

# Implication of microenvironment on the development of various forms of arthritis

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**Keywords:** arthritis • inflammation • microenvironmental network • pathogen factors

Arthritis is a common manifestation of inflammatory or autoimmune disorders and can occur by various pathways. While the clinical signs, such as effector mechanisms are mostly developed, the initial stimuli, which initiate this disorder, are less well known. Genetic susceptibility, infection, hormonal and immunological backgrounds can contribute to the development of arthritis. Among the physical, chemical, biological effects, stress, the relationship of infectious agents, the microbiomes and arthritis are widely suspected. There are several hypotheses regarding the way infectious agents could trigger or take part in the development of arthritis [1].

## The environmental factors

The role of environmental factors in the origin of the different arthritides has been widely researched. There are many pieces of evidence regarding the development of arthritis, as genetics and host and infectious milieu together can be trigger factors. The interaction of these three main factors can result in the dysregulation of the immune system or autoimmunity [2].

There are various inflammatory musculoskeletal disorders, however inflammatory, immune-mediated and ones with autoimmune origins are the critical points we should focus on. Although the exact aetiology and pathology of the three groups are unknown, based on the representative results of the research that we are aware of, new aspects of the pathomechanism of the arthritis have been revealed [3].

Reactive arthritis (ReA), seronegative spondylarthritis (SNSA/SPA), psoriatic

arthritis (PsA) and inflammatory bowel disease (IBD)-associated arthritis can be included in both the inflammatory or immune-mediated diseases (IMID) group. Precise categorization is still a source of great debate, as these conditions share common aspects of the pathomechanism [4].

## Disease-provoking agents

Firstly, the source of the disease-provoking agents can be the gut, the urinary tract and the respiratory tract. These sites are emphasized in several pieces of research [5]. In particular, the surface of the gut is home to large scale microbe communities and studies have shown that Salmonella infection during childhood is a significant risk factor for developing IBD [6]. However Öhman *et al.* emphasize the fact that gut microbiota, the enteroendocrine system, the immune system and epithelial barrier together contribute to the development of IBD [7]. Further studies have demonstrated the strong relationship between other species and IBD-associated arthritis, by enteral, colonic biopsy and faecal analysis [8]. Controversially, the existence of the different microbiota species including; *Shigella flexneri*, *Shigella dysenteriae*, *Shigella sonnei*, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Campylobacter jejuni* and *Clostridium difficile* has only been demonstrated by PCR a few times and moreover, antibiotics have only rarely resulted in remission. Otherwise, the IBD activity can trigger axial or peripheral arthritis symptoms at the same time. The human intestinal system contains a complex microflora composed of aerobic and anaerobic bacteria, therefore patients



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with IBD lose the tolerance to their own bacterial flora. However, the exact origin of these mechanisms is still unknown [9]. Reactive arthritides often develop after urinary or upper respiratory infections and the symptoms are strongly associated with *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum* or *Beta-haemolytic streptococcus*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. However, the clinical association with the pathogenic organisms has only been demonstrated by stool culture or antibody titres on rare occasions. Antibiotics may be effective during the gastrointestinal and urinary phase but not when arthritis is developed [9–11]. Other diseases also have intestinal and musculoskeletal involvements, examples include; Whipple's disease, Behcet's disease, Celiac disease, Intestinal bypasses surgery, parasitic infections and pseudomembranous colitis [12].

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### The innate immune system

Secondly, the innate immune system is highly altered in cases of all the inflammatory joint diseases. The hypothesis of the role of innate immune system and infectious agents is also well proven [12,13]. Microbial pathogens stimulate pattern recognition receptors (PRRs) as soluble opsonins on macrophages and dendritic cells. The pathogen-associated molecular patterns (PAMPs) are part of microbial pathogens, PAMPs bind to PRRs, therefore the role of PRRs is to recognize and uptake the infectious agents. There are three PRRs subclasses; secreted, endocytic and signaling. The endocytic PRRs are expressed on surface of phagocytic cells and by phagocytosis and degradation functions they have an essential role in the innate immune system [12]. The Toll-like receptor (TLR) system – a well-described signaling PRR – represents a host defense mechanism against bacteria, fungi, and viruses. TLR activates the IL-1R and NF- $\kappa$ B pathway. The NF- $\kappa$ B pathway is important in immune system as it stimulates cell functions. TLRs appear on dendritic cells, macrophages and other cell types. TLR2 is one type of TLR whose main function is to recognize gram-positive organisms, peptidoglycans from *Staphylococcus aureus*, and lipoproteins from *Borrelia burgdorferi*, *Mycobacteria*, *Listeria* and *Mycoplasma* [13]. There is some evidence regarding the role of dendritic cells and mast cells, which are involved and critical for the development of inflammatory diseases such as acute and chronic arthritis, asthma, and chronic dermatitis. Theoharis *et al.* explained that mast cells rarely degran-

ulated in autoimmune or inflammatory diseases. Mast cells have been shown in the joints and are also required for both inflammatory and autoimmune arthritis [14].

### Genetic markers

Thirdly, genetic markers are one of the most important issues in this topic. In RA, the HLA-DRB1\*04 and\*01 clusters encode the 'shared epitope,' HLA-DRB1 and PTPN22 can induce the inflammatory process, however several microorganisms have been implicated in the development of RA based on the antibodies presenting in RA [15]. One possibility is that both genetic and infectious factors are present in the pathogenetic background. In SPA, ReA and some cases of IBD-associated arthritis, it is thought that HLA-B27 may trigger the arthritis. However, despite the strong association between of these forms of arthritis and the presence of HLA-B27, infectious triggers are required for the manifestation of the observed symptoms [16]. Finally, the migrating polyarthritis, which is an important manifestation of rheumatic fever, develops rapidly two to three weeks after a streptococcal airway infection, but those with HLA-DRB1\*16 are at particular risk [17].

### Other risk factors

Finally, there is also a strong association between smoking and psoriasis and rheumatoid arthritis. Smoking is as a risk factor for the development of psoriasis and this risk factor exists in a dose-response relationship. IL-13 gene polymorphisms may indicate the development of PsA, however, there are some minor alleles that also have a protection role. Among the environmental factors, smoking is the strongest factor in the triggering of RA. RF, along with mainly ACPA production, together highly increase the risk of RA. There are also other risk factors, such as silica dust, mineral oils and further airborne exposures [18–20].

### Summary

Understanding the role of microenvironmental factors in the development of arthritis is essential. However, there is evidence that environmental factors can trigger inflammatory or autoimmune processes and we strongly emphasize that these pathomechanisms are very complex. All infectious agents, target tissues or cells, genetic markers or other exposures are needed to alter or modulate the immune system for developing arthritis. The relationship between the gut, joint manifestation and genetic factors remain unclear. Therefore, based on current research and future research results, we are required to focus on and reach the most relevant therapeutic option to restore and maintain homeostasis and the microenvironmental balance [16].

# Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employ-

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