In search of eye imaging biomarker in dementia mouse models:

Understanding the role of tau/Aβ protein in the retina

Alzheimer Society Research Program Exchange

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Research themes

Imaging the Alzheimer’s-related eye pathologies using mouse model

Retinal Tau pathology
Retina Amyloid pathology

Connection to the brain pathology
Live imaging for clinical translation

Healthy brain Demented brain

Hyperphosphorylation
Neuronal cell

Amyloid deposition

Mouse eye Human eye
Motivation – Why use retinal imaging for AD

- The retina is an extension of the central nervous system (CNS)
  
  • Sharing embryonic origin with the brain
  
  • Anatomically similar
  
  • Functionally connected
  
  • Easier to access and image
Does Alzheimer’s pathology also manifest in the eye?

- Alzheimer’s Disease
  - Complex multi-factorial disease, manifest multiple pathologies
  - vascular disruption,
  - Abnormal protein expression and aggregation
  - inflammation-related immune response
  - neural degeneration
Does Alzheimer’s pathology also manifest in the eye?

- Hallmarks of AD - two types of toxic proteins:
  - Amyloid precursor protein (APP) => \(\beta\)-Amyloid (A\(\beta\)) => plaques
  - Tau: microtubular associated protein (MAP) => hyperphosphorylated (pTau) => neurofibrillary tangles

Part 1: Imaging Tau pathology in the retina and optical nerve

• Transgenic mouse model with Tau pathology (rTg4510)
Tauopathy in mouse brain

- Hyperphosphorylated (pTau) brain staining

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<th>Region</th>
<th>Wildtype</th>
<th>rTg4510</th>
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Neurodegeneration in the mouse brain

- Cortex
- Hippocampus
- Thalamus
- Superior Colliculus
Optical Nerve Volume reduction

Wildtype Tg4510

Volume Normalised to Total Eye Volume

Optic Nerve Volume

Wildtype rTg4510

[Graph showing volume comparison between Wildtype and rTg4510]
Optical Nerve Signal Intensity increase

Wildtype  

rTg4510

Optic Nerve Signal Intensity

Wildtype  
rTg4510

Normalised T2 Signal Intensity

[Graph showing signal intensity comparison between Wildtype and rTg4510]
pTau deposition in the retina

• Immunohistochemically-stained retina sample

Retinal Ganglion Cell Layer (RGCL)
Inner Plexiform Layer (IPL)
Inner Nuclear Layer (INL)
Outer Plexiform Layer (OPL)
Outer Nuclear Layer (ONL)
Photoreceptor Layer (PRL)
Retinal pigment epithelium (RPE)
Results – pTau in retina

• pTau in the inner retinal layer of the retina
Results – pTau in retina

• pTau positive cell number and intensity

pTau immunopositive cytosolic staining cell (%)

Intensity of pTau staining (Mean Intensity/Pixel)
Results – neurodegeneration in retina

• Neuronal cell nuclear density
• Retina layer thickness

**RGCL Nuclear Density**

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**INL Nuclear Density**

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**IPL Relative Thickness**

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Summary of findings
Patient data of optical nerve volume

• Atrophic changes in optic nerve volume were similarly observed in Dementia patient with Tau pathology (−36.6 ± 2.6%).

![Optic Nerve Volume](image)
Project 2: 
*In vivo* imaging of Aβ pathology in the retina

- Transgenic mouse model with Amyloid pathology (APP/PS1)
Ex vivo Aβ immunostaining in the retina

• Significantly higher *ex vivo* retinal Ab immunoreactivity in transgenic mice.
• Retinal Aβ increased with age in the transgenic mice, but not in wildtype.
In vivo retinal fluorescence imaging

- Retinal in vivo Fluorescence After Curcumin Injection Is Higher in transgenic mouse than Wildtype Mice, and increases with age
Ex vivo Aβ immunostaining in the mouse brain

- Retinal in vivo fluorescence correlates with ex vivo cortical Aβ Loads
Connection to retinal Aβ pathology in human eye

- Levels of intracellular and extracellular Aβ retinal deposits were significantly higher in AD than controls.
Moving forward

• Integrated non-invasive multi-modal retinal imaging
  • Retinal structural change
    • Optical coherence tomography (OCT)
  • Retinal vascular change
    • Optical coherence tomography angiography (OCTA)
AD Pathogenesis model revisited

• Two-hit hypothesis
  • First hit: **vascular pathology** is an important factor in AD pathogenesis
  • Second hit: **Aβ accumulation** and **hyperphosphorylation of Tau protein**
  • Neuronal injury and **neurodegeneration**

Multi-model non-invasive retinal imaging

- Optical Coherence Tomography (OCT)
  - Structural OCT
  - OCT Angiography

- Two-photo excited fluorescence imaging
  - Retinal angiography
  - fluorescently-labelled cells
Quantitative retina morphology analysis for optical coherence tomography (OCT)

Deep-learning-based automatic retinal layer segmentation

Layer-wise retinal thickness map

RNFL  GCL  IPL  INL
Acknowledgement

Simon Fraser University
Mirza Faisal Beg
Marinko Sarunic

University of British Columbia
Joanne Matsubara
Ging-Yuek Robin Hsiung

University College London
Mark Lythgoe
Imre Lengyel

Da Ma
Daniel J. Wahl
Sieun Lee
Ahmad Sidiqi
Jing Cui
Ian F. Harrison
Roz Whitaker
Thank you

Q & A