How Herpesviridae Combined with other Viral Infections can Trigger and Drive Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) development results from an inadequate immune response to environmental challenges in genetically predisposed patients. The list of viruses associated with RA is still growing, and includes the cytomegalovirus, the Epstein-Barr virus, and the herpes simplex viruses. Several hypotheses support their causative role. Firstly, RA development may result from a polyviral community or the cumulative effect of several microbial/viral factors thus explaining the absence of a single defined pathogen. Secondly, the process of RA development from preclinical to late-stage disease may result from cumulative episodes of viral infections caused by distinct pathogens. Thirdly, viral agents may trigger RA when associated with other factors such as tobacco, ethnic differences, psychological stress, inflammation, or chronic joint tissue micro-trauma. On the other hand, others consider that RA development occurs even with ordinary infection frequency and duration and results from immune hypersensitivity to viral infections which can lead to loss of tolerance to self-antigens.

Keywords: Rheumatoid arthritis; Infections; Herpes virus

Abbreviations

RA: Rheumatoid Arthritis; CMV: Cytomegalovirus; EBV: Epstein-Barr Virus; HSV: Herpes Simplex Virus; DNA: Deoxyribonucleic Acid; Ab: Antibody; RF: Rheumatoid Factor; HVEM: Herpes Virus Entry Mediator; EGFR: Epidermal Growth Factor Receptor; SNP: Single Nucleotide Polymorphism; NK: Natural Killer

Introduction

In rheumatoid arthritis (RA) viral triggers, in particular cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Herpes simplex virus type 1 and 2 (HSV1/2), have been suggested. Moreover, compared to single infection with one of these viruses, a combined infection with at least two of them increased the risk for RA in a rate that could not be explained by a simple additive effect.

CMV infection is quite common all over the world, and in adults, its prevalence ranges between 50-85% in the United States, ~77% in Portugal, ~86% in Hungary, and ~92% in Iran Cannon, Schmid, et al. [1]. CMV, by entering lymphocytes and monocytes, establishes a lifelong latent infection following the primary infection that can be reactivated periodically in the setting of immunodeficiency with the risk of autoimmune inflammation.

EBV is a highly prevalent DNA-containing herpes virus, infecting >98% of humans by age 40, with first contact occurring typically in childhood and adolescence (the peak incidence is in the range of 15-25 years). EBV primarily infects B cells and leads to the development of a latent asymptomatic or a subclinical infection.

HSV1/2 seroprevalence in adults is found to be 60-95% worldwide, and increases with age Varga, Gorog, et al. [2] HSVs take lifetime residency in nerve cells and are transported to the mucosa during exacerbations. As a consequence, the presence of viral DNA in blood cells cannot provide comprehensive information regarding HSV infection Grinde [3].

Viral infection and RA stage

In the preclinical and early RA stages, the levels of antibodies (Ab) against the EBV viral capsid antigen and EBV viral DNA detection frequency in blood and synovial fluid cells were higher than in controls Petrov [4]. Regarding CMV, seroprevalence and the viral DNA detection rate in blood, joint fluid and synovial membrane cells are close to the general population indices Goldstein, Chibnik, et al. [5]. According to our data, individuals with clinical signs of HSV are statistically increased within the early RA group, and in first-degree RA relatives with Arleevskaya et al. [6]. Such observation is not reported by all groups, as the absence or infrequent presence of the HSV1/2 DNA in blood, joint tissues and synovial fluid cells is also reported Stahl et al. [7].

At the late RA stage, serological evidence of reactivated EBV infection is frequently observed together with a significant increase of EBV DNA prevalence and viral load in blood and synovial fluid mononuclear cells. Similarly, the level of anti-CMV antibodies (Ab) was found to increase in the RA patients with disease duration and in rheumatoid factor (RF)-positive cases. For HSV, no differences are reported regarding serum IgM anti-HSV antibody prevalence in RA Us, Cetin, et al. [8].

Lessons learned from the follow-up study

In order to further explore the interrelation between viral infections and RA development, early RA patients and their relatives were included in a 10 year follow-up study that is still ongoing Arleevskaya et al. [6]. The main results from this follow-up study were: (i) both early RA patients and their relatives suffer from more frequent and prolonged trivial infections (bacterial and viral) than those individuals without a familial history of autoimmune diseases; (ii) early RA is characterized by an elevated frequency and duration of the infectious episodes and HSV exacerbations followed by a gradual decrease when
RA is established, as observed for longer than 3 years; and (iii) among relatives who developed RA and were included in the study at the preclinical stage, the frequency and duration of the infectious episodes including HSV exacerbations started to increase one year before the RA onset, and started to decrease 2-3 years after. According to our data the ratio of persons with the clinical signs of HSV exacerbation was significantly increased in the early RA group and among the first-degree relatives of the RA patients.

In agreement with these observations, Widdifield et al. have reported an association between a history of previous infection and infectious complications during RA treatment by infliximab, an anti-TNF monoclonal Ab, or disease-modifying anti-rheumatic drugs therapy Widdifield et al. [9]. Moreover, Germano et al. supported the hypothesis that RA duration had a protective effect on the infectious syndrome Germano et al. [10].

**Hypersensitivity to viral infection in RA**

HSV spreads from cell to cell through specific receptors including the herpes virus entry mediator (HVEM), a member of the tumor necrosis factor receptor superfamily, and the epidermal growth factor receptor (EGFR). During RA, the HVEM receptor is overexpressed on most cell types within the rheumatoid synovial tissue Shang et al. [11], and soluble HVEM serum levels are increased in RA as well Jung et al. [12]. In addition to serving as a receptor for HSV, HVEM participates in the proliferation and activation of synovial fibroblasts. EGFR gene overexpression was found to occur in synovial tissue cells and bone marrow-derived mononuclear cells from RA patients and this overexpression is associated with a single nucleotide polymorphism (SNP) associated with RA risk-factor Xu et al. [13]. As a whole, it could be stated that cellular reception of the viruses can contribute to the RA progression, while it could not be excluded that HVEM and EGFR overexpression in RA are primary events and might contribute, as a consequence, to HSV dissemination.

The two pro-inflammatory cytokines, TNF-alpha and IFN-gamma, are suspected of playing an important role in protecting against HSV infection since low serum levels of any of these cytokines appears to be necessary for the recurrence and the reactivation of the virus Motamedifar et al. [14]. In this context the high serum levels of TNF-alpha in the synovial fluid that characterize RA is believed to be protective. This seems to be the case at the early RA stage since the level of TNF-alpha and IFN-gamma produced by T lymphocytes in response to infections, such as CMV/EBV, correlated with the activity of joint inflammation Davis, et al. [15]. However, it should be mentioned that, although elevated in the synovial fluids, the serum levels of TNF-alpha is similar to that observed in controls Bucht et al. [16], and that IFN-gamma producing T cells in RA patients were absent or present only in small quantities in the joint tissues. It is also possible that, in patients with RA, IFN-gamma production in response to viral stimulation is reduced. Such assertion is reinforced by the observation that the capacity of HLA-B8-restricted EBV-reactive CD8+ T cells to produce IFN-gamma in response to a panel of the virus lytic/latent peptide epitopes was significantly lower in RA patients than in controls Klatt et al. [17]. The iNK subset is another early source of cytokines and chemokines, including IFNαs and TNF-alpha, that link innate and adaptive immunity Opasawatchai [18]. A comprehensive characterization of these cells in early RA was recently presented Mansour et al. [19] showing that circulating iNKTs were reduced, and their frequency was inversely correlated to the disease activity score. It is worth noting that, in late RA, the data obtained by various authors were controversial regarding the number of iNKTs and their functions since they were found to be increased, decreased, or didn’t differ from that observed in controls (Figure 1).

![Figure 1: Features of the herpesviridae infection in patients with rheumatoid arthritis. Abbreviations: HVEM: Herpes Virus Entry Mediator; EGFR: Epidermal Growth Factor Receptor; IFN-gamma: Interferon Gamma; TNF-alpha: Tumor Necrosis Factor Alpha; Virus-Reactive CD8+ T cells; iNKTs: Invariant Natural Killer T-cells; Excessively expressed in RA factors are marked in red; Factors with reduced activity in RA are marked in blue.](image)

**Conclusion**

In conclusion, three scenarios can be proposed in order to explain how viruses could contribute to the emergence of RA in genetically predisposed individuals Konsta et al. [20]. First, in the absence of a defined pathogen, RA development at the early stage may result from a polyviral community such as CMV plus EBV, or the cumulative effect of several microbial/viral factors. Such hypothesis is reinforced by the observation that changes in the microbiome and virome, can diminish or increase the risk of RA Sandberg et al. [21]. Second, the spectrum of viral infections may vary from preclinical to late-stage RA. In other words, some pathogens may trigger RA at a preclinical stage, and subsequently lose their value at the advanced stage and vice versa. Third, viruses may trigger RA in combination with other risk factors such as tobacco, ethnic differences, psychological stress or chronic joint tissue microtrauma. Younger patients attributed their RA to previous infections more often than older patients Soderlin et al. [22].

Another scenario is that RA development is independent from viral infection and is triggered by geographical factors, differences in life style and/or is related to ethnic differences. However, the debate is not closed since the rate of viral infection in our Russian cohort is close to 75% at the onset with variations observed during the evolution while, in two Scandinavian cohorts of patients with early RA, this rate was close to 16-20%. One way to resolve these questions is to perform follow-up analyses not only with the early patients with RA but also with their relatives.

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References

1. Cannon MJ, Schmid DS, Hyde TB (2010) Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol 20: 202-213.
2. Varga M, Gorog D, Kari D, Kornyei E, Kiss E, (2011) Cytomegalovirus seroprevalence among solid organ donors in Hungary: correlations with age, gender, and blood group. Transplant Proc 43: 1233-1235.
3. Grinde B (2013) Herpesviruses: latency and reactivation - viral strategies and host response. J Oral Microbiol 5. 6.
4. Petrov AV (2005) Frequency of different infectious agents persistence in mononuclear leukocytes of blood and synovial fluid in patients with rheumatoid arthritis. Lik Sprava. 5-6: 28-32.
5. Goldstein BL, Chibnik LB, Karlson EW, Costenbader KH (2012) Epstein-Barr virus serologic abnormalities and risk of rheumatoid arthritis among women. See comment in PubMed Commons below Autoimmunity 45: 161-168.
6. Arleevskaya MI, Gabdoulkhakova AG, Filina YV, Bredberg A, et al. (2014) A transient peak of infections during onset of rheumatoid arthritis: a 10-year prospective cohort study. See comment in PubMed Commons below BMJ Open 4: e005254.
7. Stahl HD, Hubner B, Seidl B, Liebert UG, van der Heijden IM, et al. (2000) Detection of multiple viral DNA species in synovial tissue and fluid of patients with early arthritis. Ann Rheum Dis 59: 342-346.
8. Us T, Cetin E, Kasifoglu N, Kasifoglu T, Akgun Y (2011). Investigation of Epstein-Barr virus and herpes simplex virus markers by serological and molecular methods in patients with rheumatoid arthritis and systemic lupus erythematosus. Mikrobiyol Bul 45: 677-683.
9. Widdifield U, Cetin E, Kasifoglu N, Kasifoglu T, Akgun Y (2011). Investigation of different infectious agents persistence in mononuclear leukocytes of blood and synovial fluid in patients with rheumatoid arthritis. Lik Sprava. 5-6: 28-32.
10. Arleevskaya MI, Gabdoulkhakova AG, Filina YV, Miftakhova RR, Bredberg A, et al. (2014) A transient peak of infections during onset of rheumatoid arthritis: a 10-year prospective cohort study. See comment in PubMed Commons below Autoimmunity 45: 161-168.
11. Goldstein BL, Chibnik LB, Karlson EW, Costenbader KH (2012) Epstein-Barr virus serologic abnormalities and risk of rheumatoid arthritis among women. See comment in PubMed Commons below Autoimmunity 45: 161-168.
12. Jung HW, La SJ, Kim JY, Heo SK, Kim JY, et al. (2003). High levels of soluble herpes virus entry mediator in sera of patients with allergic and autoimmune diseases. Exp Mol Med 35: 501-508.
13. Xu Y, Huang Y, Cai D, Liu J, Cao X (2015) Analysis of differences in the molecular mechanism of rheumatoid arthritis and osteoarthritis based on integration of gene expression profiles. See comment in PubMed Commons below Immunol Lett 168: 246-253.
14. Motamedifar M, Sarvari J, Ebrahimpour A, Emami A (2015) Symptomatic Reactivation of HSV Infection Correlates with Decreased Serum Levels of TNF-alpha. Iran J Immunol 12: 27-34.
15. Davis JM, Knutson KL, Strausbaugh MA, Green AB, Crowson CS, et al. (2013) Immune response profiling in early rheumatoid arthritis: discovery of a novel interaction of treatment response with viral immunity. Arthritis Res Ther 15: 199.
16. Bucht A, Larsson P, Weisbrot I, Thorne C, Pisa P, et al. (1996) Expression of interferon-gamma (IFN-gamma), IL-10, IL-12 and transforming growth factor-beta (TGF-beta) mRNA in synovial fluid cells from patients in the early and late phases of rheumatoid arthritis (RA). Clin Exp Immunol 103: 357-367.
17. Klat T, Ouyang Q, Flad T, Koetter I, Bühring HJ, et al. (2005) Expansion of peripheral CD8+ CD28- T cells in response to Epstein-Barr virus in patients with rheumatoid arthritis. See comment in PubMed Commons below J Rheumatol 32: 239-251.
18. Opasawatchai A, Matangkasombut P (2015) iNKT Cells and Their Potential Lipid Ligands during Viral Infection. See comment in PubMed Commons below Front Immunol 6: 378.
19. Mansour S, Tocheva AS, Sanderson JP, Goulston LM, Platten H, et al. (2015) Structural and Functional Changes of the Invariant NKT Clonal Repertoire in Early Rheumatoid Arthritis. J Immunol 195: 357-361.
20. Konsta OD, Le Dantec C, Brooks WH, Renaudineau Y (2015). Genetics and Epigenetics of Autoimmune Diseases. 1–9.
21. Sandberg ME, Bengtsson C, Klæreskog L, Alfredsson L, Saevarsdottir S (2015) Recent infections are associated with decreased risk of rheumatoid arthritis: a population-based case-control study. See comment in PubMed Commons below Ann Rheum Dis 74: 904-907.
22. Soderlin MK, Bergsten U, Svensson B, BS Group (2011). Patient-reported events preceding the onset of rheumatoid arthritis: possible clues to aetiology. Musculoskeletal Care 9: 25-31.