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DOX Inducible IDH2 R140Q Expression in Stem Cells Results in Cell Death, Opposite of Cancerous Overgrowth

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INTRODUCTION

Mutations in the isocitrate dehydrogenase (IDH) 1 or 2 gene are found in approximately 23% of acute myeloid leukemia (AML) patients. IDH mutations have a neomorphic function and gain the ability to produce the novel molecule, D-2-hydroxyglutarate (D2HG).

D2HG production has been shown to cause DNA and histone hypermethylation, which also occurs in leukemia, although the exact mechanism by which it does so is unknown. D2HG's ability to alter the epigenetic profile of DNA also affects the transcriptional profile. Histone methylation, for example, allows for tighter packaging of genetic material which prevents access by the transcriptome and thus prevents expression.

Our lab seeks to explain the link between D2HG, hypermethylation, and the phenotype of leukemia because we hypothesize that AML is caused in part as a result of altering the epigenome in a particular way. To explore this, our lab has developed a H9 stem cell line which has stably incorporated the specific IDH2 R140Q mutation behind a promoter that allows transcription in the presence of doxycycline (DOX) and before a green fluorescent protein (GFP) gene.

Our aim is to use this cell line to understand what D2HG specifically contributes that can lead to development of leukemia. General features of leukemia include increased cell proliferation and a block to differentiation. Therefore our lab uses these phenotypes as parameters to study the onset of cancer in the stem cells.

The purpose of this experiment was to characterize the pattern of growth in cells treated with DOX and to confirm that this was correlated with the production of the mutant enzyme. Our hypothesis was that GFP, as an indicator of IDH2 R140Q, would increase over time of treatment and that the number of cells would also increase, as is seen in leukemia cells.

METHODS

In order to best mimic the environment that leukemia cells exist in, we need to perform future experiments to quantify the amount of D2HG that is produced by DOX treated cells. Then we can alter the concentration of DOX so that cells can produce a concentration of D2HG that is similar to that in leukemia samples.

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