



A Network Approach to Autism Neurobiology



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地 点: 医学院综合楼**205**会议室

报告人研究领域:

Increases of Ube3a gene dosage cause autism, while maternal Ube3a loss causes Angelman syndrome. In mature neurons, Ube3a is expressed exclusively from the maternal allele; the paternal Ube3a allele is repressed. Ube3a acts as an E3 ubiquitin ligase but also separately as a transcriptional co-activator. To determine whether excess Ube3a causes autism behavioral deficits via actions in the neuronal cytoplasm/synapse or nucleus, we engineered a nuclear importing peptide signal to the C-terminus of Ube3a. We have further engineered the Ube3a transgene to permit neuron subtype and brain region specific increases of Ube3a gene dosage to enable circuit mapping of the autism-associated behavioral defects. A detailed analysis of circuit-specific changes in gene expression (ribotag) and physiology (optogenetic manipulations and neural circuit studies) will follow. We are also now investigating the neural circuit basis of increased aggression in this autism disorder. We are also investigating the function other autism genes with direct protein-protein interacts with the Ube3a-regulated genes to identify common autism pathways. In separate projects we are investigating the functional consequences of the genomic changes that occurred during hominid evolution and might underlie human cognitive abilities. Such changes are accompanied by altered gene expression in the cerebral cortex, so we are focused on a hominid-specific non-coding RNA altered as a CNV in autism. Genome editing and transcript profiling in cell lines explores the molecular mechanisms of the hominid-specific change in gene regulation. We introduce the hominid-specific changes into the mouse genome to reconstitute the molecular step in hominid evolution in a living lower mammal to permit detailed studies of behavior, circuit physiology, and gene expression.

Selected Publications:

1. Stoppel DC, **Anderson MP**. Hypersociability in the Angelman syndrome mouse model. *Exp Neurol*. 2017 Jul;293:137-143.
2. Krishnan V, Stoppel DC, Nong Y, Johnson MA, Nadler MJ, Ozkaynak E, Teng BL, Nagakura I, Mohammad F, Silva MA, Peterson S, Cruz TJ, Kasper EM, Arnaout R, **Anderson MP**. Autism gene Ube3a and seizures impair sociability by repressing VTA Cbln1. *Nature*. 2017 Mar 23;543(7646):507-512.

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