

Editorial

Does a retrovirally encoded superantigen cause multiple sclerosis?

Retroviruses are commonly associated with neurological disease in animals, for example, inflammatory encephalomyelopathies of sheep (visna virus),¹ horses (equine infectious anaemia virus), goats (caprine encephalitis/arthritits virus)² and mice (murine leukaemia virus).³ The first retrovirus shown to be pathogenic in humans was discovered by Gallo's group⁴ who demonstrated that human lymphotropic virus type-1 (HTLV-1) was the cause of adult T-cell leukaemia (ATL). Subsequently this virus was associated with a myelopathy endemic in the Caribbean^{5,6} and Japan,⁷ a condition now called tropical spastic paraparesis (TSP) or HTLV-1 myelopathy (HAM). TSP is an inflammatory demyelinating and degenerative myelopathy predominantly affecting the thoracic and lumbar regions causing a progressive paraparesis with sphincter involvement.^{8,9} Immune mechanisms probably play an important part in the pathogenesis of this condition.¹⁰

The discovery of the association of HTLV-1 with TSP and the similarities between TSP and the primary progressive form of multiple sclerosis (MS) led to an intensive search for retroviruses in the latter condition. Two groups of workers^{11,12} claimed that an HTLV-1 like agent was indeed associated with MS and considerable excitement engendered by the observation that using DNA amplification techniques (polymerase chain reaction, PCR) sequences of DNA homologous with parts of the HTLV-1 genome were present in peripheral blood leucocytes. Unfortunately, these observations have not been confirmed;^{13,14} some of the positive results were probably due to contamination of specimens, a major problem with sensitive amplification techniques. On the other hand Perron *et al*¹⁵ have claimed that cell lines derived from CSF of MS patients contain retroviral-like particles and that reverse transcriptase, an enzyme unique to retroviruses, is produced by these cells. Recently these workers have isolated a new retrovirus from peripheral blood monocytes in about half of their MS patients, especially from those with frequent exacerbations, and shown that sera from the positive patients contain antibodies directed against the original CSF isolates.¹⁶

If these observations are confirmed, and there have been many false dawns in the virology of MS, the question arises how the CNS damage is produced. While a large number of potential mechanisms to cause CNS dysfunction in retroviral infection exist, an immune mediated one is attractive. In this article I will argue from the recent observations in several laboratories that certain retrovirally encoded superantigens (see below) are relevant to the pathogenesis of MS and could explain some of the confusing immunological features of the disease.

Immunological abnormalities in MS

There is compelling evidence of immune abnormalities in patients with MS.¹⁷ For example, in the CSF there is often a pleocytosis with local synthesis of immunoglobulins, detected as oligoclonal bands, and complement consumption. In the blood there are quantitative abnormalities of T-cell subsets with a relative paucity of CD8+ cells. Further, patients with MS have a marked immune response to a number of antigens, especially measles, both in the peripheral blood and CSF. Pathologically there is evidence of perivenular infiltration with lymphocytes and this is an early event in the genesis of the plaque.¹⁸ Finally, there are similarities between experimental allergic encephalomyelitis, particularly the relapsing and remitting model (an undoubted immune disorder), and MS.

Superantigens

For an antigen to be recognised by the immune system a number of obligatory requirements must be fulfilled. First, the antigen has to be presented by an antigen presenting cell (APC) to that set of lymphocytes bearing the CD4 marker. Secondly, the APCs must exhibit an appropriate major histocompatibility complex (MHC) group so that the peptide can neatly fit in the groove of the complex for presentation to the lymphocyte. Thirdly, the T-cell receptor (TCR) of the lymphocyte must be of the appropriate type. The major TCR has an alpha and a beta chain, both of which have a constant and variable region; within the latter are the hypervariable and junctional zones that are important for recognition of a particular peptide. The result of this complex arrangement is that for recognition of a peptide there is both MHC and TCR restriction culminating in an exquisitely specific immune response.

This system, however, is not the only one available for the initiation of an immune response. There is another, much less specific mechanism, namely: the superantigen system. Certain antigens such as Staphylococcal enterotoxin combine with the beta chain of the TCR on its lateral surface rather than being presented in combination with a particular MHC group to the whole TCR. This combination, which is thus largely independent of the MHC group, can stimulate the lymphocyte. It has long been recognised that there are minor lymphocyte stimulating (MIs) antigens that result in a relatively non-specific stimulation of T-cells; thus a mixed lymphocyte reaction can occur between cells of compatible MHC groups because of these naturally occurring antigens.¹⁹ The MIs antigens react with the beta chain of the TCR in the same manner as enterotoxin, that is, they are superantigens, and because of their lack of specificity can activate up to 10% of

all CD4+ cells compared with the minute proportion of T-cells specifically activated by a single conventional antigen.

A major breakthrough concerning these MIs antigens, also known as V_b selective elements ($V_{b,se}$), is the recent discovery in the mouse that they are encoded by a retrovirus. It has been shown that either mammary tumour virus²⁰⁻²³ or the murine leukaemia virus²⁴ (both retroviruses) encode a V_b stimulating antigen ($V_{b,se}$). How is this relevant to MS?

In experimental allergic encephalomyelitis (EAE), induced by injection of myelin basic protein (MBP) in Freund's adjuvant, there is an MHC restriction so that some inbred strains of rats and mice are totally resistant to the disease while others invariably develop it. Further, it is known that restricted parts (epitopes) of the MBP molecule are the necessary antigen for the induction of EAE. Finally, and most importantly, it has been shown that there is a marked restriction of the TCR that can be used to induce EAE²⁵. Thus in both rats and mice one particular sequence in part of the V_b chain (8·2) is obligatory for the induction of EAE. A similar situation may well exist in MS. Hafler and his group²⁶ showed that both MS patients and control subjects produced clones of lymphocytes that recognised the limited encephalitogenic regions of MBP, that this recognition was MHC restricted and that one particular V_b variable gene product was used. Subsequent work²⁷ has demonstrated that the specificity is not as complete as first suggested but there is certainly good evidence that a limited repertoire of V_b and MHC genes are used to recognise restricted epitopes of MBP in patients with MS. A problem is, however, immediately apparent. Both normal subjects and patients with MS have these competent clones yet, by definition, only the latter have the disease. In the case of one pair of identical twins discordant for MS both had such clones, an observation that is not surprising as the two subjects had an identical genetic constitution. So what distinguishes MS patients from normal subjects?

If one assumes the patients with MS were being stimulated by a superantigen, encoded by a retrovirus, it would be possible to explain all the facts. If in the MS patients a retrovirus had encoded minor lymphocyte stimulating antigens (MIs or $V_{b,se}$) such an antigen would cause a relatively non-specific activation of perhaps 10% of all the CD4+ lymphocytes. Among these would be clones to a wide variety of antigens which might well include encephalitogenic MBP epitopes. This would explain why identical twins are discordant; both have competent clones but only the twin with the retrovirus has lymphocytes that are stimulated into clonal expansion by the relatively non-specific effect of a superantigen.

Does the hypothesis explain any other features of MS? The frequent occurrence of oligoclonal bands within the CSF of the majority of patients with MS indicates an active immune response but the antigens against which most of these bands are directed is unknown as only about 10% can be adsorbed by viral and CNS antigens. This nonsense synthesis could be explained by numerous clones being activated by a superantigen ($V_{b,se}$). It is known that in TSP similar bands occur and that only a small proportion recognise HTLV-1, the retrovirus causing the disease. It may well be that HTLV-1 has encoded a $V_{b,se}$ and activated many clones only a few of which are competent against the retrovirus. Further, in the case of MS, this non-specific activation would account for the high antibody titres to many common viruses found in the serum and CSF.

There is a problem with this hypothesis. Why do patients with MS not develop other autoimmune diseases? In fact there may be an association of ankylosing spondylitis, ulcerative colitis and myasthenia gravis with MS, all three having evidence, to a greater or lesser degree, of an immune

basis²⁸ and there may be a paucity of other immune diseases in patients, particularly rheumatoid arthritis. These differences are readily explicable in terms of MHC and TCR restriction provided the restriction extends to the effector arm of the immune response. To activate a clone of cells against a peptide it is necessary for the peptide to nest within the MHC groove; in the absence of this association between peptide and MHC molecule an immune response will not occur or be limited. It is quite possible that the appropriate antigens for certain diseases are of a configuration that fits a limited number of MHC groups some of which will be satisfactory for MBP and others will be quite incompatible, with gradations in between. A similar argument also applies to the adequacy of the TCR in the recognition of a particular peptide. That this hypothesis is not fanciful is indicated by the occurrence of multisystem disorders in known retroviral diseases of humans and animals. For example HTLV-1 myelopathy is commonly associated with myositis and a pneumonitis in humans, while ovine visna (myelopathy) is accompanied by a pneumonitis (maedi) and caprine encephalitis virus also causes an arthritis. All these groupings could be explained by MHC or TCR restriction.

Finally, the retroviral hypothesis of MS could explain some of the epidemiological features of the disease. First, the geographical restriction of MS is explicable in terms of the putative retrovirus being found only in temperate zones. Second, it would explain some features of migration studies where there is evidence of a prolonged incubation period a feature typical of retroviral infection. Relevant to both these points Dean has shown that migration to South Africa, an area of low incidence, from Northern Europe (high incidence area) before sexual maturity protects the patient from MS.²⁹ Data obtained by the present author from West Indian patients with MS suggests those born in Britain have a mean age of onset of the disease of 20 years whereas those who were born in the Caribbean and are now resident in the UK develop the condition approximately 20 years after immigrating.³⁰ These observations are consistent with an incubation period that is 20 years or more and is comparable to data obtained for HTLV-1 associated myelopathy affecting a similar population. Thirdly, retroviral infections are transmitted by a variety of routes but sexual contact and suckling are among the most frequent, for example, both routes are utilised by HTLV-1 in humans and suckling by visna virus in sheep. The fact that MS, in common with HTLV-1 associated myelopathy, is rare before sexual maturity, occurs more frequently in women and, in vertical family cases, is usually associated with maternal (not paternal), disease—all consistent with MS being caused by a retroviral infection transmitted sexually or in breast milk.

In this article I have argued that a retrovirus causes MS, that the disease is immune mediated, that the immune response is triggered via a superantigen non-specifically stimulating many T-cell clones, and that this superantigen is a V_b selective element encoded by the retrovirus. The auto-antigen against which this response is generated is unknown but there is evidence that MBP is involved. That the disease is focal, that is, characterised by demyelinating plaques, rather than diffuse in nature could be explained in terms of local breakdown of the blood-brain barrier. It is clear that such a breakdown is an early, if not the first step, in plaque generation.³¹ Although there are many potential reasons for the barrier to break, a simple model of traumatic damage could account for the commonest sites of lesions being in the highly mobile optic nerve and cervical cord, especially where tethered by the dentate ligaments,³² and the periventricular areas, particularly those where acute angles occur resulting in high shear stress. The problem is

to find this elusive retrovirus, if it exists; Perron *et al*^{15 16} may have found a candidate.

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Neurological stamp

Girolamo Fracastoro 1484–1553

The origins of syphilis remain doubtful but it is generally believed that when Columbus returned to Spain in March 1493 his crew carried the infection with them. In 1494 Charles VIII of France attacked Naples. Spanish troops (possibly fighting on both sides) brought with them not only their weapons but this disease. A large scale epidemic broke out during the siege of Naples and was originally known as “Mal de Naples”. Its most common early name was “Morbus Gallicus”. In Germany where it was spread by the French army it was known as “The French Disease”. The French called it “The Italian Disease” and the Italians “The French Disease”. It spread through Germany to Poland where it was called “Deutsche Krankheit”, and from there to Russia where it became known as the “Polish Disease”.

In 1527 a Frenchman, Jacques De Béthencourt proposed that as the disease arose from illicit love it be named “Morbus Venerèus” or venereal disease.

In 1530 a Veronese doctor, Girolamo Fracastoro, described it mythologically in a poem Syphilis Sive Morbus Gallicus. The hero of the poem was a Greek shepherd, Syphilus. One day tormented by the heat he abused the sun god. As punishment he was struck with a loathsome and contagious disease which in future bore the name Syphilis. The shepherd's name soon became the adopted name of the disease. Fracastoro achieved more fame for this than his more important scientific writings. As well as being a physician he was renowned as a poet,



physicist and geographer. He gave the first accurate clinical account of typhus, contributed greatly to the knowledge of infectious and contagious diseases and came close to suggesting the germ theory of infection.

A statue of Fracastoro can be found in Verona near the place where Romeo and Juliet met. Italy issued a stamp with his portrait to commemorate the 1955 International Medical Conference at Verona. (Stanley Gibbons 915, Scott 695.)

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