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# Epigenetics and Axial Spondyloarthritis - DNA is not Destiny

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## Abstract

Epigenetics is defined as heritable changes in gene expression without changing the base-sequence of the genome, ultimately altering cell differentiation, phenotype, and function. Epigenetic modifications can take place in chromosomal deoxyribonucleic acid (DNA) or in the proteins linked with the chromosomal DNA such as histones, and have been grouped into 4 main categories: DNA methylation, histone modification, small and non-coding RNAs, and chromatin remodeling. In recent years, many epigenetic proteins have been experimentally and clinically investigated, whereas strategies for modifying the epigenetic 'machinery' have been the frontier for discovering a 'cure' for chronic ailments. Gene-environment interaction is the most plausible answer.

**Keywords:** Epigenetics; DNA; Chronic ailments; Epigenetic proteins

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## Introduction

Axial spondyloarthritis (Ax SpA) is a group of related chronic systemic inflammatory immune-mediated rheumatic diseases that afflict the spine, peripheral joints, entheses (area of insertion of a tendon, ligament, fascia or capsule into a bone), and have a potential to involve the skin, gut, is 0.9 to 1.4% of the adult population, similar to that of rheumatoid arthritis [1,2].

The aim of this article is to provide a conceptual overview of epigenetic modifications in the etiopathogenesis and management of Ax SpA. Genetics alone has not been able to account for the low concordance rate observed in monozygotic twins who share the exact same genetic information (only 11-40% falling far short of the expected 100%). This indicates an 'epi' genetic component to the etiopathogenesis of these diseases. Studies in SLE, RA, Sjogren's syndrome, scleroderma and recently vasculitis have suggested and confirmed this fact [3-6]. However, we are still in need of studies on Ax SpA where the strong association with a gene (HLA B27) was revealed almost 3 decades ago [7] and yet, the exact association between the HLAB27 gene and Ax SpA still remains unexplained.

As such, HLA-B27 is present in about 90% of patients with AS, but only about 5% of *HLA-B27*-positive individuals develop Ax SpA. This illustrates a significant gap in attributing the disease to 'genetics' only. Interactions between genetic and environmental factors may elucidate biological mechanisms for Ax SpA susceptibility and bridge these findings. The PULSAR (Program to Understand Long-term outcome in Spondyloarthritis Registry) is a nationwide effort in the United States Veterans Administration towards this end [8].

## Molecular Basis of Epigenetics

Global and high-throughput assessments of the DNA methylation profiles of white blood cells from twins discordant for an autoimmune rheumatic disease have revealed hypomethylation in the twins with the disease in comparison with their healthy siblings. A number of specific sites of hypomethylation have been identified via high-throughput analysis, showing hypomethylated in the twins 'with' the disease compared those 'without' the disease especially in CD4+ T cells [9]. Although the functional relevance of hypomethylation in these elements has yet to be determined, these findings reinforce the notion that autoimmune rheumatic diseases including Ax SpA, are associated with global and sequence-specific decreases in methylation, which cause overexpression of affected genes. A study is currently underway to analyze this aspect in PULSAR participants in the United States.

Epigenetic modifications 'outside the DNA' can work through acetylation or deacetylation of the histone proteins via histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes, respectively. The equilibrium between HAT and HDAC epigenetically regulates the transcription of the pro-inflammatory cytokine coding genes. An imbalance between HAT and HDAC in

peripheral blood mononuclear cells or synovial tissue, as well as a clear increase of the HAT/HDAC ratio has been shown in Ax SpA patients during anti-TNF therapy. HDAC-inhibition has been reported to limit production of pro-inflammatory cytokines including TNF and expression of the sirtuin 1 (SIRT1) gene is under the control of NF-kB, which is activated by TNF. It has thus been hypothesized that TNF inhibitors via deactivation of NF-kB could decrease SIRT1 gene expression and activity, and ultimately enhance HAT/HDAC ratio in PBMCs of patients with Ax SpA [10].

A major recent breakthrough in Rheumatology has been the revelation of CD41CD251/highFoxp31 regulatory T (Treg) cells, which are a subset of CD41 T cells that play an essential role in maintaining peripheral immune tolerance. Several transcriptional cofactors have been recently identified, which form complexes with transcription factor Foxp3 of Treg cells and contribute in the suppressive function of Treg cells. However, Foxp3 is still defined as a ''master'' (multiple pathway) regulator gene that controls the development and stability of Treg cells. Because of its importance, the regulatory mechanisms underlying Foxp3 expression have been a focus of intensive investigation. Recent progress suggests that the epigenetic mechanisms responsible for regulating the Foxp3 gene expression are key components of suppressive activity of Treg cells [11].

## Environmental Risk Factors: Microbial and Gut Influences?

We have several-fold more prokaryotic cells (mainly bacterial) than eukaryotic (human cells) in the form of microbiome (human cells forming only 10% of the 10 trillion cells in the body). The knowledge of gene-microbiome interactions been enhanced by high-throughput methodology [12].

The gut contains by far the most densely populated ecosystem, consisting of bacteria, A big portion of our immune system is seated in the gut in the form of mucosa associated lymphoid tissue. Archaea and eukaryotic microorganisms. The intestine of a healthy adult has been shown to contain $10^{14}$ non-eukaryotic cells, of which bacteria are the most prevalent. Within these bacterial populations are a relatively sparse number of dominating phyla, including Bacteroidetes (most abundant), Actinobacteria, Proteobacteria, Firmicutes, Verrucomicrobia and Fusobacteria. The gastrointestinal tract functions as a barrier against antigens from a variety of microorganisms. The composition of the adult human gut microbiome can be classed into three discrete and constant enterotypes, each defined by the high abundance of *Bacteroides*, *Prevotella* or *Ruminococcus*.

Microbes have been postulated to trigger altered immunity in Ax SpA through molecular mimicry. This might specifically occur in the gut through the microbiome. The etiologic role of *Chlamydiae* species and *Enterobacteria* in reactive arthritis has been posited to also apply to Ax SpA pathogenesis. Transgenic HLA-B27 murine models have also demonstrated that the introduction of bacteria is necessary for the development of Ax SpA. Proteomic analysis of *Chlamydia trachomatis* has identified peptides that interact with HLA-B27 in mouse models and also stimulate T cells from patients with Ax SpA.

Inflammation in the gut, overt or covert, has been consistently observed with Ax SpA, the classic examples being the subsets of inflammatory bowel disease (IBD) related spondyloarthritis as well as reactive arthritis triggered by inflammation in the gut. Advances in sequencing technology have allowed us to gain a more complete picture of the intestinal microbiota of patients with IBD. These data support a correlation of inflammatory disease with ***intestinal dysbiosis***—a general reduction in diversity of luminal microbiota, including a decrease in populations of 'helpful' bacterial including *Bifidobacterium, Lactobacillus and Faecalibacterium prausnitzii*, with an increase in 'pathogenic' proteobacteria. Intestinal dysbiosis is now being understood as a major cause of dysregulated immunity in Ax SpA. Diversity in the intestinal microbiome may alter immunogenetic and epigenetic factors that confer risk for this disease [13,14].

Recent insights from genetic analysis of gut microbial populations suggest that the microbiome characterizes an important environmental factor in the development of local tissue disruption and clinical disease; this is due to an alteration in commensal species resulting in the initiation of an inflammatory cascade via the innate and adaptive immune system. Research into the gut-joint axis hypothesis was prompted by knowledge that up to 20% of patients with chronic IBD have recurrent episodes of peripheral arthritis. Furthermore, reactive arthritis is known to develop following exposure to various gut bacteria, such as *Shigella, Salmonella, Yersinia* and *Campylobacter* species, further suggesting an overlap between bacteria and arthritis. The existence of epitopes on bacteria that induce immune responses cross-reactive with cartilage episodes have been described, and studies have shown a considerable degree of cross-reactivity between *Escherichia coli, Klebsiella pneumonia, Yersinia enterocolitica and Bacteroides fragilis* (all thought to be associated with IBD, Ax SpA and reactive arthritis).

One theory suggests an increased permeability of the gut wall lumen results in exposure of the immune system to commensal microorganisms that otherwise would not result in disease. Increased permeability of the gut wall lumen can lead to exposure of the immune system to microorganisms. This may lead to an immune response that, via hematological spread, results in a local inflammatory process within the joints. Ironically, NSAIDs are known to increase intestinal permeability. Increased intestinal permeability was demonstrated by Mielants et al. several decades ago in patients with Ax SpA [15].

Examination of treatment-naïve microbiome in early onset Crohn's disease (CD) shows that disease severity is correlated with intestinal dysbiosis and a decrease in microbial complexity. In patients with ileal CD in particular, a prevalence of *Escherichia coli* has been reported. Adherent-invasive *E. coli* cells isolated from the intestines of patients with CD are thought to promote increased invasion of intestinal epithelial cells and persistence within macrophages, and to exploit and promote intestinal inflammation. Decrease in the diversity of Clostridium clusters IV and XIVa, which have been shown in mouse models to induce regulatory T cells and be protective, are decreased in the context of IBD. Specific commensal bacteria in mice called segmented

filamentous bacteria tether tightly to the ileal epithelium and induce intestinal Th17 cells [16]. This novel subset of T cells is critically important in Ax SpA.

In recent years the utilization of gnotobiotic mice (germfree mice colonized with specific microbiota at various life stages) has improved our understanding of the role of the microbiome in Ax SpA. In a mouse strain designed to spontaneously develop chronic autoimmune arthritis with features similar to those in human RA. When raised in specific pathogen-free conditions, these mice remained well until exposed to curdlan (a b-1,3-glucan derived from yeast, fungal and bacterial cell walls); instead of developing disease reminiscent of RA, these mice developed a spondyloarthritis-like disease involving the ankles, feet and Achilles tendons, plantar fasciitis, spondylitis and ileitis. This provides further evidence for involvement of the bacteria in disease pathogenesis and, interestingly, although this strain was designed to represent RA (and even produces RF and anti-CCP antibodies), the CD4+ T cells have been shown to be initiated via an IL- 23 dependent pathway, which triggers production of IL-1, IL-6 and TNF alpha, all of which are known to be fundamental in the pathogenesis of IBD and Ax SpA.

Recently, alteration in the microbiota associated with abnormal humoral immune responses to commensal organisms has been shown in enthesitis-related arthritis, a *forme fruste* of Ax SpA [17].

## Other Epigenetic Factors

Cigarette smoking has also been implicated in Ax SpA susceptibility, underscoring its role in multiple inflammatory and autoimmune diseases.

Unlike most other immune-mediated rheumatic diseases, males are more likely than females to develop at least a severe form of Ax SpA, so male-specific factors e.g. testosterone may also be involved in the pathogenesis of this disease.

### Engaging HLA-B27

Hammer et al. developed a strain of rats transgenic for human HLA-B27 that developed a form of arthritis similar to human Ax SpA, associated with intestinal inflammation [18]. Interestingly, rats bred in germ-free conditions did not develop disease, but developed arthritis when exposed to specific pathogen-free enteric bacteria. Taurog et al. further implicated the role of the microbiome in an animal model of Ax SpA. They showed that HLA-B27 transgenic rats raised in a germ-free environment developed inflammatory skin and genital lesions, but not inflammatory intestinal or peripheral joint disease. This alludes to the concept that gut and joint inflammation are interconnected through the part played by the microbiome in immune homeostasis [19].

### Management strategies

**Probiotics:** Diet appears to be an important factor for the gut microbiome composition, and studies across distinct geographical locations highlight the strong association between a staple diet on the gut bacterial composition. Gut microbiome composition can also be affected by age, drug use, comorbidity, malnutrition, infections and stress. Various protective mechanisms have been adapted to protect the intestinal lamina propria and systematic circulation against gut microbiota, including: a physiological barrier (mucus layer, proteins with antimicrobial properties and IgA antibodies), tight junctions between intestinal epithelial cells (providing a physiological barrier as well as antibacterial properties) and the lamina propria innate immune system (e.g. macrophages and dendritic cells), leading to stimulation of the adaptive immune response. Due to its juxtaposition to the host's intestinal immune system and its aptitude for manipulating immune responses, the gut microbiome has a significant influence on local homeostasis.

Probiotics are viable microorganisms (bacteria or yeasts) that, if administered in sufficient quantities, beneficially affect the host by improving the intestinal microbial balance. They show favorable effects on development and stability of microflora, inhibit colonization by pathogens, influence the mucosal barrier by their trophic effect on the intestinal epithelium and stimulate both specific and nonspecific components of the immune system. Immunological studies reveal that probiotics have dose and duration-dependent immunomodulatory effects on B and T cell proliferation, reduce their response to lectin and affect pro-inflammatory and anti-inflammatory cytokine regulation. In addition to promising animal studies, research has demonstrated their favorable effects on human antibiotic-associated bowel disease, IBD, pseudomembranous colitis and rotavirus enteritis; interestingly, they also appear to be advantageous in non-intestinal pathologies, such as urinary tract infections, vaginosis, Helicobacter pylori-induced gastritis and childhood respiratory tract infections, when used in combination with antibiotic treatment. Furthermore, Colifant (probiotic bacteria *E. coli* 083) use in pre-term babies decreases the presence of pathogens, the number of infections, the need for antibiotics, and the incidence of allergies and repeated infections in later life when administered orally after birth.

Efficacy of treatment of adjuvant- induced arthritis in rats with Colifant alone, with Colifant in combination with methotrexate, and with methotrexate alone has revealed that this probiotic can enhance the effects of methotrexate treatment. It has also been discovered that in rats with tropomycin arthritis (resembling Behcet's disease in humans) and adjuvant arthritis (resembling human RA), rats fed *Lactobacillus* GG (LGG) containing yoghurt had reduced inflammation on histological examination, transcending the effects of LGG alone. Data from a very recent study are very promising [20].

### Fecal microbiota transplantation

Fecal microbiota transplantation is another potential therapeutic approach for intestinal microbiota modulation, and beneficial effects of this approach have been shown in *Clostridium difficile* infection, in IBD and for increasing insulin sensitivity in individuals with metabolic syndrome; potential benefits of this treatment have also been suggested in inflammatory arthritis. Limitations to this approach, however, include expense of donor screening, difficulties transporting donations, and infection control risk.

An alternative to this is 'synthetic stool' therapy; however, this approach remains experimental. With this data, it is possible to surmise that patients with inflammatory arthritis bear a distinctive enterotype that may activate autoimmunity in those with genetic predisposition. Additionally, certain enterotypes may be protective in predisposed individuals. The evidence grade for potential therapeutic modalities such as antibiotic/probiotic use or the use of faecal microbiota transplants remains too low to draw any strong conclusions regarding the efficacy of these treatments for inflammatory arthritis, but current data does suggest potential benefits for further research in these fields. Potential adverse reactions to these treatment options, however, needs to be considered; for example, a speculative concern about probiotic use is that organisms may be able to spread from the gastrointestinal tract into the systemic circulation; although rare, cases of probiotic related bacteremia and fungemia have been reported. Furthermore, research is needed to identify whether the possibility exists of transfer of antibiotic resistance from biotic strains to pathogenic bacteria. The possibility of artificially engineering a site-specific microbiome or of using synthetic biology to integrate inducible beneficial effects in the microbiome is an exciting therapeutic prospect. Indeed, the importance of microbiome dysbiosis in inflammatory arthritis has been suggested to be relevant in other conditions such as metabolic syndrome, type 2 diabetes, atherosclerosis and IBD. Furthermore, data from animal models needs further validation in humans owing to several dissimilarities between the two, such as microbiome variations. Additional work is needed to further elucidate the mechanisms by which microbes and their metabolites may affect the immunopathogenesis of inflammatory arthritis; this may also lead to the discovery of novel management strategies. Very recent data in the related area of cancer therapy are quite assuring about the safety and efficacy of this approach [21,22].

## Future Considerations and Summary

Despite one of the strongest associations of 'a given gene' (HLA B27) with 'an identified rheumatic disease', combined with giant leaps in genetics (including cracking of the human genome), the etiopathogenesis of Ax SpA still remains an enigma. Future risk focused on epigenetic controls and modifications in this arena should focus on safe and effective management strategies, and more importantly, prevention strategies for this challenging disease that has been with mankind for at least thousands of years [23]. In essence, DNA is not Destiny [24] and it is time to embrace lifestyle medicine [25].

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