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BSc Biology, National University of Kiev, Ukraine, 2002
MSc Biochemistry, National University of Kiev, Ukraine, 2004
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Alzheimer's disease; amyloid cascade; aggregation; seeding; synaptic impairment

Science

Accumulation of abnormally folded proteins is a key histopathological characteristic of many neurodegenerative disorders. In Huntington's disease, the polyglutamine protein huntingtin is present in intranuclear inclusions; in prion disease, infectious prion particles bind to the membrane-bound protein. In Parkinson's disease, α -synuclein aggregates as Lewy bodies in the cytoplasm of neurons. In Alzheimer's disease, both intra- and extracellular amyloids—that is, neuronal tangles containing phosphorylated tau and amyloid plaques consisting of amyloid peptides ($A\beta$)—are observed. Thus, aggregates accumulate extracellularly or in the cytoplasm, in the nucleus and at the cell membrane in different diseases.

A plausible generic explanation for the toxicity of intracellular aggregates involves the idea that the sequestration of crucial proteins together with amyloid leads to cellular dysfunction and death. Deregulated proteostasis could initiate and certainly enhance such protein failure. In Alzheimer's disease, tau aggregates occur intracellularly and could indeed theoretically trap functional proteins, such as tau itself, possibly leading to microtubule destabilization or other cellular dysfunction and death. Alzheimer's disease is somewhat unusual, however, in that there are two aggregates—intracellular tau and extracellular $A\beta$ —that potentially could result in neuronal dysfunction and death. A central question in the field is: by what mechanism might extracellular amyloid peptides such as $A\beta$ harm cells? An alternative hypothesis suggests that small soluble oligomeric structures consisting of amyloid peptides can cause cellular toxicity. Metastable oligomeric structures have indeed been described in preparations of amyloid-forming peptides such as α -synuclein, tau, prion and $A\beta$. When produced intracellularly, oligomers expose flexible hydrophobic surfaces that might contribute to trapping vital proteins, but they also, when produced extracellularly (as is largely the case for $A\beta$), cause potentially toxic alterations of cell membranes¹. This notion of a toxic $A\beta$ oligomer has been strongly promoted in Alzheimer's research because it provides potential explanations for the toxicity of the extracellular $A\beta$ peptide and for the lack of a

correlation between deposition of insoluble A β plaques and neuronal loss: A β oligomers might be able to mediate toxicity at some distance from established plaques. Further, they could subtly damage and predispose sensitive neurons to the formation of intracellular tau aggregates. The present avalanche of publications claiming the identification of various toxic A β oligomers would indeed seem to support this hypothesis. However, the exact meaning of the term 'toxic A β oligomer' is very confusing.

Recently, it has been shown that human AD brain extracts containing soluble A β aggregates induce amyloidosis in mice that otherwise never develop amyloid plaques. This suggests a connection between seeding competence and toxicity of small A β aggregate species. A seeding experiments present the strongest evidence of readily measurable A β -mediated toxic effects in brain parenchyma. Therefore, we believe there is an urgent need for new, reliable methods that allow the generation, characterization and chemical manipulation of disease-relevant, toxic A β species.

Our aim is to investigate the evidence for toxic A β oligomers, their role in Alzheimer's disease, and the question of whether it is reasonable to consider toxic oligomers as drug targets.

Recent Research Projects

ERA-Net NEURON

Period: 2012 – 2015

Title: "Preparation of amyloid-beta aggregate species from synthetic and patient-derived material to define disease-causing mechanisms"

Role: postdoc researcher

Selected Publications

Benilova, I., and B. De Strooper. "Promiscuous Alzheimer's Amyloid: Yet Another Partner." *Science* 341, no. 6152 (2013): 1354-55

Benilova, I., E. Karran, and B. De Strooper. "The Toxic Abeta Oligomer and Alzheimer's Disease: An Emperor in Need of Clothes." *Nat Neurosci* 15, no. 3 (2012): 349-57.

Chavez-Gutierrez, L., L. Bammens, I. Benilova, A. Vandersteen, M. Benurwar, M. Borgers, S. Lismont, L. Zhou, S. Van Cleynebreugel, H. Esselmann, J. Wiltfang, L. Serneels, E. Karran, H. Gijzen, J. Schymkowitz, F. Rousseau, K. Broersen, and B. De Strooper. "The Mechanism of Gamma-Secretase Dysfunction in Familial Alzheimer Disease." *EMBO J*, (2012).

Benilova, I., and B. De Strooper. "An Overlooked Neurotoxic Species in Alzheimer's Disease." *Nat Neurosci* 14, no. 8 (2011): 949-50.

Chong, S. A., I. Benilova, H. Shaban, B. De Strooper, H. Devijver, D. Moechars, W. Eberle, C. Bartic, F. Van Leuven, and G. Callewaert. "Synaptic Dysfunction in Hippocampus of Transgenic Mouse Models of Alzheimer's Disease: A Multi-Electrode Array Study." *Neurobiol Dis* 44, no. 3 (2011): 284-91.

Zhou, L., N. Brouwers, I. Benilova, A. Vandersteen, M. Mercken, K. Van Laere, P. Van Damme, D. Demedts, F. Van Leuven, K. Slegers, K. Broersen, C. Van Broeckhoven, R. Vandenberghe, and B. De Strooper. "Amyloid Precursor Protein Mutation E682k at the Alternative Beta-Secretase Cleavage Beta'-Site Increases Abeta Generation." *EMBO Mol Med* 3, no. 5 (2011): 291-302.

Benilova, I., and B. De Strooper. "Prion Protein in Alzheimer's Pathogenesis: A Hot and Controversial Issue." *EMBO Mol Med* 2, no. 8 (2010): 289-90.

Kuperstein*, I., K. Broersen*, I. Benilova*, J. Rozenski, W. Jonckheere, M. Debulpaep, A. Vandersteen, I. Segers-Nolten, K. Van Der Werf, V. Subramaniam, D. Braeken, G. Callewaert, C. Bartic, R. D'Hooge, I. C. Martins, F. Rousseau, J. Schymkowitz, and B. De Strooper. "Neurotoxicity of Alzheimer's Disease Abeta Peptides Is Induced by Small Changes in the Abeta42 to Abeta40 Ratio." *EMBO J* 29, no. 19 (2010): 3408-20. (*-equal contribution)