

Molecular mimicry between HERV-W family envelope and myelin proteins in the aetiology of multiple sclerosis

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Introduction

- Multiple sclerosis is an autoimmune disease with poorly understood aetiology
- T_H1 , T_H17 , T_C and innate immune cells, and antibodies involved in damaging myelin sheath and oligodendrocytes – immunopathology of ongoing MS is complex. $CD4^+$ T_H cells have a crucial role in initiating autoimmunity
- Target antigens are MBP, MOG and PLP
- HLA DRB1*1501 β chain pairs with DRA*0101 α chain to form the HLA DR2b heterodimer. HLA DR2b and MSR_V (member of HERV-W family) expression associated with MS
- Molecular basis for this relationship is not known

Hypothesis

- **Cross-reactive T_H epitopes in HERV-W family envelope and myelin proteins initiate MS in an inflammatory context**

Tests of Hypothesis

- Sequence homologies between MSRV envelope protein & syncytin-1 of the HERV-W family, syncytin-2 of the HERV-FRD family and MBP, MOG, PLP investigated using NCBI-BLAST
- 15 mer peptides in the HERV envelope proteins and myelin proteins potentially binding to HLA DR2b and HLA DR2a (where the β chain of HLA DRB5*0101 pairs with the α chain of DRA*0101) were investigated using the Immune Epitope Data Base (IEDB) Simplified Matrix Method (SMM). Peptides ranked according to their predicted affinity IC_{50} in nM. Core nonamers analysed

Results

- Syncytin-1 and the MSR/V envelope protein were 87% identical while syncytin-2 is more distantly related to the two HERV-W proteins

Main Regions of Homology between HERV Envelope and Myelin Proteins

<i>HERV protein</i>	<i>Myelin protein</i>	<i>E value</i>
• Syncytin-1, 8-58	MBP 223-274 ^a	0.06
• Syncytin-1, 448-460	MOG 214-226 ^b	0.038
• Syncytin-1, 411-464	PLP 114-167 ^c	1.6
• Syncytin-2, 170-271	MBP 230-273 ^a	3.8
• Syncytin-2, 483-495	MOG 214-226 ^b	0.094
• Syncytin-2, 355-369	PLP 29-43 ^d	7.2
• MSR/V envelope, 8-58	MBP 223-274 ^a	1.8
• MSR/V envelope, 411-464	PLP 114-167 ^c	0.91
• MSR/V envelope, 395-420	PLP 23-48 ^d	7.3

Principal Homologous HERV Envelope Protein and Myelin Protein Peptide Pairs Predicted to Bind to HLA DR2b and HLA DR2a

HERV peptide	Predicted binding	Homologous myelin peptide	Predicted binding
Syncytin-1: ILPFLGPLA (448-456)	DR2b High	MOG: IVPVLGPLV (214-222)	DR2b High
Syncytin-2: VLPLTGPLV (483-491)	DR2b Int	MOG: IVPVLGPLV (214-222)	DR2b High
MSRV env: TLPFLGPLA (448-456)	DR2b Int	MOG: IVPVLGPLV (214-222)	DR2b High
Syncytin-1 & MSRV env: (5-19) ^a	DR2b Int	MBP: (V)VHFFKNIV(T) (220/1-228/9)	DR2b High
Syncytin-1 & MSRV env: FLFTVLL ^b (8-14)	DR2b&2a Int	PLP: FFFLYGALL (78-86)	DR2b High

Conclusions

- *In silico* evidence supports the hypothesis that molecular mimicry between syncytin-1 and MSR/V envelope protein on one hand and the myelin proteins MBP, MOG and PLP on the other can initiate MS
- Suggests a molecular basis for the observed association between HLA DRB1*15:01, HERV-W and MS
- MSR/V envelope protein expression can play a role in initiating MS in both males and females
- Syncytin expression in placenta may convey additional risk for MS in females
- Next step - experimental verification