CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140320

Project Title:
Dissecting a Necrotic Signaling Pathway in Human Cancer Cells

Award Mechanism:
High Impact/High Risk

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

Lay Summary:

One of the ultimate goals of cancer therapy is to kill cancer cells without sacrificing normal cells. However, cancers cells are often resistant to apoptosis, the major form of cell death. Recent studies suggest that apoptosis-resistant cells are prone to non-apoptotic necrotic cell death, an alternative form of cell death. Therefore, necrosis activation could function as a novel means to selectively kill cancer cells versus normal cells. However, it is still not fully understood how necrosis is controlled. In our preliminary study, we found a small molecule compound, originally identified from a screen for anti-cancer agents, directly activates necrosis based on rigorous measurements by different assays; hereafter we name this compound as necrocide 1 (a compound that kills by inducing necrosis, abbreviated as NC1). NC1 selectively kills a subset of cultured cancer cells including breast, ovary, prostate, and pancreatic cancer cells at very low concentrations but is not toxic to normal cells until the concentration is reached 1,000 times higher. We noticed that NC1 induces necrosis through an unconventional necrotic signaling pathway. Through an unbiased genetic screen searching for proteins in a class known as kinases that are essential for NC1-induced cell death, we identified 15 kinases that protect cells from NC1-induced necrosis. In this study, we aim to find the target of NC1, to validate the functions of these 15 kinases in necrosis, and to investigate the biochemical mechanism of these “necrotic” kinases. We anticipate that critical regulators of this pathway could serve as targets for cancer therapeutics, and measurements of this type of cell death could serve as new biomarkers for therapeutic efficacy in clinical trials of chemotherapy drugs. Furthermore, a better understanding of the regulation of necrosis could expedite the development of therapeutic strategies that maximize tumor cell death.