including B cells, mast cells, macrophages, and neutrophils[57]. Initially, Syk was thought to function primarily in signaling of immunoreceptors such as Fc receptor (FcR) and B cell receptor. However, recent studies demonstrated the crucial role of Syk in the cell signaling of diverse cellular stimuli including IL-1 and TNF-α[58]. Increased levels of phosphorylated Syk have been seen in RA synovial tissue[59]. Syk activation is important in TNF-α-induced cytokine and metalloproteinase production in RA fibroblast-like synoviocytes. Interruption of Syk signaling with an inhibitor therefore may interrupt TNF-α and metalloproteinase production involved in the development of RA synoviocytes and could potentially affect disease activity[59]. Indeed, in a recent randomized clinical trial, an inhibitor of Syk produced significant clinical benefits at 12 weeks in patients with active RA[60]. Thus, Syk may be an important new therapeutic target in RA and related IMID.

*Table 2*. Genes implicated in Crohn's disease. Barrett JC, *et al*, Nat Genet 2008;40:955–62[36]; adapted with permission from Macmillan Publishers Ltd.

| Gene Association | Gene Function | Location | Phenotype |
|---|---|---|---|
| NOD2 | Peptidoglycan response | 16q12 | CD only |
| IL-23 | IL-23 receptor | 1p31 | CD, UC + other IMID |
| IL-12B | Interleukin 12p40 | 5q33 | CD, UC |
| ATG16L | Autophagy gene | 2p37 | CD only |
| PTPN2 | Tyrosine phosphatase | 18p11 | CD, UC + other IMID |
| NKX2-3 | Gut immune development | 10q24 | CD, UC |
| JAK2 | Transcription factor | 9p24 | CD |
| STAT3 | Transcription factor | 17q21 | CD |
| MHC region | Many | 6p21 | CD, UC + other IMID |

NOD2: nucleotide-binding oligomerization domain protein 2; IL-23: interleukin 23; IL-12B: interleukin 12B; PTPN2: protein tyrosine phosphatase; non-receptor type 2; JAK2: Janus kinase 2; STAT 3: signal transducer and activator of transcription 3; MHC: major histocompatibility complex. UC: ulcerative colitis; IMID: immune-mediated inflammatory disease.

## Th17 Cytokines and Their Emerging Roles in Inflammation and Autoimmunity

Th17 cells, a novel T cell subset, have been implicated in the pathogenesis of psoriasis and other autoimmune inflammatory diseases. IL-23 stimulates survival and proliferation of Th17 cells, and thus may serve as a key master cytokine regulator for these diseases.

*Characterization of IL-23-induced signal transduction*. IL-23 exerts its biological activities through the interaction with a heterodimeric receptor complex composed of IL-12Rb1 and IL-23R[55,61]. IL-23R is mainly expressed by T cells, NK cells, and, to a lesser extent, by monocytes and DC populations[55]. Like IL-12, IL-23 can directly bind the IL-12Rb1 chain through its interaction with the IL-12p40 subunit (Figure 6)[62]. Whereas IL-12 uses IL-12Rb2, IL-23 requires IL-23R as a heterodimeric partner to allow signal transduction to occur. Binding of IL-12 and IL-23 to their receptor leads to phosphorylation of STAT1, STAT3, STAT4, and STAT5. However, STAT4 phosphorylation induced by IL-23 is much weaker than that induced in response to IL-12. Thus, the responsiveness of cells to either IL-12 or IL-23 is determined by the respective expression of IL-12Rb2 and IL-23R[55].

*Th17 cells and cytokines*. IL-17-producing cells have been isolated from the dermis of psoriatic lesions[63]. Dermal localization of Th17 cells has also been documented in atopic dermatitis, with a higher percentage of IL-17-producing cells present in acute rather than in chronic lesions[64]. It is, however, interesting to note that no statistically significant differences in peripheral levels of IL-17A have been found in psoriatic patients compared with that in controls[65]. This suggests that the major site of production of IL-17A in psoriasis may be the skin lesions infiltrated by Th17 cells.

Mounting evidence also supports a major role of IL-23 and Th17 cells in the pathogenesis of IBD. IL-12, IFN-γ, IL-23, and IL-17 expression is increased in the colonic lamina propria of CD patients[66,67].

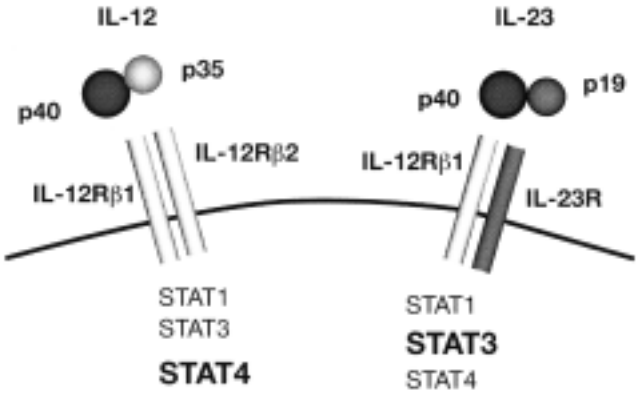


*Figure 6*. Overview of interleukin 12 (IL-12) and IL-23 ligand and receptor complexes. IL-23R: interleukin 23 receptor; IL-12Rß: interleukin 12 receptor beta; STAT: signal transducer and activator of transcription. From Boniface, *et al*, Immunol Rev 2008;226:132-46[62]; with permission from John Wiley and Sons Inc.

Strong evidence for the importance of IL-23 in CD pathogenesis is also supported by GWA studies[68,69]. In addition, it was recently reported that IL23R gene polymorphisms correlate with IL-22 serum levels in CD patients[70].

IL-23 has also been implicated in the pathogenesis of RA and SpA[71]. However, systemic levels of IL-23 appear to be strongly associated with disease activity in RA but not in SpA. The magnitude of the effect of IL-23 in PsA appears to be similar to that reported in uncomplicated psoriasis[72].

*Targeting the IL-23/Th17 pathway in the treatment of psoriasis and CD*. With regard to the IL-23/Th17 axis, targeting the common subunit, p40, of IL-12 and IL-23 has shown clinical benefits in CD and psoriasis. Two anti-IL-12p40 monoclonal antibodies have been developed: CNTO-1275/ustekinumab and ABT-874. Ustekinumab efficacy in moderate to severe psoriasis has been confirmed in 2 phase III clinical trials[73,74]. Clinical trials using anti-IL-12p40-neutralizing antibodies are also showing

promising results in the treatment of CD[75,76]. An oral IL-12/23 inhibitor has been tested in early clinical trials in CD[77].

## GENES AND THE ENVIRONMENT IN DEVELOPMENT OF IMID

Environmental factors are essential components of the pathogenesis of IMID and are primarily responsible for their growing incidence worldwide. Epidemiological, clinical, and experimental evidence supports an association between IMID and a large number of seemingly unrelated environmental factors, including smoking, diet, drugs, geographical and social status, stress, and microbial agents. Data supporting the involvement of each of these factors in predisposing to, triggering, or modulating the course or outcome of IMID vary from strong to tenuous. Smoking and the enteric bacterial flora are the ones for which the most solid evidence is currently available.

### Genes, Immunity, and Environmental Factors in Development of RA

The combined role of genes, environment, and immunity in the development of RA has been the subject of many recent investigations. However, to date smoking is the only conventional environmental factor that has reproducibly been linked to an increased risk of developing RA[78-80], whereas exposure to other substances such as silica dust and mineral oil exposures have been reported in a few studies[80-82].

Recent data support a gene-environment interaction between smoking and MHC class II HLA-DRB1 shared epitope (SE) genes in anti-citrulline peptide antibody-positive (ACPA+) RA but not in ACPA– disease[83]. However, only longterm smoking significantly increases the risk of RA, and, similarly, cessation of smoking reduced the risk only after 10–15 years[80].

In summary, data from genetic epidemiologic studies, together with information on citrullination in the lungs of smokers[84], have prompted a revision of the hypothesis for ACPA+ RA, suggesting that smoking in the context of HLA-DR SE might trigger immunity to citrulline-modified proteins and that this immunity, after several years, might cause arthritis (Figure 7)[85].

### The Human Gut Microbiome: Possible Cause of IBD?

The human intestinal microbiome coexists with the intestinal immune system and is required for normal intestinal immune development and functioning. Several mechanisms prevent luminal bacteria from damaging the body or entering it in excessive numbers. These include the epithelial-cell barrier, immune cells within the intestine, and competition with other luminal bacteria. Disruption or imbalance of these protective components can result in inappropriate intestinal inflammation.

It has long been suspected that the cause of IBD lies at the intersect of a susceptible human genome, a dysfunctional immune system, and one or more microbial pathogens[86-89]. IBD is believed to result from excessive intestinal immune activation that is driven by luminal bacteria.

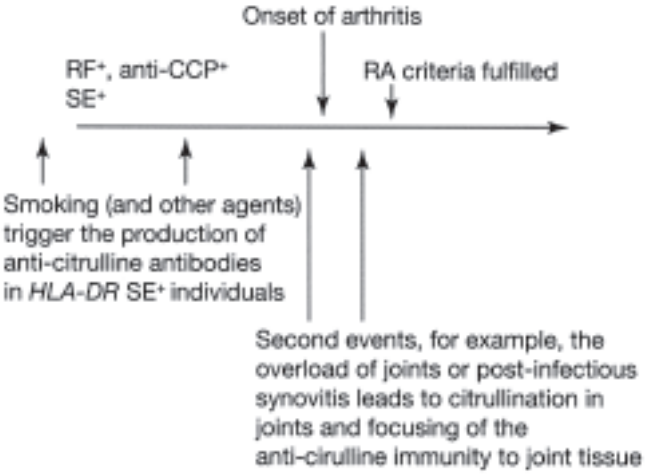


*Figure 7*. Development of anti-citrulline positive RA. From Klareskog, *et al*, Curr Opin Immunol 2006;18:650-5[85]; with permission from Elsevier.

In the host-microbial dialogue, proximity appears to be an important factor driving host responses. For example, an increased number of adherent invasive *Escherichia coli* adhere to the ileal mucosa of CD patients[90]. In addition, it has been demonstrated that multiple strains of adherent invasive *E. coli* adhere much better to epithelial cells isolated from the ileum of persons with CD than they do to cells of the same type isolated from unaffected individuals. This suggests that there are specific alterations of the ileal epithelial cells of CD patients that allow adherent invasive *E. coli* to adhere to a greater extent.

Of the various candidate proteins known to enable bacterial adhesion, both carcinoembryonic antigen-related cell-adhesion molecule 6 (CEACAM6) and CEACAM5 are overexpressed in the ileal epithelial cells of CD patients, as compared with those of controls. Further, the presence of adherent invasive *E. coli* causes an increase in the expression of CEACAM6 on the surface of cultured intestinal cells, as does incubation with proinflammatory mediators IFN-γ or TNF-α. Increased levels of IFN-γ or TNF-α are typically found in the intestine of CD patients. It has also been shown that adherent invasive *E. coli* can induce the secretion of TNF-α from cultured macrophages[91]. Therefore, adherent invasive *E. coli* may directly and indirectly induce epithelial cells to upregulate CEACAM6 to enable their own adhesion to these cells (Figure 8)[92].

Because the host response to intestinal bacteria is important for the pathogenesis of CD, autophagy may play a role in this process. Two genes in the autophagy pathway, ATG16L1[69,93] and IRGM[94], have been associated with CD (Table 2).

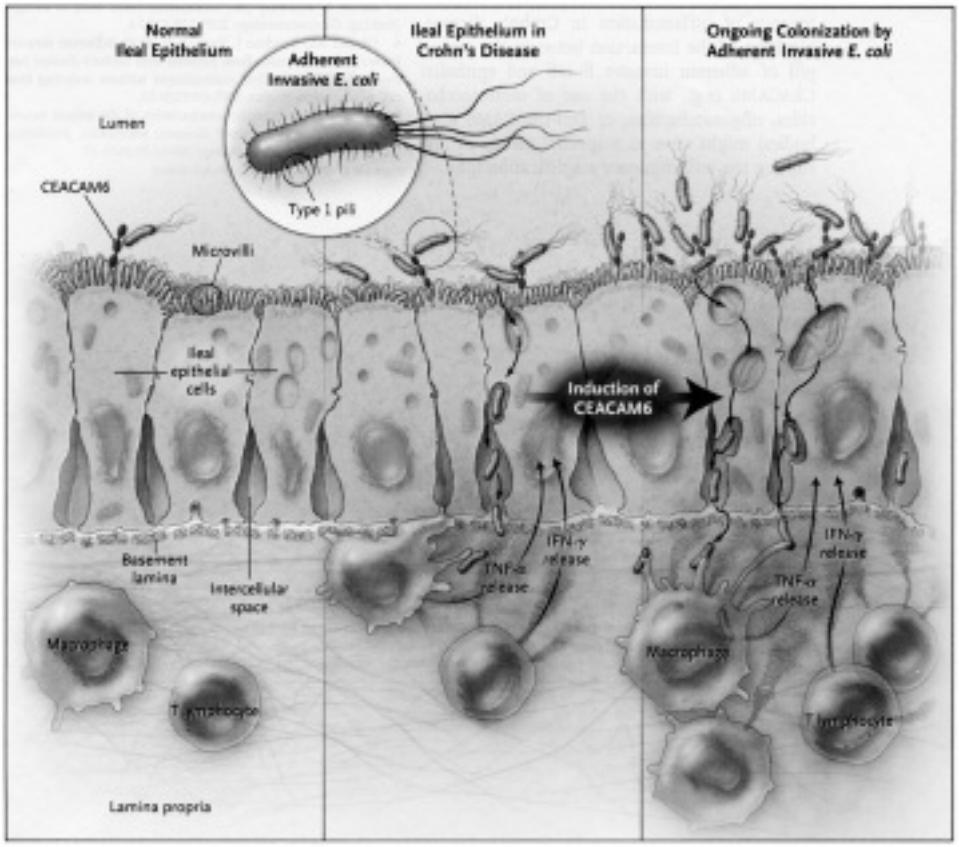


*Figure 8*. A potential model comparing the normal ileum and the ileum in Crohn's disease (CD). The presence of proinflammatory cytokines interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), as well as exposure to adherent invasive *Escherichia coli*, results in increased expression of CEACAM6 in the ileal epithelium of patients with CD. Increased CEACAM6 expression then mediates the adhesion of adherent invasive *E. coli* to the ileal epithelium. From Abraham and Cho, N Engl J Med 2007;357:708-10[92]. With permission from Massachusetts Medical Society. All rights reserved.

**Smoking and the Risk of Developing IBD**

Smoking is an important environmental factor in IBD, having different effects in ulcerative colitis (UC) and CD. Over 20 years ago, Somerville, *et al*[95] reported the relative risk of developing CD of 4.8 in those who smoked before disease onset, and 3.5 for those with a current smoking habit. Similar data were reported by a recent population-based study[96]. Both current smoking (OR 1.96) and ever-smoking (OR 1.78) were associated with increased risk to developing CD. A recent metaanalysis confirmed that current smoking is associated with a low risk of UC but a significantly high risk of CD[97]. Current smoking decreased the risk for UC (OR 0.58, 95% CI 0.45–0.75), while former smoking was associated with an increased risk (OR 1.79, 95% CI 1.37–2.34). It has also been suggested that smoking influences the phenotype of CD[98]. For example, current smokers are found to have less colonic disease than nonsmokers or ex-smokers (30% vs 45% vs 50%, respectively).

**Interactions Between Bacteria and HLA-B27 in Pathogenesis of Spondyloarthritides**

The possible interaction between bacteria and HLA-B27 may play a crucial role in models of the pathogenesis of spondyloarthritides. The fact that reactive arthritis is triggered by genitourinary infections with *Chlamydia trachomatis* or by enteritis caused by gram-negative enterobacteria[99] provides a solid background for this hypothesis. The presence of microbial antigens in the synovium of patients with reactive arthritis[100] has suggested that persistence of microbial antigens could be essential for continuing joint inflammation. About 10%–20% of HLA-B27-positive patients with reactive arthritis develop the full clinical picture of AS after 10–20 years[101].

**Environmental Triggers of Psoriasis**

Accumulating evidence indicates that body weight, alcohol, and smoking are associated with psoriasis[102,103]. For exam-

ple, Naldi, *et al*[102] found the risk of psoriasis to be higher in ex- and current smokers than in people who never smoked, with the relative risk estimates of 1.9 for ex-smokers and 1.7 for smokers. Smoking was also strongly associated with pustular lesions (OR 5.3 for smokers). The frequency of psoriasis also varied significantly in relation to body mass index (BMI) [OR 1.6 for overweight (BMI 26–29) and 1.9 for obese subjects (BMI ≥ 30)]. According to Wolk, *et al*[103], while obesity is associated with a 2-fold increased risk for psoriasis onset, smoking is associated with a 70% increased risk for onset. Stressful lifestyle also contributes to the development of psoriasis[102].

**Dendritic Cells in Immune Regulation**

DC are potent APC that possess the ability to stimulate naive T cells. They comprise a system of leukocytes widely distributed in all tissues, especially in those that provide an environmental interface (i.e., skin and intestine). DC possess a heterogeneous hemopoietic lineage, and subsets from different tissues have been shown to possess a differential morphology, phenotype, and function.

**Role of DC in Intestinal Homeostasis**

As described above, the gastrointestinal tract represents an important entry site for pathogens. It is also home to a large number and diverse array of commensal bacteria, many of which are beneficial to the host. A key feature of the intestinal immune system is its ability to protect against infection while avoiding the development of destructive inflammatory responses. A variety of subpopulations of DC are present in the organized lymphoid structures of the intestinal immune system, where they are also implicated in the generation of protective immune responses aimed at clearance of enteric pathogens. However, just as DC have been implicated in maintaining tolerance in the intestine, inappropriate or aberrant DC function may be one factor in the pathogenesis of IBD. Several studies have drawn comparisons between the phenotype and function of DC isolated from normal and inflamed intestinal tissue. For example, in CD, gut DC have been shown to express higher levels of Toll-like receptors 2 and 4 (TLR2 and TLR4) and to produce more IL-6 and IL-12[104]. Although these changes could be the result of the ongoing inflammatory response, these results also raise the possibility that changes in DC function may directly contribute to the pathogenesis of IBD. Further support for this hypothesis comes from a T cell-independent model of colitis in which direct activation of DC through CD40 leads to the development of intestinal inflammation[105].

**Plasmacytoid Predendritic Cells and Development of Psoriasis**

In recent years, there has been growing interest in the role of innate immunity to explain the interplay between environmental triggers and the exacerbation of the autoimmune T cell cascade leading to psoriasis. Nestle, *et al*[106] demonstrated that plasmacytoid predendritic cells (PDC) accumulate in the skin of psoriasis patients and become activated to produce IFN-α early during disease development. PDC are a rare cell population in the peripheral blood and secondary lymphoid organs characterized by plasma cell-like morphology and a unique surface phenotype. PDC represent key effectors in innate antiviral immunity because of their unique capacity to secrete large amounts of IFN-α in response to viruses. Further, it was demonstrated that, through the production of IFN-α, PDC drive the activation and expansion of autoimmune T cells in pre-psoriatic skin, leading to the development of psoriasis.

PDC have also been found in the inflamed tissue of patients with other autoimmune diseases, including SLE[107] and RA[108], although a functional relevance had not been elucidated.

**Joint Inflammation and Damage in RA, AS, and PsA: Commonalities and Differences**

The key role of joint-specific factors in autoimmune diseases such as RA, PsA, and AS is increasingly recognized. In the last decade, results of several clinical and animal studies have suggested that transformed synovial fibroblasts play a pivotal role in the pathogenesis of joint erosion in RA[109,110].

**Synovial Immunohistological Features of SpA and RA: Differences and Similarities**

Synovial tissue in PsA is characterized by a sublining infiltrate with T and B cells, vascular proliferation, and a relatively thin lining layer of proliferating intimal synoviocytes. A recent study compared synovial immunohistological features in SpA, including PsA, with those of RA[111]. SpA tissue exhibited significantly greater vascularity and neutrophil and CD163+ macrophage counts, whereas lining layer thickness and the number of CD83+ DC were significantly greater in RA. In RA, 44% of samples exhibited positive staining for intracellular citrullinated peptide and 46% for MHC human cartilage gp39 peptide complexes, whereas no staining for these markers was observed in SpA samples.

It has also been demonstrated that PsA PBMC readily formed osteoclasts *in vitro*[112]. In further immunohistochemical analysis of subchondral bone and synovium, receptor activator of nuclear factor-κB (RANK)-positive perivascular mononuclear cells and osteoclasts were seen. RANK ligand expression was dramatically upregulated in the synovial lining layer, whereas osteoprotegerin immunostaining was restricted to the endothelium. Thus, a proposed model for understanding the pathogenesis of aggressive bone erosions in PsA includes migration of osteoclasts, derived from TNF-α-activated PBMC, to the inflamed synovium and subchondral bone. There the osteoclasts are exposed to unop-

posed RANK ligand and TNF-α, leading to osteoclastogenesis at the erosion front.

The classic radiological features of PsA also include new bone formation at entheseal sites; for example, the hallmark pencil-in-cup type deformity results from a combination of new bone formation and osteolysis. Erosions occur less frequently in PsA than in RA, and the rate of development of new erosions is much slower. In one study of early PsA, 47% of patients had developed erosive disease at 2 years, and the number of erosions increased from a mean of 1.2 (± 2.9) to a mean of 3 (± 5.2)[113]. Although this increase was significant (p = 0.002), the number of new erosions is fewer than those described in RA[114]. In contrast, new bone formation is not a feature of RA.

Taken together, the above data confirm a histological pattern of joint inflammation in PsA similar to that in other SpA, but sharing cytokine, chemokine, and osteoclast-promoting pathways found in chronic arthropathies. The presence of common cytokine pathways certainly explains the utility of several biologic therapies, such as TNF blockers, in a number of bone-affecting IMID. Differential responses do occur, however, from which we may further clarify the relative importance of certain pathways. For example, targeting B cells in RA has proven efficacy, whereas several reports have suggested that the B cell-depleting monoclonal antibody rituximab may be associated with development of psoriasis or PsA[115]. Similarly, efalizumab — a humanized anti-CD11a monoclonal antibody — is effective in the treatment of psoriasis but appears to be ineffective in joint disease and may indeed exacerbate or trigger the onset of PsA[116].

In regard to AS, sacroiliitis is a hallmark of the disease, especially in earlier stages. In AS patients, mononuclear cells invade cartilaginous structures of sacroiliac joints and intervertebral discs, leading to destruction and ankylosis[117]. Immunohistological studies on sacroiliac joint biopsies have shown cellular infiltrates, including T cells and macrophages[118,119]. Further, molecules that regulate bone formation such as wingless (Wnt) proteins and bone morphogenic proteins (BMP) are involved. It has been shown that activation of Wnt signaling by blocking their natural inhibitor Dickkopf (DKK)-1 leads to formation of osteophytes in peripheral joints[120]. A growing number of studies using magnetic resonance imaging have shown that the most severe inflammation in AS is osteitis occurring at the bone-cartilage interface[119]. These findings have been supplemented by results of histological investigations from the sacroiliac joint and other structures affected in AS, indicating that mononuclear cells invade and erode the cartilage at different sites, particularly at early stages of AS[119,121]. Based on these findings, authors of several recent reports have proposed that the cartilage is the primary target of the immune response in SpA, including AS[122,123]. Moreover, it was demonstrated that the blockade of DKK-1 has no effect on inflammatory signs of sacroiliitis, but significantly reduces bone erosions and osteoclast counts[124]. This may indicate an important role of the Wnt signaling pathway in the structural bone changes of axial joint disease.

**Hypoxia and Angiogenesis in RA**

Angiogenesis is a prominent feature of rheumatoid synovitis. Emerging evidence based on ultrasonographic vascular imaging and angiogenic biomarkers implicates angiogenesis in the active phase of erosive disease. However, despite the luxuriant vasculature associated with RA synovitis, the joint affected by RA is hypoxic (Figure 9)[125]. Many factors contribute to the profoundly hypoxic environment that can arise within the joint affected by RA. A key regulator of the cellular response to oxygen is a transcription factor family known as hypoxia-inducible factor-1α (HIF)[126]. A growing body of evidence implicates aberrant HIF-1α regulation in the pathogenesis of rheumatoid joint disease[127]. A well documented HIF-1α-regulated gene is vascular endothelial growth factor (VEGF), a potent proangiogenic mediator. The expression of VEGF is also increased in RA[128,129]. Several studies have shown that hypoxia is a potent stimulus for VEGF induction in RA joint synovial membrane cells[130] and in RA fibroblasts[131].

The data demonstrating joint hypoxia and studies investigating the role of HIF in the tissue response to hypoxia all suggest that the angiogenesis observed in RA joint synovium is part of the normal response to low oxygen levels. Angiogenesis occurs in an attempt to restore and maintain adequate tissue oxygen homeostasis. Effects of hypoxia on synovial cell cytokine release are also demonstrated (Table 3)[125].

Repetitive cycles of hypoxia and reoxygenation, together

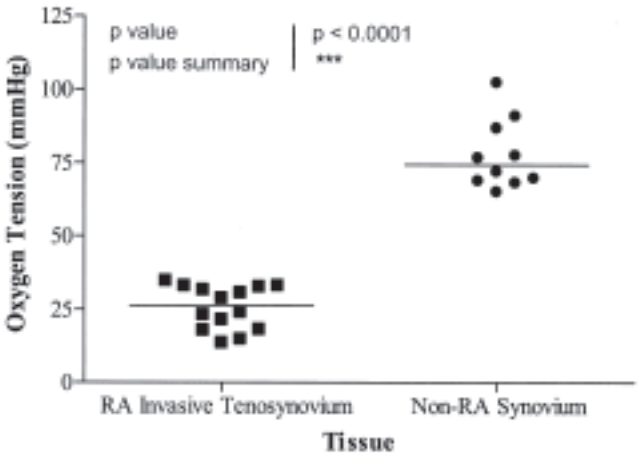


*Figure 9*. RA tenosynovium is markedly hypoxic compared with non-RA synovium. Oxygen tension (mm Hg) measurements were carried out in invasive tenosynovium of 14 RA patients or in the synovium of 10 non-RA patients. Individual datapoints are means of 1–4 replicates from a given patient and were analyzed by Student's unpaired t test, with bars showing median values. From Sivakumar, *et al*, J Hand Surg Am 2008;33:49-58[125]; with permission from Elsevier.

*Table 3*. Effects of hypoxia on synovial cell cytokine release. Tenosynovial tissue was enzymatically dissociated and cells were cultured in either 1% oxygen (hypoxia) or 21% oxygen (normoxia) for a period of 24 hours. Cytokine and receptor release (ng/ml) into supernatants was measured by ELISA. Data are shown as median (interquartile range) and were analyzed by paired t test (for Gaussian distribution: IL-10, soluble VEGF-R1, VEGF) or Wilcoxon signed-rank test (for nonparametric data: IL-6, IL-8, MCP-1) versus normoxia. Sivakumar B, *et al,* J Hand Surg Am 2008;33:49–58[125]; with permission from Elsevier.

| Variable | Normoxia | Hypoxia | n | p |
|---|---|---|---|---|
| IL-6 | 8.64 (6.03–37.45) | 7.92 (5.06–38.46) | 12 | 0.677 |
| IL-8 | 3.11 (1.85–6.37) | 3.09 (1.92–7.61) | 12 | 0.622 |
| MCP-1 | 5.37 (2.06–31.80) | 2.25 (0.80–9.41) | 13 | 0.0002 |
| IL-10 | 2.86 (1.86–4.76) | 1.76 (0.86–2.99) | 12 | 0.001 |
| VEGF | 1.97 (0.79–3.92) | 4.86 (1.798–7.02) | 11 | 0.004 |
| Soluble VEGF-R1 | 0.16 (0.10–0.29) | 0.27 (0.15–0.43) | 14 | 0.001 |

IL-6: interleukin 6; MCP-1: monocyte chemoattractant protein-1; VEGH: vascular endothelial growth factor; VEGF-R1: vascular endothelial growth factor receptor 1.

with oxidants produced by phagocytic cells, promote chronic oxidative stress within the microenvironment of the affected joint, leading to the generation of reactive oxygen species with potential to contribute to tissue damage.

## CONCLUSION

Over the past decade, our knowledge of underlying molecular and pathophysiological pathways that lead to IMID has greatly advanced. It is now understood that interruption in the regulation of innate and adoptive immunity caused by environmental triggers in genetically predisposed individuals can set off inappropriate or excessive immune response that can lead to the destruction of tissue or organs.

It is known that genetic factors play an important part in the development of immune-related disorders. However, genetic studies of IMID have so far revealed only the tip of the iceberg. More genes are yet to be found and the causal variants need to be identified. Nevertheless, the notion of shared genetic pathways creates new and powerful approaches for discovering the full repertoire and potential of susceptible genes in these potentially disabling chronic disorders.

A crucial aspect of assessing the value of recent findings from GWA studies is to examine the potential benefits to patients. For example, it is important to assess how the knowledge of shared genetic pathways can be used for predicting disease development, as well as how these findings can be applied in clinical practice. Information gathered from shared pathways might help to predict a general immune-related profile, rather than a disease-specific profile. Further, insights relating to a specific immune pathway could provide targets for therapeutic intervention. The genetic predisposition to dysregulation of a certain pathway might help to define clinical subgroups of disease and tailor pharmacotherapy to patient-specific profiles. In addition, patients with different clinical manifestations but overlapping pathways might benefit from the same treatments, which could lead to the development of shared therapeutic approaches.

The interplay between genetic factors and environmental triggers needs to be further defined. To that end, large prospective epidemiological studies are needed. By following individuals with certain genetic risks over a long period, and by monitoring their environmental exposures, such studies will be instrumental in assessing the contributions of both genetic and environmental factors to the risk of developing specific IMID. Prospective studies could determine the relationships between different risk factors and help establish key environmental triggers of disease and the timing of the development of specific conditions.

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