Hwai-Jong Cheng, MD PhD
Director and Distinguished Research Fellow
Institute of Molecular Biology
Academia Sinica
Taipei, Taiwan

Title

Integration of progenitor cells from the adult brain into mature neural circuits

Abstract

In the adult mammalian hippocampus, neurogenesis is concentrated in the subgranular zone of the dentate gyrus (DG). Adult-born neurons integrate functionally into existing hippocampal circuits, and dysregulation of adult hippocampal neurogenesis (AHN) is linked to disorders of learning, memory, and emotion. AHN declines with age. Our lab investigates how aging alters AHN in mice. We developed an efficient method to culture neurospheres from adult and aged DG neural progenitors, maintaining them as adult hippocampal neural progenitor cells (AHNPCs). We performed single-cell RNA sequencing on AHNPCs to identify intrinsic regulators of age-related changes. We transplanted AHNPCs into the mouse DG *in vivo* to assess their differentiation and integration in the mature hippocampus. Spatial transcriptomics showed that transplanted AHNPCs adopt expression profiles similar to those of neighboring endogenous granule cells. Ultimately, we aim to determine whether cultured AHNPCs can be used to treat neurological disorders.

Cheng-Chang Lien, MD PhD
Chair Professor, Institute of Neuroscience
Dean, College of Life Sciences
National Yang Ming Chiao Tung University
Taipei, Taiwan

Title

Predicting Threat in Time: A New Role for the Hippocampus

Abstract

Adaptive defensive behavior depends not only on learning that a stimulus predicts danger, but also on anticipating when an aversive outcome is expected to occur. Although the hippocampus is well known for its role in associative and contextual learning, whether and how hippocampal circuits encode internal predictions of threat timing has remained unclear. Here, we identify a previously unrecognized predictive timing mechanism mediated by mossy cells in the ventral dentate gyrus during conditioned fear learning. Using *in vivo* recordings combined with circuit-specific manipulations, we show that ventral mossy cells respond robustly to both conditioned and unconditioned stimuli during fear conditioning. Following learning, these cells exhibit a reproducible neural response during memory retrieval that is precisely time-locked to the expected onset of the unconditioned stimulus, even in its absence. This internally generated activity pattern, which we term a conditioned US-timing signal, reflects a learned prediction of threat timing rather than a sensory-driven response. Disruption of mossy cell activity or selective attenuation of this timing signal during retrieval significantly reduces freezing behavior and promotes movement, demonstrating a causal role in fear expression. These findings reveal that ventral dentate gyrus mossy cells encode temporally precise threat predictions and provide a novel hippocampal mechanism linking associative memory to behavioral control. By furnishing a temporal scaffold for information routing to downstream affective circuits, this mechanism offers new insight into how internal threat predictions guide defensive behavior and how their dysregulation may contribute to pathological fear and anxiety.

Cheng-Ting Chien, PhD
Distinguished Research Fellow
Institute of Molecular Biology
Academia Sinica
Taipei, Taiwan

Title

Protein N-glycosylation regulates dendrite self-avoidance and pruning

Abstract

We systematically screened *Drosophila* mutants with defects in glycosylation pathways to identify those exhibiting impaired dendrite arborization and pruning during metamorphosis. Two complementary studies presented here demonstrate that specific N-glycan modifications on membrane proteins play critical roles in these developmental processes.

The first study reveals that phagocytosis of fragmented dendrites by epidermal cells depends on N-glycosylation of the phagocytic receptor Draper (Drpr)/Ced-1 for proper surface membrane presentation. We further identified two galectins—Crouching tiger (Ctg) and Hidden dragon (Hdg)—that specifically recognize N-glycan-modified Drpr. Upon dendrite injury, Ctg and Hdg are induced in macrophage-like hemocytes and recruited to damaged dendrites, where they bridge the "eat-me" signal phosphatidylserine (PS) and N-glycosylated Drpr, thereby facilitating the phagocytosis of fragmented dendrites.

The second study demonstrates that an epidermal cell-derived N-acetylglucosaminidase encoded by *fused lobes* (*Fdl*), regulates dendrite self-avoidance. The cell adhesion molecule Dscam1, which mediates self-recognition between sister branches, carries multiple hybrid- and complex-type N-glycans. Fdl cleaves the GlcNAc moiety from these N-glycans, weakening Dscam1 homophilic interactions and promoting branch separation upon contact.

Collectively, these studies underscore the importance of protein N-glycosylation in epidermal cells as a regulatory mechanism for controlling specific aspects of dendrite development.

Shen-Ju Chou, PhD
Research Fellow
Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan

Title

Patterning the cerebral cortex by transcription factor gradients

Abstract

The mammalian cerebral cortex is a remarkably complex organ responsible for the perception of sensory stimuli, the execution of motor actions, learning, cognition, and consciousness. To carry out these complicated functions, it is compartmentalized into multiple functional units or cortical regions, including the newly evolved neocortex and evolutionarily older paleocortex and archicortex. Each region has unique cytoarchitectures, patterns of gene expression, and distinct sets of input and output projections to perform specialized functions. As many neurological disorders assault specific types of neurons in particular brain regions, understanding the mechanisms controlling cortical regional specification will contribute to the understanding of cortical dysfunction in disease states. We study how cortical neurons acquire region-specific properties and how boundaries between cortical regions are established during development. We found that COUP-TFI, an orphan receptor expressed in a high-caudal-lateral-to-low-rostral-medial gradient in cortical progenitors, determines the size and relative position of multiple cortical regions, and the sensory areas in the neocortex. Additionally, COUP-TFI determines the integrity of the borders between abutting cortical regions. For example, by inducing protocadherin 19 expression, COUP-TFI establishes a sharp boundary between the neocortex and the medial entorhinal cortex. Our findings suggest that the expression gradients of COUP-TFI and other patterning transcription factors in the cortical progenitors play an instructive role in cortical regional specification.