CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150053

Project Title:
Mechanisms of nuclear import and export in cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

CRM1 transports protein cargos out of the cell nucleus. In cancer, many tumor suppressor cargos are inappropriately transported by CRM1, thus preventing cancer cell death and causing resistance to therapy. Anti-CRM1 drug Selinexor reverts cargo misplacement and causes cancer cell death. The drug is in 12 Phase 1 and 2 clinical trials targeting many cancers. Selinexor is well tolerated, unlike an older CRM1 blocker named Leptomycin B (LMB), which was toxic in patients. Aim 1 of this proposal focuses on understanding how the two drugs act differently in cells. We will discover how Selinexor targets CRM1 to be destroyed or degraded and why this effect is absent with LMB. We will learn if this function of Selinexor is important for potency and/or tolerance of the drug. Aim 2 focuses on understanding how CRM1 mutants found in chronic lymphocytic leukemia (CLL) patients function differently from normal CRM1. We will determine how the mutations change arrangement of atoms in CRM1 and affect how it recognizes cargos and/or respond to drugs like Selinexor. Information obtained about basic functions of CRM1 mutants in CLL will serve as a foundation to interpret studies by our oncology collaborators of the mutants in CLL cells obtained from patients. Finally, Aim 3 focuses on a transporter named Importin-8 or Imp8, which takes the oncogenic eIF4E into the nucleus. eIF4E resides in the cytoplasm of normal cells but moves into the nucleus in acute myeloid leukemia (AML). As patients respond to an anti-eIF4E drug, their eIF4E is normal back in the cytoplasm, but at relapse the protein is mislocalized to the nucleus again. Imp8 controls eIF4E movement and its oncogene activity, but little is known about this transporter. We will determine the arrangements of atoms in Imp8 to understand how it recognizes eIF4E and releases it at the correct time. Information obtained will be critical for future efforts to design Imp8 blockers to control activities of oncogenes like eIF4E.