INTERNATIONAL INSTITUTE OF INFORMATION TECHNOLOGY
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Technology, Social Impact

Mathematical modelling of neuronal cell cycle re-entry in neurodegenerative diseases

ABSTRACT

Neurodegeneration disease (ND) is an umbrella term used to classify medical conditions associated with neuronal atrophy and gradual loss of cognitive abilities. According to recent reports of WHO, approximately 50 million individuals are affected worldwide by ND. The most common ND is Alzheimer's disease (AD). Though earlier studies considered accumulation of amyloid beta (Aβ) protein in brain as the cause of disease onset, failure of therapeutic approaches targeting Aβ aggregation points towards gaps in the understanding of disease mechanism. Current research focuses on identifying the self amplifying feedback loops that sustain disease progression even in the absence of causative agent. Intriguingly, neurons maintain a differentiated, resting state in adult brain but the degenerating neurons express cell cycle proteins. These observations motivated us to explore the consequences of cell cycle re-entry in AD. Transcriptional profiling data from different regions of AD brain versus control samples further validate the association **(Fig. 1).**

OBJECTIVE

- Development of an integrated, comprehensive molecular network in consensus with multiple experimental studies **(Fig. 2)**.
- Mathematical modeling of the different routes to neuronal cell cycle reentry and understanding its connection with neurodegeneration.
- Identification of the state transitions that contribute to irreversibility of the disease and may be targeted for therapy **(Fig. 3)**.
- Propose plausible mechanisms to bridge the missing links.

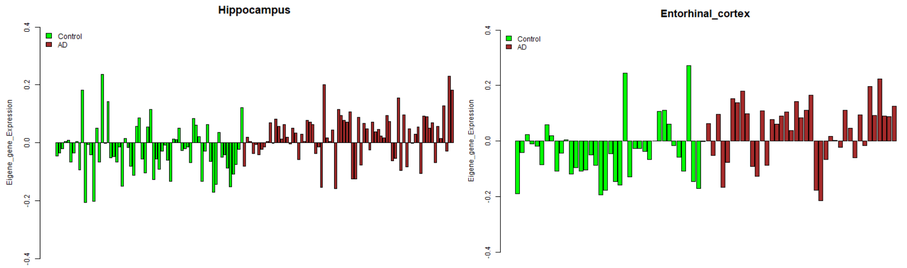

Fig. 1: Cell cycle genes under the regulation of E2F1 transcription factor show higher expression in AD brain samples from hippocampus and entorhinal cortex region. x-axis represents individual samples, y-axis represents the eigen gene expression profile.

RESULTS

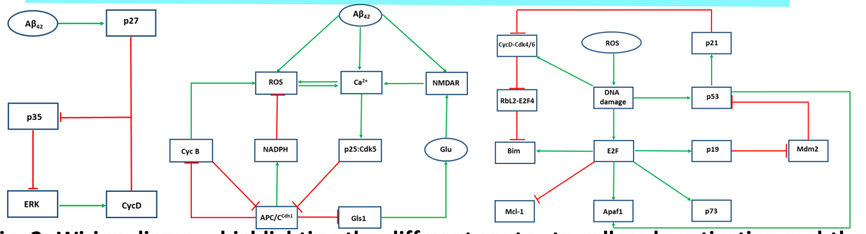

Fig. 2: Wiring diagram highlighting the different routes to cell cycle activation and the downstream effector mechanisms leading to activation of feedback.

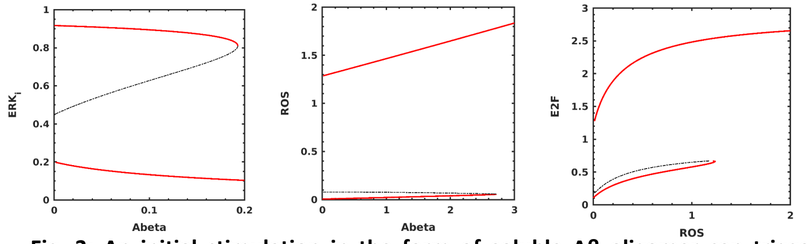

Fig. 3: An initial stimulation in the form of soluble Aβ oligomer can trigger a series of events leading to irreversible cell cycle reentry (ERK activation, E2F induction), oxidative stress and subsequently neurodegeneration.

Conclusion: Prolonged exposure to Aβ induces auto regulatory network modules which aggravate disease progression and make transition to pathological state irreversible. Hence, an efficient therapeutic approach should target these components in addition to removal of aggregates.

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