



CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

Award ID:
RP140244

Project Title:
Regulation of MDM2-Mediated Oncogenesis and Anti-Tumor Immunity by
USP15

Award Mechanism:
Individual Investigator

Principal Investigator:
Sun, Shao-Cong

Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

The immune system is vital for controlling tumor growth and progression, and it is now clear that boosting the anti-tumor immunity (or immunotherapy) is a promising strategy to treat different types of cancer. A more attractive approach is to combine the immunotherapy with chemotherapy or targeted therapies. Unfortunately, virtually all of the currently used chemotherapeutic regimens can cause immunosuppression due to killing of rapidly dividing immune cells. It is thus an important task to characterize the immunoregulatory functions of the currently explored drug targets and identify new ones whose inhibition both attenuates tumor growth and favors immune activation. This proposed research project focuses on the study of a potential drug target, USP15, which has been linked to different human cancers and shown to mediate cancer cell survival. USP15 is an enzyme that cleaves ubiquitin chains from substrate proteins and, thereby, preventing their proteolysis. Our preliminary studies demonstrated that inhibition of USP15 expression causes death of cancer cells and reduces their ability to form tumors. Furthermore, USP15 ablation also promotes immune responses against tumors. These findings suggest that USP15 may be an ideal drug target whose inhibition may both reduce tumor survival and promote tumor rejection by the immune system. The studies proposed in this application will investigate how USP15 exerts these intriguing functions and to evaluate USP15 as a therapeutic target using clinically relevant animal models of cancer therapy. For further translation of our findings into clinically applicable concepts, we will also screen for small-molecule inhibitors of USP15 and examine their therapeutic potential.