2026 ACG-IRG Pilot Grant

Mechano-regulation of Nuclear Envelope Integrity in Cancer

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Abstract:

As cancer cells invade and metastasize, they are subjected to extreme physical constraints that deform the nucleus as they traverse dense extracellular matrices and narrow interstitial pores. These mechanical stresses can cause nuclear envelope rupture (NER), a transient breach in the nuclear membrane that leads to uncontrolled nuclear-cytoplasmic exchange, DNA damage, and activation of inflammatory pathways. NER has been observed in a wide range of cancer models during confined migration and is now recognized as a hallmark of invasive tumor cells. While considerable progress has been made in identifying structural contributors to nuclear rupture and components of the repair machinery, critical gaps remain in understanding how mechanoresponsive signaling pathways regulate NER outcomes in cancer cells.

This project focuses on the role of YAP and TAZ, mechanosensitive transcriptional co-activators that are frequently activated in solid tumors and implicated in promoting invasion, proliferation, and therapy resistance. **We hypothesize that YAP/TAZ activity modulates the initiation and repair of nuclear envelope rupture in response to mechanical stress, and that the kinetics of nuclear envelope resealing encode predictive information about cancer cell fate.**

We will pursue two specific aims:

(1) Determine how YAP/TAZ signaling influences NER frequency, repair efficiency, and DNA damage in cancer cells experiencing confined migration. We will use a high-throughput nanopillar platform to impose controlled nuclear deformations and apply live-cell imaging to track YAP/TAZ dynamics, rupture events, and downstream effects following perturbation of YAP/TAZ activity.

(2) Develop a predictive model linking early resealing kinetics to cancer cell fate outcomes. By combining quantitative live-cell imaging of nuclear rupture reporters (NLS-GFP) with machine learning, we will correlate features of early repair (e.g., recovery slope, duration) with long-term outcomes such as survival, senescence, or apoptosis.

Together, these studies will reveal how cancer cells integrate mechanical cues to regulate nuclear envelope integrity, and whether YAP/TAZ plays a protective or maladaptive role in this process.

Cancer Relevance: This project will help explain how cancer cells survive nuclear damage while invading tissues, offering new insight into how metastasis might be prevented by targeting their mechanical vulnerabilities. Because nuclear envelope rupture contributes to DNA damage, chromosomal instability, and altered gene expression – all of which fuel cancer progression – understanding how cancer cells regulate rupture and repair is critical. By dissecting the role of YAP/TAZ in this process and developing a model that predicts whether a cell will survive or die after rupture, this work could identify new biomarkers of invasive potential and therapeutic strategies to eliminate metastasis-prone cells during their most vulnerable, mechanically stressed states.