Exploring the Neurobiology of Cognitive Difficulties in Down Syndrome

William Mobley
UC San Diego
Neuronal Circuits: Double Trouble in Down Syndrome

Increased Inhibition

NTF Signaling

Disrupted Axonal Function
NEURONAL CIRCUITS MEDIATE ALL BRAIN FUNCTIONS

INFORMATION

DENDRITE

SYNAPSE

AXON

CELL BODY

CHANGE IN FUNCTION

NEURON 1

NEURON 2

NEURON 3

RECEIVE

PROCESS

SEND
Hypothesis

Extra Gene(s) → Abnormal Synapses → Cognitive Problems

Research Strategy

Treatment → Gene(s) &/or Mechanism → Cognitive Phenotype
Abnormal Synaptic Architecture in Individuals with Down Syndrome

Balancing Excitation and Inhibition

Glutamate
Excitatory

Axon Terminal

GABA
Inhibitory

Axon Terminal
Mouse Models of DS

Genes:
- Hsa21
- Mmu16
- Lipi
- Mrpl39
- App
- Sod1
- Cbr1
- Fam3b
- Zfp295
- Umodl1
- Abcg1
- U2af1
- Rrp1b
- Prmt2
- Pdxk

Mouse Models:
- DSCR
- Dp(16)1Yey
- Ts65Dn
- Ts1Cje
- Ts1Rhr
- Dp(17)1Yey
- Dp(10)1Yey
Neuronal Circuits: Double Trouble in Down Syndrome

- Increased Inhibition
- NTF Signaling
- Disrupted Axonal Function
GABAergic Neurobiology in Hippocampus

- Larger GABAergic synapses.
- Molecular evidence for increased GABAergic neurotransmission.
- Physiological evidence for increased GABAergic neurotransmission.
- Cognitive performance is rescued using antagonists of GABA A or B receptors.
- Evidence implicating increased gene dose for Girk2.
Targeting Increased Inhibition in Down Syndrome

Roche Trial

GABA A Type Receptors

No Compounds Yet

GABA B Type Receptors

Girk2 Channel

Compounds Exist

GABA Compounds Exist
Neuronal Circuits: Double Trouble in Down Syndrome

Increased Inhibition

NTF Signaling

Disrupted Axonal Function
Pathology of AD in DS

The pathology of AD emerges in everyone with DS.
Endosomes Carry Trophic Signals
Growth Factors Made in Hippocampus Regulate the Function and Survival of Cholinergic Neurons

These Cholinergic Neurons Degenerate In Alzheimer’s Disease and Down Syndrome
NGF Transport is Disrupted in Ts65Dn Neurons
An Extra Copy of One Gene Plays a Conspicuous Role in Disrupting NGF Retrograde Transport and in Causing Degeneration of Cholinergic Neurons

Salehi et al., 2006
Linking APP Gene Dose to Disrupted Transport

APP gene dose

Rab 5 activity

Endosome size

Axonal transport

Neurodegeneration
APP and its Products - Finding the Culprit

APP

\[ \begin{array}{c}
\text{APP} \\
\text{Aβ} \\
\text{GFP} \\
\end{array} \]

\[ \begin{array}{c}
\text{β} \\
\text{α} \\
\text{γ} \\
\end{array} \]

\[ + \]

\[ \begin{array}{c}
\text{β-CTF} \\
\text{Aβ} \\
\text{GFP} \\
\end{array} \]

\[ + \]

\[ \begin{array}{c}
\text{α-CTF} \\
\text{GFP} \\
\end{array} \]

\[ - \]

\[ \text{AICD} \\
\text{GFP} \\
\end{array} \]

\[ - \]

\[ ? \text{ Aβ} \]
Targets to Treat or Prevent AD in DS

• Selectively reduce the effect of increased APP
  – Through reducing the levels of APP mRNA –
    • *ASOs directed specifically at APP mRNA* - *In process*
  – Through an antibody to reduce Aβ levels –
    • *AC Immune-Trial will begin soon*
  – Through disrupting Aβ aggregates
    • *Elan Trial just started – UCSD, UCI, etc*

- Through increased processing of APP – e.g. GSMs –
  • *Novel class of GSMs discovered at UCSD*

- Through restoring NE levels –
  • *Eager to pursue with Chelsea Therapeutics*
Neuronal Circuits: Double Trouble in Down Syndrome

Increased Inhibition 3 Targets

NTF Signaling

5 Targets

Disrupted Axonal Function
The neurobiology of Down syndrome features both developmental and age-related changes in cognition. Cognitive changes are linked to the dose of genes and regulatory sequences on chromosome 21. Enhanced inhibitory neurotransmission appears to play a defining role in the young brain.
Summary and Conclusions

- The changes of Alzheimer disease routinely emerge with aging.
- Here a defining role is played by APP.
- Increased APP gene dose acts, in part, through its effect on endosomal trafficking and signaling.
- In the context of DS, APP is not the only gene, but it plays a conspicuous role.
- Treatments that promise to address APP gene dose are emerging.
<table>
<thead>
<tr>
<th>Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pavel Belichenko</td>
</tr>
<tr>
<td>Alexander Kleschevnikov</td>
</tr>
<tr>
<td>Steve Wagner</td>
</tr>
<tr>
<td>Geoff Chang</td>
</tr>
<tr>
<td>Ricardo Capone</td>
</tr>
<tr>
<td>Nishant Singhal</td>
</tr>
<tr>
<td>Rachel Nosheny</td>
</tr>
</tbody>
</table>
Acknowledgements

Supported by:

- Down Syndrome Research and Treatment Foundation
- Research Down Syndrome
- National Institutes of Health
- Larry L Hillblom Foundation
- Thrasher Foundation
- Alzheimer’s Association
- Cure Alzheimer’s Fund