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Does Epstein-Barr Virus Infection Contribute to Disease Flares in Rheumatoid Arthritis?

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Abstract

Although effective treatment and good adherence to their DMARDs, some patients with rheumatoid arthritis experience transient worsening in severity of disease for which the causes remain unknown. Here the authors comment the potential contribution of Epstein-Barr virus infection in rheumatoid arthritis and the relationship between such infection and the Toll-like receptor system in the exacerbation of the inflammatory response.

Keywords: Rheumatoid arthritis; Epstein-barr virus; Anti-rheumatic drugs

Rheumatoid Arthritis

Rheumatoid arthritis (RA) affects approximately 1% of the worldwide population leading to reduced musculoskeletal health conditions in these individuals and creates an enormous economic burden. The management as well as the development of new therapeutics have considerably evolved over the last decades. Despite effective treatments currently available to RA patients and a good adherence to their DMARDs (disease-modifying anti-rheumatic drugs), some patients show several intermittent fluctuations of clinical activity of the disease [1]. Furthermore, seasonal changes may play an important role in evaluating disease activity of RA patients and should be taken into account when examining these patients [2]. Although observed for a long time, the causes of such fluctuations or "flares" are unknown and still a matter of discussion. While the origin of RA is not yet identified, it is generally believed that a combination of genetic and environmental factors are responsible for the disease and it is suspected since many years that exposure to infectious agents could be a trigger implicated in RA and might contribute to disease flares. There has been a bulk of reports suggesting that viral infections may cause acute arthralgia and arthritis [3] and notably, contribute to sustain inflammation and to increase symptom severity. A broad range of viruses have been suspected, including parvovirus B19, hepatitis B and C viruses and members of the herpesvirus family like cytomegalovirus and Epstein-Barr virus (EBV) to name a few. However, while the presence of viral genome was detected in joint tissues of patients, along with elevated serological profile, no clear evidence that viral infection can mediate arthritis has yet been confirmed.

EBV has particularly been suspected for a long time as a biologically plausible candidate in triggering autoimmune diseases including RA due to its ubiquity, its high prevalence in the population and its life-long infection after primary infection [4,5]. EBV DNA loads are higher in mononuclear cells of active RA patients compared to healthy seropositive individuals as well as EBV serology. In addition, antibodies directed against cyclic citrullinated peptides (ACPA) which are highly specific for RA diagnosis, were found to recognize a citrullinated sequence of Epstein-Barr nuclear antigen-1 (EBNA-1), supporting the association between EBV and RA [6]. EBV is also known to infect several cell types infiltrating the joint and is capable of altering host immune responses through numerous mechanisms in order to evade immune surveillance [7]. In fact, a particularity characterizing EBV is its capacity to encode proteins which share sequence similarities with host antigens. For example, the EBV envelope protein gp110 shares sequence homology with HLA-DR alleles associated with RA risk. RA patients, particularly those with active disease, have T cells that recognize epitope shared by HLA-DR4 subtype and EBV gp110 [8,9]. Such homology might thus affect the cell response to viral gp110 and generate a lower control of viral replication and ultimately might lead to chronic inflammatory response. Other examples of "molecular mimicry" associated with EBV are the sequence identity shared by EBNA-1 and the human type II collagen and by EBNA-6 with the HLA-DQ protein. EBV also encodes functional homologues of the anti-apoptotic protein Bcl-1 which protects infected cells from apoptosis, and of IL-10 recognized for its immunosuppressive properties. The molecular mimicry along with the alteration of host immune responses during the course of RA is then consistent with the plausible role of EBV as a trigger of intra-articular inflammation.

Current therapies for the treatment of RA are very effective but can exert multiple mechanisms that may affect the immune surveillance of latently EBV-infected cells with continuous viral reactivation and constant immune stimulation particularly in long-term treatment. For example, a number of reports have demonstrated that the frequency of EBV-positive lymphomas was increased in RA patients treated with a conventional drug like methotrexate, and was found to regress following methotrexate withdrawal [10-14]. Other biologic drugs that suppress innate mediator activities like adalimumab, etanercept or infliximab (TNF inhibitors), tocilizumab (IL-6 inhibitor) and abatacept, an inhibitor of T cell co-stimulation, and B cell depletion

with rituximab could all lead to remission or primary and secondary failures. These failures or relapses observed after biologic therapies might be related to a lack of the immune control of viral reactivation from latently infected cells. A recent study in patients treated with rituximab confirms the lack of immunodominant specificities within either IgG- or IgA-ACPA in predicting relapses, and suggests that the process of citrullination, rather than any particular citrullinated-antigen drives the autoimmune response in RA patients [15]. We have recently reported that patients with active RA and long-standing disease presented abnormal elevated anti-EBV titers compared to seropositive healthy individuals, and that the presence of EBV genome in blood and synovial monocytes and neutrophils was detected in a significant fraction of these patients [16]. Interestingly, increased expression levels of Toll-like receptor (TLR) 2 and TLR9 were also detected on monocyte subsets of active RA patients, which were correlated with the enhanced capacity to produce inflammatory cytokines in response to stimulation with TLR2 and TLR9 agonists, including EBV. It was thus proposed that such increase of expression of TLR2 and TLR9 on monocytes reflects the activation of monocytes and could also be associated with active RA diagnosed in these patients. TLRs are known to promote the production of cytokines in response to both cell damage molecules released by inflamed tissues and microbial ligands in the synovium, which may explain the contribution of infectious triggers in arthritis exacerbation especially in the context of disease flares [17-19]. Indeed, TLRs expressed on the cell membrane (like TLR2) can generate the production of inflammatory cytokines following recognition of debris released from damage cells (damage-associated molecular patterns: DAMPs) or of specific viral components (pathogen-associated molecular patterns: PAMPs) following infiltration of virally infected cells in the synovium. Intracellular TLRs, like TLR9, will create a second signal by binding viral DNA motifs internalized in infected cells. Such feedback loops between extracellular and intracellular TLRs could contribute to amplify and sustain inflammatory arthritis. The elevated concentrations of TLR ligands detected in the joint of RA patients [20] have highlighted the potential impact of these sensors in the regulation of the inflammatory response and also in tissue repair in the context of arthritis joints.

Although infectious agents have long been proposed to play an indirect role in RA, no specific pathogen has been linked to the disease. Nevertheless, it is plausible that in some susceptible RA patients, exposure to virus may trigger the inflammatory response through citrullination, and consequently increases prevalence of flares of disease activity. Thus, the presence of microbial ligands in synovial fluids of RA patients is susceptible to contribute to enhance inflammation and/or fluctuations in disease severity. It can be very difficult to confirm the association of a virus with disease activity, particularly because viral manifestations can be temporally detectable in inflamed joints. Nevertheless, serological testing as well as detection of viral genome/genes in joint biopsies should be considered in RA patients, especially those showing fluctuations of clinical activity. This could be valuable in older people showing less effective defense system and whose prevalence of disease flares increases with aging. In addition, given the dual role of TLRs (and other innate receptors) in immune homeostasis and in the defense against pathogens, these sensors represent promising therapeutic targets to control inflammation in joint disease, no matter if it is induced by endogenous or by viral ligands.

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