GeNeXpreSS

'Myth' Unmethylated: Novel Therapies for Methylation-Related Neurodevelopmental Disorders

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Reactivation of FMR1 by CRISPR/Cas9 (Xie et al., 2016)

Fragile X syndrome (FXS) is a CGG-repeat disorder of the *FMR1* gene caused by epigenetic gene silencing. In the presence of the elongated CGG repeat, epigenetic modifying drugs result in only transient *FMR1* reactivation. CRISPR/Cas9 genome editing was used to excise the expanded CGG-repeat in both somatic cell hybrids containing the human fragile X chromosome and human FXS iPS cells. Transcriptional reactivation was observed in approximately 67% of the CRISPR cut hybrid colonies and in 20% of isolated human FXS iPSC colonies. The reactivated cells produced fragile X mental retardation protein (FMRP) and exhibited a decrease in DNA methylation at the *FMR1* locus.

Transcriptional reactivation of the FMR1 gene (Tabolacci et al., 2016)

In Fragile X syndrome (FXS), CGG expansion and subsequent DNA methylation of the promoter region, is accompanied by additional epigenetic histone modifications that result in a block of transcription and absence of the fragile X mental retardation protein (FMRP). *In vitro* treatment of FXS lymphoblastoid cell lines with the demethylating agent 5-azadeoxycytidine for 7 days resulted in transcriptional reactivation of the *FMR1* gene and FMRP production, demonstrating that DNA methylation is key to *FMR1* inactivation. These observations demonstrate that a therapeutic approach to FXS based on the pharmacological reactivation of the *FMR1* gene is conceptually worthy of being pursued further.

Systemic delivery of MECP2 rescues behavioral and cellular deficits in female mouse models of Rett syndrome (Garg et al., 2013)

Rett syndrome is a severe X-linked neurodevelopmental disorder that is primarily caused by mutations in the methyl CpG binding protein 2 (*MECP2*) gene. Systemic administration of self-complementary Adeno-associated virus-9 (AAV9), bearing MeCP2 cDNA under control of a fragment of its own promoter (scAAV9/MeCP2), was demonstrated to be capable of significantly stabilizing or reversing symptoms in female mice with Rett syndrome. This increased MeCP2 level to 65% from 50% and resulted in improvement in motor function, tremors, seizures and hind limb clasping. Smaller body size of neurons was restored to normal. However, it could not rectify breathing deficits in the Rett-affected mice. This study has shown the first potential gene therapy for females afflicted with Rett syndrome.

Reduction of a long non-coding RNA in Angelman syndrome (Meng et al., 2015)

Angelman syndrome is caused by maternal deficiency of the imprinted gene *UBE3A*, encoding an E3 ubiquitin ligase. All patients carry at least one copy of paternal *UBE3A*, which is intact but silenced by a nuclear-localized long non-coding RNA, *UBE3A* antisense transcript (*UBE3A-ATS*). Murine *Ube3a-ATS* reduction by either transcription termination or topoisomerase I inhibition has been shown to increase paternal *Ube3a* expression. Antisense oligonucleotides

(ASOs) treatment achieved specific reduction of *Ube3a-ATS* and sustained unsilencing of paternal *Ube3a* in neurons *in vitro* and *in vivo*. Partial restoration of UBE3A protein in an Angelman syndrome mouse model ameliorated some cognitive deficits associated with the disease, although additional studies of phenotypic correction are needed.

References

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