UC San Diego
MOORES CANCER CENTER

2022 Jawsome Shark Tank – Multidisciplinary Pilot Project Program

Structural and functional identification of small GTPases that partner with RAS associated domain family protein RASSF2 to promote leukemogenesis

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Scientific Abstract:

Acute myeloid leukemia (AML) is a highly aggressive hematological cancer with a block of myeloid cell differentiation and expansion of immature myeloid progenitors in the bone marrow. The treatment for most AML patients has remained largely unchanged for decades with induction chemotherapy. Over the past several years, significant progress has been made towards understanding the genomic and molecular basis, especially regarding driver mutations, of AML. However, progress towards development of therapies that improve patient outcomes has remained limited. Signaling through small GTPases plays an important role in AML cell proliferation and survival, and therefore represents an attractive target for possible therapeutic modulation. We discovered recently that RAS associated domain family protein RASSF2 is essential for survival of human leukemia cells but is not required for normal development and growth when we analyzed Rassf2 deficient mice. These preliminary data indicate that the RASSF2 involved signaling axis is a potentially therapeutic target pool for leukemia treatment. Furthermore, although RASSF2 has a RAS association domain, it does not interact with three canonical RAS GTPases, suggesting that RASSF2 likely functions through other small GTPases in the RAS super family. Therefore, the objective of our proposed work is to conduct transdisciplinary studies for identification of a few candidate RASSF2 partner small GTPases with combined expertise of our two research groups in protein structure biology (Wang) and leukemia research (Zhang). Results of the proposed studies will be used as preliminary data for preparation of an NIH multi-PI R01 application in 2023.

Lay Abstract:

Acute myeloid leukemia (AML) is a type of blood cell cancer. The treatment for most AML patients has remained largely unchanged for decades with classical chemotherapy. Over the past several years, significant progress has been made towards understanding what kind of genetic mutations may lead to AML development or to resistance of chemotherapy. However, progress towards development of therapies that improve patient outcomes has remained limited. We discovered recently that a protein called RAS associated domain family protein (RASSF2) is essential for survival of human AML cells but is not required for normal development and growth when we analyzed Rassf2 gene knockout mice. RAS is a small GTPase and strongly promote cancer development. However, although RASSF2 has a RAS association domain, it does not interact with RAS, suggesting that RASSF2 likely functions through other small GTPases in the RAS super family. Therefore, the objective of our proposed work is to identify which GTPases work with RASSF2. Such identified GTPases can be used as new drug targets and let

scientists find ways to block their activity in order to cure AML. We propose to identify such kind of GTPases with combined expertise of our two research groups in protein structure biology (Wang) and leukemia research (Zhang). Results of our work will be used as preliminary data for applying more government funding to find approaches to control AML.