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Short Communication

Resolving the Last Piece of the Puzzle in the Cell Cycle Re-Entry Hypothesis of Alzheimers Disease?

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Alzheimer's disease has been and will be an age related puzzle for scientist to resolve as for its devastating effects on the individual and on society as a whole. Since the beginning of my work in 2007 when I received a Fulbright Scholar Program to come to Mark A Smith lab I have pursued an idea that proteins that control the post mitotic state in neurons are also related to mitosis. This has not been a new idea as the cell cycle re entry hypothesis at the time has been pursued extensively by MA Smith-s lab. Still to my view a piece of the puzzle has been missing. The last piece to the puzzle has been introduced in the view that late phase cell cycle proteins are included in the pathogenesis of AD. Thanks to open journals such as the Austin Journal of Alzheimer and Parkinson disease, these ideas may be disseminated. Hopefully a seed will fall on fertile ground.

The idea that I have been relating to the ''last piece of the puzzle'' has been embedded in the role that proteins related to the cell cycle are multifunctional which means that except for their role in segregation genetic material of to two daughter cells have a active role in maintaining the post mitotic state in neurons. This view also states that these late phase cell cycle proteins are responsible for cell cycle re entry and consequently apoptosis in AD brains. These segregation defects have been shown in papers concerning centromere instability of the X chromosome of women with AD and proteins related to these defects such as CDK 11, MAD2b, BubR1, Rad 21 and others [1].

My research activity has been mainly concentrated on multi-level expression patterns of late core cell cycle associated proteins (APC/c, CDK 11, MAD2, MAD2b, BUbR1, securin and other) that are subjected to a specific chromosomal instability phenotype in Alzheimer's disease or cohesion imbalance. He found that cohesion imbalance in Alzheimer's disease is not related only to chromosome 21 and 14 but also to chromosome X. Finding that chromosome X is imbalanced in neuronal and peripheral blood cells of Alzheimer patients opened the door to research of why women are more susceptible to Alzheimer's disease than men. This lead to an outstanding result that the X chromosome inactivation patterns in AD are altered (skewed) when compared to age matched controls. We also found that this type of instability may influence the cell cycle reentry phenotype in AD though an ectopic expression of CDK 11 phenotype and its relation to APP processing and Abeta [2-3].

So, the idea of protein multifunctionality should gain attention in the neuroscience community, i.e. a number of cell cycle core proteins, essential for cell cycle division have been found to coordinate a number of complex processes in neurogenesis (axonal pruning, dendric and spine morphogenesis and etc), neuronal survival and the maintenance of the post-mitotic state of neurons. Alzheimer's disease is represented by neuronal loss and this loss is correlated to a constant state of neuronal instability induced by intrinsic and extrinsic factors. The loss of multifunctionality of core cell cycle proteins may initiate neuronal cell cycle re entry and consequently apoptosis in the AD brain. To understand these multifunctional properties of core cell cycle proteins in Alzheimer's Disease may enhance translational research in order to find novel pathways for eliminating the burden of proteopatic seeding in affected brain regions of AD.

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