CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100483

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 out growth 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 some 25 years that Ras proteins are normally 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 then 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 both localized to the plasma membrane and there 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. In turn, pharmacological targeting of these cellular processes represents a novel approach to selectively block mutant K-Ras signaling. This proposal will investigate whether these two fascinating areas of cell biology are indeed suitable targets for K-Ras drug development.