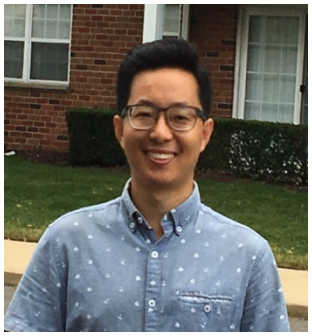
Principal Investigator: Jerry Yingtao Zhao
Grant Title: Heparan sulfate and its signaling in Kallmann syndrome

Abstract



Objectives: Kallmann syndrome (KS) is a congenital disorder characterized by hypogonadotropic hypogonadism and olfactory dysfunction. KS affects 1 in 48,000 newborns. Loss-of-function mutations in heparan sulfate 6-O-sulfotransferase 1 (*HS6ST1*) cause KS, but the underlying mechanisms remain largely unknown. Our long-term goal is to use novel mouse models to reveal how *HS6ST1* mutations contribute to KS pathogenesis, with the hope of eventually developing a cure. The two objectives are to characterize a novel mouse model of KS and to reveal the mechanisms of KS-linked signaling pathways in transcriptome.

Methods used: The methods used are nervous system-specific knockout of *Hs6st1* in mice, mouse breeding strategies to assess fertility, odor responses by behavioral test and neuronal activity, intrinsic optical imaging, RNA sequencing, bioinformatics, and gene pathway analyses.

Results: Given that the current animal models for KS are unsatisfied, our lab generated the *Hs6st1*$^{f/f}$ mice via cryo-recovery, crossed them to the *Nestin-Cre* mice, and generated the first nervous system-specific knockout of *Hs6st1* (*cKO*) mice. Given that infertility is a major symptom for individuals with KS, we examined four different breeding strategies and found that the *cKO* mice show fertility deficits. Olfactory dysfunction is another major symptom for individuals with KS. To determine the extent to which the *cKO* mice have olfactory dysfunction, we assessed *cKO* mice in response to odors at the behavioral level and neuronal activity level and found olfaction deficits in *cKO* mice. To reveal the molecular mechanisms underlying *cKO*, we carried out RNA sequencing on two important brain regions, the neocortex and the hippocampus. We obtained 396 million high-quality sequencing reads and assessed the expression levels of all mouse genes. After comparing the transcription profiles between *cKO* mice and their wild-type littermates, we found 508 and 346 genes that were differentially expressed in the neocortex and hippocampus in *cKO* mice. To determine the biological pathways affected by the *cKO*, we performed pathway enrichment analyses on the differentially expressed genes. We found that the upregulated genes are enriched in ribosome, vesicle, and response to stimulus pathways, while the downregulated genes are enriched in neuronal pathways, such as synapse, synaptic signaling, and neuron projection. These RNA sequencing results demonstrate that *cKO* alters the transcription of genes in specific biological pathways in the neocortex and hippocampus. Taken together, our results confirmed a novel mouse model for KS (the *Hs6st1 cKO* mice) and revealed new molecular mechanisms underlying *HS6ST1* and KS.