Synaptic dysfunction is rescued by targeting SUMOylation in a mouse model of Alzheimer's disease

S. Marcelli[1,2], E. Ficulle[1], F. Iannuzzi[1], L. Negri[2], R. Nisticò[1,3], M. Feligioni[1,4]

1. EBRI-European Brain Research Institute, Rome, 00143, Italy
2. Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, 00185, Italy.
3. University of Rome 'Tor Vergata', Rome, 00173, Italy
4. Department of Neurorehabilitation Sciences, Casa Cura Policlinico, Milano, 20144, Italy.

Alzheimer's disease (AD) is a progressive neurodegenerative condition recognized as the most common cause of chronic dementia among the ageing population.
Intracellular neurofibrillary tangles and extracellular senile plaques are AD histopathology hallmarks, respectively composed of hyperphosphorylated tau and aggregated Aβ peptides [1].
Recent studies have claimed 'synaptopathy' as a putative culprit at the basis of AD [2]. Indeed, synaptic dysfunction represents the first neuronal deficit at the onset of AD, causing nerve terminals degeneration and compromised neurotransmission, neuronal death and gradual decline of cognitive functions.
To confirm, several molecular modifications occur at synaptic level during early phases of the disease, including alteration of post-translational modifications.
SUMOylation, i.e. the covalent conjugation of SUMO (*Small Ubiquitin-like MOdi?er*) moieties to target proteins via a hierarchical enzymatic cascade, plays for instance a newfound role in AD pathogenesis.
Indeed, dysregulation of SUMOylation has been observed in human *post mortem* AD brain specimens, as well as in the Tg2576 transgenic AD mouse model [3]. Furthermore, pre-synaptic modulation of protein SUMOylation was shown to control synaptosomal glutamate release and calcium in?ux. In fact, an enhanced SUMOylation corresponds to a glutamate release reduction, while deSUMOylation contributes to opposite outcomes [4].
On purpose, targeting the SUMO machinery could represent a novel pharmacological avenue in AD therapy.
Our work was therefore focused on the effect of SUMO/deSUMOylation modifications in the synaptic compartment of Tg2576 mice.
Preliminarily, we found that cortical synaptosomes prepared from Tg2576 of 6 and 20 months of age (mo) showed reduced neurotransmitter release (about -30%) compared to age-matched controls in a time-lapse experiment.
Subsequently, we developed and purified two cell penetrating HIV Tat-linked peptides, namely TU-1 and TS-1, able to finely modulate the SUMO machinery either positively (TU-1, retracing the effector sequence of the SUMO-conjugating enzyme Ubc9) or negatively (TS-1, retracing the effector sequence of the SUMO-deconjugating isopeptidase SENP-1).
The effects of SUMO modulation accomplished by such peptides were tested on neuroblastoma SH-SY5Y cells and on primary cortical neurons, as well as on synaptosomes from both control and Tg2576 mice. By means of fluorescent dyes Fluo-3 (a calcium chelator indicating the cation influx/efflux) and FM 1-43 (marker of endo/exocytosis and vesicles trafficking), time-lapse recording experiments were performed to investigate Ca^{2+} influx and neurotransmitter release upon KCl stimulus in both 6 and 20 mo Tg2576 derived synaptosomes.
As expected, micromolar concentrations of TU-1 on Tg2576 synaptosomes were able to further reduce the Ca^{2+} influx and glutamate release with respect to both controls and age-matched AD mice. Conversely, TS-1 on synaptosomes was able to restore synaptic function, promoting rescued Ca^{2+} influx and glutamate release, comparable to controls.
Conclusively, the results obtained from our peptides strongly suggest SUMOylation as a potential target to modify the synaptic dysfunction characterizing AD.
Although further research is required, the improvement of specific SUMO-based drugs provides encouraging pharmacological tools for future clinical intervention in AD and related neuropathologies.

[1] A. Serrano-Pozo, et al. Cold Spring Harb. Perspect. Med., 1, 1, a006189, Sep. 2011.
[2] M. Sheng, et al. Cold Spring Harb. Perspect. Biol., 4, 5, May 2012.
[3] L. Lee, et al. Sci. Rep., 4, 7190, Jan. 2014.
[4] M. Feligioni, et al. Eur. J. Neurosci., 29, 7, 1348–56, Apr. 2009.