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Low-grade Astrocytoma Core Mutations in IDH1, P53 and ATRX Cooperate to Block Differentiation of Human Neural Stem Cells via Epigenetic Repression of SOX2

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Introduction

Low-grade astrocytomas (LGA) carry neomorphic mutations in Isocitrate Dehydrogenase (IDH), concurrently with P53 and ATRX loss. The molecular mechanisms underlying formation of LGA are not well understood.

Methods

To model LGA formation, we introduced R132H IDH1, P53 shRNA and ATRX shRNA in human neural stem cells (NSCs) derived from human embryonic stem cells.

Results

These oncogenic hits blocked NSC differentiation, increased invasiveness in vivo and led to an epigenetic and transcriptional profile resembling IDH1-mutant human LGAs. The differentiation block was caused by transcriptional silencing of transcription factor SOX2, secondary to disassociation of its promoter from a putative enhancer. This occurred due to reduced binding of the chromatin organizer CTCF to its DNA motifs and disrupted chromatin looping.

Conclusions

Our human model of IDH-mutant LGA implicates impaired NSC differentiation due to epigenetic repression of SOX2 as an early driver of gliomagenesis. This model can serve as a platform for understanding human gliomagenesis and testing new therapies.

Learning Objectives

1) To understand the main genetic alterations found in low-grade astrocytoma

2) To understand epigenetic mechanisms that may underlie astrocytoma formation

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