



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120352

Project Title:
Mechanisms of CRM1-mediated nuclear 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 hundreds of protein cargos out of the cell nucleus by recognizing a zip code-like entity known as the nuclear export signal or NES that exists in the cargos. CRM1 cargos include numerous tumor suppressors, oncogenes and proteins that control cell growth, division and cell death. Transport of protein cargos by CRM1 is essential for many normal functions of the cell and errors in this process can cause diseases like cancer. We solved the first three-dimensional structure of CRM1 in contact with a cargo. This structure revealed physical characteristics of the NES zip code in the cargo and how CRM1 recognizes the NES. This information provides us with unique knowledge, insights and probes of CRM1 function. Comparison of a CRM1 cargo database that we compiled recently with a cancer proteins database indicated that CRM1 cargos are highly enriched among tumor suppressors, their regulators and nuclear oncogene proteins. Many of these cancer-essential CRM1 cargos reside in the nucleus of normal cells but are abnormally enriched in the cytoplasm of malignant cells. CRM1 itself is found in abnormally large quantities in ovarian carcinoma, glioma, bone, pancreas and cervical cancer cells. Blocking CRM1 function in cancer cells restores mislocalized cargos to the nucleus, restores their normal functions and also increases susceptibility to other anti-cancer drugs. We will determine how tumor suppressors and oncogenes are recognized by CRM1, determine how anti-CRM1 drugs work and how CRM1 recognizes the oncogenic Nup214 protein that is fused wrongly in T-ALL and AML leukemias. Knowledge of how CRM1 recognizes these very different molecules will drive future design and improvement of anti-CRM1 drugs for increased specificity and tolerability in cancer. These studies will provide a knowledge base for the normal transport process by CRM1 and lay the foundation to future design and modification of drugs to block export CRM1 in a cargo/disease-specific fashion.