Epitope mimicry in autoimmune psychosis

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Introduction:

- Schizophrenia (SCZ) and psychosis in general has long been associated with viral infections (Epstein-Bar virus)(1).
- The potential involvement of the immune system in psychiatric disorders has been encapsulated by Dalmau's discovery of NMDAR encephalitis, which presents antibody-mediated psychosis-like behaviour.
- Here we present a theory by molecular mimicry, potentially through virus evolution, cross reactive common epitopes of SCZ related membrane proteins trigger an immune response.
- Exploring primarily the T cell response to cross reactive epitopes, taking into account MHC binding.
- Secondly, an antibody-mediated B cell response, which heavily relies on sequence matching and can only be bio logically verfied through antibody accessibility.
- The main aim is to find possible antigen targets that may be involved with brain disorders.

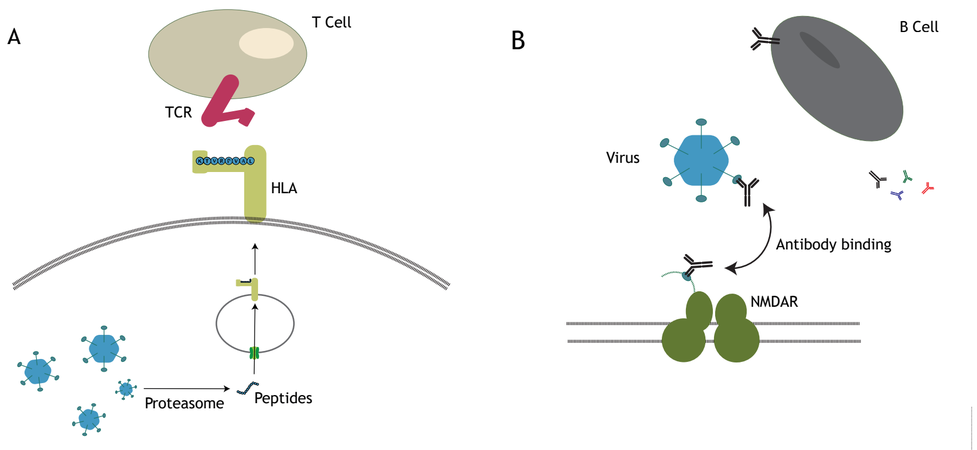

Fig. 1 Theoretical mechanisms of cross reactive epitope mimicry that could cause autoimmune psychosis.
The self protein epitope mimicked by the virus could be involved in either (or both):
A. through a T cell response once bound and presented on the MHC
B. through B cell response, through direct binding of antibodies to the common subsequence (usually recognised as a virus and triggering an immune response).

Methods:

Analysis pipeline

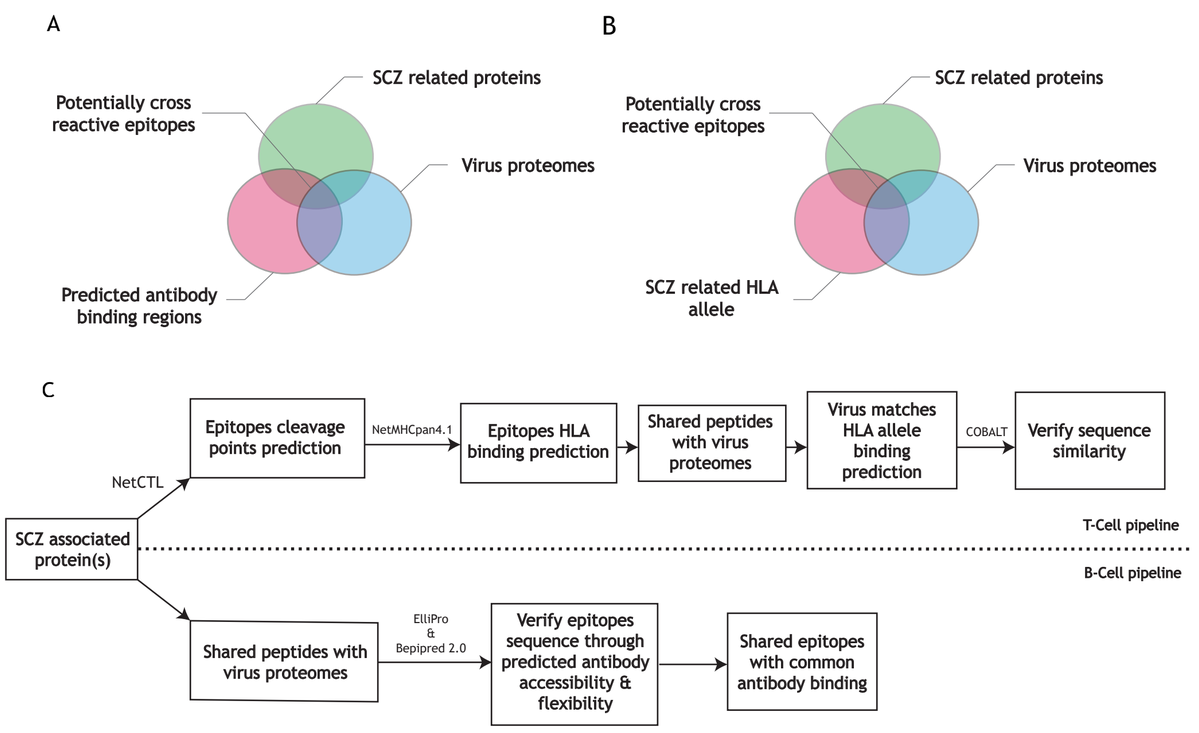

Fig. 2 B-cell and T-cell pipeline for epitope creation and analysis
Criteria for potentially B-cell (A) and T-cell (B) cross reactive epitopes. Steps involved in each pipeline and the tools used (C)

Results:

Use case: Experimentally proved reactive common epitope in type 1 Diabetes & coxsackie virus B4

Fig. 3 Proof of concept by experimentally found cross reactive epitope in type 1 diabetes.
Using the recent case of autoimmun diabetes type 1, there has been experimental evidence that shows common cross reactive epitopes between GAD65 and Coxsackievirus B4 in type 1 diabetes (2). Using the established pipline (Fig. 2c) resulted in the same epitope sequence, PVEKEK, that was experimentally found. Our matching epitopes also had a predicted binding of a common HLA allele, HLA-DQA1*03:02 - DQB1*03:02 (which is also associated with type 1 diabetes)(2, 3).

Common NMDAR & virus epitopes with shared HLA allele predicted binding

Identical Sequence	HLA allele	Protein / Virus	Epitope cut score	Epitope cut (CTL)	Binding
VRPVAL	HLA-B*08:01	GRIN2D	0.9941	DVRPVALVL	SB
VRPVAL	HLA-B*08:01	Rubella Virus	0.4395	TVRPVALPR	
AITSTL	HLA-C*07:01	GRIN1	1.0042	TFRAITSTL	WB
AITSTL	HLA-C*07:01	herpesvirus 2 (strain HG52)	0.581	YAITSTLLL	
DKSIHL	HLA-B*08:01	GRIN1	1.1898	SDKSIHLSF	WB
DKSIHL	HLA-B*08:01	Variola virus	0.5513	LDKSIHLTK	
QVHPRL	HLA-B*08:01	GRIN2A	0.9933	QVHPRLVVI	SB
QVHPRL	HLA-B*08:01	Chapare mammarenavirus	0.4423	LLSQVHPRL	
ILKKLA	HLA-B*08:01	GRIN2C	1.5315	ILKKLARVV	WB
ILKKLA	HLA-B*08:01	Epstein Bar Virus (strain B95-8)	1.9517	ILKKLAYFL	SB
ILKKLA	HLA-B*08:01	Epstein Bar Virus (strain GD1)	1.9517	ILKKLAYFL	SB

Table 1 Virus and NMDAR common epitopes
Highlighted result of virus and NMDAR common epitopes that match by a 6 AA identical sequence, predicted binding of a shared HLA allele (HLA alleles associated with SCZ by GWAS analysis) and both produced by predicted cleavage points. Only epitopes containing ILKKLA from GRIN2C and Epstein Bar Virus proteins satisfied all three criteria (4, 5).

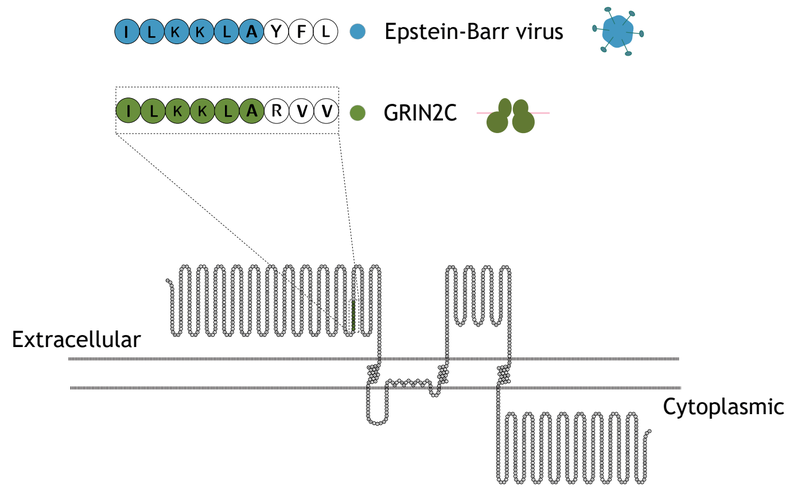

Fig. 4 Common epitope between Epstein-Barr Virus and GRIN2C
Visual representation of the common epitope (made using Protter Plot).

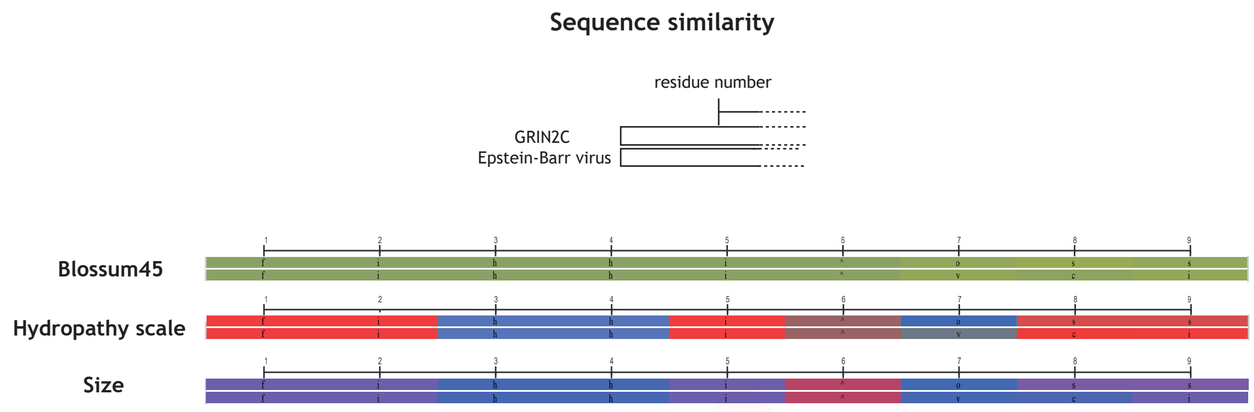

Fig. 5 Sequence similarity of the GRIN2C and Epstein-Barr Virus common epitope
Using BLAST COLBAT, analysis of the potential impact of the mismatching AA when binding to the HLA. Blossum45 shows the sequence similarity. Hydropathy scale, in which each colour reflects side chain hydropathy, with red being very hydrophobic and blue very hydrophylic. Size, where each colour represents the size of the AA. All three show a strong similarity of the mismatched AAs, further suggesting potential cross reactivity.

Conclusions

- A case for viral infection mediated SCZ has been hypothesized in recent years.
- The link between Epstein-barr Virus (EBV) and SCZ has been published
- We propose a molecular mimicry mechanism that could induce an immune response pathogenesis of SCZ.
- Through bioinformatics techniques we show a single GRIN2C epitope which is common with EBV (both SCZ related), share:
  - HLA allele binding
  - Cleavage points
  - Identical subsequence of 6AA
  - Similar sequence similarity.
- Expand the search to all neural membrane proteins and other suspected autoimmune diseases and disorders.
- Future experiments:
  - Test the epitope binding to SCZ patient blood or IGg, isolated or in HEK cells.
    - Isolating any binding antibodies.
  - Behavioural experiments (eg. testing hallucination-like behaviour, open field...) in humanized mice.
  - GRIN2C concentration & distribution

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