the immune system; pathogenesis of neuroimmune diseases

Zsolt Illes
Department of Neurology
Odense University Hospital
University of Southern Denmark
novelties in neuroimmunology, 2014

- novel treatments in MS: oral, biological
- anti-AQP4 in NMO, then anti-MOG in NMO
- novel pathogenic antibodies in myasthenia gravis: anti-Lrp4, anti-agrin
- antibody-mediated encephalitis and epilepsy syndromes

MOG: myelin oligodendrocyte glycoprotein
immune system

response to danger

pathogen invasion tumor

tolerance against self

overactivation

deficient regulation

hypersensitivity (autoimmunity)
components of the immune system

**Innate**
- Limited (pattern)
- Linear
- No
- Random
- Complement phagocytes, NK, DC FcR, CR, cytokine rec

**Adaptive ("acquired")**
- Yes
- Exponential
- Yes
- Selective
- Yes
- Antibodies
- Lymphocytes
- BCR, TCR

**Antigen specificity**
- Propagation, enhancement
- Memory
- Interaction with antigen
- Latency

**Soluble**
- Cellular receptors
autoimmunity: compartments

environment

- thymus
- genetic background
- peripheral immune
- target organ

susceptibility, tolerance
threshold liability model: gene-environment

variation in environment
(sunshine, vitamin D, salt intake, smoking)

80% SNPs
single nucleotide polymorphisms

autoimmune disease

susceptibility alleles (genome)

threshold
vitamin D levels: genes and environment

Laursen, JH, Mult Scler, 2014

- 25-hydroxylases bound to vitamin D binding protein (DBP)
- GC
- 1α-hydroxylase
- 1,25-dihydroxivitamin
- hundreds of genes (e.g. MHCII)
levels: systems biology approach

epigenetic modifications:
- do not involve a change in DNA sequence
- alter gene expression
- heritable changes, environmental effects
- DNA methylation, histone modification, nucleosome position, non-coding RNA

GENOME
 genes polymorphism

TRANSCRIPTOME
 mRNA altern splicing

PROTEOME
 proteins

linked to demyelination
DEMYome system

post-transcriptional regulation

microRNA

post-translational modification (PTM)

proteins

PTMOME
Dr. Mello recounted the phone call that he received announcing that he had won the prize.

He recalls that it was shortly after 4:30 am and he had just finished checking on his daughter, and returned to his bedroom. The phone rang (or rather the green light was blinking) and his wife told him not to answer, as it was a crank call. Upon questioning his wife, she revealed that it had rung while he was out of the room and someone was playing a bad joke on them by saying that he had won the Nobel prize. When he told her that they were actually announcing the Nobel prize winners on this very day, he said "her jaw dropped."
microRNA: complexity

genomic DNA

- microRNA
  - mRNA
    - protein
  - mRNA
    - protein

Martin and Illes, J Clin Exp Neuroimmunol, 2014
self-tolerance: protection against autoimmunity

central tolerance
thymus

target organ
regulation

peripheral tolerance
peripheral immune organs

active:
regulatory T cells

generation needs:
antigen-specific
MHC-related stimulation

Tr1
Th3

Tr1
Th3

Tr1
Th3

IL-10
TGF-β

innate, natural

NKT
CD4+CD25+ Treg

passive
antigen presentation: MHC and T cell receptor

Nara, Japan
MHC I, MHC II, MHC III: chromosome 6

- classical complement C2 C4
- cytokine TNF-α and β
- heat shock proteins

### III
- brain:
  - C1q and C3 tag synapses for elimination
  - TNF-α regulates expression of AMPARs, increases connectivity
- hsp: chaperons, elimination of misfolding proteins

### I
- on all nucleated cell
  - presented peptides: **intracellular**
  - MHC-peptide monitored by **CD8**+ Tc
  - binds to inhibitory receptors of **NK**

  - brain:
    - modulate synaptic plasticity (negatively NMDAR function and AMPAR trafficking)
    - expression regulated by neuronal activity

### II
- on antigen presenting cells
  - presented peptides: **extracellular**
  - MHC-peptide monitored by **CD4**+ Th

  - brain:
    - microglia, astrocyte, perivascular monocyte
central tolerance

- MHC repertoire?
- TCR repertoire?
- deficient selection (apoptosis)?

expressed in thymus?

bone marrow

THYMUS

positive selection
MHCII

negative selection
MHCII + Ag

blood
antigen in the thymus and autoimmune susceptibility

PLP

DM20

thymus

brain
T cell activation and signals

APC: antigen presenting cell

**Cytokines out**

**Cytokines in**

**Immune response**

**Activation**

**Inhibition**

**APC**

- APC (B)
- MHCII
- TCRα
- TCRβ

**Th**

- Th activation
- Th inhibition
- CD40
- CD40L

**Signals**

- TCR
- APC: antigen presenting cell
- cytokines "out"
- cytokines "in"
hyper-IgM syndrome

19-year old male
- CD40L deficiency
- hyper-IgM syndrome
- monthly IVIG since age of 3
T cell activation and signals

APC: antigen presenting cell
PML – progressive multifocal leukoencephalopathy

19-year old male
- CD40L deficiency
- hyper-IgM syndrome
- monthly IVIG since age of 3

- concentration and memory problems
- progressive hemiparesis
- normal CSF
- coma in 6 weeks

2 weeks later

no enhancement
immune response and autoimmunity

Break in self-tolerance leads to autoimmunity

predicted outcome

- microbes (beneficial response)
- self proteins (detrimental response)

signal 1
MHC-peptide-TCR

costimulation

signal 2

antigen

B cells

antibodies
immune response to self- vs. foreign-antigens

**Signal 1**
MHC-peptide-TCR

**Signal 2**
Costimulation

Antigen

APC

CD4 T Cell

**Beneficial**

**IL-12**

Th1

(T-bet)

IL-2, IFN-γ

**Intracellular pathogens**

**Allergy**

**Detrimental**

**Extracellular pathogens**

**Autoimmunity**

**IL-2, IL-5, IL-10, IL-13**

**Th2**

(GATA3)

**IL-4**, **IL-12**

**IL-4, IL-21, IL-23**, **IL-6**, **TGF-β**

**IL-17, IL-22**

**Th17**

(ROR-γt)

**Signal 2**

Costimulation

B7

CD28

**Th1**

(T-bet)

IL-2, IFN-γ

**Intracellular pathogens**

**Allergy**

**Detrimental**

**Extracellular pathogens**

**Autoimmunity**

**IL-4**, **IL-5, IL-10, IL-13**

**Th2**

(GATA3)

**IL-4**, **IL-12**

**IL-4, IL-21, IL-23**, **IL-6**, **TGF-β**

**IL-17, IL-22**

**Th17**

(ROR-γt)
immune response to self- vs. foreign-antigens

**Beneficial**
- Intracellular pathogens
  - Allergy
  - Autoimmunity
  - Extracellular pathogens
  - Autoimmunity

**Detrimental**
- Intracellular pathogens
  - Allergy/Asthma
  - Autoimmunity
  - Extracellular pathogens

**Signal 1**
- MHC-peptide-TCR

**Signal 2**
- Costimulation

**APC**
- CD4 T Cell

**B7**
- CD28

**Antigen**

**IL-2, IFN-γ**
- IL-4, IL-5, IL-10, IL-13
- IL-17, IL-22

**Th1 (T-bet)**
- IL-12

**Th2 (GATA3)**
- IL-4

**Th17 (ROR-γt)**
- IL-21, IL-23, IL-6, TGF-β

**Autoimmunity**
- Extracellular and Intracellular pathogens

**NMO**
- Extracellular pathogens

interference with IL23-IL17

<table>
<thead>
<tr>
<th>agent</th>
<th>target</th>
<th>company</th>
<th>clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>ixekizumab</td>
<td>IL-17A</td>
<td>Eli Lilly</td>
<td>psoriasis, RA</td>
</tr>
<tr>
<td>secukinumab</td>
<td>IL-17A</td>
<td>Novartis</td>
<td>MS (II) and many</td>
</tr>
<tr>
<td>brodalumab</td>
<td>IL-17RA</td>
<td>Amgen, MedImmune</td>
<td>psoriasis, CD, asthma</td>
</tr>
<tr>
<td>ABT-122</td>
<td>IL-17A and TNF</td>
<td>Abbott, AbbVie</td>
<td>RA</td>
</tr>
<tr>
<td>ustekinumab</td>
<td>p40 IL-12 and IL-23</td>
<td>Johnson&amp;Johnson, Janssen Biotech</td>
<td>MS (II) and many</td>
</tr>
<tr>
<td>briakinumab</td>
<td>p40 IL-12 and IL-23</td>
<td>Abbott</td>
<td>MS (II), CD, psoriasis</td>
</tr>
<tr>
<td>tildrakizumab</td>
<td>IL-23p19</td>
<td>Merck</td>
<td>psoriasis</td>
</tr>
<tr>
<td>guselkumab</td>
<td>IL-23p19</td>
<td>Johnson&amp;Johnson, Janssen Biotech</td>
<td>psoriasis, RA</td>
</tr>
<tr>
<td>AMG-139</td>
<td>IL-23p19</td>
<td>Amgen, MedImmune</td>
<td>psoriasis, CD</td>
</tr>
<tr>
<td>LY-3074828</td>
<td>IL-23p19</td>
<td>Eli Lilly</td>
<td>psoriasis</td>
</tr>
<tr>
<td>BI-655066</td>
<td>IL-23p19</td>
<td>Boehringer Ingelheim</td>
<td>psoriasis, CD, AS</td>
</tr>
</tbody>
</table>

CD: Crohn’s disease, RA: rheumatoid arthritis, AS: ankylosing spondylitis

**microbiome**: microbial ecosystem (microbiota) plus its entire genetic content

- Absence of microbial flora: milder EAE (MOG)
microbiota in early infancy

**hygiene hypothesis:**
lack of microbial exposure – immune dysregulation (Th2)

**microflora hypothesis:**
microbiota alteration – disrupt immune tolerance

**vanishing microbiota hypothesis:**
changes in microbiota – allergy/immune diseases

---

**prenatal**
- intrauterine colonization
- host genetics
- maternal nutrition (pre/probiotics)
- antibiotics

**perinatal**
- delivery (vaginal/cesarean)
- gestation time (preterm/term)
- maternal nutrition (pre/probiotics)
- antibiotics

**postnatal**
- feeding (breast/bottle)
- solid food introduction
- pre/probiotics
- antibiotics
molecular mimicry

- degenerate T cell responses
  - millions of peptides
  - affinity differs

- molecular mimicry
  - linear: 1-2 amino acids
  - charge, conformation

HLA-DRB1*1501

MBP

APC

TCR

85E N P V V H F K N I V T P R99

the complement cascade

activation

X........Xb + Xa

protease effect

Y........Yb + Ya

protease effect

Z........Zb + Za

different tissue distribution of inhibitors
the complement cascade

- **foreign surface**
- **alternative**
- **classic**
- **Ab**
- **foreign carbohydrate**
- **lectin**

**C3 activation**

- **C5 activation**
- **lytic complex**
- **terminal pathway**
- **opsonization (C3b)**

**anaphilaxins, inflammation**

**eculizumab** *(Soliris)*
- MG (2011)
- NMO (2013)

**lysis**
B cell functions

- NK, macrophage complement
- Autoantibody production (plasma cell)
- Host for EBV
- Antigen presentation
- T cell activation
- Cytokine production: IL-10, IL-6, TGF-β, TNF-α, TNF-β
effect of Abs: treatment consideration!

AchR
AQP4 M23

AchR
AQP4 M1
LGI1
NMDAR

AQP4 M1, M23
AchR?
LGI1?
NMDAR?
when does autoimmunity start?

- girl, age 15, migraine headache:
  - no focal neurological sign/symptom
  - SC-MRI, VEP, SEP, MEP negative

age 10-12?

radiologically isolated syndrome
childhood MS...

age 21:
- first symptom

CDMS
adult MS...
THANK YOU