CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150573

Project Title:
Dynamin GTPase: A novel pro-apoptotic cancer therapeutic target

Award Mechanism:
High Impact/High Risk

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

Lay Summary:

Programmed cell death, or apoptosis, plays a critical role in the normal development and maintenance of tissues by eliminating infected, mutated or damaged cells in all multicellular organisms. Not surprisingly, deficiencies in the process of apoptosis are a hallmark of cancer. Apoptosis can be triggered by a class of molecules, called death receptors, that kill target cells upon activation by their corresponding ligands. Interestingly, one of these ligands, called TRAIL, selectively kills cancer cells and is being developed as a potential anti-cancer therapeutic. The large GTPase dynamin is best known for its role in clathrin-mediated endocytosis (CME), a major process regulating the selective uptake of molecules and multiple signals into the cell. Recently, we discovered a CME independent role for dynamin-1 in providing protection against TRAIL: cells with reduced levels of dynamin-1 expression exhibited greater sensitivity to TRAIL-induced apoptosis. Strikingly, dynamin-1 is frequently overexpressed in a large number of cancers, including acute myeloid leukemia, perhaps reflecting a protective function against pathways of apoptosis. Here we propose to study this novel link between dynamins and their ability to influence cell death mechanisms. To address this, we will (1) dissect the mechanism by which dynamin regulates TRAIL-induced apoptosis by analysis of dynamin mutants and (2) establish and perform a high throughput screen for small molecule inhibitors of dynamin, as these might be potential therapeutic leads as cancer cell-specific, pro-apoptotic compounds, either alone or in conjunction with TRAIL.