CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170170

Project Title:
Prediction of nuclear export signals in proteins

Award Mechanism:
Individual Investigator Research Awards for Computational Biology

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

Lay Summary:

The goal is to efficiently find proteins that are being carried out of the nucleus of a cell into its cytoplasm (i.e. "exported") by an exporter protein called CRM1. We will develop a computer program that, taking a protein sequence as input, predicts if this protein is exported by CRM1. This program will evaluate the energy of binding between candidate cargo protein and CRM1. The major challenge is to design a mathematical formula to compute this energy accurately. To devise the formula, we will use amino acid sequences of known cargo proteins and 3D structures of complexes between CRM1 and its cargos. The values of parameters in the formula will be optimized to distinguish between proteins that bind to CRM1 and those that do not. Using this program, we will find proteins predicted to bind CRM1. We will validate cancer-relevant predictions experimentally by making these proteins and measuring their binding to CRM1. Then, our program can be used to design CRM1 inhibitors.

This project advances cancer research because cancer disrupts protein balance between nucleus and cytoplasm and causes malignant gene regulation. The nucleus is isolated from the cytoplasm by two membranes. To cross these membranes, proteins are carried through a pore by specialized transporter proteins. CRM1 is the major exporter of proteins, many of which are tumor suppressors. Exporting tumor suppressors from the nucleus, where they suppress cancer development, promotes cancer. Ovarian carcinoma, glioma, pancreatic, cervical and many other cancer cells produce more CRM1 than healthy cells, causing over-active export of tumor suppressors and thus exacerbating gene misregulation. CRM1 studies help us understand how genes are misregulated in cancer and how to reverse it for cancer treatment. Inhibition of CRM1 restores tumor suppression and kills cancer cells, but not normal cells. Selinexor is a CRM1 inhibitor currently in clinical trials, and other anti-CRM1 drugs are desired.