Hippocampus Function

The hippocampus plays a crucial role in learning and memory, and its formation requires precise coordination of patterning, cell proliferation, differentiation, and migration. Zhang et al. removed the chromatin-association capability of KDM2B in the progenitors of developing dorsal telencephalon (Kdm2bΔCxxC) to discover that Kdm2bΔCxxC hippocampus, particularly the dentate gyrus, became drastically smaller with disorganized cellular components and structure. Kdm2bΔCxxC mice display prominent defects in spatial memory, motor learning, and fear conditioning, resembling patients with KDM2B mutations. The migration and differentiation of neural progenitor cells are greatly impeded in the developing Kdm2bΔCxxC hippocampus. Mechanism studies reveal that Wnt signaling genes in developing Kdm2bΔCxxC hippocampi are de-repressed due to reduced enrichment of repressive histone marks by polycomb repressive complexes. Activating the Wnt signaling disturbs hippocampal neurogenesis, recapitulating the effect of KDM2B loss. Together, they unveil a previously unappreciated gene repressive program mediated by KDM2B that controls progressive fate specifications and cell migration, hence morphogenesis of the hippocampus [1)].

Its progressive deterioration with age is functionally linked to a variety of human neurodegenerative diseases. Yet systematic profiling of the aging effects on various hippocampal cell types in primates is still missing. Here, we reported a variety of new aging-associated phenotypic changes of the primate hippocampus. These include, in particular, increased DNA damage and heterochromatin erosion with time, alongside loss of proteostasis and elevated inflammation. To understand their cellular and molecular causes, we established the first single-nucleus transcriptomic atlas of primate hippocampal aging. Among the 12 identified cell types, neural transiently amplifying progenitor cell (TAPC) and microglia were most affected by aging. In-depth dissection of gene-expression dynamics revealed impaired TAPC division and compromised neuronal function along the neurogenesis trajectory; additionally elevated pro-inflammatory responses in the aged microglia and oligodendrocyte, as well as dysregulated coagulation pathways in the aged endothelial cells may contribute to a hostile microenvironment for neurogenesis. This rich resource for understanding primate hippocampal aging may provide potential diagnostic biomarkers and therapeutic interventions against age-related neurodegenerative diseases [2)].

Learning and memory are assumed to be supported by mechanisms that involve the cholinergic transmission and hippocampal theta wave. Using G protein-coupled receptor-activation-based acetylcholine sensor (GRABACh3.0) with a fiber-photometric fluorescence readout in mice, Zhang et al. found that cholinergic signaling in the hippocampus increased in parallel with theta/gamma power during walking and REM sleep, while ACh3.0 signal reached a minimum during hippocampal sharp waves and ripples (SPW-R). Unexpectedly, memory performance was impaired in a hippocampus-dependent spontaneous alternation task by selective optogenetic stimulation of medial septal cholinergic neurons when the stimulation was applied in the delay area but not in the central (choice) arm of the maze. Parallel with the decreased performance, optogenetic stimulation decreased the incidence of SPW-Rs. These findings suggest that septohippocampal interactions play a task-phase-dependent dual role in the maintenance of memory performance, including not only theta mechanisms but also SPW-Rs [3)].

Hippocampus plays important roles in the consolidation of information from short-term memory to long-term memory and spatial navigation.

The hippocampal formation is a brain structure integrally involved in episodic memory, spatial navigation, cognition and stress responsiveness. Structural abnormalities in hippocampal volume and shape are found in several common neuropsychiatric disorders. To identify the genetic underpinnings of hippocampal structure here we perform a genome-wide association study (GWAS) of 33,536 individuals and discover six independent loci significantly associated with hippocampal volume, four of them novel. Of the novel loci, three lie within genes (ASTN2, DPP4 and MAST4) and one is found 200 kb upstream of SHH. A hippocampal subfield analysis shows that a locus within the MSRB3 gene shows evidence of a localized effect along the dentate gyrus, subiculum, CA1 and fissure. Further, we show that genetic variants associated with decreased hippocampal volume are also associated with increased risk for Alzheimer's disease (rg=-0.155). Our findings suggest novel biological pathways through which human genetic variation influences hippocampal volume and risk for neuropsychiatric illness [4].

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