Investigating Mechanistic Insights Into PELO Dependency Across Molecular Subtypes of Gastrointestinal Cancers

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Cancer genomic alterations often create unique vulnerabilities that can be exploited for precise treatment. Inhibitors exploiting synthetic lethal relationships have recently shown clinical promise, garnering FDA approval. Previously, my lab identified PELO as a synthetic lethal target in two distinct subtypes of cancers: those with either deletion of chromosomal region 9p21.3 or microsatellite-instability high (MSI-H), which collectively account for ~20% of cancers. Both subtypes destabilize the SKIc complex, which extracts mRNA from stalled ribosomes, making these types of cancers highly dependent on PELO for survival. It's hypothesized that in SKIc-deficient cells, PELO depletion leads to an accumulation of ribosomal stress, triggering apoptotic cell death. However, the molecular mechanisms linking SKIc loss to PELO dependency and downstream effects of PELO loss remain unclear. Addressing this, I analyzed a genome-wide CRISPR screen performed in SKIc-deficient cells and identified a ribosome quality control pathway involved in translational stress signaling as a key resistance mechanism to PELO inhibition. Complementary proximity-labeling proteomics using PELO—with a loss-of-function mutation, binding to ribosomes—revealed stalled ribosomes closely associate with mRNA surveillance proteins and p-body components, highlighting a potential pathway that may compensate for the inability to decay stalled transcripts upon PELO depletion. Together, these findings reveal a rewiring of translational surveillance and provide insight into novel, specific pathways that may compensate for PELO loss in cancer cells. This study paves the way for development of precision therapies for a widespread population with 9p21.3 deletion or MSI-H cancers.

Awards Won: