Precisely Controlling Cells for Basic Research and Potential Therapeutic Applications

精準控制細胞進行基礎研究及其可能醫療應用

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Microtubules play a critical role in regulating a wide range of cellular processes. Dysfunction in microtubules is a common feature in various conditions, including neurodegenerative diseases, ciliopathies, cancers, and aging. However, the causal relationships between microtubules, intracellular transport, cellular architecture, and molecular activities remain insufficiently understood. To tackle this long-standing challenge, we have developed a suite of innovative tools that allow for the spatiotemporal control of microtubule disassembly (Liu *et al*., EMBO J, 2022; Lian and Lin, Curr. Opin. Cell Biol, 2024), tubulin post-translational modifications (Hong *et al*., Nat. Commun., 2018; Yang *et al*., Front. Cell Dev. Biol., 2021), and intracellular transport (Chen *et al*., Adv Sci, 2024).

Using these tools, we discovered that rapid microtubule removal induces the formation of contractile actin structures, increases cell stiffness, reduces vesicle trafficking and organelle dynamics, and inhibits cell division, all without causing significant cell death. These rapid effects of microtubule removal mimic the phenotypes observed in aged cells. We aim to investigate whether microtubule removal accelerates the aging process, utilizing diverse model organisms in conjunction with our tools.

In addition, we have developed sonogenetic tools that employ medical ultrasound to non-invasively modulate cellular activity. We identified and engineered several ultrasound-sensing proteins, including mPrestin(NT,NS), mPrestin(NS,VG), and eNompC. Using these proteins, we achieved transcranial activation of target neurons located deep in the brain (Huang *et al*., Nano Lett, 2020; Wu *et al*., Theranostics, 2020), and alleviated neurodegeneration and motor symptoms in a Parkinson's disease mouse model (Fan *et al*., Nano Lett, 2022). More recently, our sonogenetic tools were applied to activate GABAergic neurons and suppress hyperexcitable states in an epilepsy rat model (Phan *et al*., J. Control. Release, Accepted).

The tools we have developed offer unique and powerful approaches for the precise control of cellular activities, addressing unresolved research questions, and presenting potential therapeutic applications for currently incurable diseases.