CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160235

Project Title:
Regulation of tumor aggressiveness and immune suppression in lung adenocarcinoma

Award Mechanism:
Individual Investigator

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

Lay Summary:

Lung cancer remains the leading cause of cancer related death in the world. Recent progress in the development of targeted therapeutics against mechanisms that drive the formation and growth of a subset of lung adenocarcinoma has provided breakthrough treatment to those patients. However, the vast majority of lung cancer cases still don't have targeted therapies available. Recently, we found a novel ligand-receptor system that potentially plays a driving role in the aggressiveness of a subset of lung adenocarcinomas. This system, comprising the R-spondin (RSPO) group of secreted proteins as ligands and LGR4 as the receptor, is genetically altered to cause tumor formation in a small fraction of colon cancer patients. We discovered that one of the RSPOs, RSPO3, is produced at high levels in ~10% of lung adenocarcinomas due to a unique mechanism and RSPO3-high patients had much short survival. Blockade of RSPO3-LGR4 function in lung cancer cell lines with high RSPO3 expression led to reduced tumor growth and metastasis. We have also uncovered that LGR4 suppress the anti-tumoral function of tumor-associated macrophages which are critical to the eradication of tumors by the body's own immune system. In this proposal, we seek to establish that abnormal RSPO3-LGR4 activity functions to drive oncogenesis of lung adenocarcinoma via promoting growth and metastasis of tumor cells while suppressing anti-tumoral activity of the immune system. We also have obtained monoclonal antibodies against RSPO3 and will validate them as potential leads for the development of therapeutics targeting the RSPO3-LGR4 pathway for the treatment of cancers driven by this mechanism. Successful completion of the project will not only lead to the validation of a novel, unique mechanism but also provide actual drug leads for the development of therapeutics to treat one of the most lethal, intractable type of solid tumors.