Acetylation's role in tau structure, electrostatics and interactions: molecular dynamics studies

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Tau is a microtubule associated protein which stabilizes and promotes the assembly of microtubules in neurons.[1] In its functional form it presents minor modifications, such as phosphorylation, but a large variety of post-translational modifications are also possible.[2]

Tau post-translational modifications are directly related with tau mal-functioning, aggregation and subsequent tauopathies. Investigation on tau hyperphosphorylation has dominated in the past years, since its known role in Alzheimer's disease onset and progression. However, acetylation has gained attention, as this process is also responsible for tau pathological aggregation.[3-4]

Acetylation is a modification that occurs in lysine amino acids, adding an acyl group to the side chain NH moiety.[5] This process changes the charge of this residue, making it neutral and consequently modifying the electrostatics of the whole protein. The presence of charged groups and electrostatic interactions are the major contributors for a final protein fold. The absence of these charges, via acetylation, will contribute to significant changes in tau's structure and interactions.

Molecular Dynamics (MD) simulations take advantage of precise simulation algorithms and present themselves as a robust way to understand biomolecules' behavior, conformational preferences and interactions, even for intrinsically disordered proteins such as tau. Through this technique we are following the acetylation impact on the tau structure and its way of binding to the microtubule. In addition, it is intended to unveil the relationship between acetylation and aggregation, which results in tau associated diseases.

In the past year, Castro and co-workers shed light on tau properties by predicting its 3D structure and disclosing the interaction pattern with microtubules and the ions from the intracellular fluid[1]. The present work took this input information to generate acetylated analogs and follow the impact of this modification on tau's dynamic behavior.

Keywords: tau, molecular dynamics simulation, acetylation, Alzheimer's disease.