COGS 163 Discussion Section
Janet Tung
Week 8: May 23, 2018

HSV-1 AND A-BETA IN ALZHEIMER’S DISEASE PATHOLOGY

Two primary characteristics of Alzheimer’s Disease

Abnormal structures in Alzheimer’s Disease

- Granulovacuolar degeneration
- Synaptic loss disrupts communication between cells
- Amyloid plaques
- Neurofibrillary tangles
post-mortem Alzheimer’s brain

[Image of a brain section with annotations indicating Tau tangle and Aβ plaque]

http://sage.buckinstitute.org/amyloid-beta-and-alzheimers-disease/
herpes simplex virus 1 (HSV-1) and β-amyloid

- Why is there a cellular mechanism for APP cleavage at all?
- Recall: Aβ is found in healthy brains
- Aβ is a class of peptides: 36-43 amino acids long
- Why so many different Aβ peptides?
- What good, if any, does cleavage do for HSV-1?

Are $A\beta$ peptides good for the brain?

- Anti-microbial peptides (AMPs)
- Does $A\beta$ have antiviral properties?
Aβ peptides have a host of known antimicrobial properties

<table>
<thead>
<tr>
<th>Organism</th>
<th>Aβ$_{42}$</th>
<th>Aβ$_{40}$</th>
<th>roAβ$_{42}$</th>
<th>LL37</th>
<th>reAβ$_{42}$</th>
<th>scAβ$_{42}$</th>
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<td><em>Candida albicans</em></td>
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<td>0.78</td>
<td>0.78</td>
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<td>&gt;50</td>
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<td>1.56</td>
<td>3.13</td>
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<td>3.13</td>
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<td>12.5</td>
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<td>12.5</td>
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</table>

The antimicrobial activity of synthetic Aβ1-42 (Aβ$_{42}$), Aβ1-40 (Aβ$_{40}$), rodent Aβ1-42 (roAβ$_{42}$), LL-37 (LL-37), reverse Aβ42-1 (reAβ$_{42}$), or scrambled Aβ42 (scAβ$_{42}$) peptides were determined as minimal inhibitory concentrations (MIC) against 12 microorganisms. Reproduced from [174].

Bourgade et al., J. Alzheimer’s Disease (2016)
Aβ peptides act directly on HSV-1

β-Amyloid peptides display protective activity against the human Alzheimer’s disease-associated herpes simplex virus-1

Karine Bourgade · Hugo Garneau · Geneviève Giroux · Aurélie Y. Le Page · Christian Bocti · Gilles Dupuis · Eric H. Frost · Tamás Fülöp Jr.
Aβ peptides act directly on HSV-1

Fig. 9

Minimal model illustrating the mode of action of Aβ in preventing HSV-1 infection. HSV-1 attaches to the plasma membrane of the target cell by way of interaction of its fusogenic glycoproteins with plasma membrane receptors. Aβ interacts with HSV-1, presumably through fusogenic gB glycoprotein, and interferes with its binding/entry into the cell.
Aβ peptides act directly on HSV-1

- Acts prior to viral entry into host cell
- Viral envelope is crucial
- May interfere with viral membrane fusion
- Sequence homology between Aβ-42 and one of the HSV-1 proteins involved in membrane fusion (glycoprotein gB)
possible implications for HSV-1 mediated Alzheimer’s pathology

- Early stages: Aβ plays a protective role
- May explain BBB changes in AD: disruption of tight junctions to facilitate lymphocyte and Aβ penetration into CNS
- Middle stage is a tipping point: amnestic mild cognitive impairment (aMCI)
- Alzheimer’s Disease: tipping point, system out of equilibrium
historical context and future directions