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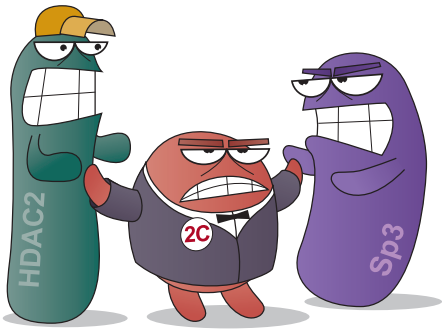
ALZHEIMER DISEASE

Blocking HDAC2–Sp3 interaction — a new approach to AD therapy?



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Upregulation of histone deacetylase 2 (HDAC2) has been linked to impaired synaptic plasticity and cognitive impairment in Alzheimer disease (AD), and blockade of this enzyme is being explored as a therapeutic strategy for AD. However, the currently available HDAC inhibitors lack selectivity for HDAC2, and carry a high risk of adverse effects. Now, a research team at the Massachusetts Institute of Technology has found a way of specifically targeting HDAC2 by disrupting its interaction with another protein, Sp3.

"We took the novel approach of trying to identify DNA-binding proteins that are required for recruitment of HDAC2 to synaptic plasticity-associated genes," explains co-first author Jay Penney. "We reasoned that if we could identify such a protein, blocking its interaction with HDAC2 could override the negative effects of overexpressed HDAC2 in AD model mice, and potentially also in humans."

The researchers used a bioinformatics approach known as weighted gene co-expression network analysis (WGCNA) to identify genes encoding proteins that could potentially bind to HDAC2 and modulate its effects on synaptic plasticity. The WGCNA screens uncovered several candidate proteins, including the transcription factor Sp3.

The team used co-immunoprecipitation and western blotting analyses to demonstrate that Sp3 could physically interact with HDAC2. The Sp3-binding domain on HDAC2 — termed 2C — was localized to the carboxyl terminus. The two proteins were shown to regulate a similar subset of genes, many of which were associated with synaptic plasticity.

"Our goal was to identify a mechanism that could prevent HDAC2-mediated inhibition of synaptic gene expression in the context of neurological disease, so we next attempted to block the HDAC2–Sp3 interaction," says Penney. "We surmised that overexpression of the 2C fragment ought to inhibit binding between endogenous HDAC2 and Sp3, thereby antagonizing HDAC2 recruitment to synaptic plasticity-associated genes."

Through *in vitro* experiments, the researchers confirmed that the 2C domain could perturb the recruitment of HDAC2 to the promoters of synaptic genes, presumably by sequestering Sp3. Moreover, in the CK-p25 mouse model, which recapitulates many of the features of AD, overexpression of 2C restored synaptic plasticity and enhanced cognitive function.

> "overexpression of 2C restored synaptic plasticity and enhanced cognitive function"

"We are testing the ability of a number of HDAC2-derived peptides to disrupt the HDAC2–Sp3 interaction, and we are also interested in identifying small molecules that can inhibit this interaction," comments Penney. "We feel that these approaches hold considerable promise for developing an AD therapeutic that could improve cognitive function in patients with this devastating disease."

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ORIGINAL ARTICLE Yamakawa, H. *et al.* The transcription factor Sp3 cooperates with HDAC2 to regulate synaptic function and plasticity in neurons. *Cell Rep.* **20**, 1319–1334 (2017)