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Review

Role of Infections in the Pathogenesis of Rheumatoid Arthritis: Focus on Mycobacteria

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Abstract: Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by chronic erosive polyarthritis. A complex interaction between a favorable genetic background, and the presence of a specific immune response against a broad-spectrum of environmental factors seems to play a role in determining susceptibility to RA. Among different pathogens, *mycobacteria* (including *Mycobacterium avium* subspecies *paratuberculosis*, MAP), and *Epstein–Barr virus* (EBV), have extensively been proposed to promote specific cellular and humoral response in susceptible individuals, by activating pathways linked to RA development. In this review, we discuss the available experimental and clinical evidence on the interplay between mycobacterial and EBV infections, and the development of the immune dysregulation in RA.

Keywords: infections; mycobacteria; immune dysregulation; genes; rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, with a reported prevalence ranging between 0.5–1% worldwide [1–3]. RA is characterized by a systemic auto-immune disease, causing joint pain, swelling, and stiffness. RA usually affects hands, feet, and wrists, leading to progressive bone and cartilage damage, resulting in deformities, joints loss of function, and reduced independence in performing daily activities [4,5]. RA clinical manifestations are usually not confined to musculoskeletal system, but also involve cardiovascular system, kidneys, lungs, liver and skin [6]. RA onset is usually insidious. The most common scenario is characterized by symmetrical inflammatory involvement of small joints. However, in a non-negligible proportion of patients, no specific diagnosis can be made at the first presentation, due to atypical clinical manifestations and negativity to RA-specific biomarkers.

RA patients suffer from premature atherosclerosis and excessive cardiovascular disease burden. However, the prompt control of systemic inflammation due to the implementation of effective treatments in the early phases of disease, has led, in the past, to two decades of a significant reduction in the excess of cardiovascular disease burden. Moreover, the relative risk of death in the RA population is still significantly increased, compared to the general population, due to cancer and infections. It has been estimated that RA patients developing infectious complications may have a significant rise in death risk (up to 52%), with respect to the RA counterpart without history of infections [7].

The etiology of RA is complex and cannot be described solely by genetic factors and epigenetic mechanisms [8]. Environmental factors such as smoking, infections, and microbiota have been identified as risk factors to develop RA in susceptible individuals [8].

The role of infections in the development of autoimmune diseases has long been considered, since the infection with different pathogens can involve multiple pathways of the immune system, potentially triggering an autoimmune response [9].

The role of *Mycobacteria* in triggering and exacerbating the RA disease is noteworthy. Over the last two decades, a significant number of in vitro and in vivo studies have convincingly shown the presence of a biological (and likely pathogenic) link between the immune response against mycobacterial infections and the development of autoimmune diseases, including chronic inflammatory arthritis [10–12]. For instance, Liao et al. showed that RA patients are 2.28 and 6.24 times more likely to be infected by *Mycobacterium tuberculosis* (Mtb), and other *Mycobacterium* species, when compared to the general population [13]. Pathobiology of the disease itself, comorbid conditions, as well as the use of immunosuppressive treatment, may play a role as well [14,15].

The purpose of this paper is to review the available evidence about the link between mycobacterial, and other common infections, and immune dysregulation in RA.

2. RA Immunopathogenesis

RA is a chronic inflammatory disease characterized by synovial inflammation and bone damage, resulting from the proliferation of synovial fibroblasts, B and T lymphocytes, neutrophils, and monocytes [16–18].

A number of different genetic factors play a crucial role in RA pathogenesis, with RA heritability accounting for about 40–60% of RA susceptibility [19]. RA has extensively been associated to HLA-DR genes and non-HLA genes variants [20]. It has been reported that HLA alleles HLA-DRB1*01 and HLA-DRB1*04 are associated with RA susceptibility, with shared epitopes (SE) mechanisms [21]. Moreover, the HLA-DRB1*1001 allele triggers an immune response against citrullinated proteins [22].

A number of different studies have investigated the non-HLA genes' role in RA pathogenesis and susceptibility, with the IL23A, PTPN22, and PAD14 genes being associated to RA [23–27].

HLA-DR genes have been linked to autoimmunity processes in RA, with the production of autoantibodies playing a central role, and with SE being the top risk factor, leading to anti-citrullinated peptide antibodies (anti-CCP) titers being significantly increased in the serum as well [19].

In particular, anti-CCP production has been linked to the induction of the autoimmune process in RA, highlighting the importance of HLA-DR genes involved in the SE mechanism.

The presence of immune cells in the synovial compartment is a typical hallmark of RA, triggered by a large number of different mechanisms, including cell–cell interactions, secretion of soluble mediators, autoantibodies, and signal transduction pathways of both innate and acquired immune response at various stages of the disease [28]. Macrophages, neutrophils, mast cells, and natural killer (NK) cells are involved in the development of inflammatory response in the joint, as a result of innate immune response activation. Antigen-presenting cells (APCs), such as macrophages, and effector cells, promote inflammation and mediate bone and cartilage destruction by releasing pro-inflammatory factors, such as tumor necrosis factor alpha (TNF-α), interleukin-1B (IL-1B), IL-6, IL-18, IL-23, reactive oxygen species (ROS), and matrix-degrading enzymes [29,30].

In particular, TNF-α plays a central role in the pathogenesis of the disease by increasing inflammatory cytokines levels, activating macrophages and lymphocytes. For these reasons, TNF-α has been extensively identified as a therapeutic target, leading to the development of several TNF inhibitors that actually represent the mainstay of treatment of moderate-severe disease modifying anti-rheumatic drugs (DMARDs) refractory RA [31].

As previously mentioned, neutrophils play an important role in the RA pathogenesis, accounting for 80–90% of the synovial fluid cells in RA patients [28–30]. These cells exacerbate inflammation

and tissue destruction by releasing pro-inflammatory cytokines, ROS, granules containing destructive enzymes, and the formation of neutrophil extracellular trap (NET) [8,32].

In addition, Toll-like receptors (TLRs) signaling pathways play an important role in the pathogenesis of RA [33,34]. TLRs receptors are divided into two main categories, extracellular receptors (TLR-1, 2, 4, 5, 6) and intracellular receptors (TLR-3, 5, 7), which interact with components of the bacterial cell surface and ligands found in the endosomal compartment, respectively. As a result of TLRs activation, pro-inflammatory cytokines and chemokines, such as TNFα and IFNα/β, are expressed via MyD88-dependent or independent pathways activation [33].

In RA patients, the chronic inflammatory processes that characterize the patients' joints may be triggered by TLRs aberrant activation. In particular, it was found that, in RA patients, TLRs are increased in both peripheral blood monocytes (TLR-2 and 4), synovial fibroblast (TLR-3 and 7), and in synovial fluid macrophages (TLR-2 and 4) [35,36]. Moreover, microbial and endogenous ligands were reported to be able to activate TLRs in patients' derived cells. In particular, bacterial LPS and peptidoglycan induced the expression of IL-6 and CXCL8, via TLR-2 binding, in RA synovial fibroblast. Moreover, macrophages with an increased expression of TLR-2 resulted in an aberrant response to bacterial peptidoglycan [36]. The same results were observed in RA patients, with upregulated response to TLR-2 and TLR-4 ligands, in peripheral blood monocytes and synovial macrophages [37]. Other than that, endogenous ligands, for instance the stress response protein gp96, could potentially result in an incorrect activation of TLRs pathway [33]. Cell culture studies with TLR-3, 7, 8, and 9 inhibitors resulted in reduced levels of inflammatory cytokines (TNFα and IL-6), while agonists significantly increased the secretion of such molecules, suggesting that a viral infection or an endogenous ligand can potentially trigger the chronic inflammation in RA patients [38]. Further to this, non-apoptotic Fas-FasL signaling, which regulates the activation threshold for macrophages and fibroblast in the synovial fluid, may be aberrant in RA patients, resulting in an increased sensitivity to TLRs activation and, therefore, a chronic inflammation [33]. Thus, upregulated expression, the presence of microbial and endogenous ligands, and increased sensitivity to TLRs signaling may confer a crucial role to TLRs in RA pathogenesis.

Despite RA being a type 1 T helper (Th1)-mediated disease, recent available evidence suggests that T helper 17 cells (Th17) are an important effector cell population in RA pathogenesis as well [39–41]. The secretion of IL-17A cytokines, by Th17 cells, activates a number of pathways such as Fibroblast-like synoviocytes (FLS), maturation and function of osteoclasts, activation of neutrophils, macrophages and B cells [40,41]. Th17 cells play an important role in RA pathogenesis, by synthesizing other cytokines and chemokines, including IL-17F, IL-22, INF-Y, TNF-α, granulocyte macrophage colony-stimulating factor (GM-CSF), and chemokine (C-C motif) ligand 20 (CCL20) [42].

Further to this, humoral immunity has been highlighted as a potential factor in RA etiopathogenesis. For instance, the presence of anti-IgG FC autoantibodies was reported in 70–80% of RA patients, as well as anti-CCP [43]. Despite the role of these auto-antibodies being still unclear, multiple studies have shown that seropositive patients are likely to develop a more severe disease when compared to seronegative patients [44,45]. Serum rheumatoid factor (RF) and anti-CCP are currently used as biomarkers for the diagnosis of RA [6]. These antibodies (Abs) appear many years prior to RA onset, during the so-called "pre-clinical" course of the disease [46,47]. This finding supports the hypothesis that early steps of RA pathogenesis may originate in an extra-articular environment, such as the mucosal interface of gastrointestinal tract and respiratory system [48–51].

To date, different molecular mechanisms have been reported to play a role in autoimmune processes, such as pathogen/host interaction, and molecular mimicry [52,53]. Moreover, it has also been shown that cross-reactive Abs produced in the context of microbial infections have the potential to cause damage to host tissues [54,55].

In the presence of unfavorable conditions, the host's immune response to pathogens, as well as the pathogen's direct attack against the host, may lead to self-tissue damage and release of auto-antigen, resulting in the development of a self-specific immune response mounted to the host tissue [56,57].

In addition, bacterial infections can lead to the proliferation, and differentiation, of B and T lymphocytes, without their antigenic specificity, resulting in direct inflammatory responses against the host, triggering the polyclonal lymphocyte activation [58]. Other than that, microbial infection may trigger inflammatory pathways, by activating reactive lymphocyte cells, leading to autoimmune responses, called bystander activation [58].

Different studies have demonstrated that molecular mimicry between *Epstein–Barr virus* (EBV), *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and host peptides acts as an RA pathogenic mechanism. MAP and EBV infections can lead to the deregulation of the Interferon regulatory factor 5 (IRF5) pathway. The frequency of Abs reactivity against IRF5 was increased in RA patients compared to healthy controls (56% vs. 9%, $p < 0.0001$) [59]. A similar trend was found for Abs against the EBV tegument protein called BOLF1, where the frequency of reactivity was 44% vs. 9% ($p < 0.0001$), in RA patients and healthy controls, respectively [59]. Finally, it was found that Abs against MAP_4027 have a higher reactivity in RA patients compared to the control group (21% vs. 9%, $p < 0.0076$) [59].

Experiments with antigen-induced arthritis performed in IRF5 conditional KO mice strengthened the hypothesis that Abs generated against the three homologues peptides are cross-reactive. This discovery supports the hypothesis that IRF5 is a potential auto-immune target of RA. However, further studies in a larger group of patients are needed to further confirm these findings [60].

3. The Role of Mycobacterial Infections in Rheumatoid Arthritis

Mycobacterium genus has more than 170 species, most of which are environmental organisms [61]. Mycobacterial infections include tuberculosis and non-tuberculous mycobacterial infections, which cause subacute clinical symptoms with granulomatous inflammation [62].

Different studies showed the link between the immune response to mycobacterial infections and autoimmune diseases, especially autoimmune arthritis [10–12,63–66]. Poncet et al. presented the first study on this association in the late 19th century, after reporting that a type of aseptic polyarthritis was developed in patients with active tuberculosis, later named Poncet's disease [67]. In addition, this association was strengthened after the observation of a seronegative form of oligoarthritis following immunotherapy with Bacillus Calmette–Guerin (BCG) vaccine [68]. Various studies have shown the presence of mycobacterium antigens in RA patients' joints [69–72]. Moreover, increased levels of Abs against *Mycobacterium* in the serum [73–75] and the presence of active T cells in the synovium have been reported in RA patients [76,77]. In a collagen-induced arthritis (CIA) mice model, mice treated with collagen plus killed Mtb developed severe arthritis, while, on the contrary, mice treated with collagen emulsion alone did not develop arthritis [78].

In CIA, arthritis is normally induced by immunization with autologous or heterologous type II collagen in adjuvant. Susceptibility to collagen-induced arthritis is strongly associated with major histocompatibility complex class II genes, and the immune-pathogenesis of CIA involved both a T-cell and B-cell specific response to type II collagen [79]. The pathological features of CIA include a proliferative synovitis with the infiltration of polymorphonuclear and mononuclear cells, pannus formation, cartilage degradation, erosion of bone, and fibrosis. As in RA, pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα) and interleukin (IL)-1β, are abundantly expressed in the arthritic joints of mice with CIA, and the blockade of these molecules results in a reduction of disease severity [79].

Mycobacterium is a potent immunogen, often causing uncontrolled immune responses that are likely to play a role in RA pathogenesis [80]. Complete Freund's adjuvant (CFA), which contains inactivated *Mycobacteria*, is used as immunopotentiator (booster), to develop several animal models of autoimmune diseases, such as adjuvant-induced arthritis [81]. Moreover, studies have shown that components of *Mycobacteria*, such as muramyl dipeptide, glycolipids, and lipoarabinomannan (LAM) are all capable of replacing *Mycobacteria* in CFA for immunity induction [81] (Figure 1).

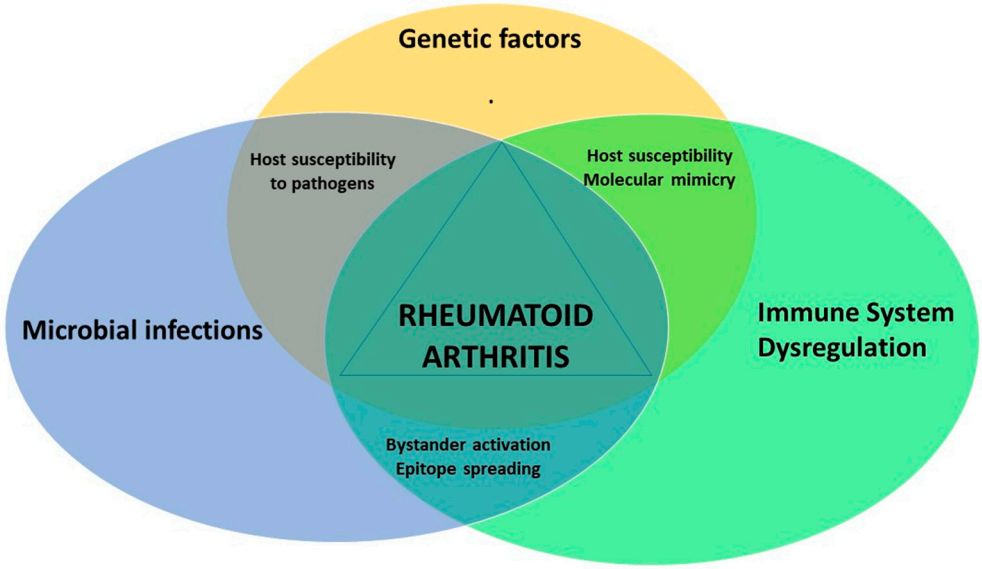

Figure 1. Interaction between different factors in driving rheumatoid arthritis (RA) pathogenesis.

Other studies have shown that in RA patients some mycobacterial lipids, named pathogen associated molecular patterns (PAMPs), are able to increase the immune response via TLR-2 and TLR-4 binding, resulting in the increased maturation of dendritic cells, ROS production, synthesis of pro-inflammatory RA cytokines (such as IL-1, IL-6, IL-17 and IL-23), and TNF-α secretion by neutrophils [82].

Gene expression analysis, and subsequent gene ontology study, revealed that genes belonging to T cell receptor signaling pathway, TLR signaling pathway, and virus defense signaling pathway, such as TLR-5, TNFSF10/TRAIL (tumor necrosis factor (ligand) family, member 10/TNF-related apoptosis-inducing ligand), PPP1R1613/TIMAP (protein phosphatase 1 regulatory subunit 16B), SIAH1 (E3 ubiquitin protein ligase 1), PIK3IP1 (phosphoinositide-3-kinase protein 1) and IL-17 are significantly dysregulated in TBC and RA patients [83].

Molecular mimicry between mycobacterial antigens and host proteins is one of the possible explanations regarding the role of immune response against *Mycobacteria* in the development of autoimmune diseases such as RA [84,85]. Supporting this preposition, immunization against *M. tuberculosis* has been reported to cause arthritis due to cross reaction with cartilage proteoglycans [86]. In addition, some studies have shown a non-negligible prevalence of anti-CCP and anti-arginine-containing peptide (anti-CAP) positivity in the serum of patients with mycobacterial infections [87–90]. Moreover, polyclonal antibodies against human lactoferrin, cross-reacted against *mycobacterial* antigens, further support the role of such molecules in triggering molecular mimicry mechanisms in RA [86,91]. There is ample evidence suggesting that TB-reactive T cells can be potentially arthritogenic, as they react, specifically, against both cartilage and *Mtb* antigens [65,92]. In a case-control study, Bo et al. found increased levels of Abs against two main proteins of MAP, named protein tyrosine phosphatase A (PtpA) and protein kinase G (PknG), in RA patients compared to healthy controls. This finding of a previous exposure of RA patients to MAP infection suggests a potential role of MAP infection in the RA pathogenesis [75].

It is important to highlight that a number of mycobacterium antigens, such as Mtb, are associated with autoimmune diseases, such as autoimmune arthritis, sarcoidosis, systemic lupus erythematosus [65,86,91,93–98], where the most prevalent mycobacterial antigen detected was the heat shock protein 65 (HSP65) [65,86,91,93,94]. The latter is an immunodominant protein similar to several human proteins, such as lactoferrin transferrin, alphaB-crystallin in terms of sequence and conformation [86,91,95]. HSP65 region between aa180–188 can stimulate auto-reactive T lymphocytes that react with cartilage-resident self-proteins [99]. HSP65 increases the responses of mononuclear cells

in the synovial fluid of RA patients, and the clonal expansion of T cells against mycobacterium HSP65 was detected in RA patients' blood and synovial fluid [82,83]. Mycobacteria Heat shock protein 16 (HSP16), 70 (HSP70) and HSP65 demonstrated 18–60% identity to their human homologues [95,100,101]. Autoimmune response to Mycobacterial (Myc) HSP70 and human binding immunoglobulin protein (Bip), a member of the human HSP70 family, has also been reported in RA patients [102]. Shoda's study showed that the similarity between Myc HSP70 $_{287–306}$ and human Bip$_{336–355}$ epitopes can lead to a broken immune tolerance, triggering an auto-immune response as a result of the T cells' inability to distinguish between self- and pathogens' antigens [103] (Figure 1).

A different approach to investigate the similarities between the virulence factors of Mtb and human proteins are bioinformatics models. HLA class I and II restricted T cell epitopes from host proteins that share bacterial and homologues human HSP60 specialty KPLVIIAEDVDGEALSTLVLN, bind to many HLA class I and class II alleles, including HLA-DRB1: *01:01, *03:01, *04:01, *07:01*, 08:02, *11:01, *13:01, *15:01, A*01:01, A*02:01, A*03:01, A*011:01, A*024:02, A*07:02, A*08:01 [104].

Findings indicated the presence of matching 22 B-cell, 79 human leucocyte antigen (HLA) class II and 16 HLA class I specific predicted epitopes in these virulence factors having human homologs [105]. In addition, in silico analysis showed that T cell cross-reactive epitopes between *M. tuberculosis* and the human proteome can be considered as vaccine candidates [106–108].

Genomic analysis showed that single nucleotide polymorphism (SNPs) in immune related genes play a role in increasing the severity of mycobacterial disease, and its association with autoimmune diseases [109–112]. One of the most common genes studied in this context is the *SLC11A1* gene (solute carrier family 11 member a1). The protein encoded by the *SLC11A1* gene, named natural resistance associated macrophage protein 1 (NRAMP1), plays an important role, activating macrophages and the innate immune system [113]. The expression of NRAMP1 causes acidification of the phagosome, eventually leading to the destruction of the intracellular pathogen, whilst mutations in *SLC11A1* gene cause intracellular pathogens survival [114]. According to several mutational screenings, mutations in *SLC11A1* are linked to autoimmune diseases, such as RA [109,115], multiple sclerosis [116,117], inflammatory bowel disease [110,118], and type 1 diabetes mellitus [111,119]. Examination of SNPs in *TNF-α* gene, and its receptors (*TNFRSF1A/TNFRSF1B*), in RA patients compared to HCs, reported that some SNPs, TNFRSF1A:rs767455 and TNFRSF1B:rs3397, are linked to TNFRSF1B downregulation, increased susceptibility to MAP infection, increased inflammation and osteocalcin deficiency, and, possibly, increased osteoporosis [120]. Sharp et al. showed that the SNPs in *PTPN2/22* genes (protein tyrosine phosphatase non-receptor type 2 and 22) are linked to increased sensitivity to MAP infection and, therefore, increased T lymphocyte response, and IFN-γ expression in RA patients [112] (Figure 1, Table 1).

Table 1. In vivo and in vitro studies of microorganisms related to RA.

Presence of microbial contents in RA patients tissues and serum	*Mycobacteria*, *P. gingivalis*, EBV, *Mycoplasma*, *Bordetalla*, *Haemophilus*, *Acinetobacter*, *Parvovirus*, CMV, Bacterial cell wall
Presence of immune response to infection in RA patients tissues and serum	*Mycobacteria*, *P. gingivalis*, EBV, HTLV, *Mycoplasma*, *Parvovirus B19*, *Papilloma virus*, HERV
Induction of Arthritis by Infections in Animal Models 	*Mycobacteria*, *P. gingivalis*, *Mycoplasma*, *EBV*

Furthermore, infection is one of the most important complications in RA patients [121]. The risk of infectious diseases increases in the RA, due to immunological dysfunction, immunosuppressive therapy, and associated comorbidities [122]. The activation of latent tuberculosis is a major concern during the treatment of RA patients. The risk of tuberculosis, as well as the risk of *non-tuberculous Mycobacteria*, increases from about 1.6 to 25 times during the treatment with TNF blockers [123,124].

In addition, there are reports of some other species of Mycobacterium associated with RA disease that make it difficult to treat the disease. There have been case reports of other Mycobacterium species in infections and arthritis and other parts of the body in RA patients around the world [125–132]. Furthermore, the risk of death in RA patients with mycobacterial infection was higher than that in patients without infection [13].

The breakdown of different mechanisms ultimately leads to the activation of molecular mimicry, bystander activation, and epitope spreading. Triggering such mechanisms, along with the presence of either microbial infections, genetic variants, and immune system dysregulation, results in the development of RA disease.

4. Other Infections Associated with RA

The evidence of an association between microorganism's infection and RA disease dates back to the 1870s, with suspected pathogens still being added to this list [133]. Using different laboratory methods, have allowed the detection in RA patients' joints, and serum, of several microorganisms, or their components, such as *Porphyromonas gingivalis* [134,135], *Mycoplasma* [136–138], *Bordetella* [139,140], *Haemophilus* [139,140], *Acinetobacter* [140], Parvovirus [141,142], Epstein–Barr virus (EBV) [143–147] and Cytomegalovirus (CMV) [144] (Table 1).

Immune responses against microbes, such as *Porphyromonas gingivalis* [148–150], EBV [151–156], Human T-Lymphotropic Virus (HTLV) [157], *Mycoplasma* [158,159], Parvovirus B19 [160], Papilloma Virus [161], and Endogenous retroviruses (HERV) [162], have been reported in RA patients. On the other hand, some animal models of arthritis were developed, exploiting the infection of some pathogens, such as *P. gingivalis* [163–166], *Mycoplasma* [167], and EBV [168,169] [Table 1].

Laboratory and clinical studies have shown that *Porphyromonas gingivalis* is the most common microorganism associated with RA etiopathology [170]. Of note, it has been reported a similarity of up to 82% between *P. gingivalis* enolase and human α-enolase within the 17-amino acid immunodominant region, and Abs levels against bacterial enolase were related to the levels of Abs against the human enolase [171–173].

Reports of both microbial components, and the immune response against them, in RA patients' joints tissue and serum were exploited to develop mice models of RA, through the injection of different microorganisms in the mouse joints.

Another microorganism associated to RA is EBV. Again, a cross-reaction mechanism was detected between anti-p107 EBV Abs and human denatured collagen and creatine. This molecular mimicry mechanism may increase autoreactive T cell activation and proliferation [173]. As previously mentioned, Abs against EBV and MAP antigen BOLF1, MAP_4027$_{18–32}$ human homologous (IRF5 epitope) were significantly higher in RA patients than healthy controls, indicating that these microorganisms may be involved in RA pathogenesis, with the production of cross-reactive Abs being a central mechanism to trigger autoimmune disease [174].

Proteus mirabilis is another RA-related pathogen [175,176]. Studies by serological and proteomics methods have shown that there are similarities between hemolysin (ESRRAL) and urease (IRRE7) sequences in *P. mirabilis*, with HLA-DR (EQRRAA) and collagen XI (LRREI) antigen epitopes [177–179]. In addition, cross-reactivity is present between bacterial hemolysin and urease enzymes with human proteome, which, subsequently, activates B lymphocytes and stimulates the production of autoantibodies. Moreover, Abs against ESRRAL and EQRRAA have been detected in RA patients [177,179].

Another RA-related pathogen is *Escherichia coli*. The QKRAA motif of the dnaJ class of heat-shock proteins from *E. coli* is as well present in HLA-DRB1 antigens. QKRAA motif strongly activates the T cells in the synovial region in RA patients. This activation may result in a cross reaction against the host dnaJ heat-shock proteins that are expressed in the synovial microenvironment [23,180].

Another non-specific inflammatory response, named bystander activation, can be exploited by microorganisms to exacerbate RA. In vitro and in vivo studies have shown that bacterial

lipopolysaccharides stimulate osteoclast formation and bone resorption through TLRs pathway activation [181–183]. Lipopolysaccharide (LPS) can stimulate macrophages to secrete pre-inflammatory cytokines [184,185]. *Porphyromonas* LPS stimulated the activation of monocytes and the production of RA-related cytokines, such as IL-1 and IL-23, via TLR pathway [186,187], ultimately promoting osteoclast formation and the bone resorption [188,189]. Concomitant injection of LPS with moramil dipeptide (MDP) also increases the expression of pro-inflammatory cytokines by monocyte cell culture [190,191]. *Mycoplasma* Glycolipid antigens (GGPL-III) significantly increased the production of TNF-α and IL-6 in the peripheral blood and the proliferation of synovial fibroblasts [136].

The EBV DNA increased the secretion of pro-inflammatory cytokines, such as IL-17, IL-23 and TNF-α in mice, which could lead to, or exacerbate, autoimmune diseases [192]. In addition, EBV and *E.coli* DNA ligation to endosomal TLR-9 leads to increased IL-17A expression, which is an essential cytokine in the synovial environment [193]. The EBV infection in human lymphocytes under in vitro conditions could cause the expansion of non-specific B lymphocytes and $TCD8^+$ cells, leading to the production of polyclonal antibodies and the activation of cytotoxic T lymphocytes [151,152,194]. Accordingly, T lymphocyte response to EBV [153,154] and CMV [195] has been reported in inflamed joints of RA patients.

Generation of neo-antigen and epitope spreading is another mechanism triggered by microorganism infections involved in RA pathogenesis. For instance, *Porphyromonas gingivalis* is the only bacterium that produces the peptidylarginine deiminase (PAD)-enzyme with citrullination activity. Host proteins post-translation modifications are catalyzed by this enzyme, resulting in the production of new antigens. It has also been reported that *P. gingivalis,* through PAD-enzyme activity, is able to generate neo-antigens in the joint, including citrullinated-fibrinogen, α-enolase and vimentin, resulting in the stimulation of the auto-immune response [196–198].

By producing proteinase enzymes, *Porphyromonas* increases apoptosis in chondrocyte cells, thereby destroying cartilage tissue and deforming the joint, which is an important mechanism in RA pathogenesis [170,199].

5. Conclusions

There is ample evidence showing a link between different microbial pathogens and RA development and progression. On the other hand, favorable genetic background, different environmental factors, including lifestyle and immunosuppressive treatment, are also involved in the increased risk of infection in various stages of RA, from the pre-clinical phase to the established/late phase. A better comprehension of the intricate relationship between microbial pathogens and RA may help in the future to develop effective strategies to block early pathogenic steps of disease, thus preventing the development of the clinical phase of RA.

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