Neuroinflammation in Alzheimer’s Disease

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Neuroinflammation is an Invariant Feature in Neurodegenerative Diseases

• Microglia, the brain’s resident macrophage, performs immune surveillance, but is now understood to have a broad range of brain-specific functions.

• Microglia are highly dynamic and continuously extend and retract processes throughout the brain parenchyma.

• The brain undergoes complete surveillance by microglia every few hours with each microglia surveying an area with a radius of about 80µm.

• **Neuroinflammation arises from disease-related perturbations in the brain that subsequently induce a pro-inflammatory response by microglia, which exacerbates disease severity and accelerates disease progression, resulting in neuronal loss.**
Ontogeny of microglia:
Microglia are derived from early yolk sac derived myeloid precursors that invade and populate the developing brain.

Microglia self renew from endogenous progenitors.
In many CNS disorders blood borne monocytes infiltrate the brain.

CNS Disease:
CCL2-mediated infiltration of monocytes into the brain

Sieweke & Alan, 2013
Amyloid deposition results in the accumulation of macrophages on and around the plaque.

The plaque associated macrophages exhibit a proinflammatory phenotype but are inefficient phagocytes.
Nasu-Hakola Disease: Demonstration that perturbation of microglia is alone sufficient to cause Neurodegenerative Disease

- Nasu-Hakola disease (aka PLOSL) is a progressive neurodegenerative disease that arises from mutation of the myeloid specific gene, TREM2 or its signaling adapter protein DAP12 (TyroBP)

- In the brain TREM2 and DAP12 are exclusively expressed by microglia.
TREM2 is expressed on myeloid cells and exclusively on microglia in the brain.

Its ligand(s) are unknown are are postulated to be:
- Lipids, including phospholipids/ApoE.
- Cell surface proteins that interact with heparin sulfate-containing proteoglycans.

TREM2 phospholipid binding does not result in signaling.

The function of TREM2 remains controversial:

It has been postulated to be a phagocytic receptor.

TREM2 has been shown in vitro to suppress inflammatory responses. However, this conclusion is not supported in several in vivo settings.
TREM2 variants are associated with neurodegenerative diseases

GWAS have identified a number of TREM2 variants linked to neurodegenerative diseases.

R47H increases the risk for AD by approximately 3 fold, an effect size similar to that observed with APOE4.

The TREM2 R47H variant is linked to AD, FTD/FTLD, ALS.
AD-linked TREM2 mutations are confined to a surface ligand binding domain that alters binding affinity.

Nasu-Hakola and other LOF mutations are buried and affect folding and stability.

TREM2 extracellular domain

Kober et al. eLife 2016;5;e20391
Plaque-associated macrophages express high levels of TREM2

TREM2 is focally expressed at plaque interface, curbing plaque growth and abrogating microglial barrier function

Plaque-associated macrophages bear markers of peripheral monocytes

Resident microglia do not associate with plaques in AD Mouse Models

TREM2+, CD45$^{hi}$ myeloid cells are elevated in the brains of 2 different AD models.
Plaque associated macrophages are absent in the TREM2 KO

APPPS1

APPPS1; TREM2-/-

Iba1 6e10

TREM2 Deficiency Regulates Aβ Deposition in an Age and disease progression-Dependent Manner
TREM2 Deficiency Reduces Proliferation of Resident Microglia At Late Disease Stages
Trem2 deficiency is linked to microglial ‘alternative activation’ phenotype
TREM2 deficiency reduces amyloid internalization in plaque associated macrophages
# The TREM2 R47H Mutation Increases AD Risk

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Amyloid burden is modestly reduced in $Trem2^{+/R47H};$APPPS1 mice

$Trem2^{+/+};$APPPS1  $Trem2^{+-};$APPPS1  $Trem2^{+/R47H};$APPPS1  $Trem2^{-/-};$APPPS1

ThioS 

6E10 

4 months

ThioS Plaque Number

6E10 % Area

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Cortex  Hippocampus

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**  **

$Trem2^{+/-};$ APPPS1

$Trem2^{+/-};$ APPPS1

$Trem2^{+/R47H};$ APPPS1

$Trem2^{-/-};$ APPPS1

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Cortex  Hippocampus

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**  ***  **

$Trem2^{+/-};$ APPPS1

$Trem2^{+/-};$ APPPS1

$Trem2^{+/R47H};$ APPPS1

$Trem2^{-/-};$ APPPS1

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Plaque associated Iba1+ cells are significantly reduced in *Trem2*^{+/R47H};APPPS1 mice

**Iba1+ Cells / Plaque**

- *Trem2*^{+/-}; APPPS1
- *Trem2*^{+/-}; APPPS1
- *Trem2*^{+/-}; APPPS1
- *Trem2*^{-/-}; APPPS1

![Images showing plaque associated Iba1+ cells across different genotypes](image-url)
CD45, a marker of peripheral myeloid cells, is significantly reduced in $\text{Trem2}^{+/R47H};\text{APPPS1}$ mice.
Plaque associated myeloid cell proliferation is significantly reduced in *Trem2*^{+/R47H}/; APPPS1 mice

*Trem2*^{+/+}; APPPS1  *Trem2*^{+/−}; APPPS1  *Trem2*^{+/R47H}; APPPS1  *Trem2*^{−−}; APPPS1

Plaque associated myeloid cell proliferation is significantly reduced in *Trem2*^{+/R47H}/; APPPS1 mice.
Plaque associated neuritic dystrophy is modestly increased in Trem2^{+/R47H};APPPS1 mice.
Human R47H carriers exhibit impaired Myeloid Cell Barrier and enhanced Plaque Associated Neuronal Dystrophy

Plaque regions poorly covered by myeloid cell processes have more neuritic dystrophy

Yuan et al., Neuron (2016)

TREM2 R47H reduces myeloid barrier index and increases neuritic dystrophy
Soluble Trem2 extracellular domains are released from microglia

Proteolytic cleavage

Alternatively spliced mRNAs

Alternatively spliced mRNAs have not been shown to be translated

* FTD-like (homozygous)
° FTD (heterozygous)
# AD-risk (heterozygous)
Conserved cysteine residues

Klineberger et al.

Jin et al.
sTREM2 stimulates proinflammatory gene expression in microglia

sTREM2 acts in an autocrine or paracrine manner to drive microglial activation

These data force a reevaluation of TREM2 actions in the brain and its roles in neurodegenerative diseases

Zhong et al. JEM 2017
sTREM2 appears in CSF after amyloid deposition and concurrent with other disease markers in dominantly inherited forms of AD.
Summary

• Perturbation of microglial function through loss of TREM2 is sufficient to cause neurodegenerative disease

• TREM2 deficiency (−/− > +/−) reduces plaque associated peripherally-derived macrophages

• TREM2 deficiency results in reduced microglial proliferation

• Age and disease progression-dependent phenotypes preclude firm conclusions with regard to effect of TREM2+/R47H mutation on plaque and neuritic dystrophy

• The preliminary findings suggest the TREM2R47H variant appears to be LOF

• CSF levels of sTREM2 may be a useful biomarker for AD
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Erin Reed-Geaghan

Crystal Miller

Paul Cheng-Hathaway

Bruce Lamb

Richard Ransohoff
Acknowledgements

Landreth Lab
Julie Savage
Taylor Jay
Tarja Malm
Colleen Karlo
Shweta Mandrekar
Rebecca Skerrett
Paul Cheng-Hathaway
Monica Mariani
Brad Casali
Victoria von Saucken
Miguel Mouhinto

Supported by:
NIH/NIA
Alzheimer’s Association
Weston Brain Institute

Collaborators:
Bruce Lamb- Indiana Univ
Richard Ransohoff-Biogen

Stark Neurosciences Research Institute
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