“Nothing in biology makes sense except in the light of evolution”
(Th. Dobzhansky)

Alzheimer’s disease -
an evolutionary perspective

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3rd Alzheimer’s Focused #C4CT Concussion Awareness Summit at United Nations
Prevailing concepts

amyloid cascade hypothesis

PSEN1/2 & APP FAD mutations

\[ \text{NH}_2 \rightarrow \beta \alpha \gamma \text{ secretases} \rightarrow \text{A}\beta\text{-peptide} \rightarrow \text{A}\beta\text{-aggregates} \]

A\beta-plaques

\[ \text{hyperphosphorylation and aggregation of tau-protein} \]

\[ \text{neurofibrillary tangles} \]

\[ \text{Neuronal dysfunction and death} \]

\[ \text{loss of synapses} \]
Why do we get Alzheimer´s disease?

- AD is unique to human
- major genetic risk factor: ApoE polymorphism is unique to human

Cerebralization:
accelerated brain growth in hominid evolution
increase in:
- cortical synapses
- brain plasticity
- cognitive capacity
Why do we get Alzheimer’s disease?

Brain regions, highly vulnerable to AD-pathology have been elaborated in most recent hominid evolution.

Allometric volume plots
Development of neurofibrillary degeneration inversely recapitulates brain development

progression of myelination
[acc. to Flechsig]

brain structure: last in – first out

development

progression of neurofibrillary degeneration
[acc. to Braak]

primary sensory & motor cortex
primary sensory association cortex
non-primary association cortex
limbic cortex

degeneration / regression?
Reversal of developmental behavioural hierarchy in AD

"last in - first out"

Sequence at which function is acquired during development (J. Piaget)

- Perform complex activities of daily life
- Put on clothing properly
- Perform mechanics of toileting correctly
- Maintain urinary continence
- Maintain fecal continence
- Say a few intelligible words
- Walk independently
- Sit up independently
- Smile
- Hold up head independently

Sequence at which function is lost in AD
expansion and laminar elaboration of primate neocortex:

accelerated cell-cycle kinetics with delayed maturation

• extended duration of cell cycle
• more total rounds of cell division

Achilles heel

• increased risk of mitotic errors
• special requirements of differentiation control
Re-expression of cell cycle markers in AD

The human brain is a mosaic with hyperploid neurons

AD: 50% increase in single cell DNA content

**Slide based cytometry**

- **2n peak**
- **4n peak**

**PCR amplification of alu repeats**

<table>
<thead>
<tr>
<th>single-neuron DNA content (pg)</th>
<th>control</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2n</td>
<td>0</td>
<td>2n</td>
</tr>
<tr>
<td>4n</td>
<td>0</td>
<td>4n</td>
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</tbody>
</table>

**Number of neurons [%]**

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2n - 4n</td>
<td>12%</td>
<td>29%</td>
</tr>
<tr>
<td>4n</td>
<td>0.4%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

**References**

Hyperploidy is an early (preclinical) event

Arendt et al. Am.J.Pathol. 2010, 177: 15-20
Hyperploidy occurs prior to cell death

additional challenge: consuming reparative/compensatory capacity

- concussion
- oxidative stress
- chronic intoxication
- metabolic imbalances
- latent infections

number of hyperploid neurons (mm⁻²)

disease progression

Arendt et al. Am.J.Pathol. 2010, 177: 15-20
Selective cell death of hyperploid neurons

entorhinal cortex (n=28)

- Total loss of neurons: 67
- Loss of diploid neurons: 7 (~10%)
- Loss of hyperploid neurons: 60 (~90%)

Arendt et al. Am. J. Pathol. 2010, 177: 15-20
Cell cycle proteins subserve alternative functions in differentiated neurons: regulation of synaptic plasticity

**Constitutive expression**

- **cyclin D**
- **CDK 4**

**Axonal localisation**

- **CDK 4**
- **Cyclin D**

**CDK 4 regulates structural plasticity**

- **Control**
- **siRNA CDK 4**

The dual functions of cell cycle regulators in neurons

“canonical cell cycle regulators”
(e.g. CDKs, cyclins, CDK-inhibitors …)

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development

alternative effector pathways

maturation (differentiation)

developmental switch

control of the cell cycle

neurodegeneration (de-differentiation)
degenerative switch

adult

control of synaptic plasticity
'Dr. Jekyll & Mr. Hyde concept'

Is the **risk of a phylogenetic regression** based on the persistence of developmentally primitive aspects in a highly developed biological system.

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**non-neuronal dividing cells**
(e.g. fibroblasts)

- loss of neighbouring cells
- loss of contact inhibition
  - proliferation
  - tissue repair

**Cellular evolution:**

- synapse formation on the expense of the ability to proliferate

**Regression:**

- loss of synaptic input is mis-regarded as loss of contact inhibition
- triggers ancient program of repair that involves cell cycle activation

**postmitotic neurons**
(non-dividing)

- network re-organisation
  - functional deafferentation
  - re-activation of proliferation
  - neuronal death
Hibernation: a model for repeated cycles of synaptic regression

- metabolic rate
- depression
- body temperature
- energy expenditure
- reversible
  “brain shrinkage”

- metabolic rate (mlO₂ h⁻¹)
- heart rate (BMP)

- body temperature (°C)

- heart rate

- spine density (spines/µm)

- eupthermic
  - torpor
  - arousal

- CA3 apical

- spine density (spines/µm)

- EU
  - TL
  - AL

- ***
  - **
  - ***
AD (PHF)-like phosphorylation of tau in hibernation

Euthermic                  Torpor                 Arousal

pS202+pT205 (AT8)

Hamster (Cricetinae)

Brown bear (Ursus arctos)

Arctic ground squirrel (Spermophilus parryii)

European ground squirrel

Linking metabolic depression (diabetes ?) to AD-type pathology

Stieler et al. (2008), Stieler et al. PlosOne (2011)
Accumulation of PHF-tau at postsynaptic sites coincides with synaptic detachment of excitatory afferentation.

Synaptophysin (stratum lucidum): mossy fibre input

MAP 2 (green) / PHF-tau: AT8 (red)

Synaptic detachement
Gradual re-appearance of synaptic afferentation
Blocking cell cycle activation by p16\textsuperscript{INK4A} is neuroprotective

conditional (tet), neuron-specific (CamKII) expression of p16\textsuperscript{INK4A} protects against NMDA-induced cell death

expression of the transgene

excitotoxic cell death

Fluoro-Jade B

lesion volume (µm\textsuperscript{3})

Arendt 2000; 2003
Expression of p16\textsuperscript{INK4a} as universal mechanism of neuroprotection

ischemic cell death (middle cerebral artery occlusion; MCAO)

Arendt 2000; 2003
Our vision: neuroprotection by gen-transfer of p16\textsuperscript{INK4A}

Fluoro-Jade

anti-p16

NMDA-induced neurone death (Fluoro-Jade)

Lesion volume [%]

\[ p<0.01 \]
Cell cycle dysregulation on peripheral lymphocytes as diagnostic blood biomarker of AD


CD69 expression after mitogenic stimulation (PHA, 12µg/ml)
FACscan flow cytometry

AD: MCI: control:
n=43; n=14; n=18
n=27; n=45

stimulation index

AD - patient

LymPro Test®

r=0.73
r=0.63
The evolutionary 'Dr. Jekyll & Mr. Hyde concept' of AD and emerging diagnostic & therapeutic targets.

- Synaptic detachment & abnormal synaptic turnover
- Amyloid cascade
- Phylogenetic regression
- LymPro Test®
- Cell cycle activation & partial DNA replication
- \( p16^{INK4a} \)
- Gentherapy
- Second challenge – consuming reparative capacity
- Neuronal death
Support by the families of our patients is gratefully acknowledged.