Genome-wide shRNA Screening Defines the SUMO-activating Enzyme (SAE1/2) as a Novel Therapeutic Target for Tumors Driven by c-Myc Oncogenesis

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Learning Objectives

By the conclusion of this session, participants should be able to:

1) Describe the importance of the c-Myc ongene for tumorigenesis, especially in medulloblastoma.

2) Discuss, in small groups, exciting new approaches for drug discovery using genome-wide siRNA technology, and how these techniques could be used for multiple brain tumor types

3) Identify a potentially novel target for tumors driven by c-Myc oncogenesis

Introduction

The c-MYC oncogene is a pivotal regulator of tumorigenesis in many human cancers, and is often associated with particularly aggressive tumors in breast cancer and medulloblastoma. c-Myc has proven difficult to target pharmacologically, highlighting the need for alternative therapeutic approaches. We exploited the principle of "non-oncogene addiction" to identify genes required by c-Myc for the maintenance of its tumorigenic phenotype in order to define novel drug targets.

Methods

We performed an RNAi genome-wide screen looking for c-Myc-synthetic lethal shRNAs (using a library of 74,905 total shRNAs targeting 32,293 unique transcripts) in the HMEC human epithelial cancer cell engineered with an inducible a c-Myc-estrogen receptor fusion transgene. Top-scoring shRNAs lethal to cells with overexpressed c-Myc but not in cells without c-Myc overexpression were validated in vitro with cell proliferation assays and in mice with implantable c-Myc-dependent tumors. Gene expression data for nearly 1,300 tumors from patients harboring c-Myc-dependent tumors was stratified according to whether their tumor c-Myc activity was high or low, and associations between lethal genes and c-Myc status was assessed.

Results

We uncovered a novel role for the SUMO-activating enzyme (SAE1/2) in the maintenance of the c-Myc oncogenic phenotype. Inactivation of SAE1/2 drives synthetic lethality with c-Myc to promote mitotic catastrophe and cell death selectively in cancer cells but not normal cells. Mechanistically, SAE2 inhibition switches a transcriptional subprogram of c-Myc from activated to repressed. A subset of these genes are required for mitotic spindle function and to support the c-Myc tumorigenesis. SAE2 is required for growth of Myc-dependent tumors in mice, and gene expression analyses of Myc-high human cancers suggest that low SAE1 and SAE2 abundance in the tumors correlates with longer metastasis-free survival of the patients.

Conclusions

Inhibition of SAE1/2 merits investigation as a novel therapy for Myc-driven human cancers, such as breast cancer and medulloblastoma.

References

Recently published as:

Kessler JD, Kahle KT, Sun T, Meerbrey KL, Schlabach MR, Schmitt EM, Skinner SO, Xu Q, Li MZ, Hartman ZC, Rao M, Yu P, Dominguez-Vidana R, Liang AC, Solimini NL, Bernardi RJ, Yu B, Hsu T, Golding I, Luo J, Osborne CK, Creighton CJ, Hilsenbeck SG, Schiff R, Shaw CA, Elledge SJ, Westbrook TF. A SUMOylation-dependent transcriptional subprogram is required for Myc-driven tumorigenesis. Science. 2012 Jan 20;335(6066):348-53.

Featured in:

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