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GENETIC DISORDERS

Steps towards epigenetic therapy for PWS

Prader–Willi Syndrome (PWS) is an imprinting disorder caused by a deficiency of paternally expressed genes along a specific region of chromosome 15 (15q11–q13) and is characterized by neonatal hypotonia, failure to thrive, childhood onset obesity and intellectual disability. Current treatment of PWS largely consists of growth hormone administration, and occupational and behavioural therapy. Now, writing in *Nature Medicine*, Jiang and colleagues demonstrate that a small-molecule inhibitor of euchromatic histone lysine *N*-methyltransferase 2 (EHMT2; also known as G9a) restores expression of PWS-associated genes, which significantly improves growth and survival in a mouse model of PWS.

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Imprinted gene expression at 15q11–q13 is controlled by a regulatory element defined as an imprinting centre (PWS-IC). Normally, genes associated with PWS are repressed epigenetically on the maternal chromosome 15 but are active on the paternal chromosome. However, in PWS, the critical region on the paternal chromosome is either inactive or missing. Although the mechanism that underlies imprinting of PWS-associated genes is still unclear, allele-specific patterns of DNA methylation and histone modification in the PWS-IC have been reported. Therefore, Jiang and colleagues set out to explore whether epigenetic therapy could restore expression from the maternal copies of PWS-associated genes.

First, the authors carried out a cell-based high-content screen of 9,157 small molecules for their ability to activate the expression of small nuclear ribonucleoprotein N polypeptide (SNRPN), which is a PWS-IC-controlled gene within the 15q11–q13 region. The screen identified 32 potentially active compounds, including UNC0638 and UNC0642 (previously characterized as selective G9a inhibitors); both compounds were validated in additional *in vitro* assays.

Next, Jiang and colleagues investigated whether the G9a inhibitors derepressed maternal PWS-associated genes in a patient-derived cell model of PWS; a human skin fibroblast cell line in which the paternal copy of the 15q11–q13 region is deleted. Both UNC0638 and UNC0642 activated the expression of *SNRPN* and the small nucleolar RNA *SNORD116* from the maternal chromosome in the cell model.

In a mouse deletion model of PWS, intraperitoneal injection of UNC0642 from postnatal day 7 onward improved survival (the majority of mice survived past 2 weeks and about 15% survived long term), growth and weight gain. Notably, the expression of *Snrpn* and *Snord116* was detectable in the brain and liver — two organs relevant to PWS pathogenesis. Importantly, there were no signs of toxicity. The compound also effectively activated maternal genes in an adult (6-week-old) mouse model of PWS.

Finally, the authors investigated the mechanisms that mediate the effects of UNC0638 and UNC0642. Using a combination of bisulfite genomic sequencing and chromatin immunoprecipitation and accessibility assays, the compounds were shown to reduce dimethylation of histone H3 lysine 9 at the PWS-IC without changing DNA methylation, which resulted in more open chromatin across the imprinted region.

These findings provide a proof of principle to develop small-molecule-based epigenetic therapy for PWS, and further investigation of G9a inhibitors is warranted.

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ORIGINAL ARTICLE Kim, Y. *et al.* Targeting the histone methyltransferase G9a activates imprinted genes and improves survival of a mouse model of Prader–Willi syndrome. *Nat. Med.* http://dx.doi.org/10.1038/nm.4257 (2016)