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Study of Rare Cancer Yields Therapeutic Clues to Combat Drug Resistance

Results point to combination therapy for patients with NUT midline carcinoma; may apply to other forms of cancer

Boston, MA — Stephen Elledge, PhD, and his team did not set out to find therapies that could render tumors less resistant to therapy or make existing drugs more potent against a rare form of cancer. But these are precisely the clinical insights that their most recent study has yielded.

Elledge, together with his graduate student Sida Liao, set out to explore cancer drivers that allow NUT midline carcinoma – a rare, aggressive cancer that can arise in multiple organs – to become impervious to drugs.

Their results, published recently in *Genes & Development*, may apply to several forms of cancer fueled by the same mutated driver gene, and their approach may be applicable to other types of cancer whose genomes have been sequenced.

“Our idea here was to take a cancer that’s dependent on a particular gene, turn that gene off, and see what replaces it,” said Elledge, Gregor Mendel professor of Genetics and of Medicine at Brigham and Women's Hospital and Harvard Medical School.

That idea led to new biological insights, which in turn led to preclinical work that has set the stage for a clinical trial for patients with NUT midline carcinoma.

“We always hope that our findings will turn into something that can help people. We hope that this is the case here,” Elledge said.

NUT midline carcinoma affects fewer than 100 people in the United States each year, with an average patient survival of 9.5 months. Most cancers have many genetic mutations and rearrangements that shuffle some of the pieces of the genome, turning on molecular machinery that shouldn’t be active. In the case of NUT midline carcinoma, there is only one chromosomal abnormality: the *NUTM1* gene breaks off and fuses with a partner gene. In about three-quarters of cases, NUTM1 fuses to a BET protein. Today, patients with this form of NUT midline carcinoma can be treated with bromodomain and extraterminal domain inhibitors (BETi), which interfere with BET proteins.

BET inhibitors are currently being evaluated in clinical trials. However, cancer cells can develop resistance against the drug through a variety of mechanisms. Elledge and colleagues set out to identify these mechanisms. To do so, they used gene editing tools to meticulously look at the effects of a list of cancer drivers previously identified by the lab. They uncovered six general classes, or families, of genes that appeared to help drive cancer resistance to BET inhibitors. In particular, they found evidence that genes targeted by another class of drugs – known as CDK4/6 inhibitors – seemed to be involved in resistance. In preclinical experiments carried out in the lab and in animal models, combining pre-clinical versions of the two drugs – BET inhibitors and CDK4/6 inhibitors – completely stopped tumors from growing.

In addition to NUT midline carcinoma, BET inhibitors are currently being explored as a treatment of certain leukemias and multiple myeloma. More broadly, the approach of using a list of cancer drivers predicted by the algorithm TUSON Explorer, which relies on data from fully sequenced cancer genomes, could bring to light the drivers of resistance for other cancer types.

For patients with NUT midline carcinoma and clinical experts in the field, the results also represent hope for better clinical trial design and outcomes.

“These findings come at a crucial time for this aggressive lethal orphan cancer, especially after BET inhibitors that directly target BRD4-NUT have uniformly failed to be curative in recent trials,” said Christopher French, MD, of the BWH Department of Pathology, who studies NUT midline carcinoma. “The Elledge lab discovery provides a scientifically rational direction to improve the efficacy of BET inhibitors, by combination with CDK4/6 inhibitors. I think you will see the impact of their findings in the next round of BET-inhibitor based clinical trials for this disease and others.”

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