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Poster présenté par l'associaton Positifs

Multiple sclerosis (MS) and Epstein-Barr virus (EBV): Molecular homology between Myelin Basic Protein (MBP) and HTLV-1, -2 Gag p15, EBV EBNA-1 at the triproline motif.

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INTRODUCTION

Epstein-Barr Virus (EBV) infections when occuring late in adults (infectious mononucleosis) enhanced 20 fold the relative risk to contract MS *(Review in: Ascherio A, Ann Neurol 2007)*. Oligoclonal IgG antibodies (or OCB= O ligo c lonal B ands) in cerebrospinal fluid, a hallmark of Multiple Sclerosis, are directed against EBV EBNA-1 repeat amino acid sequence Alanine-Glycine-Alanine-Glycine-Glycine-Alanine AGAGG *(Cepok S, 2005)* . Human T-cell leukaemia virus-1 (HTLV- 1) infects some 20 millions individuals worldwide; only 2-5% will develop a chronic encephalomyelopathy, H TLV-1 a ssociated M yelopathy / T ropical S pastic P

araparesis (HAM/TSP)
(Beby-Defaux A., 1999)
. HTLV-2 has also been found in TSP among Amerindiens, with a periventricular demyelinisation
(Beilke M.A., 2005; Araujo A., 2004)
. HAM/TSP possibly mimics MS
(Reddy E.P., 1989)
.

Five viruses were found in MS:

EBV: Carriers of the HLA DR15 allele with elevated anti-EBNA-1 antibody titers may have a markedly increased risk of MS; The relative risk of MS among HLA DR15-positive women with elevated (>1:320) anti-EBNA-1 titers was ninefold higher than that of DR15-negative women with low (<1:80) anti-EBNA-1 titers *(De Jager PL, 2008)*.

Measles virus, with a molecular homology between MBP and measles virus hemagglutinin *(Old stone MBA, 1987) (See the results).*

Canine Distemper virus, a paramyxovirus like Measles virus *(Cook S.D., 1995; Rohowsky-Kochan C., 1995),* indu
cing in dogs a demyelinizing disease similar to MS.
We found an homology between Canine Distemper virus and
m
yelin
o
ligodendrocyte
g
lycoprotein (MOG).

Human Herpes Virus type 6 (HHV-6) *(Challoner, P. B, 1995; Friedman J.E., 1999)* and

Multiple Sclerosis Retrovirus MSRV *(Perron H., 1999; Komurian-Pradel F., 1999)*.

Herpes simplex virus type 1 may be also a very surprising candidate, as Herpes simplex virus type 1 ICP4 (NP_04462) sequence **AAQARP** is identical to an *encephalitogenic* peptide from modified (Alanine in position 4 instead of Lysine) MBP 1-
AA
Q
A
R
P
-6
(Pearson CI, 1999)
. for which we found an homology with bovine MBP NH2-terminus 1-
AA
Q
K
R
P
-6. Bee Propolis which is more efficient than acyclovir in the treatment of herpes simplex virus type 1.

OBJECTIVE

To link demyelinisation in MS and HAM/TSP to these viruses. METHOD: We compared amino acid sequences of MBP (human P02686), EBV, HTLV-1,-2, HHV-6 and MSRV.

RESULTS

Abbreviations used

A = Ala, Alanine; **B** = Asn or Asp, Asparagine or Aspartic acid; **C** = Cys, Cysteine; **D** = Asp, Aspartic acid;
E
= Glu, Glutamic acid;
F
= Phe, Phenylalanine;
G
= Gly, Glycine;
H
= His, Histidine;
I
= Iso, Isoleucine;

K
= Lys, Lysine;
L
= Leu, Leucine;
M
= Met, Methionine;
N
= Asn, Asparagine;
P
= Pro, Proline;
Q
= Gln, Glutamine;
R
= Arg, Arginine;
S
= Ser, Serine;
T
= Thr, Threonine;
V
= Val, Valine;
W
= Trp, Tryptophane;
X
= unknown;
Y
= Tyr, Tyrosine;
Z
= Gln or Glu, Glutamine or Glutamic acid

1°) We looked for MBP critical epitopes inducing in various experimental animals an experimental allergic encephalomyelitis (EAE): For example, the tryptophan is crucial, as its deletion abolished completely the encephalocitogenicity of MBP sequence RFSWGAEGQR;

A computer BLAST research on MBP sequence RFSWGAEGQR revealed that Rhesus Cytomegalovirus (*Hansen SG, 2003*) contained the motif RFSWG identical to the motif we found manually in canarypox virus RFSW; interestingly, it has been published that a monkey cytomegalovirus may be found in multiple sclerosis. Another match was observed with influenza virus (B/Lee/40) ns1 protein sequence RFSW. Influenza virus C antibodies has been found in MS, and MS is aggravated by influenza infection; finally, we found manually RFSW motif also in Hepatitis B HBs surface antigen used in HBV vaccination, complicated by exacerbation and/or

occurrence of MS in France (Revhab Association).

MBP crucial residues for encephalitogenicity **W QR**

MBP encephalitogenic sequence **SLSRFSWG**A**E**G**QR**PGF

Rhesus Cytomegalovirus 128-**RFSWGRD** I **RR**-137

Measles virus nucleocapside 142-**SRF**G**WF ENK**E-151

Canarypox virus 218 **RFSWVR**Y**DD**FEII

Influenza virus type B ns1 **rfswqr**al**d**ypg

Hepatitis B virus surface antigen HBs (vaccine) **SVRFSWL**SLLVPF

2°) **VACCINIA VIRUS EPITOPE ILPDDIE**

Concerning vaccinia virus and MVA (modified vaccinia Ankara strain), another result was found by analyzing Canine distemper virus (CDV) hemagglutinin epitope 234
LVPDDIE
REFDTREI 248
(Rohowsky-Kochan C, 1995);
CDV is a measles-like neurotropic dog virus implicated by
Cook SD (1995)
in multiple sclerosis in Faroe Islands. Antibodies against this epitope 234-48 was found in sustained elevated titers in spinal fluid of MS patients, suggesting that MS is a zoonotic disease

transmitted by dogs. We found by manual comparison an homology with
marsupial
m
yelin
o
ligodendrocyte
g
lycoprotein (MOG) 15 LVGDEIE 21; by computer BLAST research, we extended this core alignment to Murray Valley encephalitis, Venezuelian Equine encephalitis virus and vaccinia virus (serine protease inhibitor):

Canine distemper virus hemagglutinin	234 **LV**P**DDIE** 240
Myelin Oligodendrocyte Glycoprotein (MOG)	15 **LV**G**DEIE** 21
Murray Valley encephalitis	168 **AVI**GP**DDIE** 176
Venezuelian Equine encephalitis virus	**A**S**LV**P**NEIE**
Vaccinia virus (serine protease inhibitor)	215 **VIIL**P**DDIE** 221

Very interestingly, the Myelin Oligodendrocyte Glycoprotein (MOG) sequence 1-22 (containing 15- LVGDEIE-21) is encephalitogenic when injected in Biozzi AB/H mice
(Amor S 1994)
, confirming that the homology is really of biological significance.

3°) We noticed also manually a striking homology of Canine Distemper Virus with **interferon-beta**
VPEEIEQ:

Canine distemper virus epitope 233 **VPDDIER EFD**T**RE** 247

Interferon-beta **V**P**EEIEQ**AQ**QFQ KE**

Interferon-beta is efficient in some cases of multiple sclerosis, but the relationship between Canine Distemper Virus infected patients and the interferon response has not been explored until now.

4°) Concerning the sequence Alanine-Glycine-Alanine-Glycine-Glycine-Alanine AGAGGA *(Cep ok S, 2005),*
we found also an homology with Lyme's disease Borrelia Burgdorferii, which is coherent with the presence of oligoclonal bands (OCB) in Lyme's disease. Neurological symptoms of Lyme's disease may present like and be confounded with multiple sclerosis. We found also this motif in HHV-6, a very good causal candidate for MS.

5°) A perfect molecular mimicry **Proline-Arginine-Arginine-Proline-Proline-Proline** between HTLV-2 Gag p17 and EBV EBNA-1 permitted to center the triproline alignment:

MBP shark **Lys Lys**
MBP human 228-**Val Thr Pro Arg Thr Pro Pro Pro Ser Gln Gly Lys Gly**-240

HHV-6 U24 **Pro Arg Thr Pro Pro Pro Ser**
MSRV **Ser Pro Gln Ser Pro Pro Pro**
HTLV-2 Gag p15 **Val Gln Pro Arg Arg Pro Pro Pro Gln**
HTLV-1 Gag p15 **Val Pro Lys Lys Pro Pro Pro Gly Lys Ala**
EBV EBNA-1 **Ser Pro Pro Arg Arg Pro Pro Pro Gly Arg**

CONCLUSION

The demyelinisation observed in HAM/PST and MS is explained by a molecular mimicry/homology centered on a triproline motif PPP between myelin MBP and the 5 viruses found in these neurologic diseases: EBV, HHV-6 and MSRV (for MS), HTLV-1, -2 (HAM/TSP) ;

this is a molecular confirmation which reinforce and complete virus isolations. Interestingly, this MBP epitope is restricted by HLA DR2 (= DR15 = DR B1*1501), a crucial marker of susceptibility to MS; when injected to *B10RIII (H-2r)* mice, the 89-101 myelin basic protein peptide induced a chronic experimental allergic autoimmune encephalomyelitis *(Jansson T, 1991)*
. It is rational to treat HAM/TSP and MS with antivirals specific of retrovirus and herpes viruses, including EBV. Interestingly, a published clinical trial with an anti-herpes drug in MS showed some results. Perhaps the results would be more convincing if a selection of MS patients restricted them to those infected by herpes virus family, avoiding non response from those infected by paramyxovirus and/or retrovirus: Thus, in the future, it would seem more efficent to define in a first step the different viral sub-groups and only then to treat them specifically with the corresponding anti-viral.

Some kinds of anti-viral therapeutic vaccine like the dendritic cell vaccines (Srivasta P; and Nventa HSP-E7 against human papillomavirus) have proven their remarquable efficiency and constitute a promising avenue in the anti-viral armamentorium. Bee Propolis is also interesting against the herpes virus family.

Addendum:

The sequence mimicking Myelin Basic Protein PRTPPP, containing the triproline motif PKTPPP, is also present in T Antigen of Polyomavirus JC (Stoner GL, 1986a, 1986b, 1993), the etiologic agent of progressive multifocal leukoencephalopathy (PML), a demyelinating disease encountered in AIDS.

BIBLIOGRAPHY

- Amor S, Groome N, Linington C, Morris MM, Dornmair K, Gardinier MV, Matthieu JM, Baker D. Identification of epitopes of myelin oligodendrocyte glycoprotein for the induction of experimental allergic encephalomyelitis in SJL and Biozzi AB/H mice.
- J Immunol. 1994, 153: 4349-56.
- Araujo A, Hall WW. Human T-lymphotropic virus type II and neurological disease.
- Ann Neurol. 2004, 56(1):10-9. Review.
- Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007, 61: 288-99. Review.
- Beby-Defaux A, Frugier F, Bourgoin A, Moynet D, Hajjar C, Sainte-Foie S, Guillemain B, Agius G. Nucleotide sequence analysis of human T-cell lymphotropic virus type I pX and LTR regions from patients with sicca syndrome. J Med Virol. 1999, 59: 245-55.

- Beilke MA, Japa S, Moeller-Hadi C, Martin-Schild S. Tropical spastic paraparesis/human T leukemia virus type 1-associated myelopathy in HIV type 1-coinfected patients. Clin Infect Dis. 2005, 41(6):e57-63. Epub 2005 Jul 29.
- Cepok S, Zhou D, Srivastava R, Nessler S, Stei S, Büssow K, Sommer N, Hemmer
- B. Identification of Epstein-Barr virus proteins as putative targets of the immune response in multiple sclerosis. J Clin Invest. 2005, 115: 1352-60. Epub 2005 Apr 14.
- Challoner PB, Smith KT, Parker JD, MacLeod DL, Coulter SN, Rose TM, Schultz ER, Bennett JL, Garber RL, Chang M, Schad PA, Stewart PM, Nowinski RC, Brown JP and Burmer GC. Plaque-associated expression of human herpesvirus 6 in multiple sclerosis. Proc Nat Acad Sci USA 1995, 92: 7440–4.
- Cook SD, Rohowsky-Kochan C, Bansil S, Dowling PC. Evidence for multiple sclerosis as an infectious disease. Acta Neurol Scand Suppl. 1995, 161: 34-42.
- De Jager PL, Simon KC, Munger KL, Rioux JD, Hafler DA, Ascherio A. Integrating risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis. Neurology. 2008, 70(13 Pt 2):1113-8. Epub 2008 Feb 13.
- Friedman JE, Lyons MJ, Cu G, Ablashl DV, Whitman JE, Edgar M, Koskiniemi M,
- Vaheri A, Zabriskie JB. The association of the human herpesvirus-6 and MS. Mult Scler. 1999, 5: 355-62.
- Hansen SG, Strelow LI, Franchi DC, Anders DG and Wong SW. Complete Sequence and Genomic Analysis of Rhesus Cytomegalovirus. J. Virol. 2003, 77: 6620-36.
- Jansson L, Olsson T, Höjeberg B, Holmdahl R. Chronic experimental autoimmune encephalomyelitis induced by the 89-101 myelin basic protein peptide in B10RIII (H-2r) mice. Eur J Immunol. 1991, 21: 693-9.
- Komurian-Pradel F, Paranhos-Baccala G, Bedin F, Ounanian-Paraz A, Sodoyer M,
- Ott C, Rajoharison A, Garcia E, Mallet F, Mandrand B, Perron H. Molecular cloning and characterization of MSRV-related sequences associated with retrovirus-like particles. Virology. 1999, 260:1-9.
- Oldstone MBA. Molecular mimicry and autoimmune disease. Cell 1987, 50: 819–820.
- Perron H, Seigneurin JM. Human retroviral sequences associated with extracellular particles in autoimmune diseases: epiphenomenon or possible role in aetiopathogenesis? Microbes Infect. 1999, 1: 309-22. Review.
- Reddy EP. Amplification and Molecular Cloning of HTLV-I Sequences from DNA of Multiple Sclerosis Patients. Correction. Science. 1989, 246 (4926): 10-1.
- Rohowsky-Kochan C, Dowling PC, Cook SD. Canine distemper virus-specific antibodies in multiple sclerosis. Neurology. 1995, 45: 1554-60.