RESEARCH HIGHLIGHTS

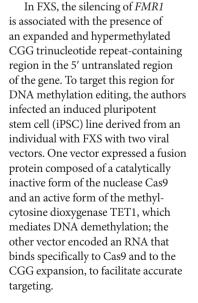
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The cause of fragile X syndrome (FXS) has been shown to be the epigenetic silencing of the FMR1 gene in individuals carrying disease-causing genetic mutations, suggesting that manipulations that can relieve this repression could reverse the neurological deficits associated with the disorder. In their new study, Jaenisch and colleagues show that a tool that allows targeted demethylation of specific nucleotide sequences can be used to reactivate FMR1 and to reverse some phenotypic abnormalities in cells derived from individuals with FXS.

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In 'edited' iPSCs, the methylation of the FMR1 CGG expansion was drastically reduced, when compared with non-edited cells, and FMR1 expression was restored to 90% of its level in healthy human embryonic stem cells. When postmitotic neurons generated from FXS iPSCs were infected with the vectors, the effects were similar (although less robust), suggesting that this approach can also reactivate FMR1 expression in differentiated cells. Furthermore, when neural precursor cells derived from edited FXS iPSCs were injected into the brains of mice, the cells differentiated into neurons that maintained FMR1 activation several months after injection, showing that FMR1 reactivation can be sustained in vivo.

The hypermethylation of the *FMR1* CGG expansion is thought to promote the formation of heterochromatin, a highly compacted form of chromatin characterized by the presence of repressive epigenetic marks and inaccessibility to RNA polymerase, at the *FMR1* promoter. The authors found that the *FMR1* promoter in edited FXS iPSCs exhibited an increase in the presence of markers of active chromatin and a reduction of repressive marks, suggesting that demethylation of the CGG expansion drives the *FMR1* promoter to adopt an active conformation that enables gene expression.

To investigate the effects of reversing the hypermethylation of the FMR1 CGG repeat on neuronal function, the authors differentiated edited and non-edited FXS iPSCs into neurons and examined their electrophysiological properties. In keeping with the hyperexcitability that has been observed in neurons from individuals with FXS, neurons derived from non-edited iPSCs displayed higher than normal firing rates; however, firing rates were restored to control levels in neurons derived from edited iPSCs. Electrophysiological properties were similarly rescued to control levels in neurons in which demethylation was induced after differentiation.

This study demonstrates the utility of DNA demethylation editing as a tool to investigate the contribution of DNA methylation to disease and suggests possible avenues for the rescue of neuronal function in FXS through the reversal of the DNA methylation-driven silencing of *FMR1*.

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ORIGINAL ARTICLE Liu, X. S. et al. Rescue of fragile X syndrome neurons by DNA methylation editing of the *FMR1* gene. *Cell* **172**, 979–992 (2018)

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