Jordan L Holtzman, J Alzheimers Dis Parkinsonism 2014, 4:5
http://dx.doi.org/10.4172/2161-0460.S1.006

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Alzheimer's Disease and Dementia
September 23-25, 2014 Valencia Convention Centre, Spain

New cellular models for drug discovery in Alzheimer's disease

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Background: It is currently thought that the dementia of Alzheimer's disease is due to the neurotoxicity of the aggregates or deposits of amyloid-β (Aβ) found in the cerebral cortex of patients. As a result the search for therapies has been based on the development of agents which clear Aβ in mouse models transfected with mutant genes associated with early onset disease in humans. A major philosophical problem with these models is that although these mice exhibit many of the pathological and clinical manifestations of the human disease, individuals with late onset Alzheimer's disease lack these mutations. Hence, the question arises whether they are valid models of the late onset disease seen in humans. Furthermore, 11 clinical trials of drugs that reduced the plaque burden in transgenic mice were found to be ineffective in patients. These finding suggest that rather than being the cause of the dementia, plaque and soluble aggregates are biomarkers for an age related decline in the posttranslational, protein processing in the endoplasmic reticulum (ER). This paradigm is supported by our published observation that in human cerebrospinal fluid there are no aggregates, instead all of the Aβ is N-glycosylated and bound to two chaperones, ERp57 and calreticulin. Our data indicate that plaque and aggregates appear when the cell can no longer form this complex. Since the complex is produced in the ER and most membrane proteins also undergo posttranslational processing in this organelle, these findings suggest that the dementia seen in Alzheimer's disease is secondary to a decline in the capacity of the cell to produce the synaptic membrane proteins that are necessary for memory. Both the activity of the N-glycosylation pathway and the content of the chaperones in the ER declined with age. These declines may be major factors in the decreased capacity of the cell to catalyze the posttranslational protein processing in the ER.

Methods: The traditional approach to develop such models is to construct a complex in which the promoter region of the gene for the target protein is bound to a gene for a reporter protein, such as luciferase. Unfortunately, these constructs fail to fully identify agents which regulate protein synthesis through cytosolic and nuclear regulatory elements, such as small RNA's, histone modifications, epigenetic DNA adducts, protein kinase cascades, variations in the 3'untranslated segment of the mRNA and cytosolic and nuclear receptors. These cellular components are now known to play major roles in the control of both transcription and translation.

Results: Author proposes a potentially more robust system in which embryonic stem cells are transfected with fluorescent proteins, such as GFP, into exons of ER chaperones and one of the 15 MST's which catalyze the synthesis of the oligosaccharide complex involved in N-glycosylation.

Conclusions: Such constructs are widely used in cell biology because they only minimally disrupt the structure of the target protein and have little or no effect on the regulatory elements of the cell. For drug discovery in Alzheimer's disease the cells would be transformed into neurons by the addition of the appropriate growth factors. The effect of potential therapeutic agents on fluorescence would then be determined in microtiter plates after incubation of the cells for hours to days. Major strengths of this cell based system is that it can identify agents which act through regulatory elements other than the classic promoter region and would allow rapid screening of large libraries of potential therapeutic agents.

Biography

Jordan L Holtzman, Graduated from University of Chicago, the Pritzker School Of Medicine in 1959. He Complete internship from University Ill Rsc/Ed in 1960. He Completed Residency training from University of Minnesota in 1973, Department of Medicine, University of Minnesota Minneapolis, MN, USA at present he is in Department of Pharmacology, University of Minnesota Minneapolis, MN, USA. Department of Environmental Health Sciences, University of Minnesota Minneapolis, MN, USA.

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