Mechanism study: how circadian clocks mediate intercellular communications in brain pathologies to enhance brain repair systems

機制研究：晝夜節律鐘在腦病中介導細胞間通訊以增強神經修復系統

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Research Background

Circadian clocks are intrinsic in nearly every cell in the body, including neural cells, such as neurons, astrocytes, microglia, and oligodendrocytes. Circadian clocks are built on a transcriptional-translational negative feedback loop and target thousands of clock genes to automatically generate a 24h cycle in their expression. Clock gene products are involved in various physiological processes, including metabolisms, so these processes exhibit oscillations in their activities based on clock gene expression patterns. Therefore, alterations in circadian clocks were considered detrimental events due to abnormal physiological processes.

Recent studies published in 2020, including our recent work, started providing a new perspective on relationships between altered circadian clocks in glia (oligodendrocytes, astrocytes, and microglia) and brain pathologies such as demyelination, amyloid-β (Aβ) accumulations, and neuroinflammation. They showed that altered clocks were not merely detrimental to brain damages because they could enhance brain repair systems (remyelination and toxin (Aβ) clearance) and prevented neuroinflammation. Our recent work showed that astrocyte BMAL1 (the circadian transcription factor) responded to demyelination to express new target genes, including secreted frizzled-related protein (SFRP) 1 and 5. SFRP1/5 signaled to the subventricular zone (SVZ), where adult neural stem cells (NSCs) reside, to reduce BMAL1 levels in NSCs. These subsequent BMAL1 changes in astrocytes and NSCs recruited NSCs to the lesions for remyelination. Another study by Lananna et al. also reported a beneficial effect of reduced BMAL1 in astrocytes on Aβ clearance. They showed that the expression of Chi3l1/Ykl-40, a well-known cerebrospinal fluid biomarker of Alzheimer's disease, was regulated by BMAL1 in astrocytes. Deleting Bmal1 in astrocytes reduced CHI3L1/YKL-40, resulting in the induced phagocytosis activity of astrocytes to clean up Aβ. Wang and colleagues found that reduced Bmal1 in another glial cell type, microglia, prevented neuroinflammation. Bmal1 deficiency in microglia reduced pro-inflammatory cytokine expression but induced anti-inflammatory factor expression. These studies support the beneficial effects of altered glial clocks on brain pathologies and suggest various beneficial

functions in different pathological conditions. However, not much-supporting mechanism studies are available to explain the beneficial effects of altered clocks.

Research Objectives

Objective 1) Understanding how circadian clocks in brain lesions mediate intercellular communications.

Objective 2) Study how clock-medicated intercellular communications regulate adult neural stem cells to enhance brain repair systems.