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In This Issue

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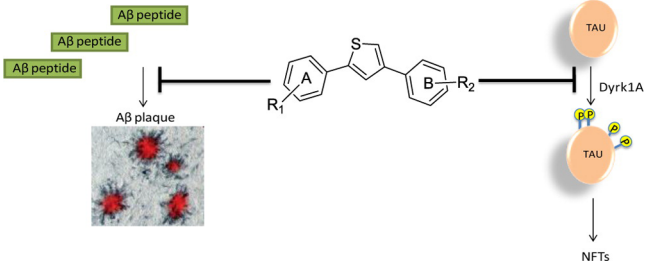
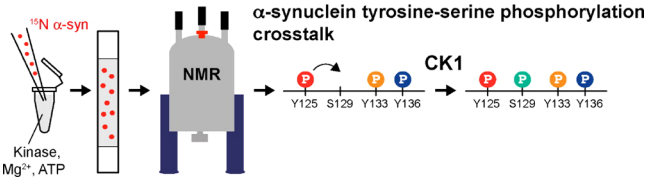
DUAL INHIBITORS TARGETING ALZHEIMER'S DISEASE



Alzheimer's disease (AD) is an increasing burden on an aging society and is already the sixth leading cause of death in the United States. Current treatments can slow down the disease progression; however, AD cannot be cured. Because AD is a result of multiple factors rather than a single cause, therapeutic agents that address only one pathogenic mechanism may fail to succeed. In the current issue, Mariano et al. (DOI: 10.1021/cn5001815) report the development of novel small molecules which have two in-built functions, directed against two of the major pathogenic processes.

The authors describe dual inhibitors that on one hand block the interaction of the so-called β-amyloid peptides which precedes amyloid plaque formation in the brain. On the other hand, they can also inhibit an enzyme called Dyrk1A, which, in the diseased brain, attaches phosphate groups to the so-called tau protein. These excess phosphate groups abolish the normal function of tau in the cytoskeleton and promote the formation of toxic aggregates, the neurofibrillary tangles.

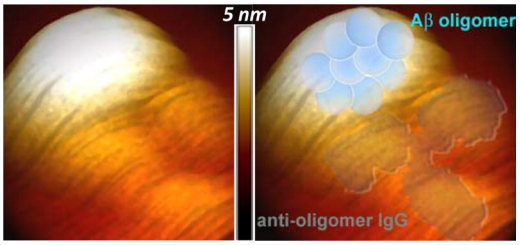
CHARACTERIZING THE ROLE OF PHOSPHORYLATION IN PARKINSON'S DISEASE



Phosphorylated α-synuclein is abundantly found in brain lesions of Parkinson's disease patients but not in healthy individuals. Especially phosphorylation of α-synuclein Ser129 serves as a pathological hallmark of the disease, which led Kosten et al. (DOI: 10.1021/cn5002254) to investigate how the establishment of this modification is influenced by other phosphorylation events at neighboring substrate sites.

Using real-time NMR spectroscopy, the authors simultaneously studied multiple phosphorylation events at closely spaced, C-terminal α-synuclein modification sites and showed that phosphorylation of Tyr125 is a prerequisite for the modification of Ser129 by the broadly acting and constitutively active enzyme casein kinase 1 (CK1). This result suggests that modified Tyr125 may contribute to the high levels of Ser129 phosphorylation found in Parkinson's disease patients.

SIZING UP NEUROTOXIC Aβ OLIGOMERS



Aggregation of the Aβ peptide into soluble oligomers plays a central role in the pathogenesis of Alzheimer's disease (AD). However, the size of neurotoxic Aβ oligomers (AβOs) is still debated, in part due to technical issues in isolating particular species from complex samples such as tissue extracts. Uncertainties on the size of the toxic AβOs have strong implications for drug and diagnostic developments for AD. Now, Sebollela et al. (DOI: 10.1021/cn500156r) describe a novel approach for in-solution sequestration and biochemical analysis of a toxic AβO.

The strategy combined antioligomer monoclonal antibody targeting (for isolation of a single Aβ species by gel-filtration chromatography) with visualization of the antibody–oligomer complex by atomic force microscopy (AFM). When applied to a complex AβO preparation, this approach allowed the authors to determine the apparent molecular mass of a toxic oligomer retaining neuronal binding activity. Furthermore, the authors were able to directly observe the antibody–oligomer complex by AFM. This strategy may be applicable in the isolation of toxic oligomers directly from AD brain extracts, as well as oligomers responsible for other diseases such as Parkinson and prionoses.

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