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IN THE HELMHOLTZ ASSOCIATION

Contribution ID: **8** Type: **POSTER**

Regulation of DVL2 Condensates by CK1 and DDX3X in Wnt Signaling

Biomolecular condensates formed via phase separation are emerging as key modulators of signal transduction. In Wnt signaling, Dishevelled proteins (DVL), particularly DVL2, form such condensates ("signalosomes") upon pathway activation, but how these condensates are regulated remains poorly understood. This project investigates the regulatory roles of casein kinase 1 (CK1) and the RNA helicase DDX3X—an oncogene and CK1 activator—in modulating DVL2 condensation and phosphorylation.

We hypothesize that CK1-mediated phosphorylation reduces DVL2 condensation, and that co- condensation of CK1 and DVL2 may inhibit kinase activity due to substrate inhibition, a process that DDX3X can rescue by enhancing CK1 turnover. Using a combination of in vitro reconstitution assays and live-cell imaging of endogenously tagged DVL2, we aim to: (1) determine how phosphorylation influences DVL2 condensation; (2) assess whether CK1-DVL2 condensates lead substrate inhibition on CK1 activity; and (3) test whether DDX3X relieves the substrate inhibition to restore efficient DVL2 phosphorylation; and (4) investigate whether DDX3X-CK1-DVL2 condensates leads to site-specific phosphorylation on DVL2.

By linking kinase kinetics with biomolecular condensation, this project addresses fundamental questions about how phosphorylation is regulated within DVL2 condensate in the Wnt signal pathway. Specifically, it investigates how the physical and biochemical environment of DVL2 condensates influences CK1 kinase activity and how this is modulated by the oncogenic RNA helicase DDX3X. Uncovering these mechanisms will not only shed light on the dynamic regulation of signalosomes in Wnt signaling, but also provide broader insights into how phase-separated condensates fine-tune enzymatic reactions within cells.

Research type

Basic research

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Session Classification: Poster presentation