CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130059

Project Title:
K-ras Spatiotemporal Dynamics: Novel Therapeutic Targets

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

Ras is a protein that operates as a molecular switch, toggling between an active “on-state” and an inactive “off-state” in response to growth signals received by the cell. When Ras is in the “on-state” it activates a signaling network that instructs the cell to divide. Unfortunately 15-20% of all human tumors acquire mutations that lock the Ras switch in the “on-state”. Cells with a mutant Ras switch therefore receive a constant signal to undergo cell division, resulting in the outgrowth of a tumor. The major clinical problem is with a form of Ras called K-Ras that is mutated in >90% of pancreatic cancers, ~50% of colon cancer and ~25% of non-small cell lung cancer. We have known for over 25 years that Ras proteins are anchored to the inner surface of the cell limiting membrane, called the plasma membrane. The anchors used for this purpose are attached to the Ras protein on the surface of endoplasmic reticulum (ER), which is an extensive set of membranes inside the cell. However, the transport or trafficking mechanism that delivers K-Ras from the ER to the plasma membrane is not understood. There are currently no drugs that directly target mutant Ras, but there is a wealth of experimental data to show that K-Ras must be localized to the plasma membrane and then organized into small clusters in order to activate its signaling network. Identifying how K-Ras is trafficked from the ER to the plasma membrane and the processes that then regulate the spatial organization of K-Ras on the plasma membrane are important cell biological challenges. One aspect of the grant is to study these cell processes. In addition, we have recently identified drugs and small molecules that prevent the normal association of K-Ras with the plasma membrane and selectively kill tumor cells transformed by mutant K-Ras. The second aspect of this grant will be to work out how these drugs are working and determine whether they have clinical utility as new anti-K-Ras cancer agents.