OFFICIAL ABSTRACT and CERTIFICATION

Identification of the Cyclin Responsible for the Activation of Cancer Dependency CDK11

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According to the National Cancer Institute, over 600,000 people in the United States die from cancer every year. One promising area of research to address this crisis is the identification of cancer dependencies as drug targets. CDK11, a cyclin-dependent kinase responsible for cell cycle progression through phosphorylation of target proteins, was recently discovered to be a cancer dependency. CDK11 must first be activated by a cyclin in order to phosphorylate, but currently, which cyclin is responsible for its activation is unknown. 11 recombinant plasmids were designed and harvested expressing GFP, ampicillin resistance, and a guide RNA targeting either cyclin L1, cyclin L2, or both. These were used to create lentivirus to infect three different Cas9-expressing cancer cell lines, A375 (melanoma), HCT116 (colon cancer), and MDA-MB-231 (breast cancer), using CRISPR/Cas9 to induce a double-stranded break on the genes responsible for coding certain cyclins. These samples were subjected to dropout assays, a type of competition assay measuring relative percent GFP+ to GFP-, to test their viability. If the cyclin targeted is responsible for activating CDK11, those cells will die, since it has already been proven that cancer cells need CDK11 in order to survive. The "knock-out" of targeted cyclins was then confirmed using Western blotting and genomic DNA sequencing. The identification of the activating cyclin of CDK11 can help researchers understand the true function of CDK11, especially as a cancer dependency, characterize the structure of CDK11 itself, synthesize novel therapeutics targeting CDK11, and identify a new potential drug target for cancer therapies.

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