Atlas of Science
another view on science
https://atlasofscience.org

Is multiple sclerosis triggered by immunological cross-recognition between an ancient virus and brain cell proteins?

Multiple sclerosis (MS) is an autoimmune disease where immune cells (T cells) and antibodies progressively damage the myelin sheath surrounding nerve cells leading to their loss of function. We have a reasonable understanding of the disease process in MS but not the events that initiate it. Genome studies have established that one type of molecule on antigen processing and presenting cells that displays peptide fragments of protein antigens to T helper-type T cells is strongly associated with MS. This molecule is termed HLA-DR2b. Myelin oligodendrocyte glycoprotein (MOG) is one major myelin sheath protein recognised by autoimmune T helper cells. Indeed, immunisation of mice with mouse MOG can induce an autoimmune disease similar to human MS. The human genome contains remnants of many different ancient viruses (termed HERVs) that became permanently incorporated millions of years ago. HERV-W is one of several families of retroviruses. One HERV-W member found to be expressed strongly in MS patients was termed the MS-associated retrovirus (MSRV). The gene for the envelope protein of another HERV-W member has been functionally co-opted during evolution as Syncytin-1, a molecule that now performs an essential function in the human placenta.

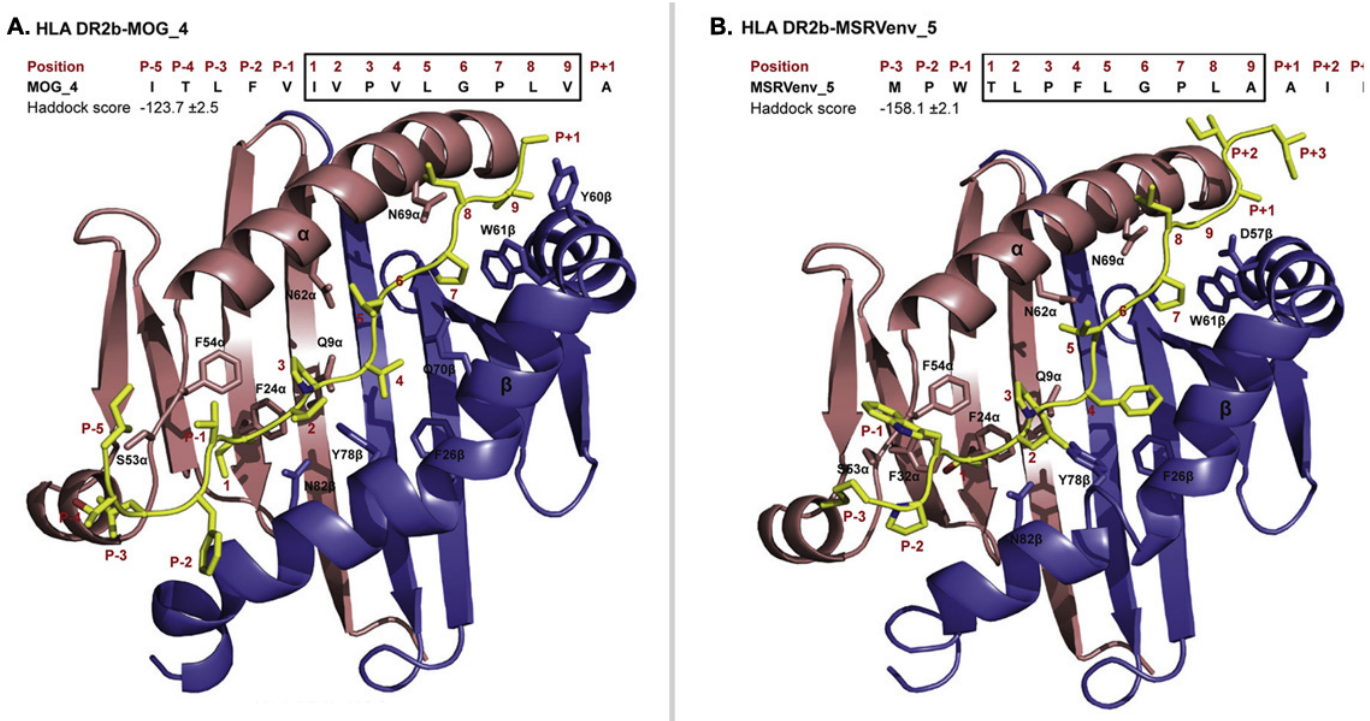

Fig 1.

Studies on the theoretical binding abilities of 15 amino acid peptides from the MSRV envelope protein (MSRVenv) and MOG identified a pair of structurally similar peptides that can both bind with sufficient affinity to HLA-DR2b to be potentially responsible for cross-recognition by T helper cells and the initiation of autoimmunity. Follow-up experimental studies showed that the two 15 amino acid peptides from MSRVenv

and MOG are able to bind with sufficient affinity and stability to HLA-DR2b molecules to support a role for them in the primary induction of MS. Figures 1 and 2 respectively show the ball and stick model structures of the two 15 amino acid peptides from MOG and MSRVenv peptides and how they might bind to the antigen binding groove on an HLA-DR2b molecule shown in a ribbon format. The calculated high negative Haddock scores in both figures suggest potentially strong binding affinity. There is strong sequence homology between the two peptides in the core nonamer amino acid sequences that bind to the HLA-DR2B peptide-binding cleft. Amino acid residues P1, P4, P6 and P9 in the nonamers serve as anchor residues which slot into the HLA-DR2b antigen binding groove, whereas side chains at P-1, P2, P5 and P8 are surface exposed and are predicted to bind with the antigen receptor on an interacting T helper cell. It is noteworthy that residues P-1, P2, P5 and P8 are either identical or strongly conserved in the MOG and MSRVenv peptides suggestive of the possibility that they can bind to the same T helper cell antigen receptor. This is a requirement for the peptide from MSRVenv being able to stimulate T helper cells that can subsequently recognize MOG peptide in the central nervous system to initiate the autoimmune reaction causing MS.

Two other observations regarding the autoimmune origin of MS require a measure of rationalization. Firstly, other pairs of structurally-related peptides between endogenous virus and exogenous virus peptides on one hand and nerve cell proteins on the other have been identified by us and others. We reported on such homology between a nerve cell protein synuclein 1 and an Epstein-Barr virus protein termed EBNA-1, both of which can bond to HLA-DR2b. MSRVenv – MOG molecular mimicry may be regarded as a better candidate pair for initiating autoimmunity because of the ready establishment of MS-like disease in mice with MOG immunisation. Secondly, there is strong evidence that Epstein-Barr virus infection is a necessary prerequisite for MS. A clear immunological explanation for this has not been established but it could involve immune dysregulation by EBV or molecular mimicry between EBV proteins and nerve cell proteins. Also, EBNA-1 promotes alternative splicing of cellular genes and is widely produced in EBV infected cells, so that its splicing activity may have a role in producing functional MSRVenv molecules.

Ranjan Ramasamy
ID-FISH Technology Inc., 797 San Antonio Road, Palo Alto, CA 94303, USA

Publications

HLA DR2b-binding peptides from human endogenous retrovirus envelope, Epstein-Barr virus and brain proteins in the context of molecular mimicry in multiple sclerosis
Ranjan Ramasamy, Fiyaz Mohammed, Ute-C Meier
Immunol Lett. 2020 Jan

Potential molecular mimicry between the human endogenous retrovirus W family envelope proteins and myelin proteins in multiple sclerosis
Ranjan Ramasamy, Blessy Joseph, Trevor Whittall
Immunol Lett. 2017 Mar