Inhibition Effect of Magnetic Field on Liquid-Liquid Phase Separation of Tau-441 and Its Perspectives

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The biological effects of magnetic fields (MFs) have long been controversial, with their underlying physical mechanisms remaining elusive. In this report we will show that a 16 T static MF reduces apoptosis by suppressing Tau-441 LLPS, thereby providing a novel mechanism for understanding magnetobiological effects and potential therapeutic strategies for LLPS-related diseases.

Alzheimer's disease (AD) and other neurodegenerative disorders are closely linked to abnormal aggregation of Tau proteins, with LLPS acting as a critical early step in this process. Our research shows that, upon arsenite induction, Tau-441 undergoes LLPS in the cytoplasm, forming droplets that recruit hexokinase (HK). This reduces the pool of free HK, which normally competes with Bax for binding to the voltage-dependent anion channel (VDAC I) on mitochondrial membranes. A decrease in free HK increases Bax-VDAC I binding, promoting Bax-mediated apoptosis.

The major findings include:

1) MF inhibition of LLPS: A 16 T MF significantly reduces the number and size of Tau-441 droplets, decreases solution turbidity, and a 0.48 T permanent magnet yields similar effects. Circular dichroism (CD) and thioflavin T (ThT) fluorescence analyses confirm that MFs reduce LLPS-induced β-sheet formation, stabilizing Tau-441 secondary structure.

2) Reduced HK recruitment and improved metabolism: MF-suppressed LLPS decreases Tau-441-mediated HK sequestration, increasing free HK levels and activity. This enhances glucose metabolism, as evidenced by increased glucose consumption and glucose-6-phosphate production.

3) Apoptosis suppression: Elevated free HK enhances VDAC I binding, reducing Bax-VDAC I interactions. This mitigates mitochondrial membrane potential damage, reactive oxygen species (ROS) production, and caspase-3 activity, ultimately decreasing apoptosis.

To explain our findings, we propose that MFs affect LLPS through two pathways: (1) When droplet size exceeds a critical value, magnetic energy overcomes thermal energy to disrupt LLPS; (2) Lorentz forces decrease diffusion of charged molecules (e.g., Tau-441, HK), thereby inhibiting LLPS process.

Our study links the MF effect to LLPS and proposes a new physical mechanism of magnetobiological effects. It confirms that MFs can modulate apoptosis by modulating LLPS, providing potential for non-invasive physiotherapy (e.g., the use of permanent magnets) for LLPS-related diseases such as AD.

[1] W. J. Lin, W. P. Shi, W. Y. Ge, L. L. Chen, W. H. Guo, P. Shang, D. C. Yin, Research 6 (2023) 0146.