ILSI Europe Satellite Workshop on ‘Nutrition for the Ageing Brain: Towards Evidence for an Optimal Diet’

03-04 July 2014, Milan, Italy
Neurodegeneration and Synaptic Dysfunction/Loss: are Alzheimer’s disease and Neurodegenerative Dementia primarily Metabolic diseases?

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03 July 2014, Milan, Italy

Organised by
The ILSI Europe Nutrition and Mental Performance Task Force
Presentation outline

- A multi-factor network analysis of Alzheimer’s disease
- Modeling of the neurodegenerative dementia network
- Exploring the Links Between Diabetes and Alzheimer’s
- Autophagy and healthy aging: role of nutrition
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A multifactor analysis of Alzheimer’s disease

Caberlotto L., Lauria M., Nguyen TP, Scotti M. PLOS ONE (2013) 8, 11, e78919
Alzheimer’s disease

Prevalence:
1-2% age 65-75; 50% over age 85

Pathology:
Amyloid plaques
Neurofibrillary tangles
Neuronal death and brain atrophy

Pharmacological treatment (FDA approved):
Cholinesterase inhibitors
  Donepezil
  Galantamine
  Rivastigmine
  Tacrine
NMDA receptor antagonist
  Memantine
Alzheimer’s project overview

Alzheimer relevant genes

mRNA expression

SNPs

Drug Targets

 Identification of AD candidate genes and/or Biomarkers

OMIM
Online Mendelian Inheritance in Man

ILSI Europe
Functional enrichment analysis

- Superior frontal gyrus
- Hippocampus
- Enthorinal cortex
- Medial temporal gyrus
- Visual cortex
- Posterior Cingulate Cortex

GO terms Biological Functions

- Synaptic Transmission
- Inflammation
- Metabolism
- Autophagy
- Circadian Rhythm
- Neurotransmitter Signaling
- Metabolism & Autophagy
- Circadian Rhythm
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Modeling of the neurodegenerative dementia network

Caberlotto L & Nguyen TP. (2014) *BMC Systems Biology*
Dementia

Multiple cognitive deficits manifested by:
memory impairment and one (or more) of the following cognitive disturbances:
(a) aphasia (i.e., speech impairment)
(b) apraxia (i.e., motor planning)
(c) agnosia (i.e., object recognition)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
Neurodegenerative Dementia

Individual neurodegenerative dementia diseases share the symptom of dementia, but they are characterized histologically by varying grades of neuronal loss, gliosis, and abnormal accumulation of proteins.

How Neurodegenerative diseases with dementia are related?

Diseases

- Alzheimer
- Frontotemporal dementia
- Frontotemporal dementia with parkinsonism-17
- Lewy bodies disease
- Progressive supranuclear palsy
- Corticobasal dementia
- Pick’s disease
- Prion disease
- Huntington’s disease
- Familial Dementia
Neurodegenerative Dementia’s project overview

Disease genes

Protein-protein interaction network (I2d database)

Drug targets

Network reconstruction integrating dementia DGs ad DTs

Network Analysis

Highly ranked proteins
Set of candidate genes linking DGs and DTs
Dense sub-networks of candidate genes

Functional annotation analysis

GO terms Biological Processes
Analysis of specific GO term-associated genes
Neurodegenerative Dementia’s network

Disease proteins

Drug targets

Mediator

Cell surface receptor signaling pathway

Immune response & Inflammation

Metabolic Process
**Autophagy** (from the Greek words, *auto* "self" and *phagein* "to eat"), is the basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes.
Disease Genes: Autophagy Subnetwork

Disease Genes-Mediators

- FTD
- AD
- ALSPD
- FTD/AD

AMPK
Drug Targets: Autophagy Subnetwork

An okadaic acid-induced model of tauopathy and cognitive deficiency

Zhang Zhang\textsuperscript{a}, James W. Simpkins\textsuperscript{a,b,*}

PP2A blockade inhibits autophagy and causes intraneuronal accumulation of ubiquitinated proteins

Amandine Magnaudeix\textsuperscript{a}, Cornelia M. Wilson\textsuperscript{a,b}, Guylène Page\textsuperscript{c}, Chantal Bauvy\textsuperscript{d}, Patrice Codogno\textsuperscript{d}, Philippe Lévêque\textsuperscript{e}, François Labrousse\textsuperscript{f}, Manuela Corre-Delage\textsuperscript{f}, Catherine Yardin\textsuperscript{a,b}, Faraj Terro\textsuperscript{a,b,*}
Human Autophagy network

Topological

Autophagy interactions subnetwork

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Exploring the Links Between Diabetes and Alzheimer’s Disease
Alzheimer’s disease and Type 2 diabetes

- Insulin resistance and particularly T2DM increases risk of Alzheimer’s
- Type 2 diabetics have deposits of amyloid beta in their pancreas
- Experimental brain diabetes shares many features with AD, including cognitive impairment
- Anti-diabetic drugs are in clinical trial for the treatment of Alzheimer’s
Alzheimer’s Disease and Diabetes: cross-disease analysis

Separate analysis of networks (GO terms, Pathways)

Human T2DM

Network analysis

Human Alzheimer’s

Network analysis

Analysis of overlapping genes (GO terms, Pathways)
Functional annotation analysis: role of autophagy

OMIM

SNPs

OMIM AD

OMIM T2DM

PIOGLITAZONE

SQSTM1↑

GABARAPL1↓
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Autophagy and Healthy Aging:
Role of Nutrition
AMPK, Autophagy and Aging

Table: Polyphenol Source Effect on Autophagy

<table>
<thead>
<tr>
<th>Polyphenol</th>
<th>Source</th>
<th>Effect on Autophagy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Tumeric (urcuma longa)</td>
<td>Induction</td>
</tr>
<tr>
<td>Epigallocatechin gallate</td>
<td>Green tea (Camelia sinensis)</td>
<td>Induction</td>
</tr>
<tr>
<td>Genistein</td>
<td>Soybeans</td>
<td>Induction</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Onions, apples, berries, caperrs, grapes</td>
<td>Induction</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Grape skins, Nuts</td>
<td>Induction</td>
</tr>
</tbody>
</table>

(Sardi B, 2011)

(Pallauf K., 2013)
Curcumin effects on AMPK-PP2A-autophagy pathways in microglia

* Resveratrol in neocortex
Thank you!