Spatio-temporal Control of Arl4 GTPases Drives Organelle Homeostasis and Divergent Oncogenic Pathways

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Membrane trafficking and cytoskeletal remodeling are highly coordinated processes that require precise spatio-temporal control to govern cell growth, polarity, and migration. The loss of this coordination is a hallmark of oncogenesis, often driven by the deregulation of Ras superfamily small GTPases. Functioning as molecular switches, these GTPases integrate signaling cascades via their guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). Our laboratory focuses on the Arl4 family (Arl4A, Arl4C, and Arl4D), a subset of Arf GTPases that are developmentally regulated and frequently overexpressed in various cancers. We have characterized the Arl4 family as key modulators that integrate spatial distribution with temporal activation to maintain organelle homeostasis and drive divergent oncogenic pathways. We also identified a critical spatial mechanism where endosomal Arl4A attenuates EGF-induced EGFR degradation, thereby prolonging oncogenic signaling. I will detail our recent findings on a sophisticated spatio-temporal feedback loop involving the Arl4A/D-Pak1 axis. We demonstrated that Arl4A/D are novel substrates of Pak1; this phosphorylation event provides protein stabilization and effector cooperation that is essential for driving directional cancer cell migration on fibronectin. Crucially, we have uncovered a lipid-based and kinase-driven positive-feedback mechanism that dictates how extracellular cues are translated into localized Arl4-Pak1 signaling at the cell periphery. By elucidating the extracellular signals and intracellular mechanisms that govern the spatio-temporal dynamics of Arl4A/D, our research provides a molecular basis for exploring Arl4 GTPases as high-precision diagnostic markers or therapeutic targets in human cancers.