

MECP2 Is a Frequently Amplified Oncogene with a Novel Epigenetic Mechanism That Mimics the Role of Activated RAS in Malignancy - DTU Orbit (08/11/2017)

MECP2 Is a Frequently Amplified Oncogene with a Novel Epigenetic Mechanism That Mimics the Role of Activated RAS in Malignancy

An unbiased genome-scale screen for unmutated genes that drive cancer growth when overexpressed identified methyl cytosine-guanine dinucleotide (CpG) binding protein 2 (MECP2) as a novel oncogene. MECP2 resides in a region of the X-chromosome that is significantly amplified across 18% of cancers, and many cancer cell lines have amplified, overexpressed MECP2 and are dependent on MECP2 expression for growth. MECP2 copy-number gain and RAS family member alterations are mutually exclusive in several cancer types. The MECP2 splicing isoforms activate the major growth factor pathways targeted by activated RAS, the MAPK and PI3K pathways. MECP2 rescued the growth of a KRAS(G12C)-addicted cell line after KRAS downregulation, and activated KRAS rescues the growth of an MECP2-addicted cell line after MECP2 downregulation. MECP2 binding to the epigenetic modification 5-hydroxymethylcytosine is required for efficient transformation. These observations suggest that MECP2 is a commonly amplified oncogene with an unusual epigenetic mode of action. MECP2 is a commonly amplified oncogene in human malignancies with a unique epigenetic mechanism of action. *Cancer Discov*; 6(1); 45-58. ©2015 AACR. This article is highlighted in the In This Issue feature, p. 1.

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Authors: Neupane, M. (Ekstern), Clark, A. P. (Ekstern), Landini, S. (Ekstern), Birkbak, N. J. (Intern), Eklund, A. C. (Intern), Lim, E. (Ekstern), Culhane, A. C. (Ekstern), Barry, W. T. (Ekstern), Schumacher, S. E. (Ekstern), Beroukhir, R. (Ekstern), Szallasi, Z. I. (Intern), Vidal, M. (Ekstern), Hill, D. E. (Ekstern), Silver, D. P. (Ekstern)

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