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In This Issue

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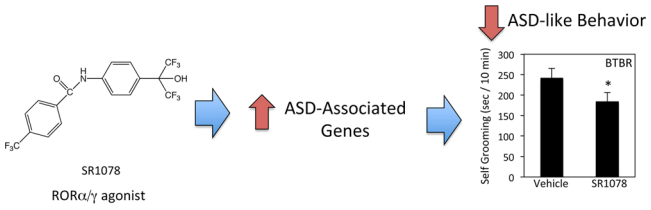
NOVEL THERAPEUTIC TARGET FOR AUTISM

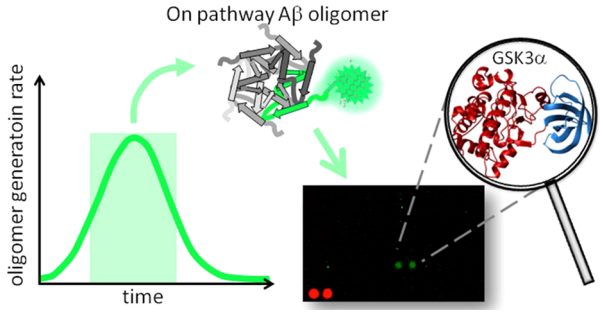


Autism Spectrum Disorder (ASD)

The expression of nuclear receptor RORα has been shown to be reduced in the brains of many individuals with autism. This appears to be due to epigenetic alternations in the *RORA* gene. The decrease in expression of RORα leads to decreased expression of a number of RORα target genes that are known to be associated with autism in humans. In the current issue, Wang et al. (DOI: 10.1021/acschemneuro.5b00159) demonstrate that a synthetic agonist (SR1078) for the nuclear receptors RORα and RORγ, that the authors recently developed, activates the expression of a number of genes that are known to be suppressed in individuals with autism.

The authors also demonstrate that treatment of BTBR mice (a model for autism) with SR1078 leads to a therapeutic effect. Given the prevalence of autism as well as the lack of pharmacological therapeutics that target the pathology of the disease, this study suggests that ROR may be a valid target for treatment of autism.

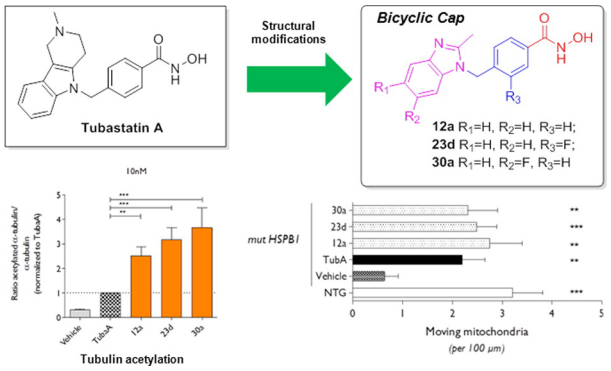
UNCOVERING A NEW MOLECULAR LINK IN ALZHEIMER'S DISEASE



Alzheimer's disease is the most common form of dementia. Hallmarks of this disease are deposits of aggregated proteins and neuronal death. The aggregated proteins are amyloid β peptide (Aβ) and tau. The aggregates can be large fibrils with thousands of copies of the same protein, or smaller aggregates, oligomers, with some 2−50 copies. The oligomers seem to kill the neuronal cells, but why this happens on a molecular level is not known. Now, Dunning et al. (DOI: 10.1021/acschemneuro.5b00262) provide some work in an attempt to address this question.

The authors use protein arrays, microscope slides with over 9000 different kinds of human proteins printed on them. They probe these arrays with fluorescently labeled Aβ oligomers as they form and reform during an aggregation reaction. The authors identify and validate binding of Aβ oligomers to the enzyme glycogen synthase kinase 3α, and find that this increases its phosporylation of tau. This result uncovers a direct and functional molecular link that may be of importance in Alzheimer's disease.

IMPROVED LEAD COMPOUND FOR CHARCOT−MARIE−TOOTH DISEASE



Charcot−Marie−Tooth (CMT) disease is a disorder of the peripheral nervous system for which no pharmacological treatment is currently available. Recently, it has been shown in an animal model of the axonal form of CMT that histone deacetylase 6 (HDAC6) can serve as a potential target for the development of a therapy.

By investigating HDAC6 inhibitors containing a bicyclic cap as the structural scaffold from which to build upon, Shen et al. (DOI: 10.1021/acschemneuro.5b00286) have developed several analogues that possessed improved enzymatic potency, restored mitochondrial axonal transport defects characteristic of this disease, and achieved better druglike properties compared to selective HDAC6 inhibitor tubastatin A. These results suggest it will be valuable to advance the best in class compound into the CMT mutant mouse studies.

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