DRUG RESISTANCE

Overcoming resistance in acute myeloid leukaemia treatment

Resistance to the acute myeloid leukaemia (AML) therapy cytarabine (Ara-C) is a major therapeutic challenge in the treatment of this disease. A previous study from the Borden laboratory had shown that treatment of AML in a Phase II trial with the eukaryotic translation initiation factor 4E (eIF4E) inhibitor ribavirin produced effective initial responses, including remission in patients who had relapsed after Ara-C treatment, but all patients eventually developed resistance and relapsed. A new study from the same group, by Zahreddine and colleagues, has shown that this resistance to both drugs is due to the sonic hedgehog (SHH) pathway transcription factor glioma-associated oncogene (GLI1).

To investigate the mechanism underlying this resistance, the authors generated resistant cancer cell lines by prolonged treatment with ribavirin. Examination of the transcriptome of these resistant cells showed upregulation of *GLI1* mRNA. Similarly, nine of nine patients from the ribavirin trial who had relapsed had increased GLI1 mRNA and protein levels. Furthermore, analysis of AML samples from The Cancer Genome Atlas showed that increased *GLI1* expression is consistently associated with poor prognosis in AML.

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Can GLI1 be directly targeted to resensitize cells to ribavirin or Ara-C? Pretreatment of resistant cells with the drug GDC-0449, which inhibits SHH signalling upstream of GLI1, prior to ribavirin or Ara-C treatment caused a 60% reduction in growth compared with cells that were not pretreated with GDC-0449.

What is the molecular mechanism that underlies resistance to ribavirin and the restoration of sensitivity with GDC-0449? Immunoprecipitation experiments showed that eIF4E could bind to ribavirin in control cells but this interaction was lost in cells that overexpressed GLI1. Furthermore, treatment of resistant cell lines with GDC-0449 or GLI1 knockdown restored eIF4E–ribavirin complex formation. The authors hypothesized that GLI1-dependent modification of ribavirin might prevent complex formation. As protein levels of the UDP glucuronosyltransferase (UGT1A) protein family were also elevated in ribavirin-resistant and Ara-C-resistant cells, and as UGT1As are known to modify drug activity by the addition of glucuronic acid (glucuronidation), the authors examined the potential role of UGT1As in further detail. Protein levels of UGT1As were reduced with knockdown of GLI1 or inhibition by GDC-0449. However, as GLI1 did not affect *UGT1A* mRNA levels, the authors proposed that GLI1 affects the stability of UGT1A. These results correlated with the clinical data — patients with AML who had relapsed after either Ara-C or ribavirin treatment had increased UGTA1 levels in addition to elevated GLI1 levels. Furthermore, mass spectrometry analysis showed that both ribavirin and Ara-C were glucuronidated in resistant cells but not in parental cells, and glucuronidation was lost in resistant cells following treatment with GDC-0449.

Collectively, although the sample sizes in this study are small, and further work is required, these results highlight GLI1 and, more generally, the SHH pathway as a potential therapeutic target to counter resistance to Ara-C and ribavirin in AML.

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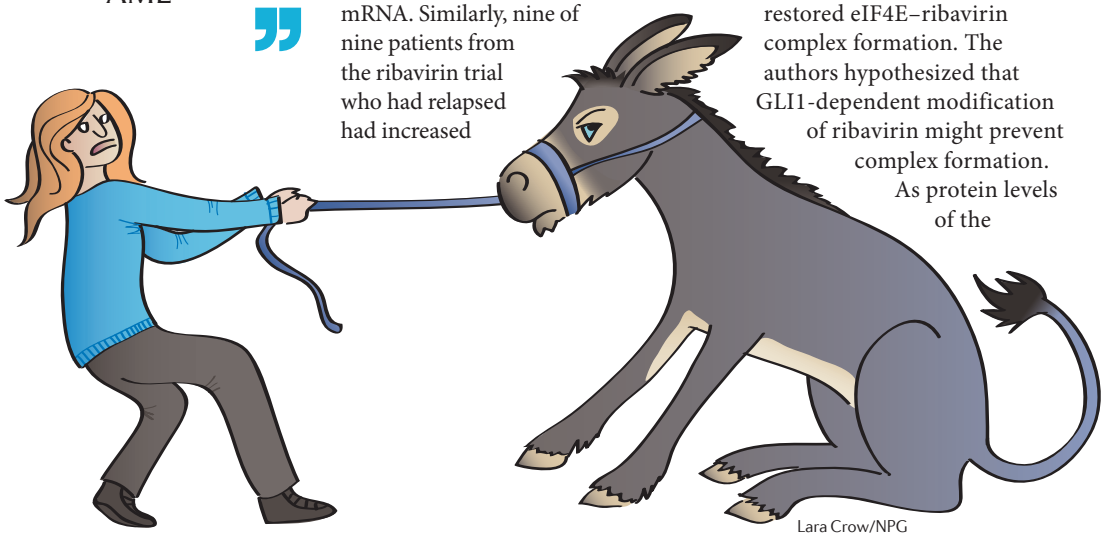

Lara Crow/NPG

ORIGINAL RESEARCH PAPER Zahreddine, H. A. *et al.* The sonic hedgehog factor GLI1 imparts drug resistance through inducible glucuronidation. *Nature* http://dx.doi.org/10.1038/nature13283 (2014)

FURTHER READING Assouline, S. *et al.* Molecular targeting of the oncogene eIF4E in acute myeloid leukemia (AML): a proof-of-principle clinical trial with ribavirin. *Blood* **114**, 257–260 (2009)