An overview of the possible therapeutic role of SUMOylation in the treatment of Alzheimer's disease

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ABSTRACT

Nowadays, Alzheimer's disease (AD) is recognized as a multifactorial neurological pathology whose complexity is the cause of our still low achievements in the understanding of the associated mechanisms as well the discovery of a possible definitive cure. Clinicians are aware of the few possibilities offered by medicine to cure Alzheimer's patients, restore their memory and take them back to normal life. Unfortunately, the therapeutic tools available today are not able to contrast the pathology.

In the last years the tendency of the research is to formulate new hypotheses that can help to develop future effective drugs.

Here we propose an overview about an interesting intracellular mechanism called SUMOylation which belongs to the post-translational modification family. SUMOylation is currently studied from few decades and it has been observed to be implicated in the molecular mechanisms of several neurological disorders including AD.

Interestingly, the unbalance between SUMOylation/deSUMOylation seems to be involved in the switch from physiological to pathological behaviours of several proteins implied into AD etiology.

Nevertheless, there are no pharmacological treatments known to modulate SUMOylation/deSUMOylation equilibrium. We hereby listed some natural compounds that, due to their effects on this molecular mechanism, they deserve attention for inspire the development of future convincing therapies.

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1. A clinical overview in alzheimer's disease

In the last ten years, the definition of Alzheimer's disease (AD) has been modulated by the increasing awareness of its complex and multifactorial nature, leading some experts to state that AD should not be considered a disease, but rather a syndrome in which the classically recognized combination of memory loss and behavioural changes results in a varied spectrum of clinical phenotypes [1,2].

The original NINCDS/ADRDA diagnostic criteria presented in 1984 considered AD as a distinct clinical and pathological condition with evidence of dementia combined with possible or confirmed AD neuropathology [3]. In 2011 the National Institute on Aging and the Alzheimer's Association commissioned a workgroup to review the 1984 criteria. The group, while respectful of an important part of the previous work, redefined significantly the diagnostic criteria for possible or probable AD dementia by also incorporating CSF and imaging biomarkers. Thus, the new criteria pointed out the importance of distinguishing AD from other well defined causes of dementia, such as vascular dementia [4], dementia with Lewy bodies [5], behaviour variant of frontotemporal dementia [6,7] and primary progressive aphasia [8]. The phenotypic variability of AD presentation at onset was revised and, besides the more frequent amnestic form, non-amnestic presentations were highlighted, such as the language, the visuospatial and the executive variants [9].

The diagnostic guidelines introduced the concept that AD manifests across a "*continuum*", with a long pre-symptomatic phase during which the pathophysiological process develops, leading patients to progress from the preclinical stage to mild cognitive impairment (MCI) and to dementia [10,11]. The disease progression, from an asymptomatic state to a definite AD, represents therefore the mirror of a biological *continuum* and this led experts to consider the increasing importance of using AD biomarkers, measurable indicators that can contribute to evaluate and follow the progress of AD pathology. Direct AD biomarkers of AD pathology, or biomarkers of brain amyloid-beta (Aβ) protein deposition, are reduced $A\beta_{42}$ in the cerebrospinal fluid (CSF) and the evidence of Aβ deposition in the brain at PET imaging [12]. Indirect biomarkers, or biomarkers of downstream neuronal degeneration, are elevated CSF tau protein, decreased uptake of 18-fluorodeoxyglucose (FDG) on PET in the temporo-parietal cortex and disproportionate atrophy in the medial, basal, and lateral temporal lobes, and medial parietal cortex at structural MRI [9]. Although biomarkers presence is considered to increase the certainty of AD pathophysiology process beyond the clinical presentation of probable AD, the working group did not suggest to use AD biomarkers in the diagnostic routine, but only in the research contest, due to the invasive nature of some of them, the costs-benefits ratio and the lack of standardisation [9,13]. To date an important focus is placed on the detection of possible AD biomarkers in the plasma [14,15], but research is still far from the discovery of a valid and standardised peripheral blood biomarker for diagnostic purposes.

In the last years, the pathophysiology of AD has been widely investigated. The paradigm of the "*amyloid cascade hypothesis*" [16,17], in association with tau-mediated toxicity [18] as the main responsible of the neurodegenerative process, still represents a cornerstone of the AD pathology. On the other hand, mitochondrial dysfunction [19–21], cell signalling alterations [22–24], inflammatory and immunologically response [25–27] and, more recently, the possible involvement of the dopamine network [28] have been taken into account and proposed as parallel or alternative pathophysiologic hypothesis in AD. Alteration of synaptic SUMOylation profiles in AD patients is a field of investigation that has been recently studied by our group and that could open to new therapeutic perspectives after further studies [29].

All the unanswered issues described above find their more evident consequence in the lack of available treatments able to stop or considerably modify the progression from the prodromal phase to the full clinical expression of dementia due to AD. If the portfolio of the treatment for AD can be already considered very poor, unfortunately no drug is available for the treatment of the MCI. Three cholinesterase inhibitors (rivastigmine, donepezil and galantamine) and one N-methyl-D-aspartate (NMDA) receptor antagonist (memantine) have been the only drugs approved from FDA in the last 20 years for the management of the different stages of AD dementia [30–36]. In the last 30 years, researches on treatment strategies have focused on targeting the underlying causes of neurodegeneration in AD [37], with the aim of finding a "disease modifying therapy", and many drugs have been candidate for AD clinical trials [38]. Most of the work was addressed to target the amyloid cascade in order to prevent the accumulation of amyloid aggregates. The majority of the studies were conducted only in the preclinical setting. γ-secretase inhibitors and modulators were tested in mice models [39]; β-secretase (BACE) inhibitors were studied in mice and beagle dogs and results were reproduced on healthy humans volunteers, but later stages of clinical trial were prevented because of the drug's toxicity [40]. Anti-tau protein antibodies reduced biochemical markers of tau in two transgenic mouse models [41].

Many expectations have surrounded the good results of anti-Aβ antibodies in pre-clinical studies, but their efficacy in the clinical setting is still to be demonstrated: bapineuzumab and solanezumab failed in producing significant results in three phase III, placebo controlled clinical trials in patients with AD compared to healthy controls [42], [Lilly Announces Top-Line Results of Solanezumab Phase 3 Clinical Trial, Available from: https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871. Last updated 2016, Accessed on 2016]. Experts are "cautiously optimistic" [37] for adacanumab, another anti-Aβ antibody under investigation in a phase III, double blind, randomised, placebo controlled clinical trial [NCT02477800 and NCT02484547], after the encouraging results of Ib phase in slowing the accumulation of Aβ plaques and cognitive decline in patients with prodromal or mild AD [43]. Finally, promising results are attended from other two phase III studies on anti- Aβ antibodies: Crenezumab, which recognizes oligomeric and fibrillar Aβ species and amyloid plaques with high affinity, for prodromal-to-mild AD (Clinical Trial Identifier: NCT02670083) and Gantenerumab, a conformational antibody against Aβ fibrils, in patients with mild AD (Clinical Trial Identifier: NCT02051608 and NCT01900665) [38].

In order to study new possible pharmacological targets in AD, the basic research has to be taken in consideration. This review reports an update of the classical molecular features of this pathology, attempting to show that going back to natural compounds