T CELL IMMUNE RESPONSES, MOLECULAR MIMICRY AND INFLAMMATORY CNS DISEASE
GENERATION OF AN IMMUNE RESPONSE
INDIVIDUALITY OF AN IMMUNE RESPONSE: ARE THERE SUSCEPTIBILITY FACTORS?
INDIVIDUALS (EVEN TWINS) ARE DIFFERENT DUE TO THE STOCHASTIC NATURE OF TCR AND Ig RECEPTOR REARRANGEMENTS
HLA/MHC:
GENES THAT CONTROL THE IMMUNE RESPONSE – SUSCEPTIBILITY FACTOR
WHAT IS MOLECULAR MIMICRY?

Organism: L S W A Q G A F R Y Q B L
Host: F V G A Q G A F R R N I P

Epitope Similarity

CAN OCCUR AT THE B CELL AND T CELL RECEPTORS
CONFORMATION EPITOPE

LINEAR EPITOPE

MICROBE

HOST
HETEROLOGOUS IMMUNITY

LCMV Infection → 5 weeks → PV or VV Infection
INFECTION WITH CROSS-REACTIVE VIRUSES (LCMV/PV)

• Infection of LCMV immune mice with PV leads to expansion of the subdominant cross-reactive CD8\(^+\) T cells.

• This leads to a significant reduction in the frequency of the rest of the non-cross-reactive LCMV-specific CD8\(^+\) T cells.

• All mice exhibited the same pattern of expansion of T cells specific to the cross-reactive epitope.

Kim et al JEM 2005
LCMV IMMUNE MICE INFECTED WITH VV

• Challenge of LCMV immune mice with VV lead to a much less predictable response.
• T cells specific to different epitopes were favored in different mice.
• No predictable increase of CD8+ T cells specific to any particular LCMV epitope
• Expansion pattern varied between individual mice.
• However, there were overall preferences in responses to some epitopes over other epitopes.

Kim et al. JEM 2005
MODELS/HYPOTHESES OF MULTIPLE SCLEROSIS

• Virus infection triggers autoimmunity?
  – Molecular mimicry between virus and host cell
  – Virus prime – challenge
  – Autoreactive T cells and antibody attack host cells
  – Immune responses in the brain damages myelin in a bystander fashion

• Can we use molecular mimicry to vaccinate against autoimmune disease?

• Virus infection?
  – Animal model: Theiler’s virus infection – Molecular mimicry

–
MS – EPIDEMIOLOGICAL DATA FACTORS:

• GENETICS
• GENDER
• AGE
• ENVIRONMENT
VIRUS PRIME CFA CHALLENGE

RECOMBINANT VIRUS

5 weeks

CFA

PRIME

CHALLENGE
VIRUS PRIME
VIRUS CHALLENGE

$V V_{PLP}$

5 weeks

$V V_{WT}$
LCMV
MCMV

PRIME

CHALLENGE
POTENTIAL CROSS-REACTIVITY BETWEEN VIRUS AND SELF

Molecular mimicry between CNS proteins and virus

CNS EPITOPE

VIRUS EPITOPE
SUMMARY

Viruses can silently prime for autoimmune disease that can be triggered by infection.
CAN WE USE VIRUSES TO PROTECT AGAINST AUTOIMMUNE DISEASE?
PROTECTION EXPERIMENTS

Vaccinia Inoculation
(Tail Scarification or ip)

5 weeks

MBP$_{1-20}$ Challenge
PROTECTION EXPERIMENTS

Vaccinia Inoculation
(Tail Scarification or ip)  5 weeks  MBP Challenge
VIRUSES CAN PROTECT/VACCINATE AGAINST AUTOIMMUNE DISEASE
VIRUSES CAN GENERATE CROSS-REACTIVE CD8+ T CELL RESPONSES: AUTOIMMUNE DISEASE
AUTOREACTIVE CD8\(^+\) T CELL

- *In vitro* characterization of autoreactive cell
  - Cytotoxic T cell or Natural killer cell?
    - Syngeneic vs Allogeneic killing
    - NK cell assay
  - Mechanism of killing
    - Cell-to-cell contact vs Soluble factor
    - Fas vs Perforin pathway
    - CD3, or CD8 mediated killing but not CD4
  - Viral capsid proteins contribute to its induction

- Characterization of T Cell hybridomas/Adoptive transfer of autoreactive cells into naïve mice
CONCLUSIONS

• Theiler’s virus induces an autoreactive killer cell that is different from cytotoxic T cell and NK cell.
• Killing requires direct cell-to-cell contact and is mediated by Fas and CD3, or CD8 but not by CD4.
• Viral capsid proteins contribute to induction of autoreactive cells.
• Transfer of autoreactive cells causes CNS pathology.