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NEUROBLASTOMA

As a matter of FACT

> FACT inhibition with the small-molecule inhibitor CBL0137 … delayed tumour growth

Up-regulation of the MYC homologue MYCN is a well-known hallmark of neuroblastoma — a devastating childhood malignancy of the sympathetic nervous system. But drugging MYC itself has proved to be maddeningly challenging, so efforts have focused on targeting downstream targets of MYC.

With this in mind, a team led by Glenn M. Marshall and Michelle Haber re-examined a cluster of genes known to be upregulated in *MYCN*-amplified neuroblastoma. The histone chaperone FACT (facilitates chromatin transcription) immediately piqued their interest, because of its known involvement in several cancer types. FACT is a transcription elongation factor that comprises the structure-specific recognition protein 1 (SSRP1) and the protein SUPT16H subunits. Knowing that it accumulates at the *MYC* promoter in fibrocarcinoma cells, the authors asked whether FACT regulated *MYCN* expression. Obliterating SSRP1 and SUPT16H expression using small interfering RNA (siRNA) led to a marked decrease in MYCN transcript and protein levels. Moreover, cycloheximide chase experiments revealed that knockdown of either SSRP1 or SUPT16H decreased the half-life of MYCN, suggesting that FACT regulates MYCN both transcriptionally and post-translationally.

As their data suggested a positive feedback loop between FACT and MYCN, the authors next probed the consequences of FACT inhibition. Using mice that express *MYCN* from the tyrosine hydroxylase (*TH*) promoter (*TH-MYCN*$^{+/+}$ mice), which develop a disease that closely resembles human neuroblastoma, the group showed that FACT inhibition with the small-molecule inhibitor CBL0137 — a curaxin-based agent that targets the FACT complex — delayed tumour growth when delivered perinatally. Tumours that did develop contained a higher number of ganglion-like cells, leading the team to speculate that CBL0137 might induce differentiation in neuroblasts that persists after birth.

What about established disease? Intravenous administration of the inhibitor attenuated tumour growth in *TH-MYCN*$^{+/+}$ mice with advanced tumours. Not only did CBL1037 lead to long-term regression of established tumours, it also blocked the development of lung metastases. Furthermore, combining CBL0137 with clinically relevant chemotherapy regimens significantly delayed tumour formation in *TH-MYCN*$^{+/+}$ mice, and the authors noted that the drug combinations were generally well tolerated.

How was FACT inhibition mediating this robust antitumour effect? FACT has been implicated in the cellular response to genotoxic stress, so the authors asked whether CBL0137 affected DNA repair following exposure to chemotherapeutic agents. They discovered that FACT inhibition increased the DNA damage markers phosphorylated histone H2AX (γH2AX) and p53 binding protein 1 (53BP1; also known as TP53BP1) after treatment with etoposide and hydroxyurea, but not after vincristine treatment. On the basis of their results, the authors posit that CBL0137 might potentiate the effects of genotoxic agents rather than microtubule poisons, although this will need to be confirmed experimentally.

Neuroblastoma is a highly metastatic disease — often presenting at an advanced stage — so these results might be the first step towards a new treatment strategy for this malignancy. Time will tell whether this turns out to be the case.

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