Cell Cycle/Chromosome Segregation Defects in Diseases of Aging: Focus on Alzheimer’s Disease and Atherosclerosis

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ALZHEIMER’S DISEASE

Dementia on the rise
Alzheimer’s Patients in the U.S.

EPIDEMIC IN THE US
• >5 Million diagnosed Patients
• ~$215 Billion annual cost in US
• 10% of people over age 65
• 50% of people over age 85

RESEARCH TODAY: MEMORIES FOREVER
BRAIN PATHOLOGY IN ALZHEIMER’S DISEASE AND DOWN SYNDROME

Typical Brain

AD/DS Brain

Plaques and tangles

George Glenner and Caine Wong 1984

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGV VIA

$A\beta$ Peptide

RESEARCH TODAY: MEMORIES FOREVER

THE AMYLOID PRECURSOR PROTEIN GENE IS ENCODED ON CHROMOSOME 21

The ‘Swedish’ Alzheimer’s Disease Family Inherits a Mutant APP Gene

RESEARCH TODAY: MEMORIES FOREVER
The Genetics of Alzheimer’s Disease

- Amyloid Precursor Protein (APP)
  Chromosome 21
- Presenilin 1 (PS1)
  Chromosome 14
  (Most early-onset cases)
- Presenilin 2 (PS2)
  Chromosome 1
- Apolipoprotein E4
  Chromosome 19

THE AMYLOID CASCADE IN AD and DS

Amyloid Precursor Protein

\[ \beta \text{-secretase} \rightarrow s\text{APP} \]
\[ \gamma \text{-secretase} \rightarrow A\beta \]
\[ \alpha \text{-secretase} \rightarrow s\text{APP} \]

ApoE4

Aβ protofibrils

Aβ deposition in plaques
A RECIPROCAL AD—DS CONNECTION


Review and Hypothesis: Alzheimer Disease and Down Syndrome—Chromosome 21 Nondisjunction May Underlie Both Disorders

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TRISOMY 21 MODEL OF ALZHEIMER’ DISEASE

Predictions:

1) Alzheimer’s Disease Individuals Should Show Trisomy 21 Mosaicism

2) Trisomy 21 Mosaicism Should Predispose Individuals to Develop Alzheimer’s Disease

3) Genes/Proteins Carrying FAD Mutations Should Affect Chromosome Segregation and/or the Cell Cycle

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RESEARCH TODAY: MEMORIES FOREVER
COUNTING CHROMOSOMES

Aneuploidy/Trisomy 21 In Alzheimer’s Disease

Geller and Potter 1999
Iourov et al., 2009
Arendt et al., 2010
TRISOMY 21 MODEL OF ALZHEIMER’ S DISEASE

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INCREASED RISK OF NON-DISJUNCTION AND SUBSEQUENT AD IN YOUNG MOTHERS OF DOWN SYNDROME CHILDREN


FISH analysis results (non-disjunction)  

<table>
<thead>
<tr>
<th>Chr 13</th>
<th>Chr 21</th>
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<tbody>
<tr>
<td>Controls (n=10)</td>
<td>0.28 ± 0.18</td>
</tr>
<tr>
<td>MDS (n=12)</td>
<td>0.88 ± 0.65</td>
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* Results obtained by analyzing 1000 binucleated lymphocytes.  

* P<0.01 MDS subject vs. controls.
TRISOMY 21 MODEL OF ALZHEIMER’ DISEASE

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TRISOMY 16 IN NEURONS OF FAD-PS1 TG-MICE

A

B

C

NON | WT | M146L | M146V

p=0.01

p=0.03

p=0.001

NON | PS KI

RESEARCH TODAY: MEMORIES FOREVER
MITOTIC SPINDLE ABNORMALITIES INDUCED BY PS-1 OVEREXPRESSION/MUTATION

MULTI-CHROMOSOME ANEUPLOIDY INDUCED BY PS-1 OVEREXPRESSION OR MUTATION
PS-INDUCED ANEUPLOIDY REQUIRES γ-SECRETASE

FAD APP/Aβ INDUCES CHROMOSOME MIS-SEGREGATION
NORMAL MITOSIS

1. Interphase
2. Prophase
3. Prometaphase
4. Metaphase
5. Anaphase
6. Telophase

XENOPUS LAEVIS EGG SPINDLES

CONTROL + Aβ 1-42
FRONTOTEMPORAL LOBAR DEGENERATION

- **NEUROFIBRILLARY TANGLES**
  <HALF OF SPORADIC PLUS MAPT MUTANT FAMILIAL

- **TDP-43 INCLUSIONS**
  >HALF OF SPORADIC
  PROGRANULIN MUTANT FAMILIAL
  C9ORF72 GGGGCC REPEAT EXPANSION-MOST FAMILIAL
  (ALSO CAUSE MOST FAMILIAL ALS)

RESEARCH TODAY: MEMORIES FOREVER
ANEUPLOIDY IN SPORADIC AND FAMILIAL FTLD

ANEUPLOIDY IN FTLD/MAPT MUTANT MICE

RESEARCH TODAY: MEMORIES FOREVER
FTLD MUTANT MAPT INDUCES ANEUPLOIDY IN CULTURED CELLS

FTLD MUTANT MAPT INDUCES MITOTIC SPINDLE DEFECTS
Aβ INHIBITS CERTAIN MITOTIC MOTORS

EG5 IS INHIBITED IN APP/PS MOUSE BRAIN
MONASTROL, AN EG5 INHIBITOR INDUCES CHROMOSOME MIS-SEGREATION

CHOLESTEROL INDUCES ANEUPLOIDY IN MICE, CELLS, AND NIEMANN-PICK C PATIENTS
AD and CVD Link

• Risk for AD (epidemiological evidence)
  – Hypercholesterolemia
  – High mid and late life plasma cholesterol level
  – Atherosclerosis
  – Hypertension
  – Obstruction in cerebral blood flow (hypoperfusion)
  – High saturated fat diet

• AD Risk Reduction
  – Statin therapy
  – MeDi

CHOLESTEROL INDUCES ABNORMAL SPINDLES

A

B

University of Colorado
Anschutz Medical Campus
Department of Neurology
Atherosclerosis

Chromosomal Abnormalities in Atherosclerotic Plaques

- Trisomy and tetrasomy 7
- Trisomy 8
- Monosomy 11
- Monosomy 13
- Y deletion

Bonin et al., 1999; Matturi et al., 2001
LDL INDUCES ANEUPLOIDY IN HUMAN AORTIC SMOOTH MUSCLE CELLS

ETHANOL ATTENUATES LIPOPROTEIN-INDUCED ANEUPLOIDY
Conclusions

1. All forms of AD show neuronal aneuploidy/trisomy 21

2. All forms of FTLD show neuronal aneuploidy/trisomy 21
   Relevance to ALS

3. LDL/cholesterol induces aneuploidy/trisomy 21
   Relevance to NPC, AD, CVD

4. Preliminary results show aneuploidy/trisomy 21 in Huntington’s Disease

4. Trisomy 21/Aneuploidy is a key feature of multiple neurodegenerative diseases
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