Research advances in animal models for OCD/PANDAS

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Disclosures

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PANDAS Network
<table>
<thead>
<tr>
<th>Antibody target</th>
<th>Disease</th>
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<tbody>
<tr>
<td>NMDAR</td>
<td>Autoimmune Encephalitis</td>
</tr>
<tr>
<td>GlyR</td>
<td>Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)</td>
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<tr>
<td>AMPAR</td>
<td>Limbic Encephalitis</td>
</tr>
<tr>
<td>VGKC complex</td>
<td>Limbic Encephalitis</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt;R</td>
<td>Paraneoplastic or immune-mediated limbic encephalitis</td>
</tr>
<tr>
<td>D2R, D1R</td>
<td>Basal ganglia encephalitis (Sydenham’s chorea, PANDAS)</td>
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<tr>
<td>GAD65</td>
<td>Stiff Person Syndrome (Cerebellar Ataxia)</td>
</tr>
</tbody>
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Autoantibodies disrupt communication between neurons in autoimmune encephalitides

Access to the brain?
The blood-brain barrier: an important gatekeeper between the blood and central nervous system

- Maintains brain homeostasis
- Limits CNS entry of
  - pathogens
  - immune cells
  - drugs
Hypothesis 1: Destruction of tight junctions between endothelial cells

Engelhardt & Ransohoff, 2012 *Trends Immunol*
Huppert, J. *et al.*, 2010 *FASEB*
Okada & Khoury, 2012 *JCI*
Risau W. *et al.*, 1990 *JCB*
Hypothesis 2: Selective transport of antibodies from endothelial cells into the brain

Zhang, D. et al., 2012 Brain Behav Immun
Abuqayyas & Balthasar, 2012 Mol Pharmaceutics
Okun, E. et al., 2010 Neuromol Med
Diamond, B. et al., 2013 Ann Rev Immunol
Group A $\beta$-hemolytic *Streptococcus pyogenes* causes a plethora of autoimmune diseases

Implicated in autoimmunity

- Scarlet fever
- Rheumatic fever
- Glomerulonephritis
- Sydenham’s chorea
- PANDAS
- Heart
- Kidney
- Skin (viral toxin)
- Brain
Neurological symptoms in SC and PANDAS

**SC**
- Chorea
- Hypotonia
- Cardiac involvement
- Hyperactivity
- Obsessions

**PANDAS**
- Choreiform movements
- Tics
- Severe separation anxiety
- Urinary frequency
- Food refusal / anorexia
- Emotional lability
- OCD-like symptoms
- Contamination fears

![Before, During, After images]

**Legend**
- **Before**
- **During**
- **After**

**Graph**
- **Symptom severity**
- **Time**
*S. pyogenes* activates both the humoral (antibodies) and cellular (Th17 cells) immune system.

**Generation of Th17 cells after multiple intranasal infections**

A novel intranasal rodent model to understand cell-mediated immunity after *S. pyogenes* infections

Dileepan T *et al.*, (2011) *PLoS Pathogens*;
Dileepan T, Smith E. *et al.*, 2016 *J Clin Invest*
Hypothesis: Dysregulated Th17 immune response to *S. pyogenes* infections is key to understanding “autoimmune” complications associated with this pathogen.
Novel pathway for T cell entry into the CNS

Dileepan T., Smith E. et al., 2016 J Clin Invest
Outline

1. What is the role of GAS-specific Th17 cells in post-infectious basal ganglia encephalitis?

2. How do CD4+ T cells gain access to the brain?
Th17 and Th1 cells are present in the CNS after multiple GAS infections
Outline

1. What is the role of GAS-specific Th17 cells in post-infectious basal ganglia encephalitis?

2. How do CD4+ T cells gain access to the brain?
Blocking the recruitment of T cells into the CNS may be beneficial for the disease.
Acknowledgements

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