Identification of a Novel Target for Inhibition of Leukemia

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BACKGROUND

Rho-family small (~21kDa) GTPases are essential for regulation of numerous cellular functions. There are 20 members of the Rho family in mammals, of which four (Rac1, Rac2, Rac3, RhoG) belong to the Rac subfamily. Each Rac GTPase functions as a molecular switch by cycling between an active GTP-bound form and an inactive GDP-bound form. In addition to their normal cellular functions, Rac GTPases contribute to cancer development as downstream effectors of growth factor receptor signaling and oncogenic mutations in the Ras pathway. Rac GTPases represent attractive targets for therapy in hematologic cancer, however direct targeting of small GTPases has proved difficult and largely ineffective. A thorough understanding of the diverse mechanisms controlling Rac activation in cancer will therefore be essential towards identifying new therapeutic avenues and improving outcomes in patients

One insight into the regulation/activation of the Rac GTPases involves examining Ras proteins and their signal transduction pathways since mutations that produce abnormally active Ras proteins are found in 30% of all human cancers. Moreover, after activation, RAS signaling is mediated through interaction with RAS-binding domains or through the domain RAS association (RA), transmitted to downstream effectors. Notably, many downstream effectors are oncogenes or tumor suppressor genes that are mutated or silenced in cancers independently of RAS. Ras proteins are involved in Ras association domain-containing protein 2 (RASSF2) and it has recently been shown that in Acute myeloid leukemia cells with low expression of RASSF2 are more resistant to pharmacological inhibition of Dedicator of cytokinesis protein 2 (DOCK2), a guanine nucleotide exchange factor (GEF). Acute myeloid leukemia cells with high expression of RASSF2 are sensitive to pharmacological inhibition of DOCK2.

TECHNOLOGY DESCRIPTION

Researchers at UCSD have identified a previously-unappreciated signaling mechanism linking non-canonical functions of mammalian Hippo kinases with control of Rac GTPase activation in hematologic cancer through biochemical and functional characterization of RASSF2 in leukemia models. The researchers identify RASSF2 as a gene that is differentially expressed across AML subtypes and perform the characterization of RASSF2 function in myeloid leukemogenesis. They find targeting this pathway via shRNA-mediated perturbation or through the use of a small molecule inhibitor of the atypical Rac-specific GEF, DOCK2, to be therapeutically effective in AML.

APPLICATIONS

Targeting Rac GTPases through inhibition of DOCK2 may be an effective therapy in acute myeloid leukemia, and our invention describes a biomarker that is predictive of when this therapy would be most effective.

ADVANTAGES

This represents a novel approach to treat AML.

STATE OF DEVELOPMENT

The invention is in the concept stage and experimental data stage

INTELLECTUAL PROPERTY INFO

The invention is patent-pending and is available for licensing and collaborations.

PATENT STATUS

Patent Pending

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OTHER INFORMATION

KEYWORDS

AML, RAS, Rac, cancer, GTPases, signal transduction, Acute myeloid leukemia cells, Ras association domain-containing protein 2, RASSF2

CATEGORIZED AS

- Medical
  - Disease: Cancer
  - Therapeutics

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