Rheumatoid arthritis: a viral aetiology?

Viruses are often proposed as potential aetiological agents in rheumatoid arthritis (RA). However, this hypothesis is based primarily on circumstantial evidence rather than on experimental data. This editorial discusses specific viral candidates for RA and highlights some of the difficulties in proving disease causation.

WHY ARE VIRUSES IMPLICATED IN RA?

RA has a complex multifactorial aetiology likely to require both genetic and environmental components. Genetic factors are implicated by studies showing a concordance rate of around 20% in monozygotic twins and this susceptibility is linked, at least in part, to specific major histocompatibility complex (MHC) alleles (Nepom and Nepom, 1998). At the same time, this low concordance rate implies that environmental factors also have a strong influence.

Although many environmental agents could potentially influence RA, infection is widely regarded as the most likely contributory factor and viruses are attractive candidates because of their ability to induce immune activation and dysregulation. Moreover, a number of viruses including rubella and parvovirus induce a transient, self-limiting arthritis soon after infection.

WHAT ARE THE CANDIDATE VIRUSES?

Any candidate aetiological virus should have a pattern of infection that matches the epidemiology of RA. RA shows a worldwide prevalence of around 1% with little geographical variation (Silman and Hochberg, 1993). In addition, RA does not have the characteristics of a classical infectious disease; there are no epidemics. This suggests that RA may arise in genetically predisposed individuals following infection with a common or ubiquitous virus. Given the chronic, progressive nature of disease in RA, the most likely viral candidates are those viruses that establish a persistent infection. These include retroviruses, parvovirus B19 and herpesviruses.

Retroviruses

Retroviruses are regarded as potential aetiological agents in RA because there is an established animal model of RA caused by a retrovirus. Goats infected with caprine arthritis encephalitis virus develop a chronic erosive arthritis strongly reminiscent of RA. The course of disease is MHC dependent and is greatly influenced by the age at infection; young goats develop neurological disease, adult goats get arthritis.

Infection with human retroviruses is also associated with joint disease. A subset of patients infected with human T-cell leukaemia virus type-1 (HTLV) or human immunodeficiency virus (HIV) type-1 suffer a mild arthritis and HTLV is able to infect synovial fibroblasts (Kitajima et al, 1991). Although neither HTLV nor HIV are thought to cause RA, retrovirus-like particles have been observed in RA synovial fluid using electron microscopy (Stransky et al, 1993). Unfortunately, this putative virus has not been characterized further.

More recently, we have described a novel infectious human retrovirus in synovial tissue from patients with various forms of arthritis, including RA (Griffiths et al, 1999). This new virus, denoted human retrovirus-5 (HRV-5), appears to be a common infection in humans but is present at an increased viral load in synovial tissue and peripheral blood in RA. Present data on HRV-5 are limited but studies are ongoing to determine the epidemiology of infection and investigate potential mechanisms for pathogenesis.

Parvovirus B19

Parvovirus B19 is almost ubiquitous in adults with a worldwide distribution, and causes a transient polyarthritis in around 1% of infections. In a minority of cases, parvovirus-induced arthritis may persist for several months or even years and for this reason parvovirus B19 has been proposed as an aetiological agent for RA.

In the most complete study (Takahashi et al, 1998) parvovirus DNA and RNA were detected in RA synovial tissues much more frequently than in osteoarthritis or other control tissues. These data correlate with evidence of active parvovirus replication in RA joints.

Herpesviruses

Herpesviruses have often been cited as potential agents in RA, in particular Epstein–Barr virus (EBV). However, increased EBV replication in RA almost certainly reflects a deficiency in local T-cell control of the virus in these patients (Tosato et al, 1984). In light of this, the increased detection of HRV-5 and parvovirus B19 in RA must be interpreted with caution.

DIFFICULTIES IN ESTABLISHING CAUSATION

The initial identification of a candidate virus in RA is merely the first step towards establishing an aetiological role. Developing these initial findings into a model of disease causation and pathogenesis may be extremely difficult. How can we

prove causation for a disease where the candidate viral triggers are ubiquitous? Animal models may help but are of limited use for viruses such as parvovirus B19, which has a restricted species tropism.

Other confounding issues include the effect of virus strain variation and the possibility that several environmental factors may interact to elicit disease. In addition, any aetiological virus may not actually be present at disease onset. A virus could initiate immunopathological mechanisms and subsequently be cleared from the body. Finally, given the clinical heterogeneity of RA, viruses may act as co-factors for disease severity rather than as initial triggers of disease.

CONCLUSIONS

Despite these difficulties, the identification of HRV-5 and recent data on parvovirus B19 show that progress is being made and provide specific candidates for future research. Proof of causation for a viral agent in the development of RA would be an enormous breakthrough since it would provide a specific target for therapeutics. Perhaps more importantly, it would raise the possibility that RA could ultimately be prevented by immunization. HM

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Griffiths DJ, Cooke SP, Hervé C et al (1999) Detection of human retrovirus 5 in patients with arthritis and systemic lupus erythematosus. *Arthritis Rheum* **42:** 448–54

Kitajima I, Yamamoto K, Sato K et al (1991) Detection of human T cell lymphotropic virus type I proviral DNA and its gene expression in synovial cells in chronic inflammatory arthropathy. *J Clin Invest* **88:** 1315–22

Nepom GT, Nepom B (1998) Genetics of the major histocompatibility complex in rheumatoid arthritis. In: Klippel JH, Diepe PA, eds. *Rheumatology.* 2nd edn. Mosby International, London: 7.1–7.12

Silman AJ, Hochberg MC (1993) *Epidemiology of the Rheumatic Diseases.* Oxford University Press, Oxford

Stransky G, Vernon J, Aicher WK, Moreland LW, Gay RE, Gay S (1993) Virus-like particles in synovial fluids from patients with rheumatoid arthritis. *Br J Rheumatol* **32:** 1044–8

Takahashi Y, Murai C, Shibata S et al (1998) Human parvovirus B19 as a causative agent for rheumatoid arthritis. *Proc Natl Acad Sci USA* **95:** 8227–32

Tosato G, Steinberg AD, Yarchoan R et al (1984) Abnormally elevated frequency of Epstein-Barr virus-infected B cells in the blood of patients with rheumatoid arthritis. *J Clin Invest* **73:** 1789–95

KEY POINTS

- Viral involvement in rheumatoid arthritis is often assumed but there is limited direct evidence available.
- The epidemiology of rheumatoid arthritis suggests a role for a common virus infection in genetically predisposed subjects.
- Virus detection in rheumatoid arthritis synovium is insufficient to confirm an aetiological role.
- Current viral candidates include human retrovirus-5 and parvovirus B19.
- If rheumatoid arthritis does have a viral aetiology, could a vaccine be developed?