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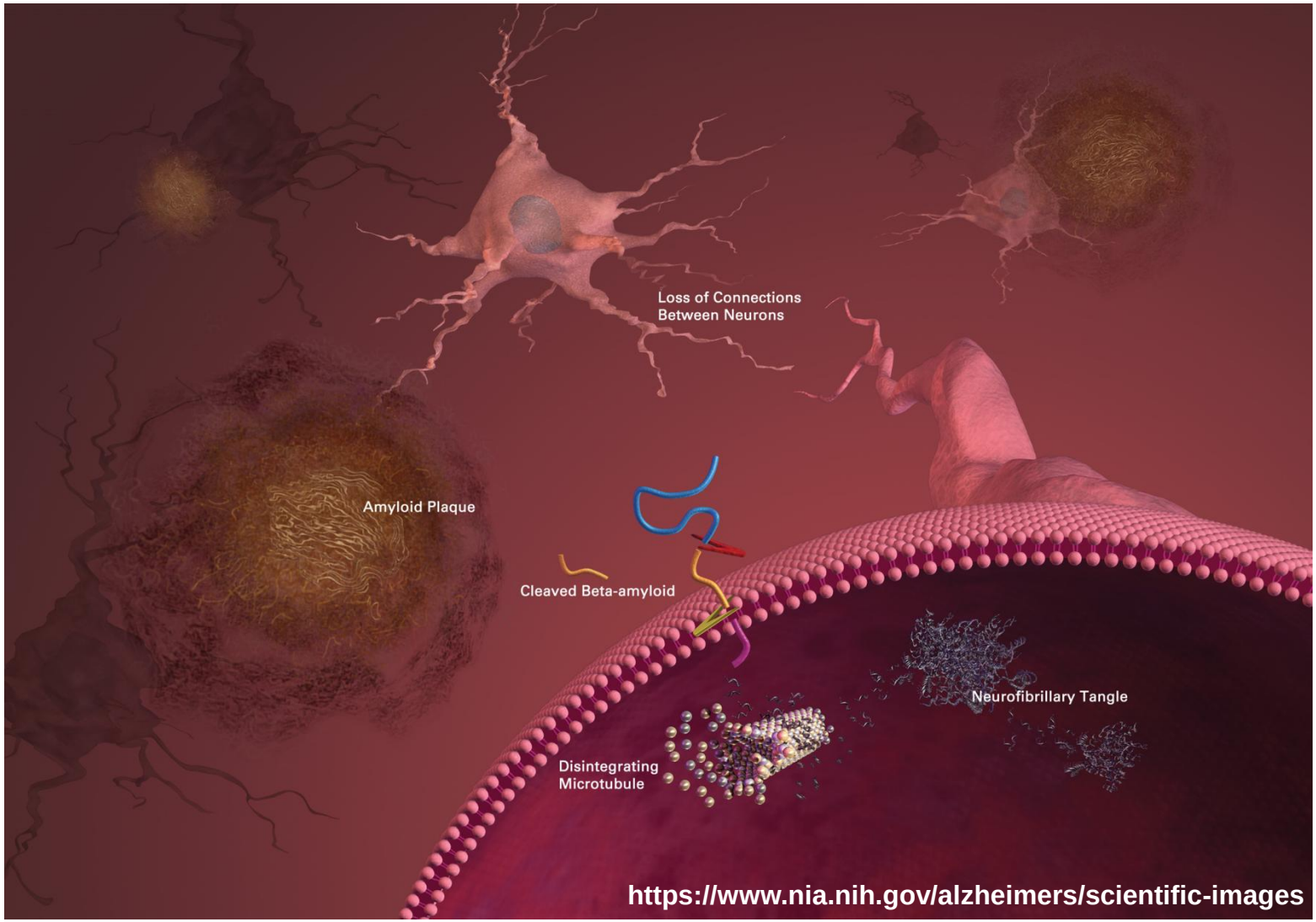
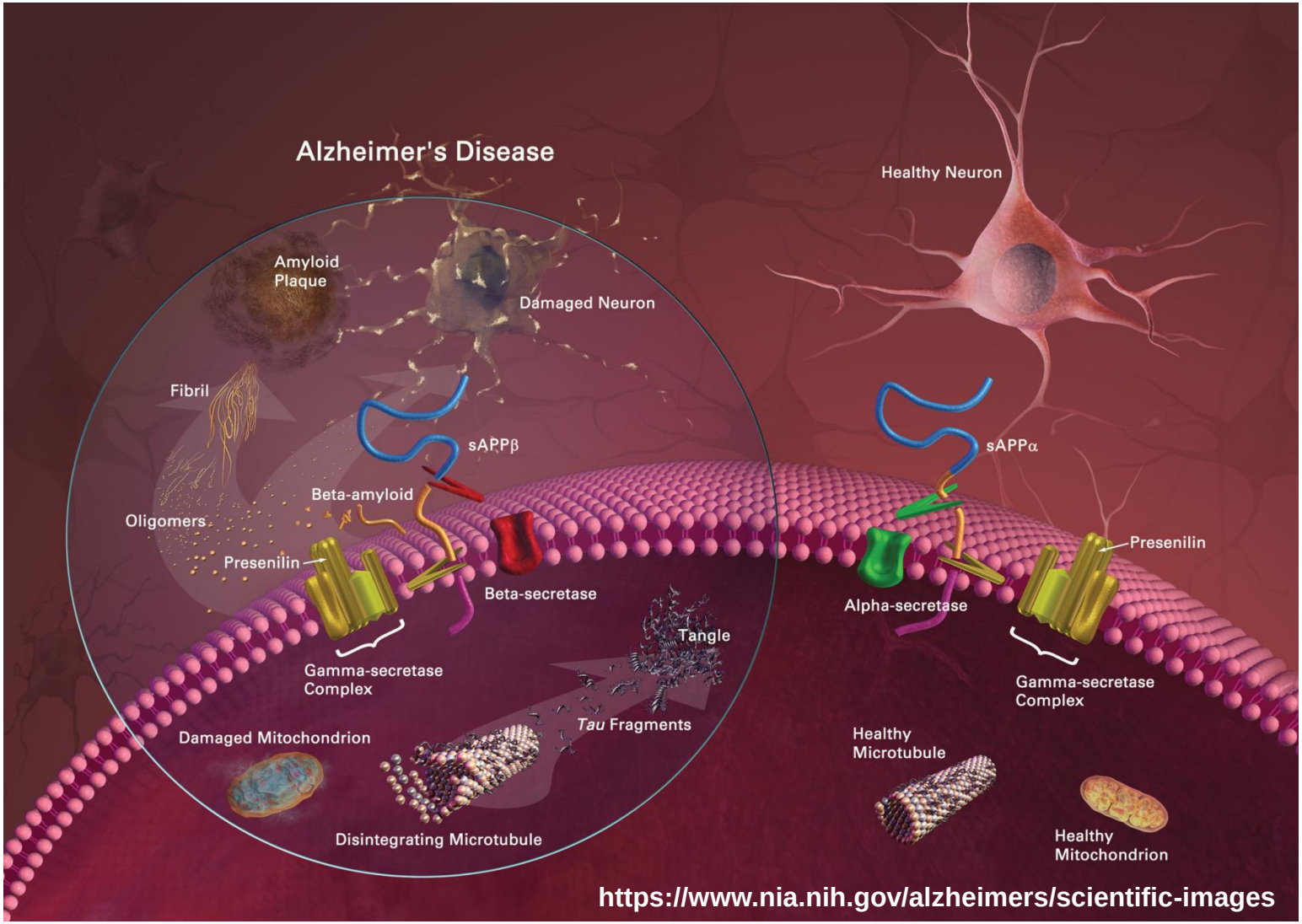
Prof.ssa Elena Tamagno

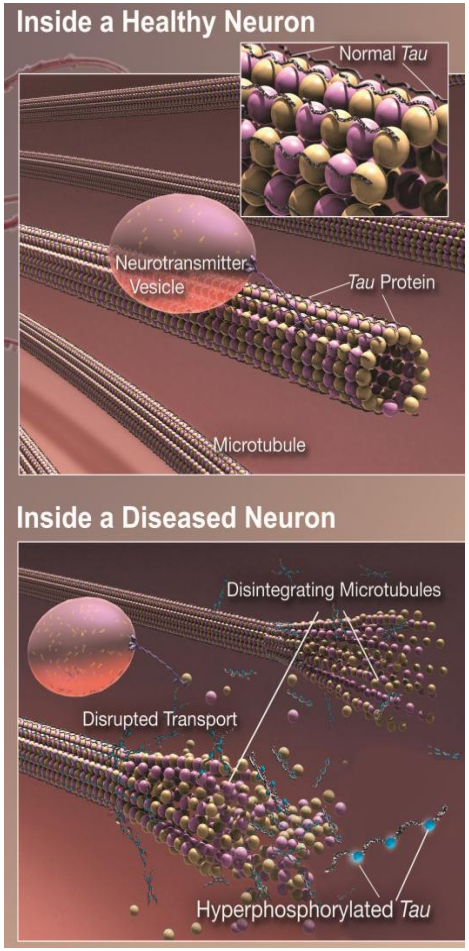
Alzheimer's Disease

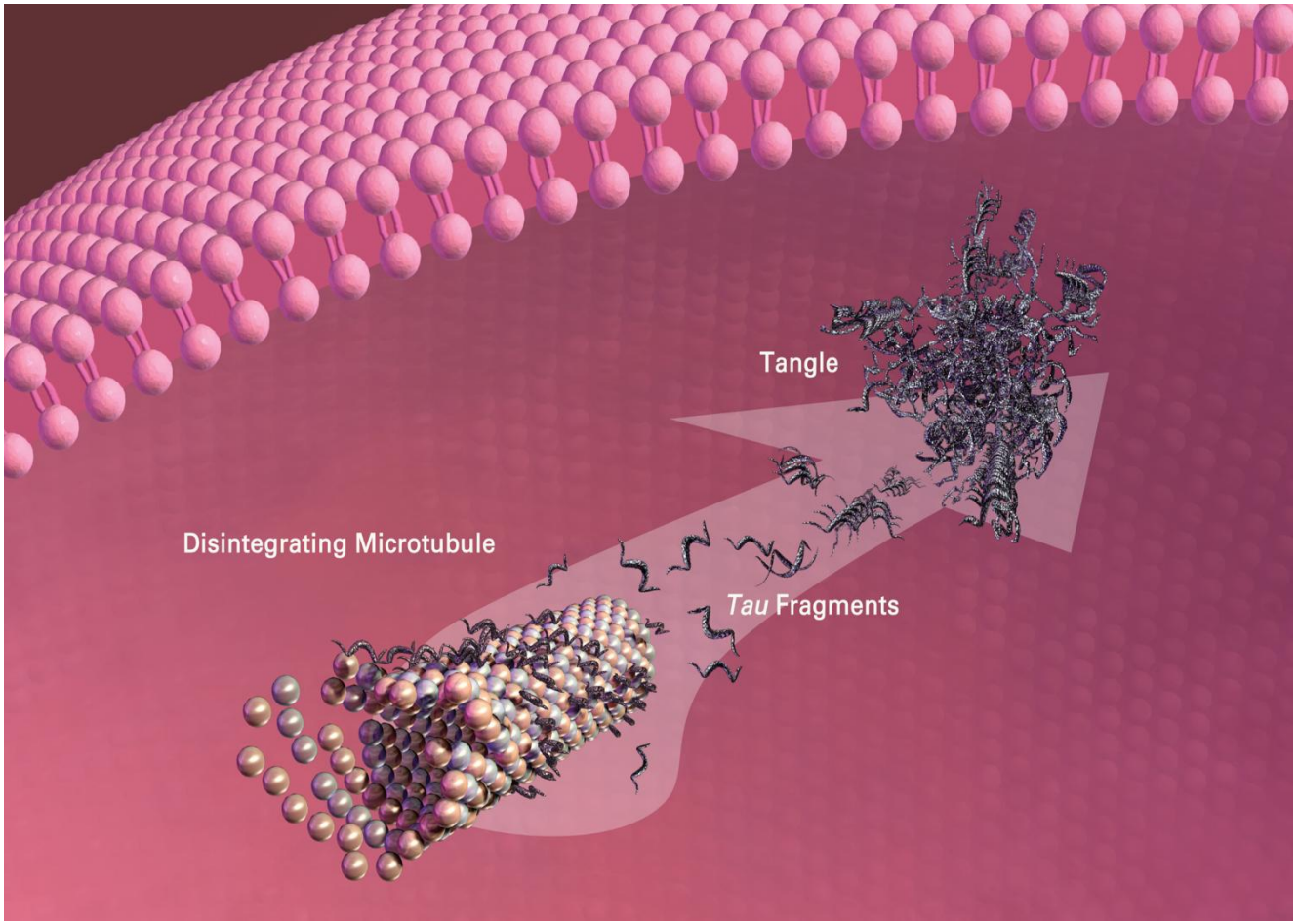


Amyloidogenic vs NON-Amyloidogenic pathways



Formation of Tau tangles



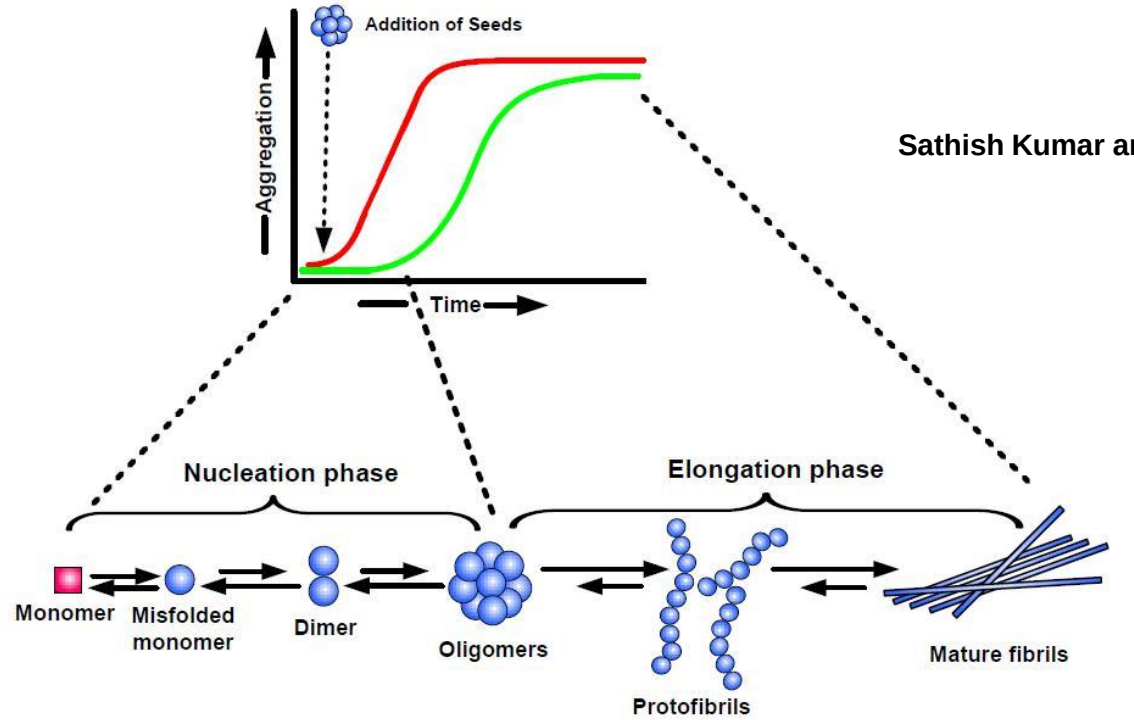


https://www.nia.nih.gov/alzheimers/scientific-images

Aβ aggregation - routes to neurotoxic assemblies

Aβ is a proteolytically processed fragment that occurs in different length variants:

- 40 amino acid residues (Aβ40)
- 42 amino acid residues (**Aβ42**)



Sathish Kumar and Jochen Walter, 2011

In the nucleation phase/lag phase, **monomers undergo conformational change** /misfolding **and associate to form oligomeric nuclei**.

In elongation phase/growth phase, nuclei rapidly grow by further addition of monomers and form larger polymers/fibrils until saturation.

Alzheimer's Disease

Therapy

symptomatic

depressive symptoms
psychotic-like symptoms

pathogenetic

- Phatogenetic therapy-Block accumulation of Aβ

- < production
- > disposal Aβ-42
- < aggregation

UBIQUITIN C-TERMINAL HYDROLASE-L1

Uch-L1

Cell

Ubiquitin Hydrolase Uch-L1 Rescues β-Amyloid-Induced Decreases in Synaptic Function and Contextual Memory

Bing Gong,[1] Zixuan Cao,[1] Ping Zheng,[2] Ottavio V. Vitolo,[1] Shumin Liu,[1] Agnieszka Staniszewski,[1] Donna Moolman,[1] Hong Zhang,[1] Michael Shelanski,[1,*] and Ottavio Arancio[1,*]
[1] Department of Pathology and Taub Institute, Columbia University, New York, NY 10032, USA
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DOI 10.1016/j.cell.2006.06.046

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Neurochemistry International 51 (2007) 105–111
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www.elsevier.com/locate/neuint

Review

The functions of UCH-L1 and its relation to neurodegenerative diseases

Rieko Setsuie [a,b], Keiji Wada [a,*]
[a] Department of Degenerative Neurological Diseases, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo 187-8502, Japan
[b] Japan Health Sciences Foundation, Kyodo Building, 13-4 Kodenmacho, Nihonbashi, Chuo-ku, Tokyo 102-0001, Japan

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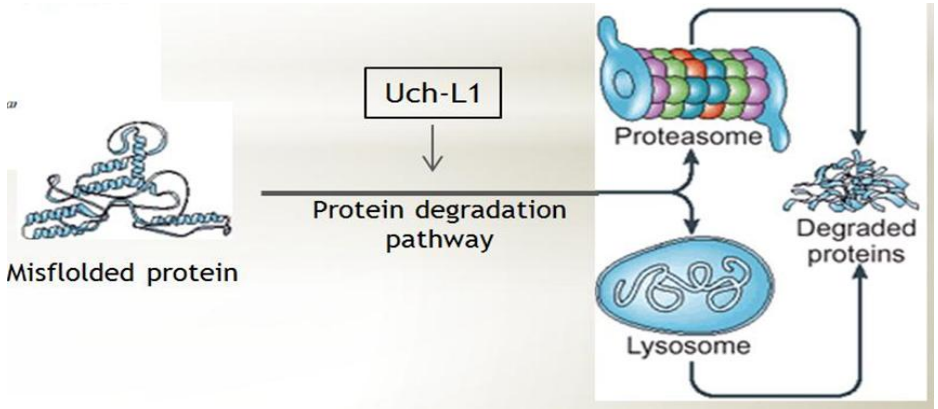
© 2004 by The American Society for Biochemistry and Molecular Biology, Inc. Printed in U.S.A.

Oxidative Modifications and Down-regulation of Ubiquitin Carboxyl-terminal Hydrolase L1 Associated with Idiopathic Parkinson's and Alzheimer's Diseases*

Received for publication, December 23, 2003
Published, JBC Papers in Press, January 13, 2004, DOI 10.1074/jbc.M314124200

Joungil Choi‡, Allan I. Levey‡§, Susan T. Weintraub¶, Howard D. Rees‡§, Marla Gearing‡§, Lih-Shen Chin‡, and Lian Li‡**

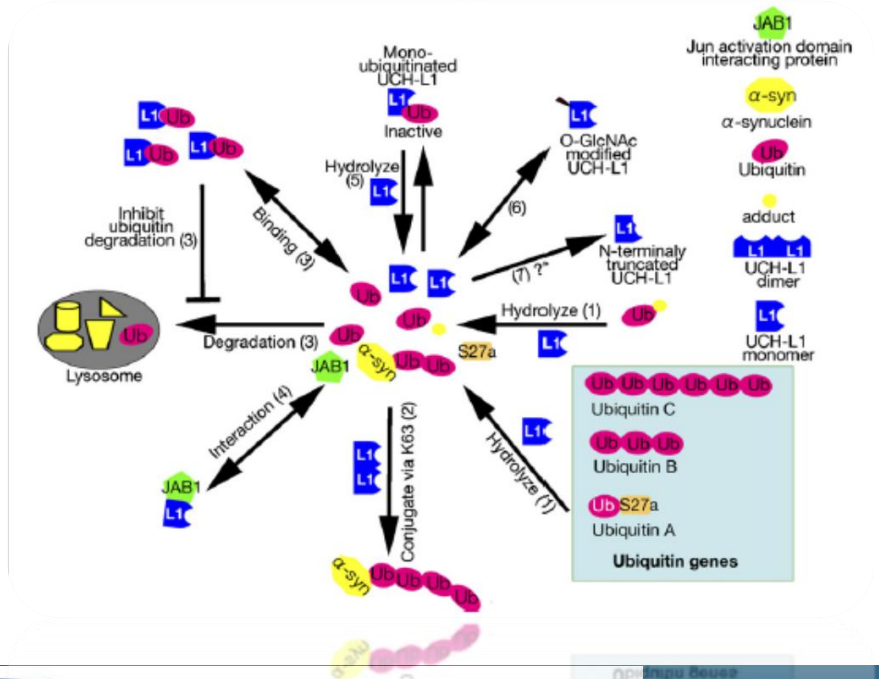


Uch-L1

- Uch-L1 is an enzyme highly expressed in neuron, know to decrease in the brain of Alzheimer's patients.

- Several lines of evidence suggest that Uch-L1 function is impaired in AD and that this enzyme might be involve in the pathogenesis of AD.

- Uch-L1 is responsible for the protein ubiquitination and for directing them to degradation by proteasome or by lysosomes.

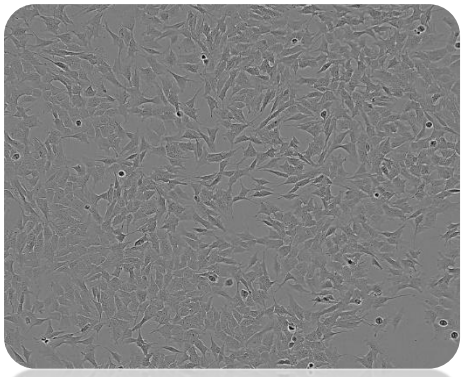


Uch-L1 have three activities:

- **Hydrolase;**
- **Ligase;**
- **Mono-Ub stabilizer.**

EXPERIMENTAL MODEL

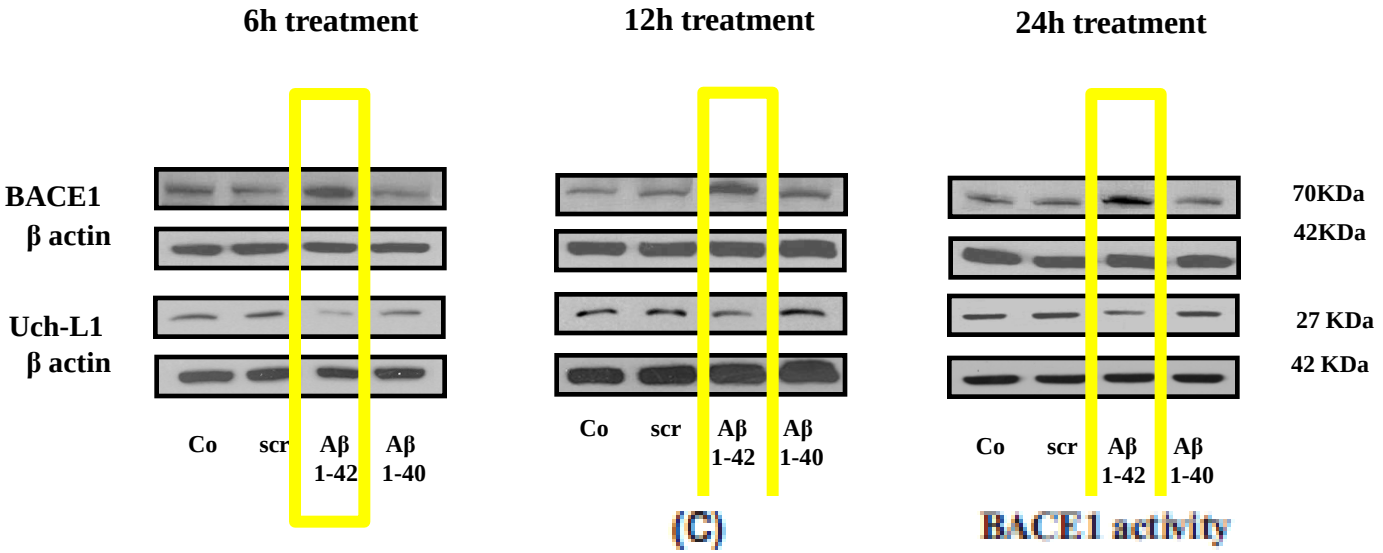
SH-SY-5Y



Monomeric

- **Aβ 1-42**
- **Aβ 1-40**
- **scramble**

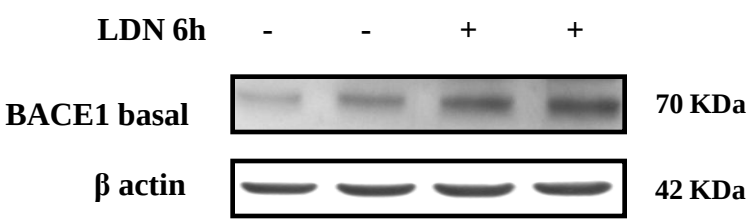
Aβ1-42–MEDIATED INCREASE OF BACE1 AND DECREASE OF Uch-L1 ARE RELATED EVENTS



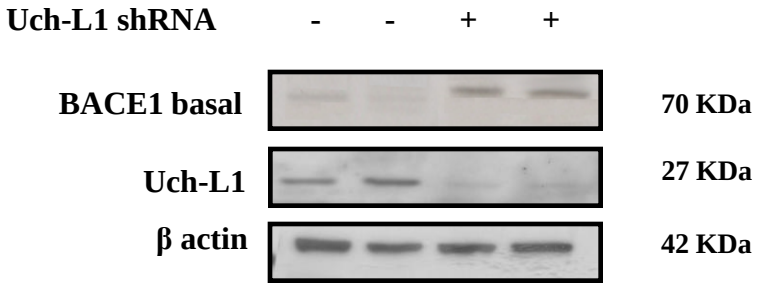
BACE1 activity was significantly higher in cells exposed to Aβ1-42 and to LDN compared to control cells.

Guglielmotto M. et al., Aging Cell, 2012

Aβ1-42-MEDIATED INCREASE OF BACE1 AND DECREASE OF Uch-L1 ARE RELATED EVENTS



RNA Interference



Guglielmotto M. et al., Aging Cell, 2012

BACKGROUND

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 283, NO. 15, pp. 10037–10047, April 11, 2008

NFκB-dependent Control of *BACE1* Promoter Transactivation by Aβ42*

Received for publication, August 8, 2007, and in revised form, January 24, 2008 Published, JBC Papers in Press, February 8, 2008, DOI 10.1074/jbc.M706579200

Virginie Buggia-Prevot[‡1], Jean Sevalle[‡], Steffen Rossner[§], and Frédéric Checler[‡2]

From the [‡]Institut de Pharmacologie Moléculaire et Cellulaire, UMR6097 CNRS/UNSA, Equipe Labellisée Fondation pour la Recherche Médicale, 06560 Valbonne, France and the [§]Department of Neurochemistry, University of Leipzig, 04109 Leipzig, Germany

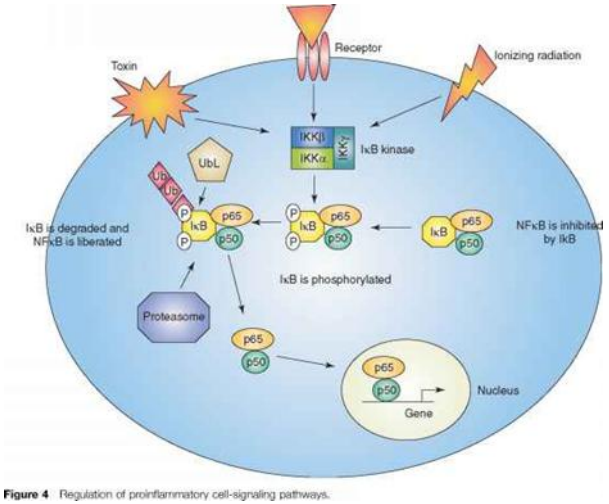


Figure 4 Regulation of proinflammatory cell-signaling pathways.

- Aβ42 is able to modulate BACE1 through the NF-kB pathway

Journal of Neurochemistry JNC

JOURNAL OF NEUROCHEMISTRY | 2011 | 116 | 1160–1170 doi: 10.1111/j.1471-4159.2011.07172.x

NF-κB signaling inhibits ubiquitin carboxyl-terminal hydrolase L1 gene expression

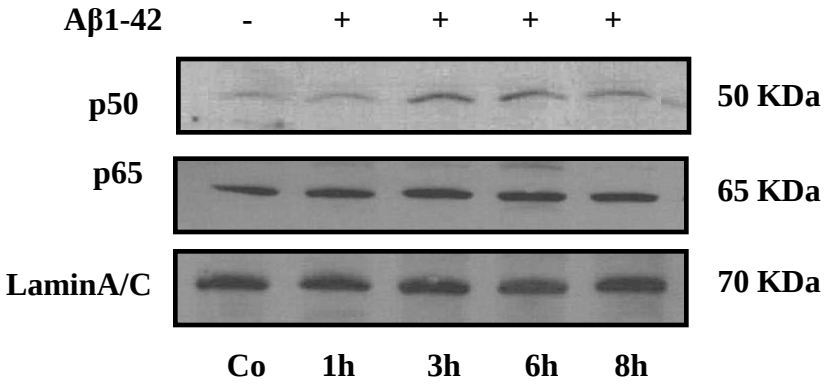
Ruitao Wang,*·†·[1] Mingming Zhang,*·[1] Weihui Zhou,* Philip T. T. Ly,* Fang Cai* and Weihong Song*

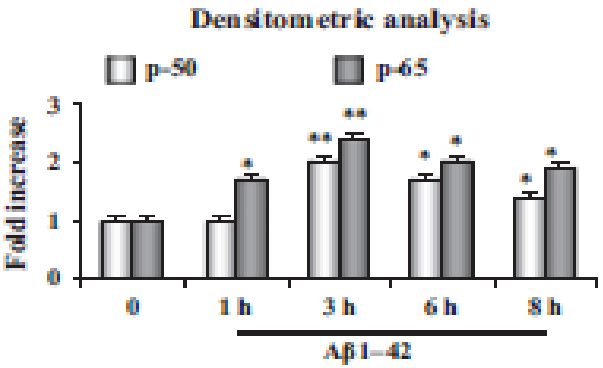
**Townsend Family Laboratories, Department of Psychiatry, Brain Research Center, Graduate Program in Neuroscience, The University of British Columbia, Vancouver, British Columbia, Canada*

†Department of Geriatrics, The Second Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, China

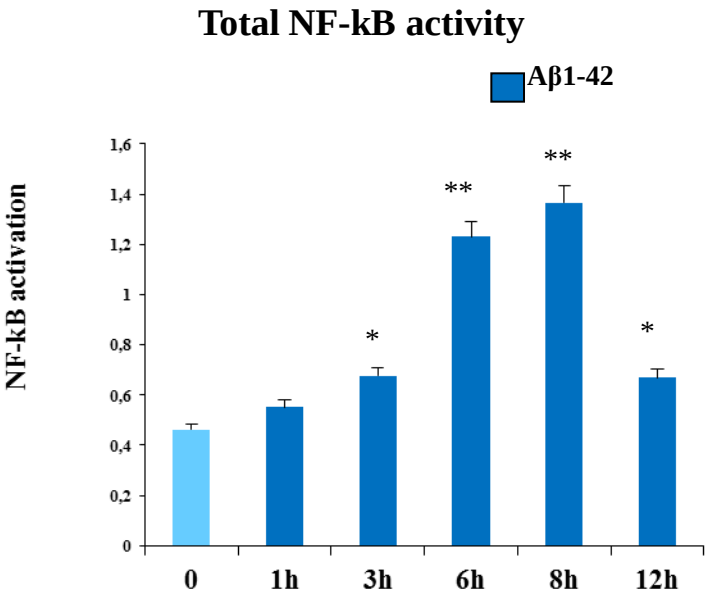
- NF-kB has its responsive element identified in the promoter region of Uch-L1 gene and therefore the expression of NF-kB suppresses Uch-L1 gene transcription.

THESE EVENTS ARE DEPENDENT ON NF-κB PATHWAY





Guglielmotto M. et al., Aging Cell, 2012



BACKGROUND

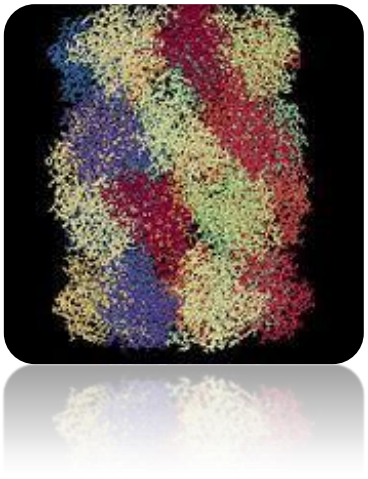
The FASEB Journal express article 10.1096/fj.04-1994fje. Published online August 2, 2004.

Degradation of BACE by the ubiquitin-proteasome pathway

Hong Qing,* Weihui Zhou,* Michelle A. Christensen,* Xiulian Sun,[†,*] Yigang Tong,* and Weihong Song,[†,*,¶]

*Department of Psychiatry, Brain Research Center, [†]Graduate Program in Neuroscience, The University of British Columbia, Vancouver, Canada. [¶]Holder of Canada Research Chair in Alzheimer's Disease.

Corresponding author: Weihong Song, Department of Psychiatry, The University of British Columbia, Vancouver, BC V6T 1Z3, Canada. E-mail: weihong@interchange.ubc.ca



THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 280, NO. 37, pp. 32469–32504, September 16, 2005

BACE Is Degraded via the Lysosomal Pathway*

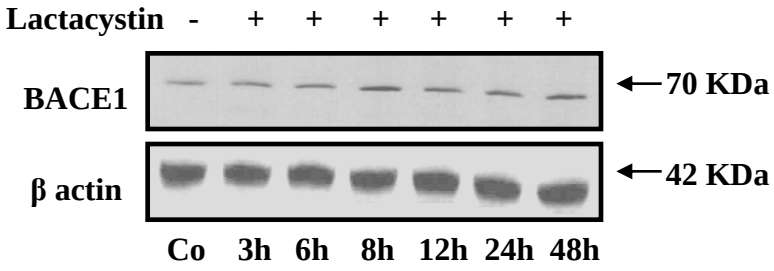
Received for publication, June 7, 2005, and in revised form, July 19, 2005 Published, JBC Papers in Press, July 20, 2005, DOI 10.1074/jbc.M506199200

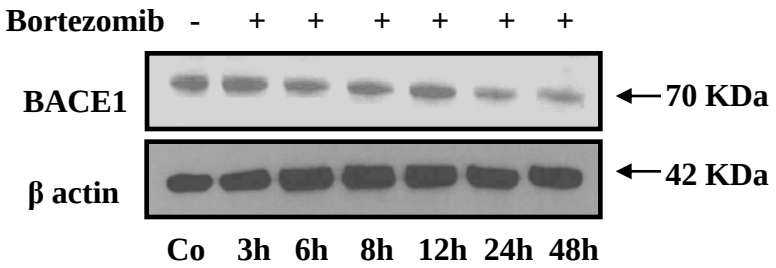
Young Ho Koh[§], Christine A. F. von Arnim[¶], Bradley T. Hyman[¶], Rudolph E. Tanzi[§‖], and Giuseppina Tesco[§‖]

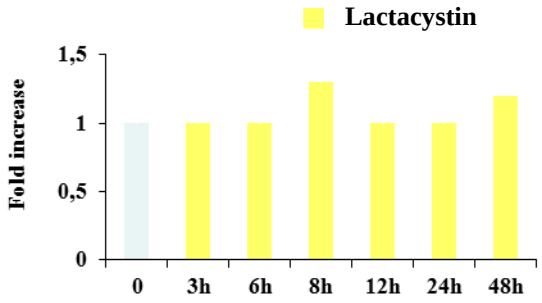
From the [§]Genetics and Aging Research Unit and the [¶]Alzheimer Disease Research Laboratory, MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital, Charlestown, Massachusetts 02129

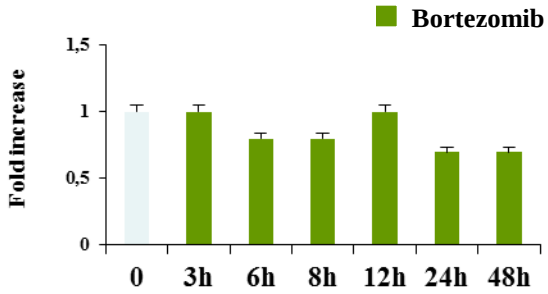
THE TURNOVER OF BACE1 PROTEIN IS NOT MEDIATED BY UBIQUITIN-PROTEASOME SYSTEM

Guglielmotto M. et al., Aging Cell, 2012





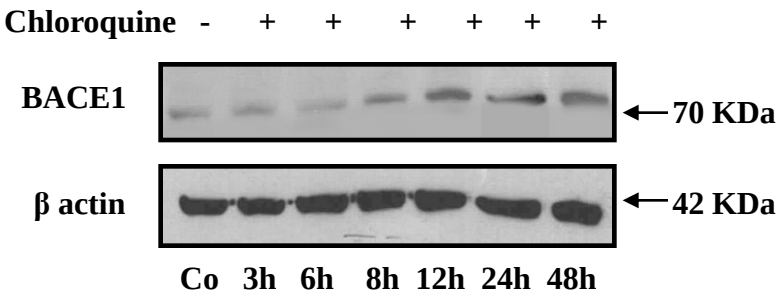


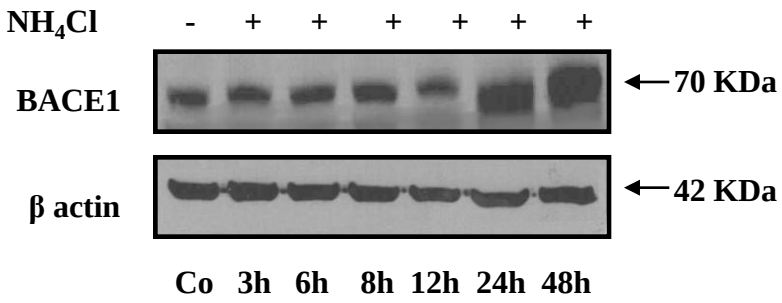


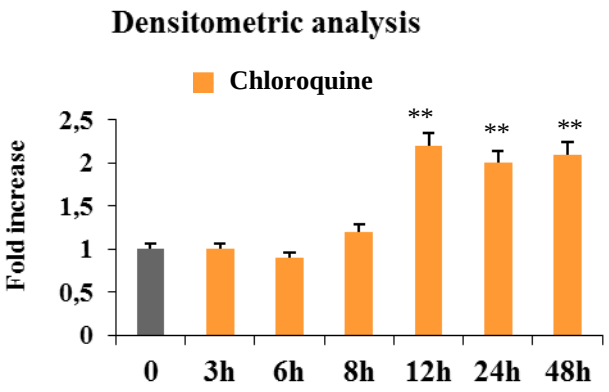
The proteasome inhibitors have no effect on BACE1 protein levels.

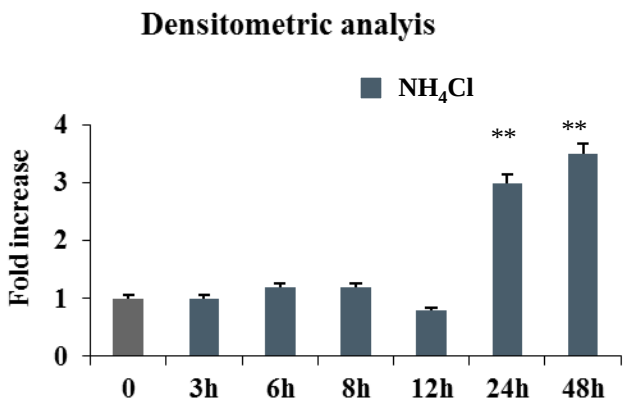
THE TURNOVER OF BACE1 PROTEIN IS MEDIATED BY LYSOSOMAL SYSTEM

Guglielmotto M. et al., Aging Cell, 2012









Chloroquine and NH_4Cl inhibit lysosomal hydrolases by reducing the acidification of endosomal/lysosomal compartments

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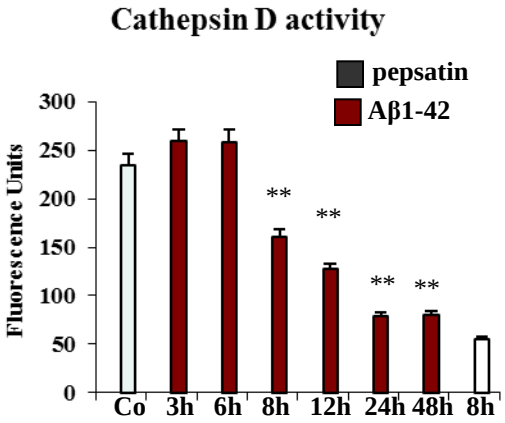
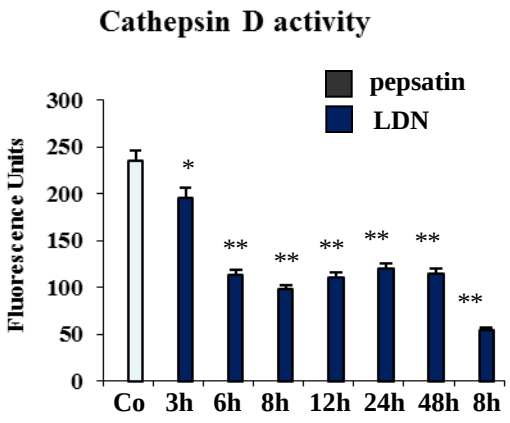
Aβ1-42 –MEDIATED DECREASE OF Uch-L1 INTERFERES WITH BACE1 LYSOSOMAL DEGRADATION

Guglielmotto M. et al., Aging Cell, 2012





CATHEPSIN D ACTIVITY

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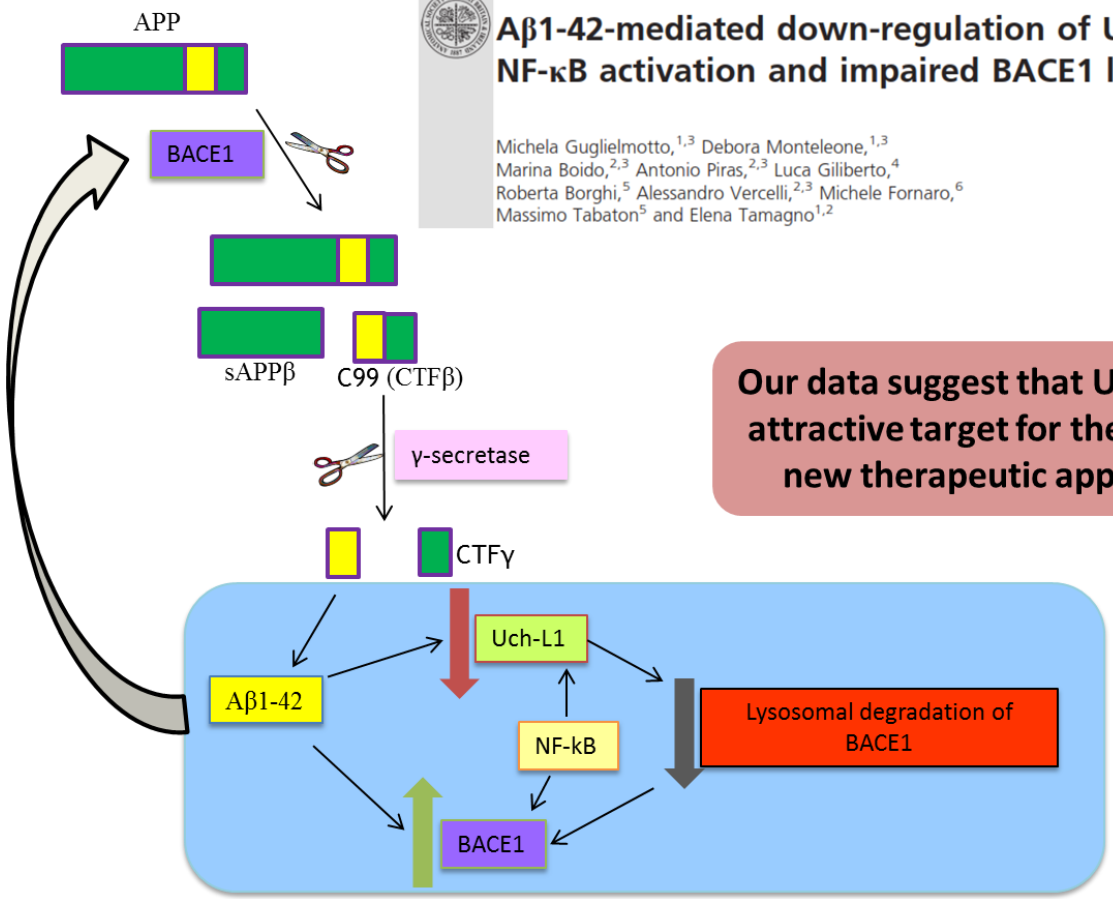
*Significantly different from controls (P < 0.05); **Significantly different from controls (P < 0.01).

CONCLUSION 1

Aging Cell (2012) **11**, pp834–844 Doi: 10.1111/j.1474-9726.2012.00854.x

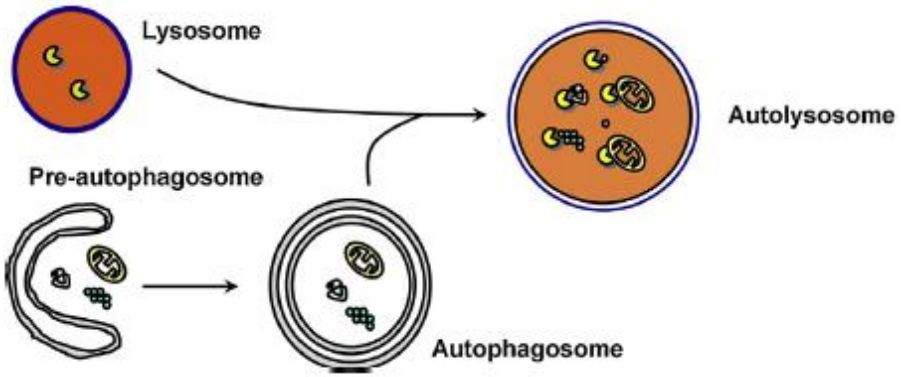
Aβ1-42-mediated down-regulation of Uch-L1 is dependent on NF-κB activation and impaired BACE1 lysosomal degradation

Michela Guglielmotto,[1,3] Debora Monteleone,[1,3] Marina Boido,[2,3] Antonio Piras,[2,3] Luca Giliberto,[4] Roberta Borghi,[5] Alessandro Vercelli,[2,3] Michele Fornaro,[6] Massimo Tabaton[5] and Elena Tamagno[1,2]



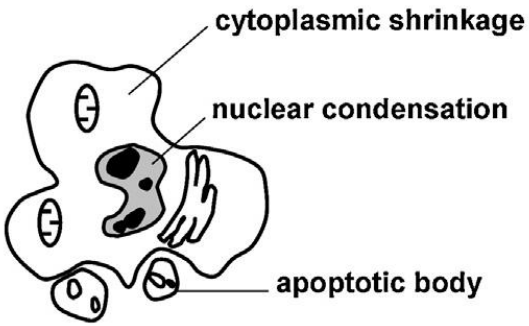
Our data suggest that Uch-L1 could be an attractive target for the development of new therapeutic approaches for AD

Autophagy



Autophagy involves sequestration of portions of the cytoplasm and intracellular organelles within autophagic vacuoles that are sent to lysosomes for degradation

Apoptosis



Apoptosis is the best-known form of programmed cell death and involves the activation of catabolic pathways that lead to the rapid destruction of cellular organelles.

Autophagy and Apoptosis are likely to be connected with each other in Alzheimer disease

Autophagy, amyloidogenesis and Alzheimer disease

Ralph A. Nixon
Center for Dementia Research, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962, Departments of Psychiatry and Cell Biology, NYU School of Medicine, New York, NY 10016, USA

Disruption of autophagy leads to Aβ accumulation in vacuoles and cell death…

JCB: ARTICLE

Macroautophagy—a novel β-amyloid peptide-generating pathway activated in Alzheimer's disease

W. Haung Yu,[1,2] Ana Maria Cuervo,[4] Asok Kumar,[1] Corrinne M. Peterhoff,[1] Stephen D. Schmidt,[1] Ju-Hyun Lee,[1,2] Panaiyur S. Mohan,[1,2] Marc Mercken,[5] Mark R. Farmery,[6] Lars O. Tjernberg,[6] Ying Jiang,[1,2] Karen Duff,[1,2] Yasuo Uchiyama,[7] Jan Näslund,[6] Paul M. Mathews,[1,2] Anne M. Cataldo,[8] and Ralph A. Nixon[1,2,3]

Journal of Neurochemistry JNC
JOURNAL OF NEUROCHEMISTRY | 2011 | 118 | 317–325 doi: 10.1111/j.1471-4159.2011.07314.x

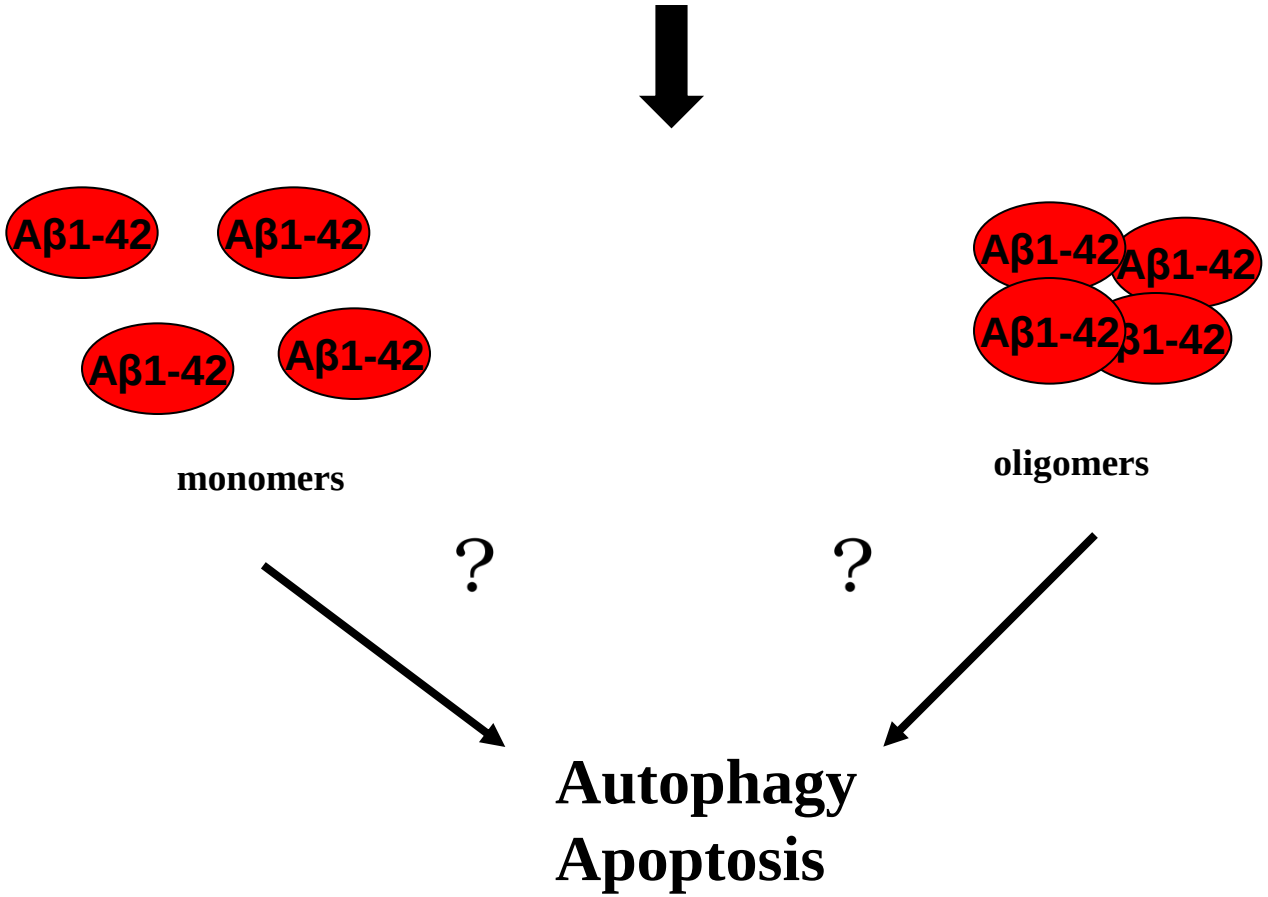
REVIEW

Autophagy deregulation in neurodegenerative diseases – recent advances and future perspectives

Zelda H. Cheung and Nancy Y. Ip
Division of Life Science, Molecular Neuroscience Center and State Key Laboratory of Molecular Neuroscience, The Hong Kong University of Science and Technology, Hong Kong, China

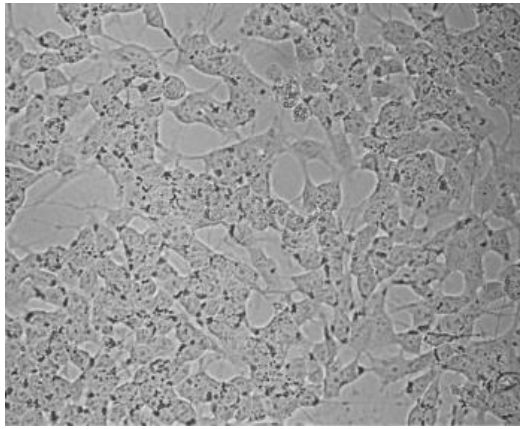
… in turn Aβ has been shown to affect autophagy

Given the relevance of soluble Aβ peptides



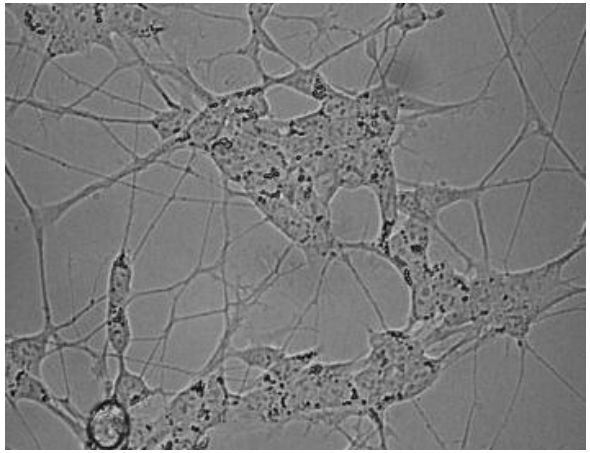
in vitro experimental model

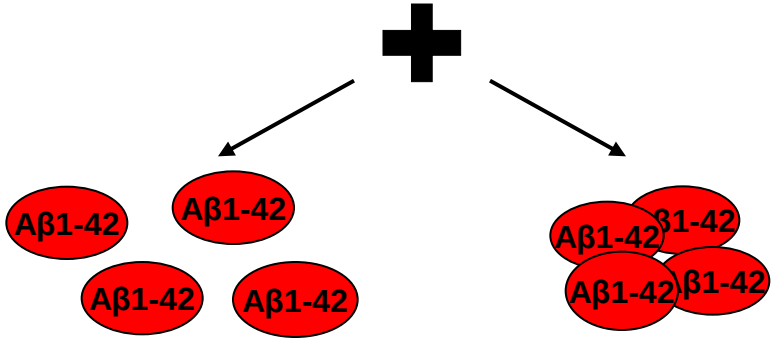
SK-N-BE



Retinoic Acid
10µM for 10 days

Differentiated SK-N-BE





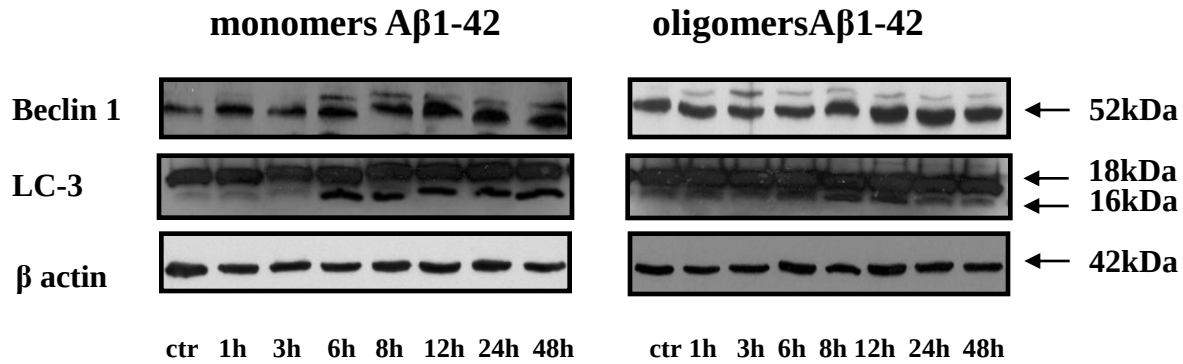
monomers

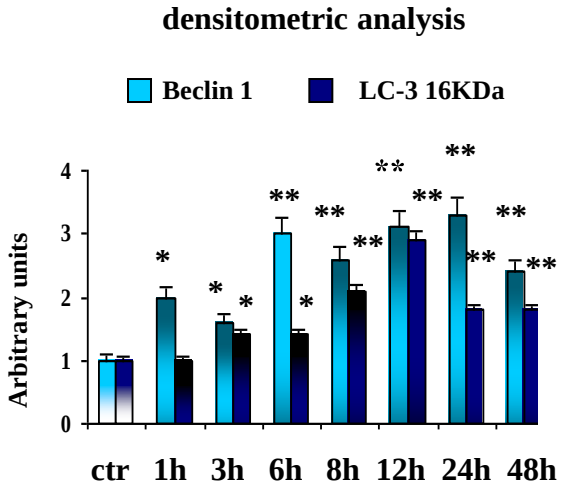
1µM

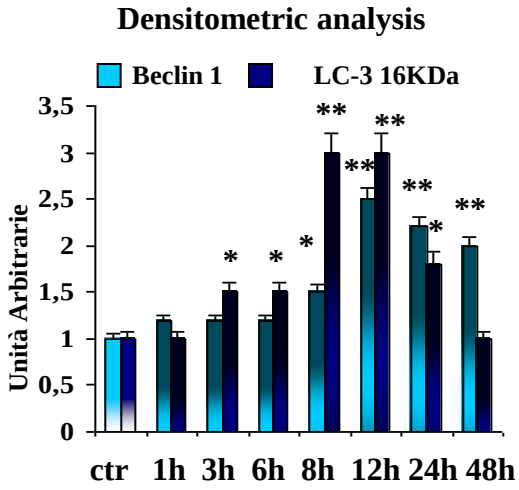
oligomers

1µM

Aβ1-42 Monomers and oligomers affected autophagy



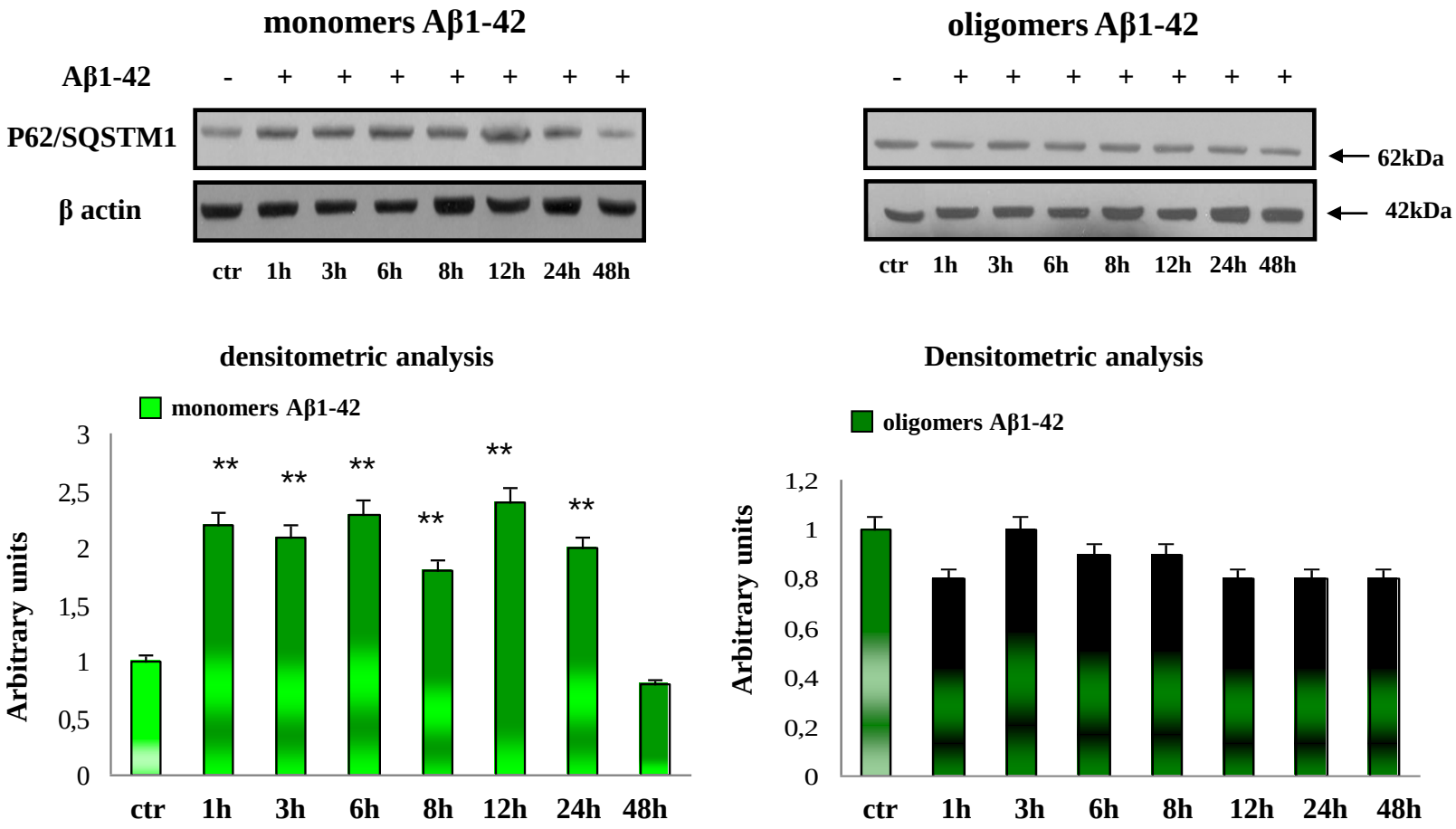




Guglielmotto M. et al., Autophagy 2014

Aβ1-42 monomers and oligomers affected autophagy

Guglielmotto M. et al., Autophagy 2014



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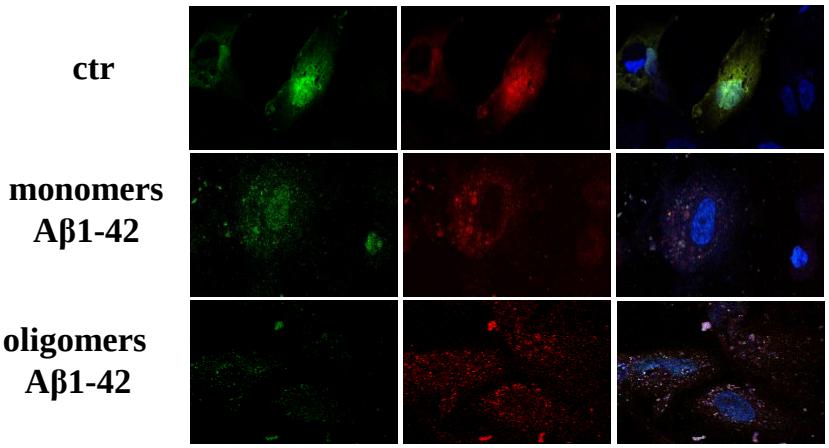
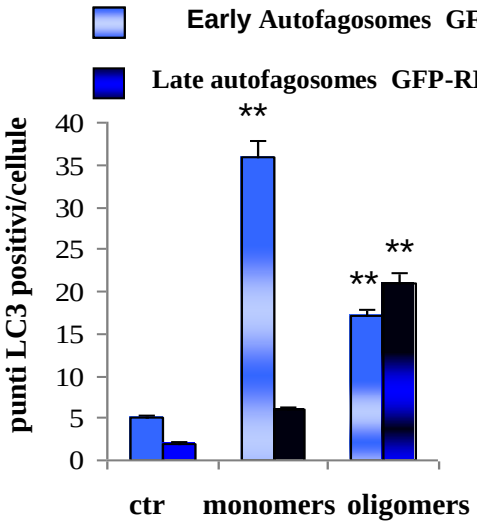
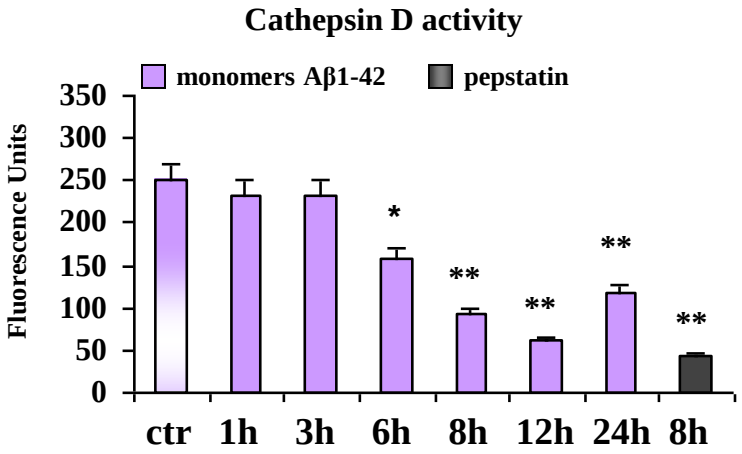
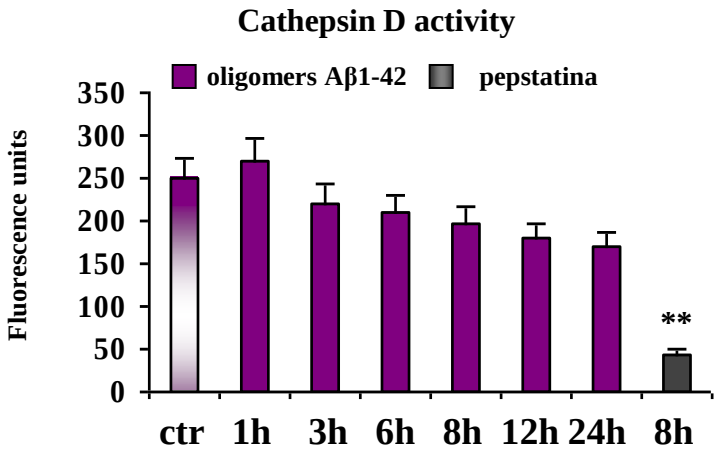
Aβ1-42 Monomers and oligomers affected autophagic flux

Guglielmotto M. et al., Autophagy 2014



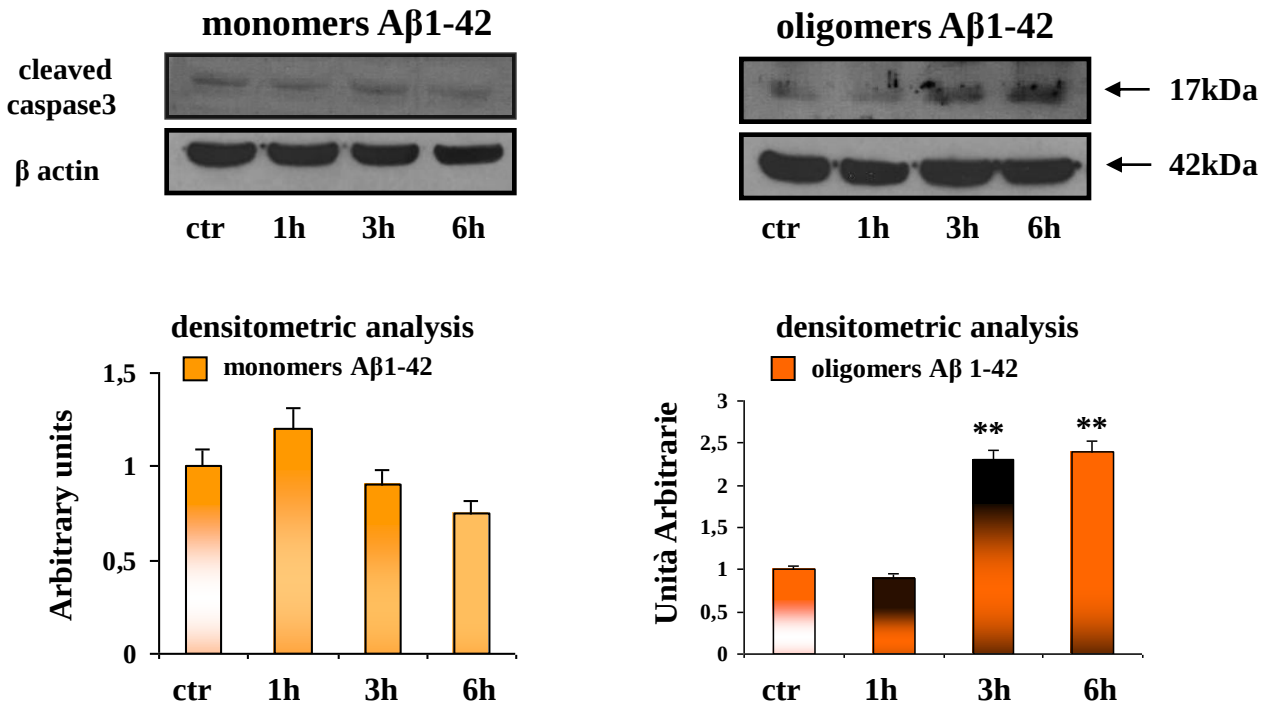






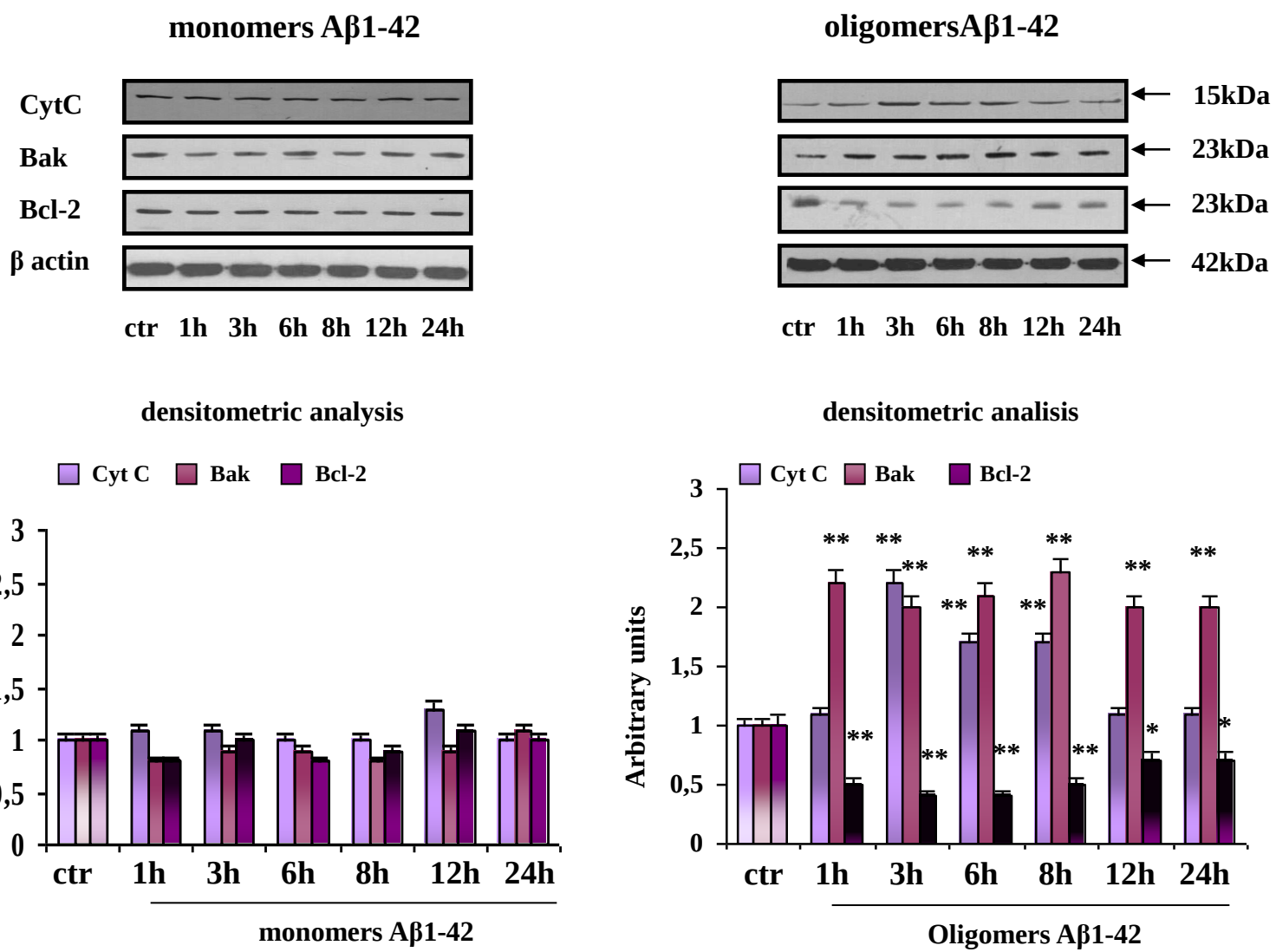
Aβ1-42 oligomers affect apoptotic intrinsic way

Guglielmotto M. et al., Autophagy 2014



Aβ1-42 oligomers affects apoptotic intrinsic way

Guglielmotto M. et al., Autophagy 2014



Bcl-2 /Beclin 1 complex

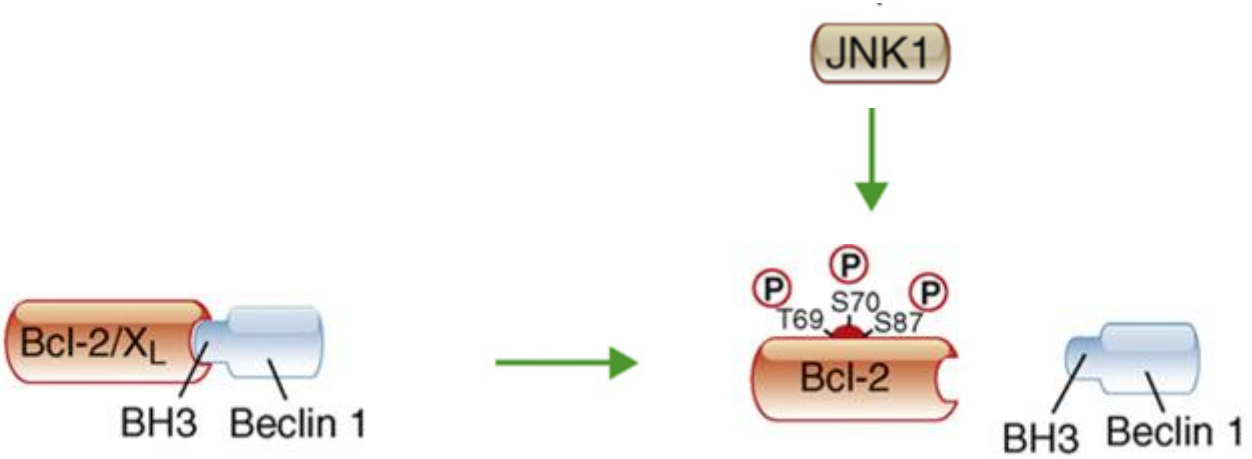
Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Cell Biology

The Beclin 1 interactome

Congcong He[1,2] and Beth Levine[1,2,3]

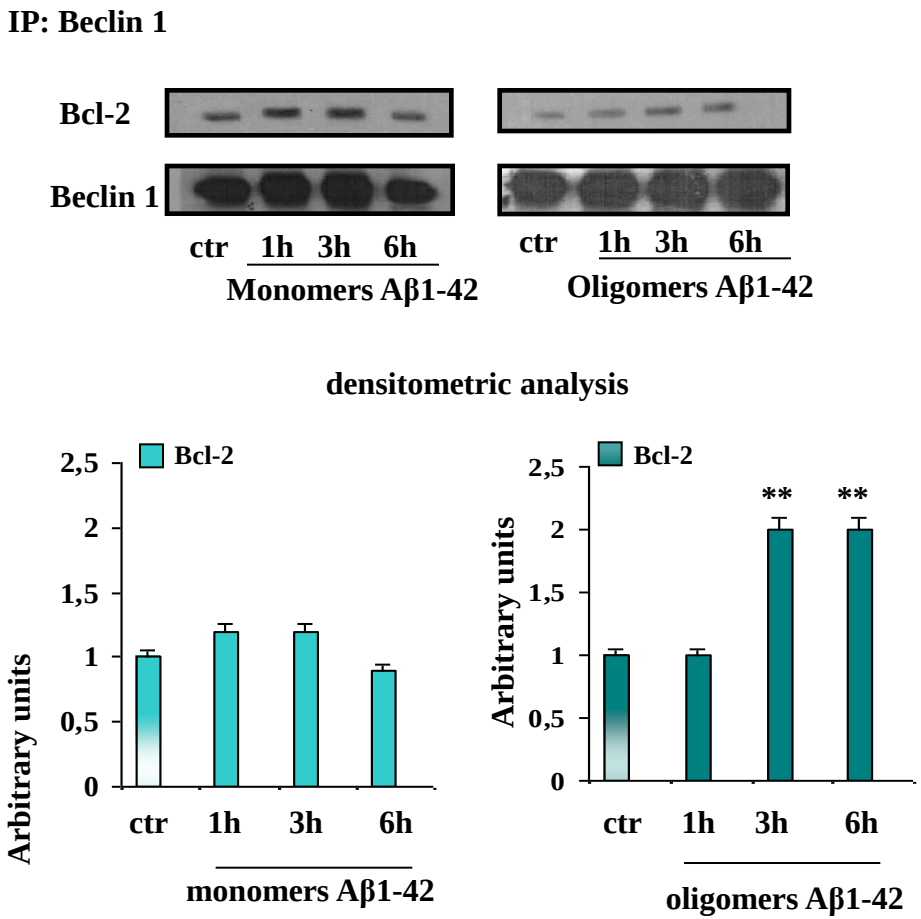
Self-eating and self-killing: crosstalk between autophagy and apoptosis

M. Chiara Maiuri[*‡||], *Einat Zalckvar*[¶], *Adi Kimchi*[¶] *and Guido Kroemer*[*‡§]



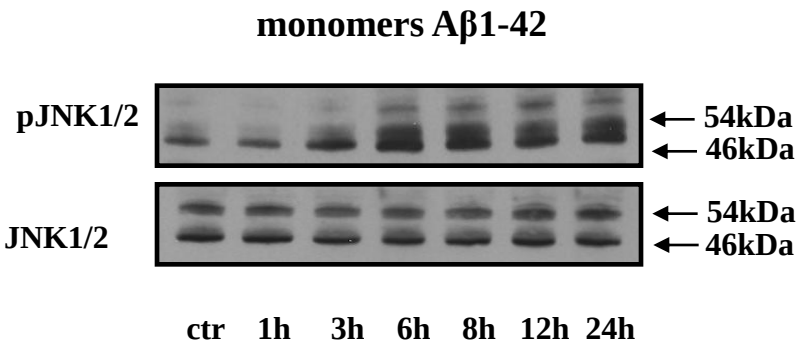
Oligomers of Aβ1-42 favour Bcl-2/Beclin 1 complex

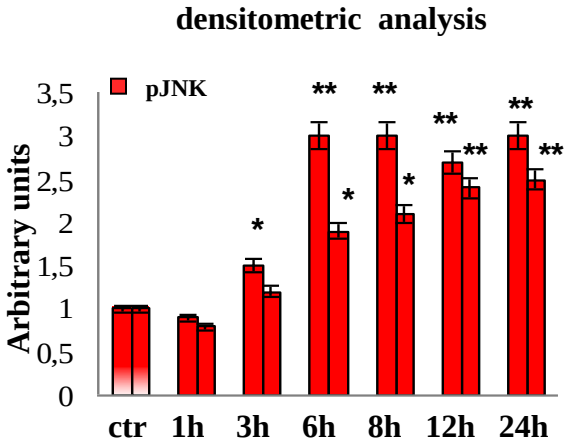
Guglielmotto M. et al., Autophagy 2014

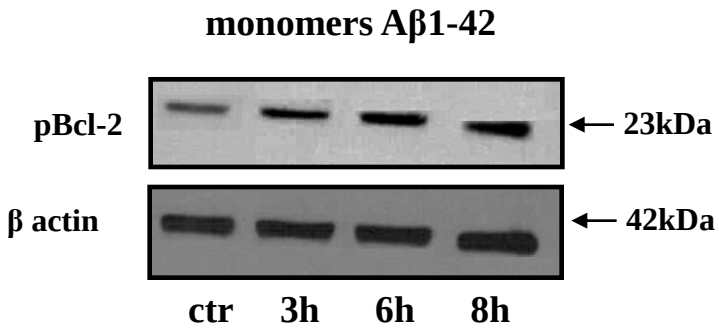


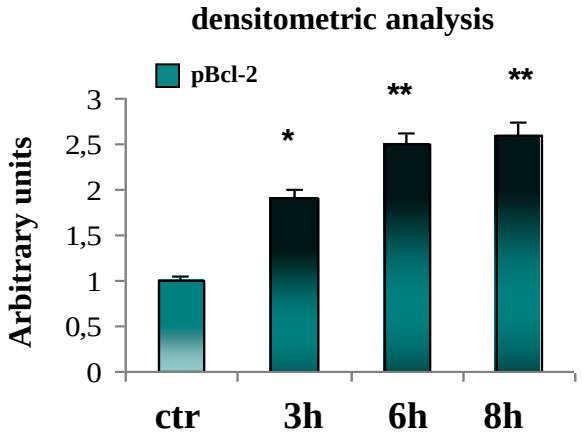
Monomers of Aβ1-42 activate JNK pathway

Guglielmotto M. et al., Autophagy 2014



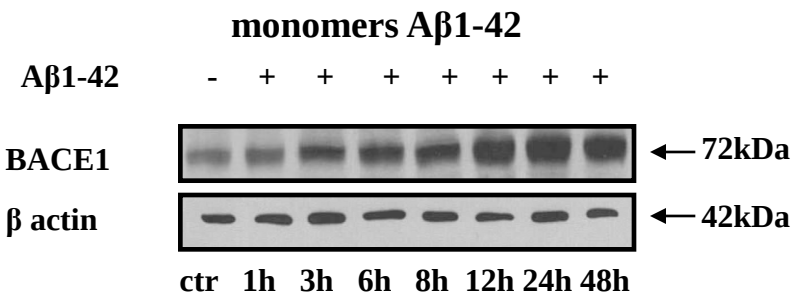


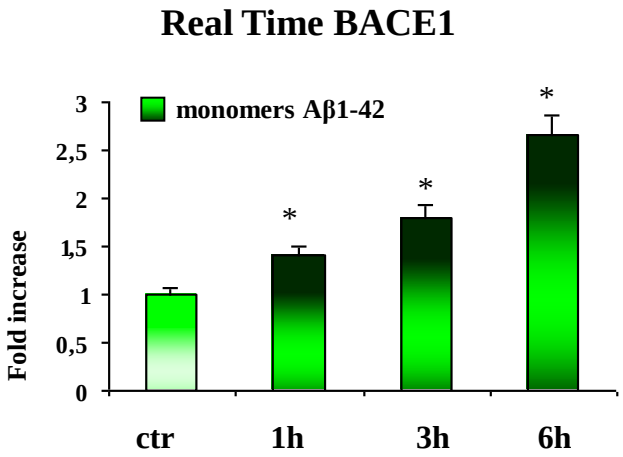


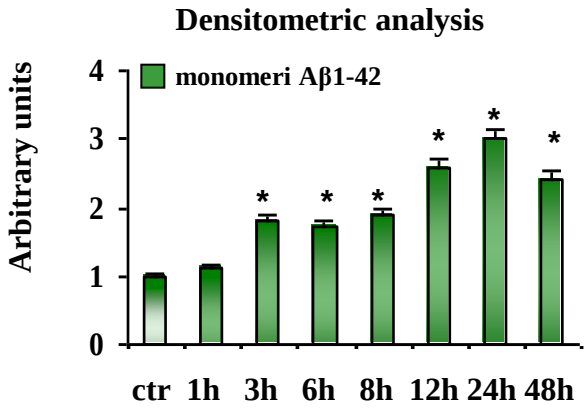


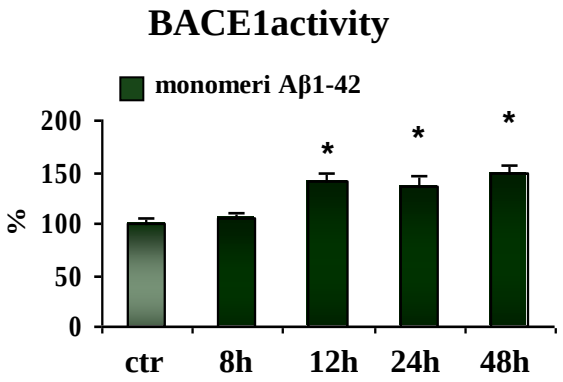
Monomers of Aβ1-42 induce an over-expression of BACE1

Guglielmotto M. et al., Autophagy 2014

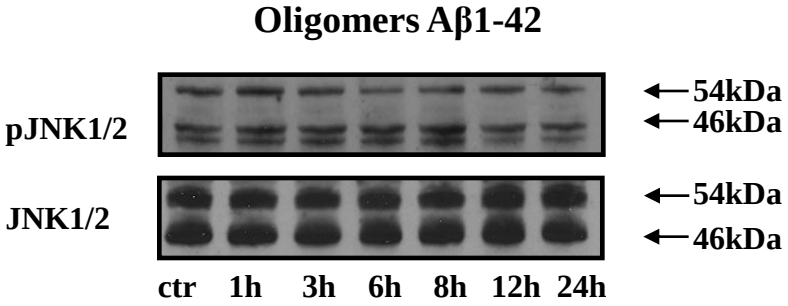


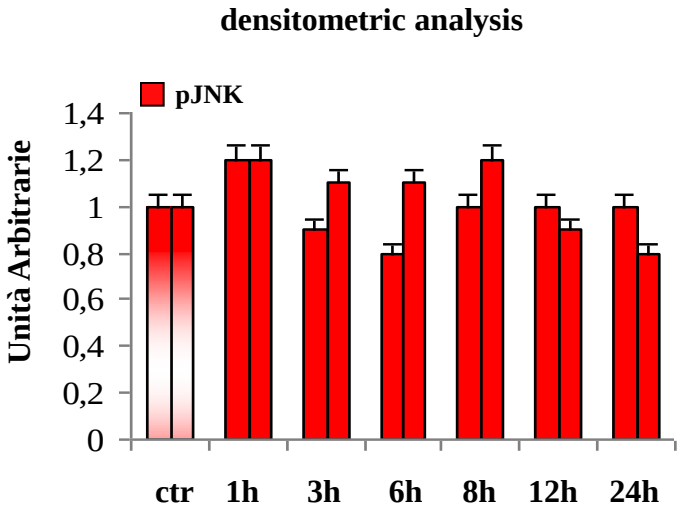






Oligomers of Aβ1-42 do not activate JNK pathway

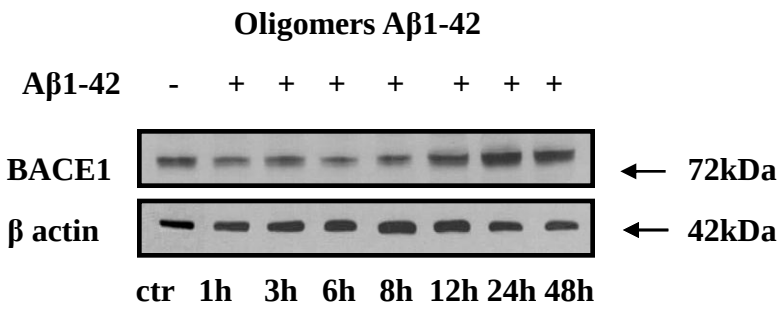


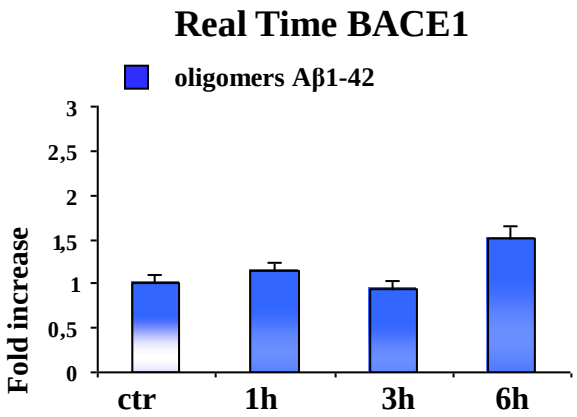


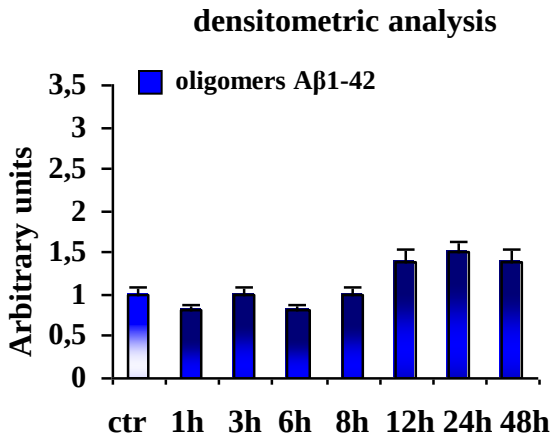
Guglielmotto M. et al., Autophagy 2014

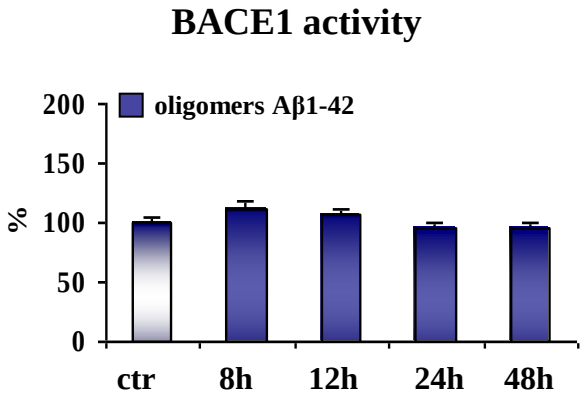
Oligomers of Aβ1-42 do not induce BACE1 over-expression

Guglielmotto M. et al., Autophagy 2014

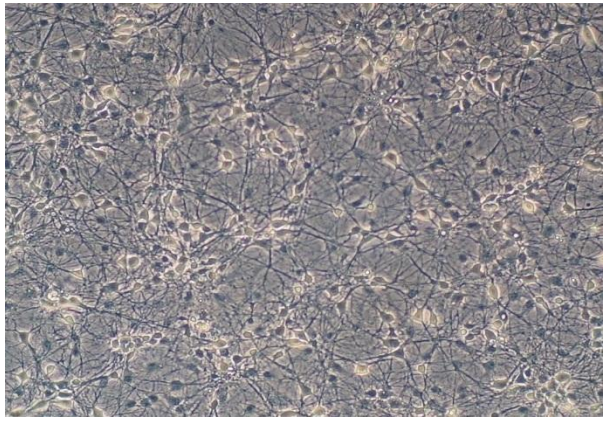


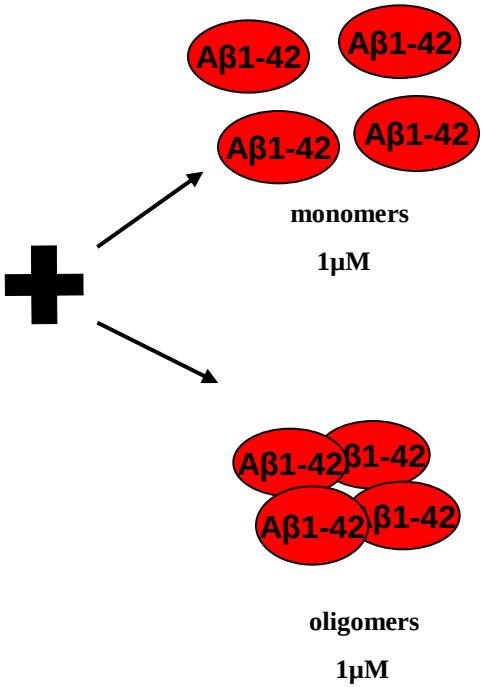






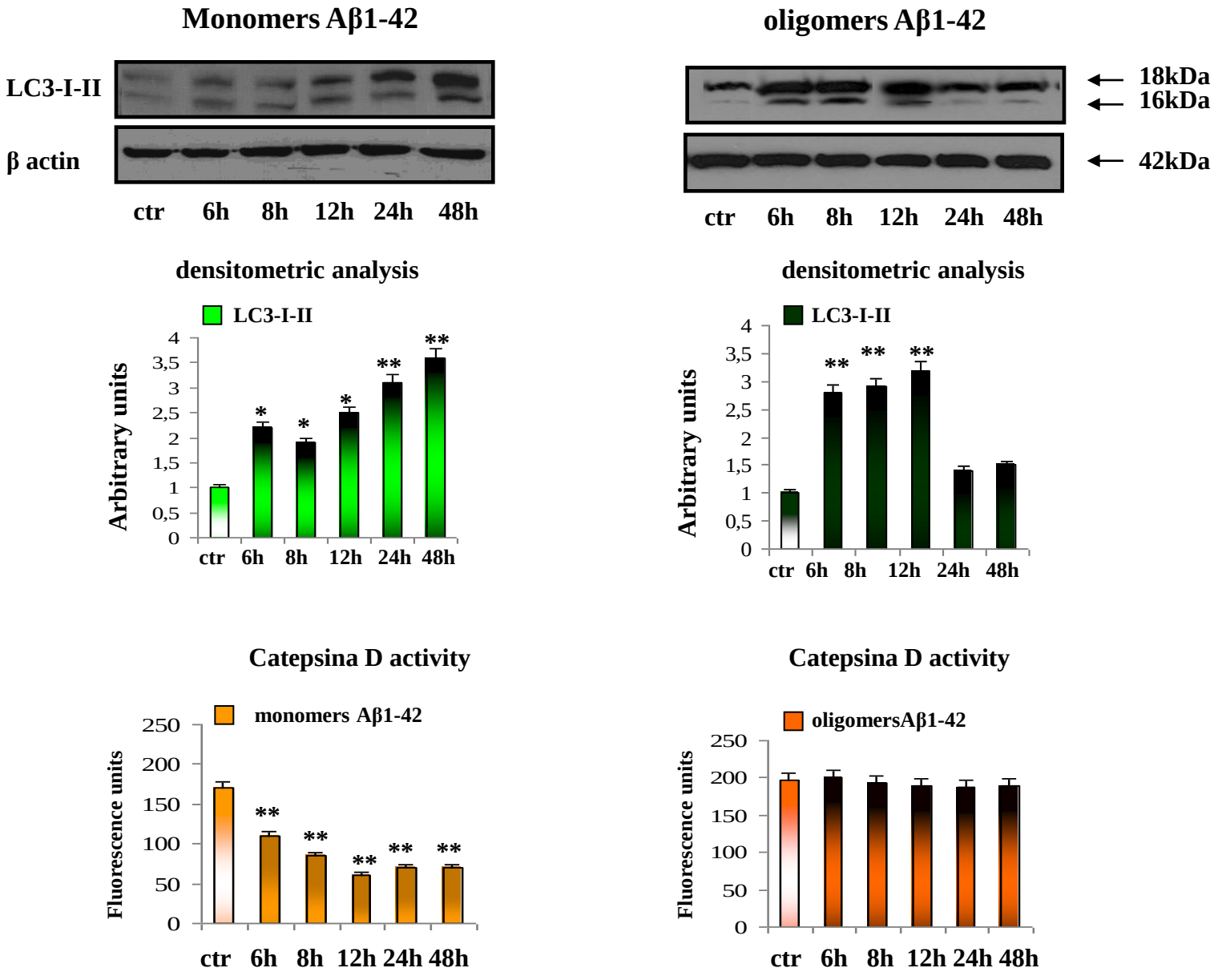
Experimental model in vitro





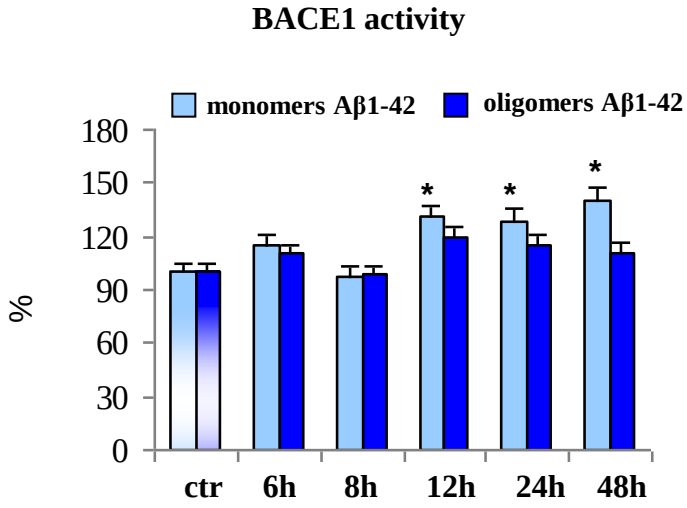
Primary cortical neuron cultures confirm data on autophagy…

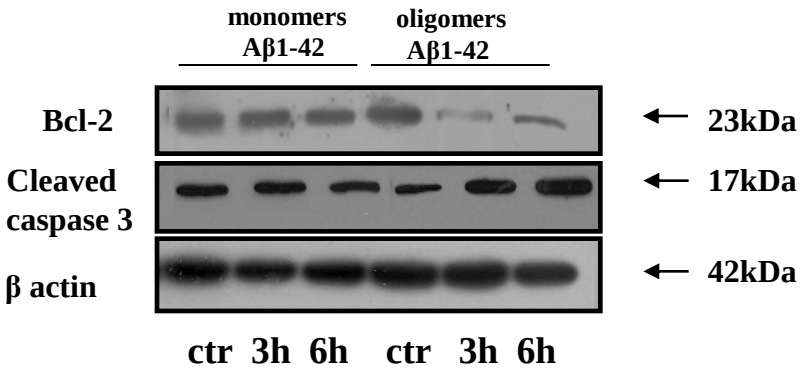
Guglielmotto M. et al., Autophagy 2014

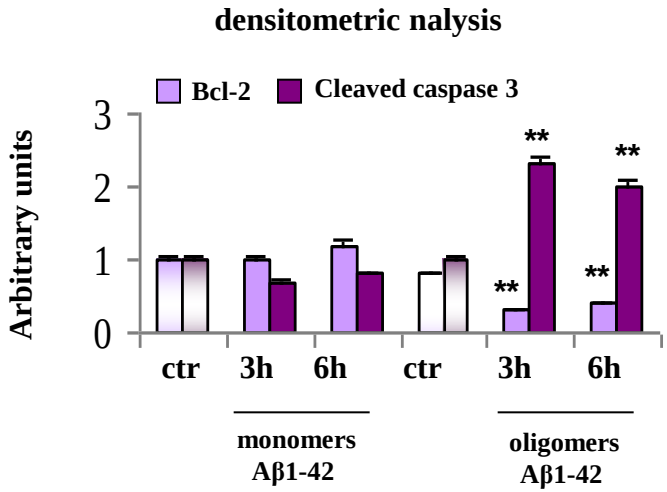


… and on BACE1 over-expression and apoptosis

Guglielmotto M. et al., Autophagy 2014







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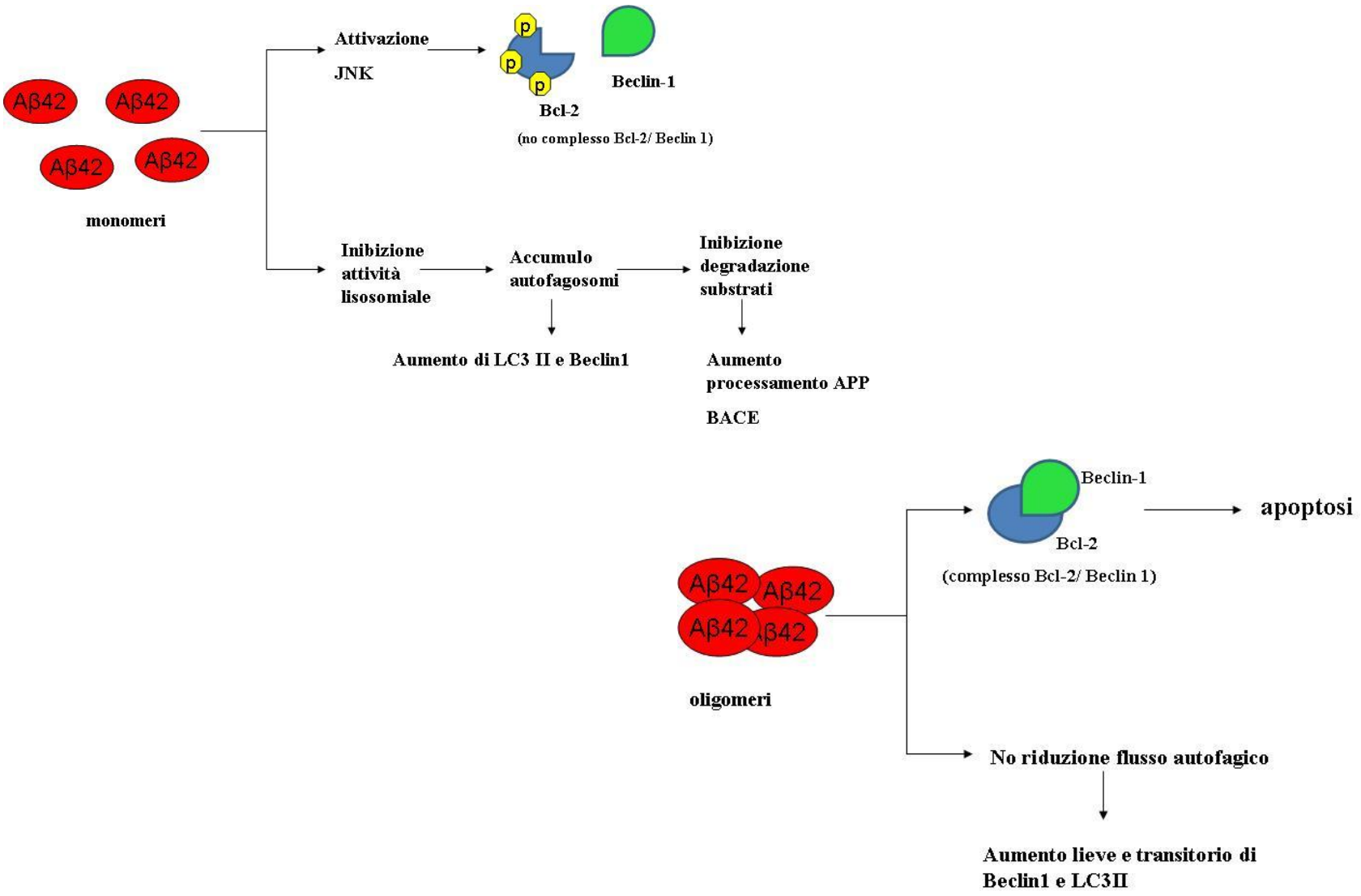
Conclusions



Several evidences indicate that, in AD, accumulation and aggregation of Aβ peptides in the brain are the primary events that induce degeneration, the latter characterized by Tau pathology.

How Aβ peptides induces Tau alteration and aggregation remains uncertain

Three major mechanisms have been proposed:

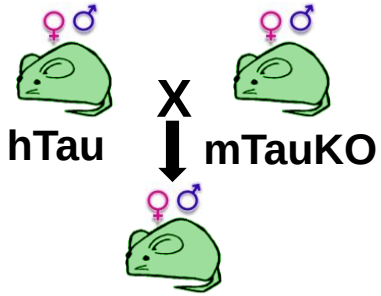
Aβ ACTIVATES KINASES THAT PHOSPHORYLATE TAU

Aβ ALTERS THE PROTEOSOMAL DEGRADATION OF TAU

INTRACELLULAR Aβ HAVE A NUCLEATION EFFECT ON TAU

EXPERIMENTAL PLAN

2 month-old



In *vivo*

ICV

After
3h or
4days

- **GROUPS**

- ctr (saline)
- oligomeric Aβ42
- monomeric Aβ42

Aβ ANASPEC

- ctr (saline)
- oligomeric Aβ42
- monomeric Aβ42

Aβ DEPSI

- ctr (saline)
- monomeric Aβ42

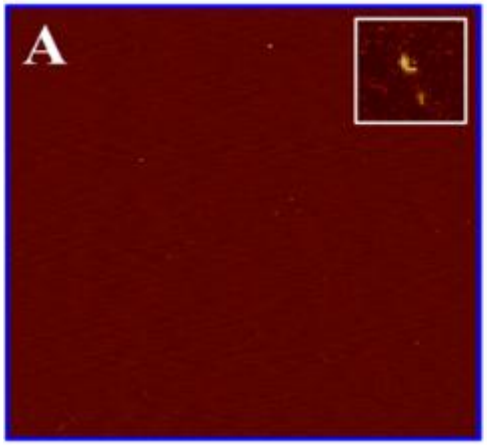
SP
PD
AZD
+ Aβ ANASPEC

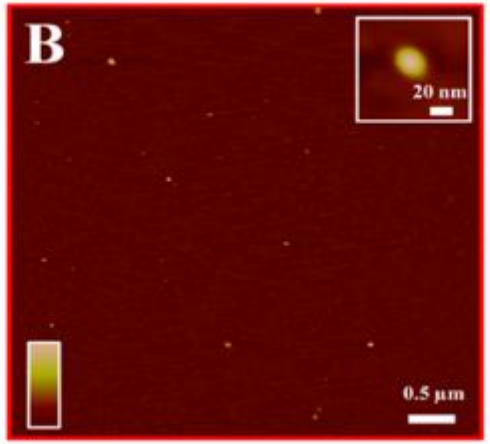
- atomic force microscopy
- WESTERN BLOT
- qPCR
- IF
- proteasome assay

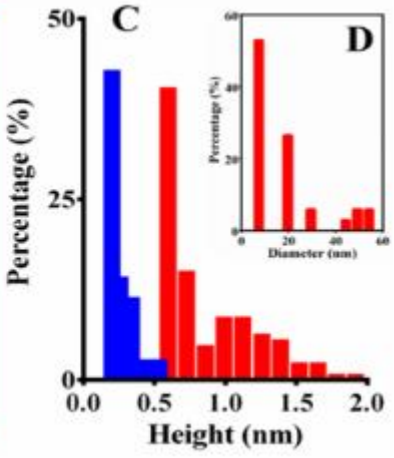
- Tau conformation
- Tau phosphorylation

Aβ42 monomers induce a conformational change of Tau protein

Aβ
ANASPEC
3h







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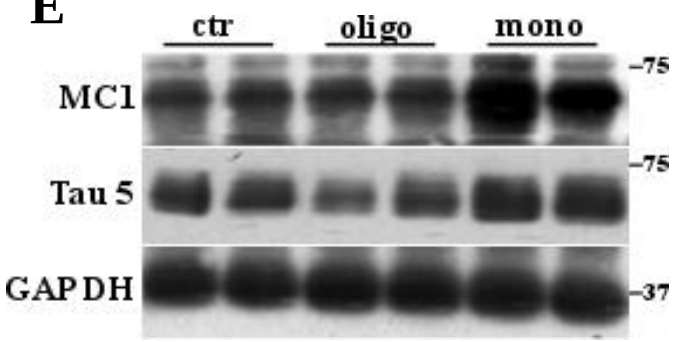

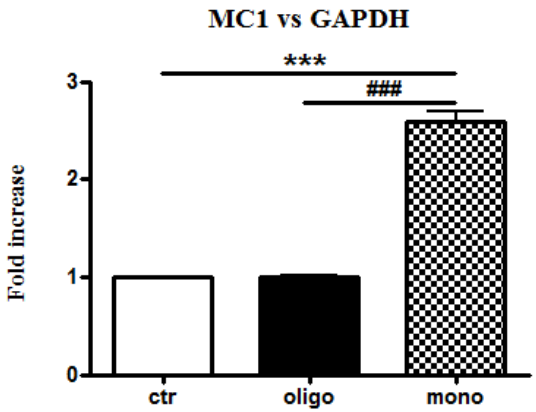

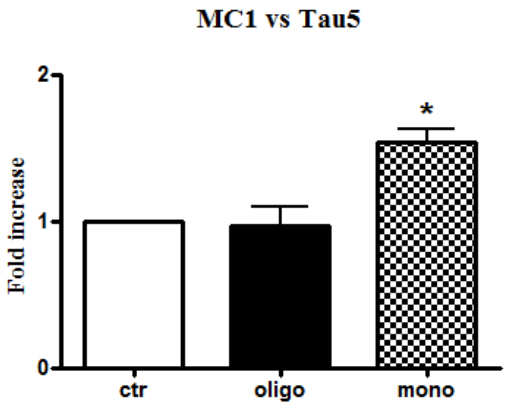

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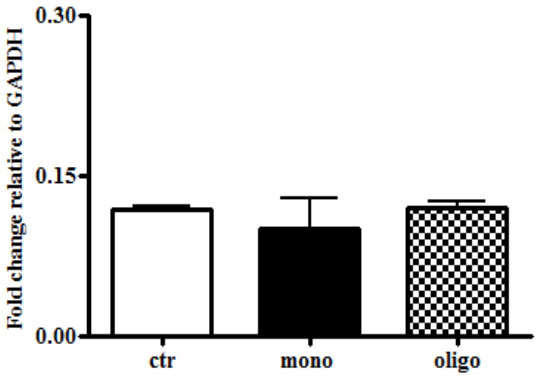

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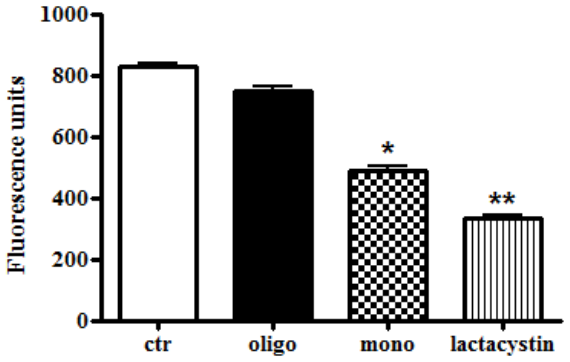
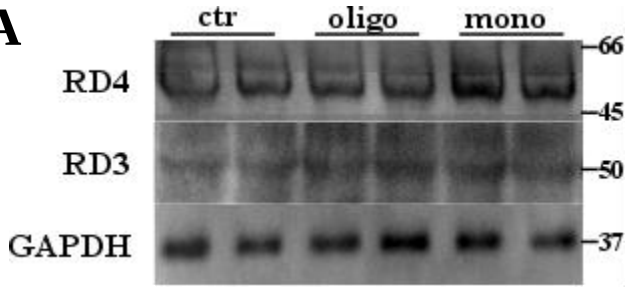
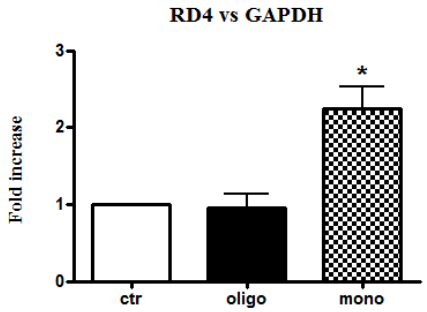
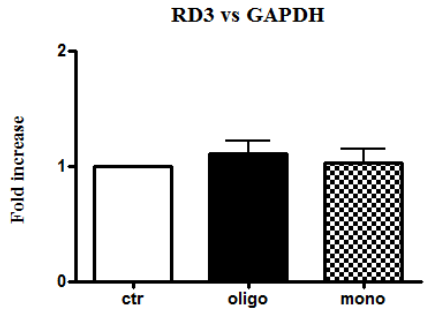


Aβ42 monomers produce alternative splicing, insoluble Tau aggregates and hyper-phosphorylation of Tau protein

A







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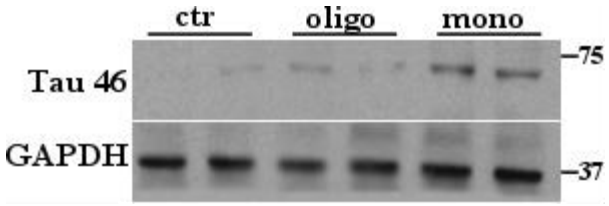
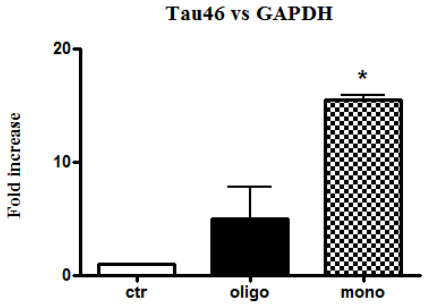
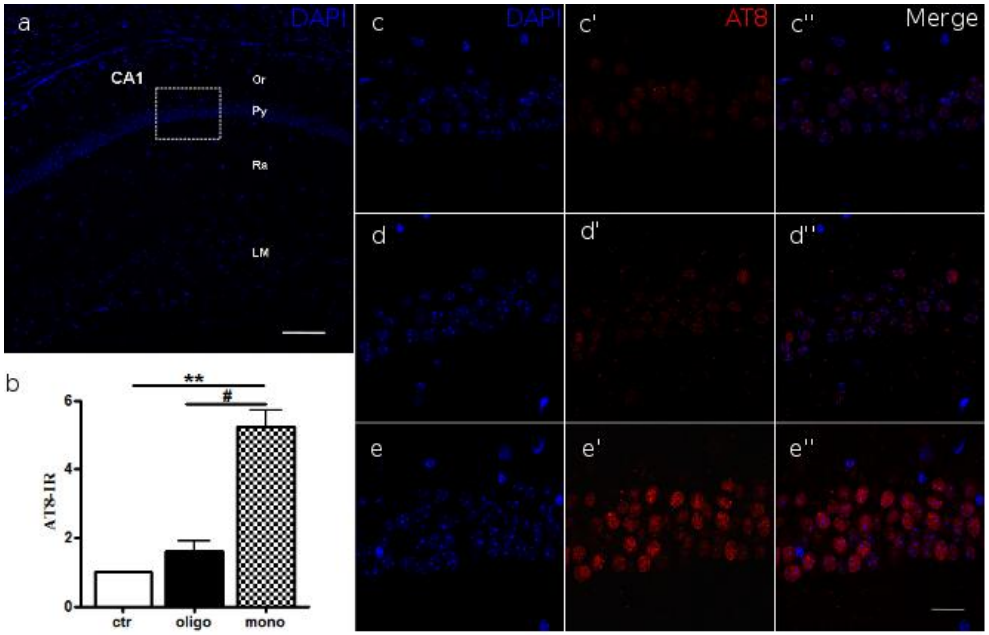
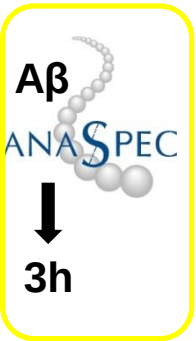




Manassero G. et al., Aging Cell 2016

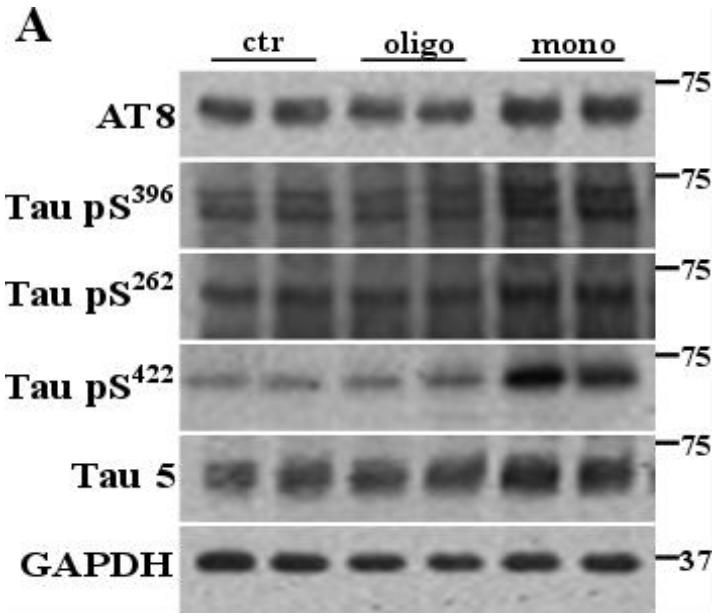
C

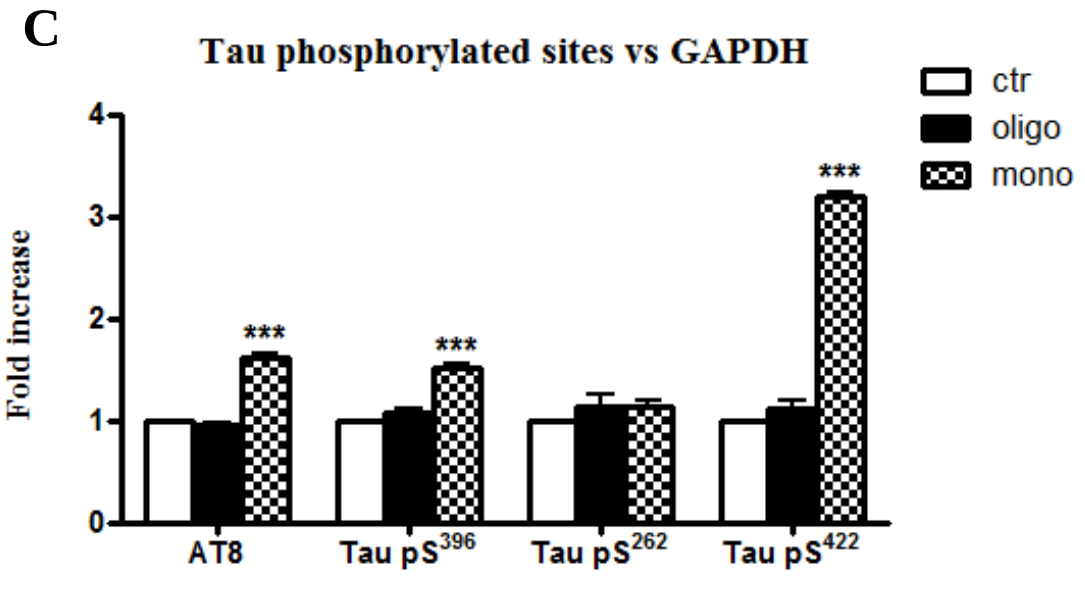


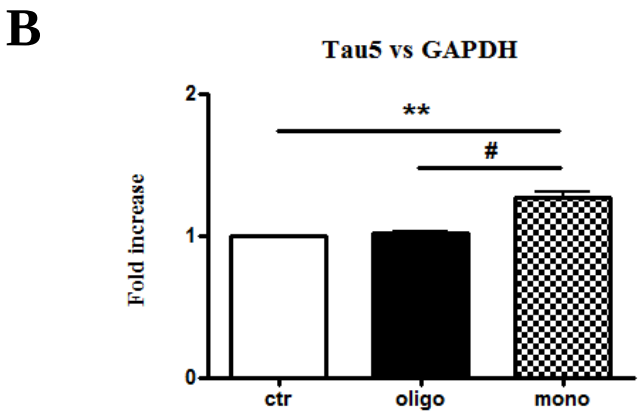


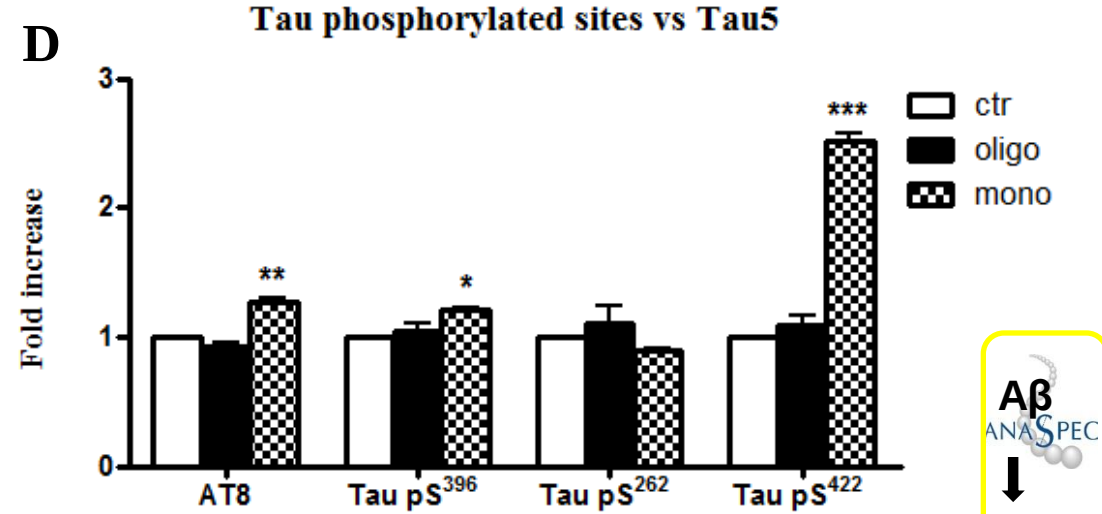
Aβ42 monomers promote phosphorylation at particular sites that have been related to AD progression

Manassero G. et al., Aging Cell 2016

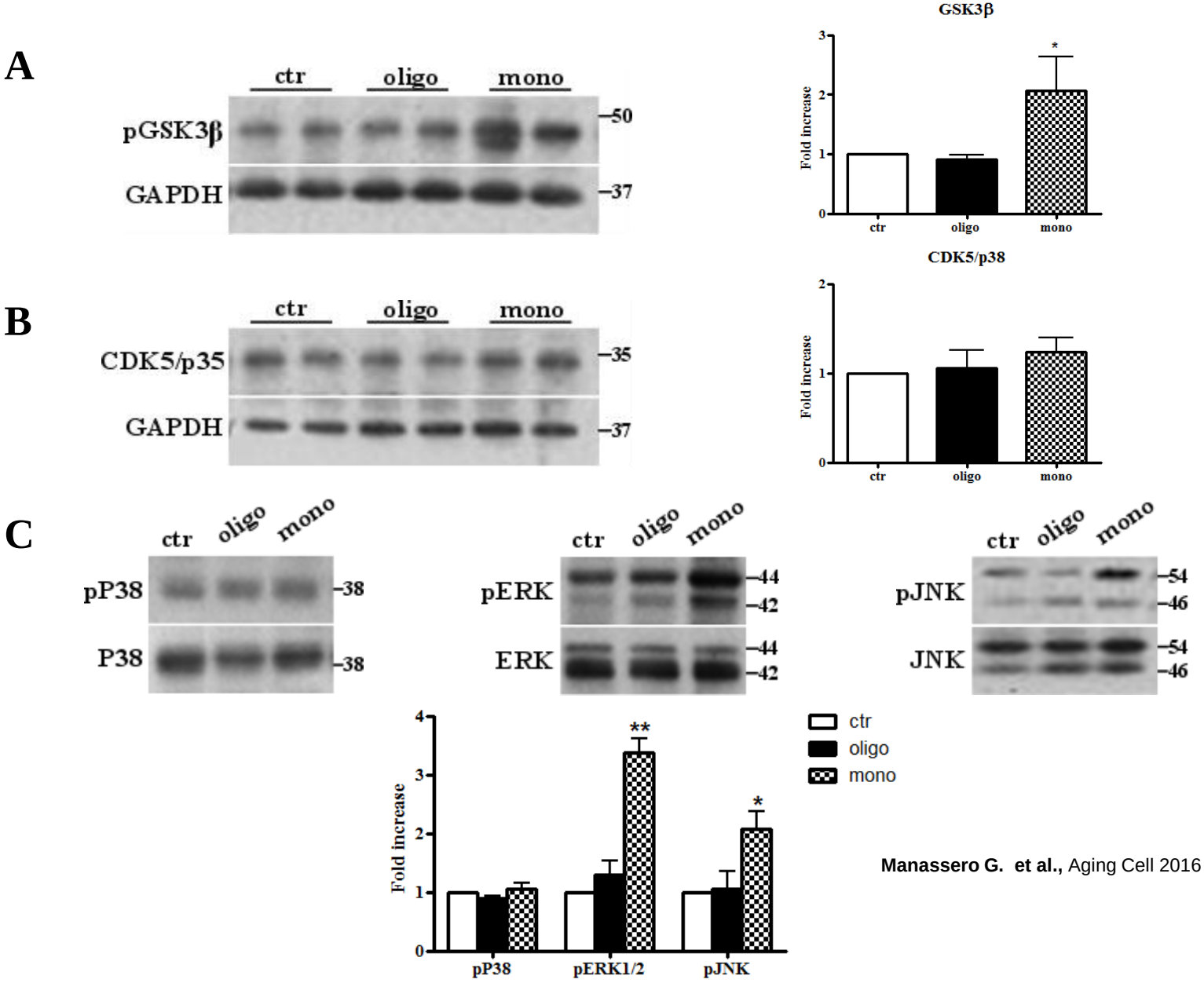








Aβ42 monomers affect Tau phosphorylation through GSK3β, ERK1/2 and JNK kinases activation

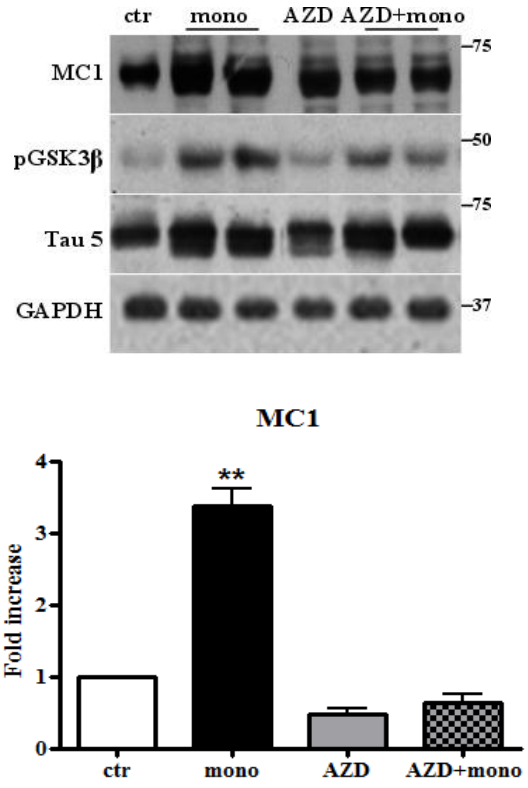


Manassero G. et al., Aging Cell 2016

Aβ ANASPEC 3h

The activation of JNK, ERK1/2 and GSKβ is required to mediate the conformational change of Tau protein induced by Aβ42 monomers

A



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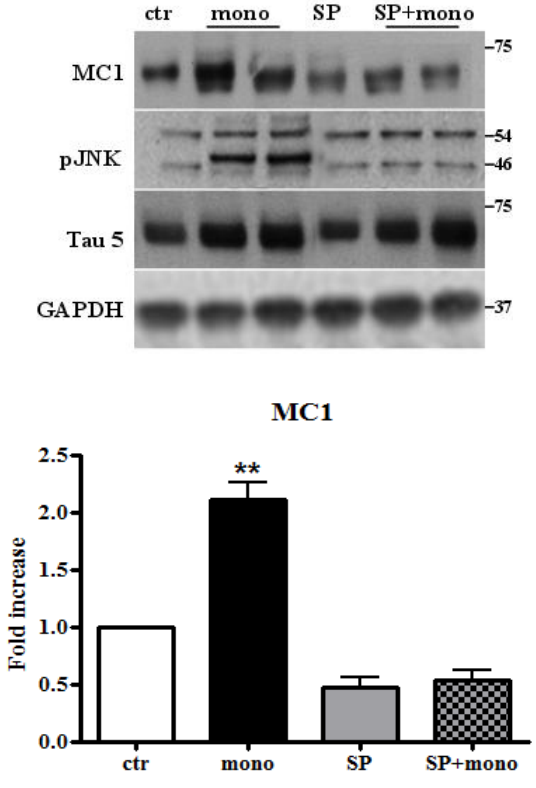

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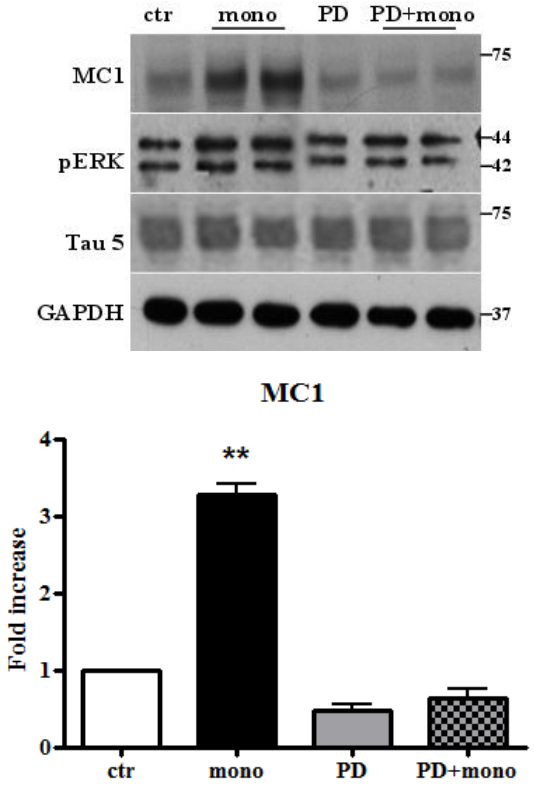

Manassero G. et al., Aging Cell 2016

SP
PD
AZD
+
Aβ
ANASPEC

CONCLUSIONS

- **Aβ42 monomers alter Tau conformation through two mechanisms: hyperphosphorylation and increase of total Tau levels.**
- **Aβ42 does not have a direct nucleation effect on Tau.**
- **Our results have practical implications; currently the major efforts of Alzheimer's disease therapy are focused on removal of Aβ oligomers, and not monomers.**

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