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Editorial

# Cohesin and Cohesin Related Proteins: A New Frontier for Alzheimer Disease Exploration

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Recently, Rao CV., *et al.* [1] produced a mice model of Late onset Alzheimer's disease (LOAD) in which a protein, Shugoshin 1 ("guardian spirit" in Japanese), that is known for its binding properties to chromatids by protecting [2] a central protein, cohesin is altered leading to cognitive changes and neurodegeneration [3].

Using this model the authors showed for the first time that Alzheimer type dementia can be produced when the mice hit a certain age, suggesting that this model can reflect LOAD.

Shugoshin 1 is fundamental to the cohesion process and to the cell cycle [4,5] and dependently works with the central core cohesion protein, Cohesin [6].

Cohesin is a complex protein that is organized through its subunits, SMC1 and 3, (SA1) Rad 21 and SA2 [7,8]. A number of cohesin related proteins have been elucidated in the processes of cell mitosis and the regulation neuronal development, migration and maturation [9]. These late phase cell cycle proteins that regulate the cohesion process by addressing the cohesion protein, cohesin, have been heavily reviewed [10-12].

In 2004, a group led by Prof Biljana Spremo Potparevic [13] found that the cohesion process is altered in peripheral blood lymphocytes in AD patients. The alteration coined by Vig., *et al.* [14] as premature centromere division showed that the X chromosome is especially susceptible to cohesin degradation before its time. Phenotypically, chromatids appear to have no cohesion between their chromatids [15,16]. This work was extended to neurons. We found that neurons of women are indeed more prone to PCD than men. These results were published in Neurochemistry in 2008 [17].

In 2007 the cohesion theory was recognized by my dear friend and colleague, Prof. Dr Mark A Smith *(more than 15.000 citations and 800 papers) and I was able to come to his laboratory as a Fulbright scholar.

The question that we put at hand is how cohesion and, or cohesion related proteins that phenotypically express PCD are altered in AD? As I have elaborated previous literature about how cohesion-cohesin is altered in different syndromes and cancer models and disease that express PCD [10-15], I have chosen and was given three antibodies to work with, Rad 21, CDK 11 and Rad 51.

Our work was published for cohesion related mechanisms and CDK 11 in normal and AD subjects in 2008, 2009 and 2011 [18-20]. CDK 11 shows differential expression in AD versus age matched controls. Rakkaa., *et al.* [21] showed that shugoshin 1 and Bub1 where not present at the centromeres if CDK1158 was depleted.

Results for Rad 21 haven't been published yet. Preliminary research showed that Rad 21 (a cohesion subunit) is decreased in Abeta neuroblastoma transfected cells [22]. Rad 51, a protein important in DNA repair showed inconclusive evidence. The rationale for its use was that RAD 51 is a hub protein in survival vs apoptotic processes in cells/bacteria exposed to xenobiotics [23].

We believe that the neuronal regulation of last phase cell cycle proteins are the cap stone to the cell cycle re-entry hypothesis. For that, in 2016 we published a paper in which we suggest that late phase cell cycle proteins have a value to be explored as potential drugs for AD treatment [24].

Beforehand, as a DAAD fellow in 2011. I was introduced to Prof Thomas Arendt's Lab in Leipzig, Germany. We explored a number of cohesin related proteins, MAD2, MAD 2b, Bub R1, Bub 1. All of these proteins in our preliminary research show alterted expression in AD brain tissue using immunohistochemistry and Western blot methods. Results were reported on a number of Congresses [25,26].

Our work, with the work of Prof Dr Biljana Spremo Potparevic have been published as the cohesion-aneuploidy hypothesis of AD [27].

Interestingly enough, late phase cell cycle proteins have been found to be deregulated not only in AD [27], neuro-development syndromes (Roberts syndrome, Corney de Lang) [28,29] but also in diabetes [30,31] suggesting a connection between these disease and secondary roles of cohesin and cohesin related proteins [9,24,27,32].

The new frontier to AD research is opened as the new mouse model may give us new insights of how all these proteins are regulated in normal versus affected neurons, suggesting how age and environment influences the effect on the neurodegenerative process. These new insights may lead us to new avenues for treatment and cure of Alzheimer's disease.

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