What Causes CNS Inflammation in MS?

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Is the CNS an immune-privileged site?

- CNS Viral infections
- Clearance of apoptotic cells/inflammation
- Immune surveillance/opportunistic infections (HIV)
- Autoimmunity
CNS immunity gone wrong…

• Multiple sclerosis
  
  – Immune mediated inflammatory disease characterized by destruction of myelin, damage to CNS resident cells, and resultant loss of mobility/cognition
  
  – Both white and grey matter affected
  – Different types of MS likely due to different underlying immune mechanisms

Pathology of MS Lesions

• Acute and chronic active lesions
  – axons commonly preserved, with presence of macrophages that have taken up myelin debris

•Inactive lesions
  – loss of axons and oligodendrocytes with few macrophages present

•Cortical plaques
Etiology of MS

- Not well understood
- Antigens may be myelin proteins, neuronal proteins, and/or astrocytic proteins
- Multiple genetic factors with moderate effect on susceptibility
  - Mutations (IL-2R & IL-7R)
  - MHC HLA-DR2B
- Environmental factors
  - Vitamin D/Latitude effect
  - Virus/infection
  - Gut and Lung immunity
- Gender
  - ~66% of MS patients are female
- Central role for the immune response in disease pathogenesis

Molecular Mimicry and Bystander Activation – Fact or Fiction?

- Molecular Mimicry: non-self antigens share homology with self-antigens leading to autoimmune disease
  - Data supporting this concept are weak
- Bystander Activation: systemic immune response against foreign antigen leads to immune response directed against self
  - T cells with dual TCRs identified that could recognize “self” with 1 TCR and “non-self” with another
  - Priming of T cells in the gut in response to specific microbiota could result in autoimmunity
Immune Cells Implicated in CNS Inflammation

- Lymphocytes
  - T cells (CD4+ and CD8+)
  - B cells
- Monocytes
- Microglia
- Dendritic Cells
- Antibodies
- Macrophages
- Granulocytes
- NK Cells

Components of autoimmunity

1. Auto antigen
2. APC activation
3. CD4 “help”
4. CD8 T cells
T cells

- CD4+ and CD8+ T cells specific for myelin antigens circulate harmlessly until activated by environmental stimulus
- How do myelin-specific T cells escape tolerance and what leads to their activation?
  - Genetics? Environment? Infection?
- What is the phenotype of pathogenic T cells in MS?
- What do these T cells do in the CNS?

Phenotype of Pathogenic T cells in MS

- Naïve CD4+ T Cell
  - IFNγ and IL-12
  - Or
  - TGF-b, IL-6, IL-23, and IL-1b
- Th1 and Th17 Cells
  - Secrete pro-inflammatory cytokines: IFNγ/IL-17, TNFα, and LT
  - PATHOGENIC
- Th2 and Treg Cells
  - Secrete Anti-Inflammatory cytokines: IL-4, IL-5, IL-10, TGF-B and IL-13
  - PROTECTIVE
**B cells**

- B cells with myelin-specific BCRs become activated and pass thru BBB into CNS
- Secrete antibodies that can mediate damage to axons
- Some patients have presence of B cell follicles in the meninges
- Also may play an important role in repair and remyelination by promoting clearance of myelin debris via opsonization

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**B cells in MS pathogenesis**

Monocytes/Macrophages/Microglia and Dendritic cells

- Damage to CNS tissue = activation of CNS resident immune cells
  - MICROGLIAL CELLS
    - Sense changes in CNS and immune regulation
    - upregulate MHC (also known as HLA in humans) and COSTIMULATORY MOLECULES
    - release CYTOKINES and CHEMOKINES, paving the way for the entry of …
  - MONOCYTES, lymphocytes and DENDRITIC CELLS into the lesion
  - DCs play central role in antigen presentation to invading T cells
  - MACROPHAGES - release proinflammatory cytokines and toxic molecules
    - nitric oxide, interleukin (IL)-1, IL-6, tumor necrosis factor- (TNF-) and matrix metalloproteinases—which cause damage to oligodendrocytes and neurons

Microglia as immune activators/APCs

Activated microglia/macrophages can be detected in CNS lesions with immunostaining

Monocytes/Macrophages activated in the periphery migrate across the endothelium into the CNS

Science & Medicine; Vol. 10(2):112 (April 2005)
Pathogenic concept for development of multiple sclerosis

Immunopathology in the MS lesion


Inflammation in the CNS results in axonal damage

- Axonal damage and loss are most important determinants of permanent neurological disability
- Axonal damage occurs even in early stages of disease
- Hypotheses for a link between an aberrant inflammatory response in the CNS and axonal damage include:
  - Activation of CD8+ T cells that directly target neurons
  - Vigorous CD4+ T-cell responses that recruit macrophages, leading to release of inflammatory mediators and toxic molecules
  - Binding of antibodies to neuronal surface antigens, followed by COMPLEMENT activation or antibody-mediated phagocytosis of axons
  - MS-specific immune response may trigger a program in CNS resident cells resulting in secondary inflammation-independent neurodegeneration
  - Indirect mechanisms, such as loss of protective myelin, mitochondrial dysfunction, dysregulation of ion channels, or release of glutamate or nitric oxide
Summary

- Etiology of MS is unknown but immune system plays a central role in disease pathogenesis – grey and white matter lesions exist
- Invasion of the CNS by T cells and B cells may be the initiating event of MS
- May be secondary to the activation of microglia and macrophages, and the local release of self or foreign antigens
- Highly focused and persistent acquired immune response in MS may be driven by a small number of antigens—the identity of which is currently unknown—that are presented in the CNS
  - Among the possible candidates are myelin or neuronal antigens, and also antigens from infectious agents that have been epidemiologically associated with MS