Signaling complexes in neurodegeneration

Jian Zhao
Pathological hallmarks of Alzheimer’s Disease

- Amyloid plaque
- Neurofibrillary tangles
- Neuronal/synaptic loss
Multifactorial basis of AD

Cell (2012)
Sequential cleavage of APP and γ-secretase complex

Monomers and oligomers: neuronal toxicity
GPCR signalosomes

- Largest class of cell-surface receptors: >1,000 genes
- Activated by a diverse range of ligands
- Activate a wide range of signaling molecules and effector systems
- Critical roles in virtually every organ system
- Involved in multiple human disease states
1. GPCRs as novel targets for AD

2. β-arrestin mediates the amyloid generation

3. Conclusions and perspectives
β2-Adrenergic Receptor (β2AR) interacts with γ-secretase.

Activation of β2AR increases Aβ production and γ-secretase activity.

Blockade of receptor endocytosis abolishes β2AR-induced γ-secretase activity.

Blockade of postendocytic trafficking abolishes β2AR-induced γ-secretase activity.

Opioid receptors are widely expressed in CNS including hippocampus and cortex

Opioid receptors play important roles in synaptic activation, learning and memory

Expression of endogenous opioid peptide and opioid receptors is altered in postmortem brains of AD patients

Enkephalin elevations contribute to AD pathogenesis

Activation of DOR increase Aβ production *in vitro*
Blockage of DOR improve cognitive deficits in AD mice

Teng, et al., Cell Research (2010)
Blockage of DOR by NTI retards Aβ pathogenesis in mice

Teng, et al., Cell Research (2010)
Knockdown of DOR retards AD pathogenesis in mice

Teng, et al., Cell Research (2010)
NTI treatment reduces $\beta$- and $\gamma$-secretase activity for APP processing

Teng, et al., Cell Research (2010)
Activation of DOR enhances APP processing

Teng, et al., Cell Research (2010)
Activation of DOR specifically enhances APP processing

Teng, et al., Cell Research (2010)
DOR complexes with $\beta$- and $\gamma$-secretase

Teng, et al., Cell Research (2010)
Postendocytic sorting of activated DOR defines $\beta$- and $\gamma$-secretase trafficking

Teng, et al., Cell Research (2010)
C-tails of DOR but not that of MOR interact with endosomal sorting protein GASP

Heydorn A et al. J. Biol. Chem. 2004;279:54291
Postendocytic sorting of activated DOR defines $\beta$- and $\gamma$-secretase trafficking and activities

<table>
<thead>
<tr>
<th>receptor</th>
<th>Interaction with GASP</th>
<th>Interaction with secretases</th>
<th>Enhancement of secretase activity</th>
<th>Postendocytic sorting of secretase to lysosomes</th>
<th>Notch processing</th>
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<tbody>
<tr>
<td>DOR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>MOR</td>
<td>–</td>
<td>+</td>
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<tr>
<td>DMT DOR with MOR c-tail</td>
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</tbody>
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Teng, et al., Cell Research (2010)
1 GPCRs as novel targets for AD
2 β-arrestin mediates the amyloid generation
3 Conclusions and perspectives
Basic functions of β-arrestins
β-arrestin1 is upregulated in brains of sporadic AD patients and AD mouse models

Liu, et al., Cell Research (2013)
β-arrestin1 deficiency ameliorates behavior deficits and Aβ pathology in APP/PS1 mice.

**Novelty seeking**

**Morris water Maze**

Liu, et al., Cell Research (2013)
β-arrestin1 deficiency ameliorates behavior deficits of APP/PS1 mice.

Liu, et al., Cell Research (2013)
β-arrestin1 modulates γ-secretase activity.
β-arrestin1 modulates γ-secretase activity.
β-arrestin1 interacts with APH-1 but not other γ-Secretase components
The β-arrestin1/APH-1 interaction dependent enhancement of γ-Secretase activity

**Interaction (Co-IP)**

**Secretase activity**

**Secrestase complex on Blue Native PAGE**

**Wild-type cells**

**PS1/2 ko cells**
Model: $\beta$-Arrestin1 modulates $\gamma$-secretase complex assembly

Liu, et al., Cell Research (2013)
Blockage of β-arrestin1/APH-1 interaction inhibits γ-secretase complex formation and Aβ production.
Blockage of β-arrestin1/APH-1 interaction inhibits γ-secretase complex formation and Aβ production.

Liu, et al., Cell Research (2013)
1. GPCRs as novel targets for AD

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Versatile function of γ-secretase

<table>
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<tr>
<th>Protein</th>
<th>10</th>
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<th>Shedase(s)</th>
<th>Shedase Regulation</th>
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<td>Alcadecin γ</td>
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<td>APLP1</td>
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<td>N-glycosylation</td>
<td>[102, 103]</td>
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<td>APP</td>
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</table>

| E-cadherin  |     |     |     |            |                    |           |
| EphrinB1    |     |     |     |            | ionomycin, mechanical scraping | [132-134]|
| EphrinB2    |     |     |     |            | EphrinB2            | [136, 137]|

| LRP         |     |     |     |            | Vitamin-D binding protein | [157]    |
| LRP1B       |     |     |     |            | Wnt3a                |           |
| LRP2        |     |     |     |            | ionomycin, NMDA agonist | [159, 160]|
| LRP6        |     |     |     |            | ND                   |           |
| N-cadherin  |     |     |     |            | ND                   |           |
| Nectin1a    |     |     |     |            | ND                   |           |
| Notch1      |     |     |     |            | Delta, Jagged        | [164, 165]|
| Notch2      |     |     |     |            | ND                   |           |
| Notch2c     |     |     |     |            | ND                   |           |
| Notch3      |     |     |     |            | ND                   |           |
| Notch4      |     |     |     |            | ND                   |           |

| SorLA       |     |     |     |            | head-activator        | [182-185]|
| Sortlin     |     |     |     |            | ND                   |           |
| Syndecan3   |     |     |     |            | ND                   |           |
| Tyrosinase  |     |     |     |            | ND                   |           |
| TYRP1       |     |     |     |            | ND                   |           |
| TYRP2       |     |     |     |            | ND                   |           |
| VEGF-R1     |     |     |     |            | ND                   |           |
| VGSC β2     |     |     |     |            | ND                   |           |
| VLDLR       |     |     |     |            | apolE, reelin, α2-macroglobulin | [105] |

Drug development in AD

Lancet Neurol (2010)
Conclusion & perspective

- GPCRs forms complexes with secretases and modulate their activities;
- Some GPCRs may be novel potential therapeutic targets for specific inhibition of Aβ production to protect or against Alzheimer’s disease;
- Specific reduction of Aβ pathology can be achieved by regulation of the γ-secretase assembly or endocytotic sorting;
- Small chemicals that interfere the assembly of secretase complexes and cellular localization should be helpful for addressing the underlying pathology of Alzheimer's disease;
- Using a feasible screening model based on newly defined mechanisms to looking for the effective nature products or TCM may provide effectively strategies to modulate AD pathogenesis with fewer side effects.
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