Brain – immune interactions in health and disease

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Neuroimmunology:

Studying bi-directional interactions between the nervous system and the immune system and their relevance to health and disease

Key areas:

• The role of the nervous system in regulating immune processes and inflammation (mostly immune / inflammatory readouts in the periphery or the CNS)

• The role of immune / inflammatory processes in the CNS (mostly concerning CNS development, normal CNS function and CNS pathology)
Inflammation

.....a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue.
Periphery – how are inflammatory processes regulated?

Infection, Injury:  \[\rightarrow\]  Inflammation

- Inflammatory mediators
- Chemokines
- Adhesion molecules
- Leukocyte infiltration
- Pathogen killing, local tissue damage

Serhan et al., NATURE IMMUNOLOGY VOLUME 6 NUMBER 12 DECEMBER 2005
Recruitment of inflammatory cells: not restricted, but signal/organ-dependent

Potential recovery: usually high

but...: chronic inflammation can cause serious tissue damage and irreversible harm

-Leukocyte apoptosis
-Phagocytosis of debris and inflammatory cells
-Antiinflammatory eicosanoids and cytokines
-Tissue regeneration
Central Nervous System

- Blood Brain Barrier
- CSF – Blood barrier
- Blood flow autoregulation
- Regulated physiological traffic for small populations of blood-borne cells

Infection, Injury: \[\rightarrow\] Inflammation

Resident inflammatory cells

Exonegous (blood-borne) cells – restricted

Replacement of injured neurons is very limited, so inflammation in the CNS is a dangerous game
Gates to neuroinflammation: effective barriers in the CNS to keep leukocytes out

How quickly get central and peripheral immune cells recruited after acute brain injury?
Choroid Plexus – a key place for leukocyte entry into the CNS
What happens to CNS antigens – is there any „classical” immune response in the brain?
Inflammation: a previously unrecognised contributor to brain disease

Limited success in translation so far – what are the mechanisms involved?
Microglia and inflammation: what did we learn?

An interesting „cell” changes in the brain after rabies infection…..

Victor Babes
1880

Pío del Río Hortega
(1920)

Silver-carbonate staining

Alois Alzheimer

Nissl staining
How do microglia (main immune cells of the brain) get into the CNS during development?
Microglia-mediated neuroinflammation in the CNS

Perry et al., Nature Reviews Immunology 7, 161-167

Wallerian degeneration (anterograde degeneration): injured axons denegerate distal to the injury
The role of microglia in demyelination and neuronal injury

Rivest et al., Nature Reviews Immunology 9, 429-439
Microglia respond rapidly to mechanical injury or endogenous danger signals

Davalos et al., Nature Neuroscience 8, 752 - 758 (2005)
Impaired neuron-microglia interactions in Cx3Cr1 −/− mice

Increased neuronal loss in a Parkinson’s model

Smaller infarct size after stroke

Cardona et al., Nat Neurosci. 2006

Denes et al., JCBFM 2008
A novel model to selectively deplete microglia via CSFR1 blockade:

- 98% depletion by apoptosis – no inflammation
- No visible effect on other brain cells or peripheral immune cells

Szalay et al., Nature Communications, 2016
Absence of microglia results in markedly increased brain injury

- Feeding mice a CSF1R inhibitor (PLX) for 3 weeks prior to cerebral ischemia leads to elimination of microglia and a 60% increase in infarct size.

- This effect is not influenced by the presence of the drug and is fully reversed in response to repopulation of microglia.

Szalay et al., Nature Communications, 2016
Microglia interact with neurons in an activity-dependent manner

Absence of microglia results in dysregulated neuronal network activity after brain injury

Calcium oscillations (GCaMP6s) and increased calcium load after brain injury in the absence of microglia

Szalay et al., Nature Communications, 2016
How are immune processes regulated by the CNS?

The autonomic nervous system controls all main physiological processes in the body. It also controls immune processes.
A number of ways for neuro-immune interactions:

Silver stained section through mouse spleen showing nerve fibres radiating from an arteriole.
TH+ nerve fibres (arrows) associated with lymphocytes in thymus and spleen.

(Felten, 1991)
Immune organs and cells are under central autonomic control.
Perivascular cells completely ensheathe blood vessels and form an effective barrier to cell movement.

Perivascular cells are targeted by nerve fibres that synapse onto them.

Yamazaki & Allen (1990)
Am.J.Anat. 187(3): 261-76
Inflammatory cytokines stimulate the brain (primarily circumventricular organs)

This leads to autonomic activation (E, NE release) and HPA activation (cort. release)

Vizi and Elenkov, 2000
Adrenaline (Epinephrine, E) and noradrenaline (norepinephrine, NE) inhibit proinflammatory responses
The cholinergic anti-inflammatory pathway

- Reduced cell activation
- Reduced TNF production
- Reduced mortality in sepsis

The α7 nicotinic acetylcholine receptor is expressed on macrophages

But….*the spleen does not have cholinergic innervation* – how does this work???
Acetylcholine-Synthesizing T Cells Relay Neural Signals in a Vagus Nerve Circuit
Rosas-Ballina et al., Science, 2011
How do cells recognise early events of injury or infection?

- DAMPs (Damage Associated Molecular Patterns)
- PAMPs (Pathogen Associated Molecular Patterns)
- Alarmins – released by injured tissues

### Intrinsic and extrinsic danger signals and outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Infectious inflammation</th>
<th>“Sterile” inflammation</th>
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<tbody>
<tr>
<td>Signals</td>
<td>PAMPs</td>
<td>DAMPs (including alarmins)</td>
</tr>
<tr>
<td>Sources</td>
<td>Extrinsic</td>
<td>Endogenous</td>
</tr>
<tr>
<td>Targets</td>
<td>TLRs</td>
<td>NOD receptors (NLRPs)</td>
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<tr>
<td>Location</td>
<td>Cell surface</td>
<td>Cytosol</td>
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<td>Examples of ligands or factors:</td>
<td>LPS, Lipoteicoic acid, CpG-DNA, Flagellin, Poly IC</td>
<td>Heat shock proteins, Uric acid crystals, Hyaluronin, Heparin sulfate, Defensins, Cathepsin G, HMGB1</td>
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<tr>
<td>Responses:</td>
<td>Proinflammatory mediator production, Complement activation</td>
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</tbody>
</table>

*Abbreviations:
- PAMPs: Pathogen associated molecular patterns
- DAMPs: Danger associated molecular patterns
- PRRs: Pattern recognition receptors
- TLRs: Toll-like receptors
- NOD-like receptors: Nucleotide oligomerization domain (NOD) receptors (NLRs)
- NLRPs: NOD-like receptor proteins

Ward et al., EMBO Mol Med, 2012
Inflammasomes: multiprotein complexes recognizing host- and pathogen-derived signals

Inflammasome activation → release of IL-1 and IL-18 → Inflammation
Inflammation contributes to brain injury in apparently healthy animals

RAPID COMMUNICATION

Interleukin-1 Receptor Antagonist Inhibits Ischaemic and Excitotoxic Neuronal Damage in the Rat

JANE K. RELTON AND NANCY J. ROTHWELL

Department of Physiological Sciences, University of Manchester, Oxford Road, Manchester M13 9PT, UK

Received 3 February 1992
Does inflammasome activation contribute to brain injury?

Markedly reduced brain injury in mice with deficient inflammasome signaling after cerebral ischemia

PNAS, 2015
Infections mean the greatest risk to survival

Rapid and powerful mechanisms are needed to prevent and eliminate infection

Direct detection of pathogens

Detection of pathogens by means of tissue injury

TLRs
NLRs
etc..

“PAMP Universe”

“DAMP Universe”
Chronic diseases increase in developed countries

In 2004, 133 million Americans had at least one chronic condition
Infant mortality rate world map (deaths/1,000 live births)
Type 1 Diabetes

ZACCONE et al., 2010
Cancer Incidence Worldwide

Breakdown of the estimated 12.7 million new cases, age standardised incidence rates and the most commonly diagnosed cancers by the different regions of the world, 2008.

http://info.cancerresearchuk.org/cancerstats/
Does systemic inflammation change the brain prior to brain injury?

Patients at risk of stroke and obese, atherosclerotic rodents display increased microglial, vascular inflammation in the brain and leukocyte recruitment into the choroid plexus.

Drake et al., BBI, 2010
Preceding systemic inflammation leads to impaired outcome after stroke

Szigeti et al., JCBFM 2015

Denes et al. J neuroinflammation, 2011
Preceding systemic inflammation change BBB injury and brain perfusion after stroke

Szigeti et al., JCBFM, 2015
Blockade of IL-1 actions by IL-1Ra reduces brain injury both in „normal” aged rats and in aged rats with systemic inflammation

Pradillo et al., JCBFM 2012
*Streptococcus pneumoniae* infection induces systemic inflammatory responses that drive atherogenesis and augment cerebrovascular pathologies in ischaemia via IL-1- and platelet-mediated mechanisms.

Larger aortic plaques after infection in C57Bl/6 mice fed atherogenic (Paigen) diet and cerebrovascular inflammation

Larger brain injury after experimental stroke in infected mice and rats, which is reversed by IL-1Ra

Ann Neurol 2014
Summary:

- The CNS has a bi-directional communication with the immune system.
- Microglia are largely self-renewing in the brain, regulate central immune responses, phagocytose cell debris and remove non-functioning synapses / nerve fibers.
- Inappropriate activation or dysfunction of microglia could contribute to various brain diseases. Recruited leukocytes are also capable of causing injury in the brain.
- The nervous system controls immune responses in health and disease.
- Peripheral inflammatory factors reach the brain and lead to HPA / autonomic activation.
- HPA / autonomic / cholinergic activation can blunt proinflammatory responses.
- Systemic inflammatory diseases commonly involve chronic immune activation and deficient neuro-immune regulation.
- Systemic inflammatory conditions contribute to several common brain diseases.