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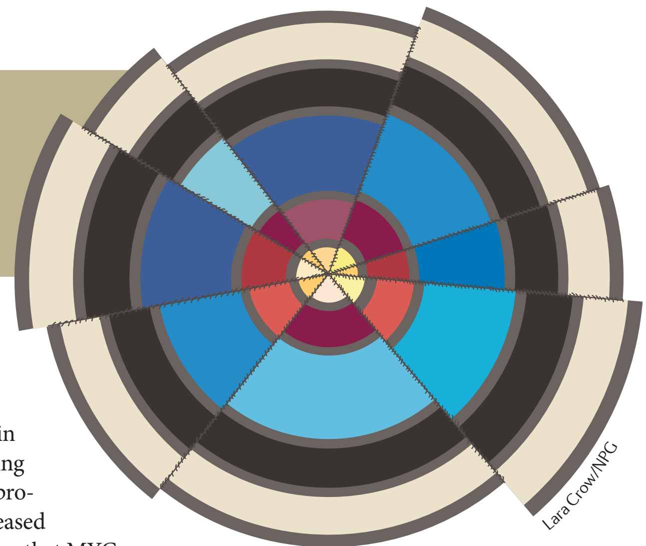
MYC

Splicing up your survival


Lara Crow/NPG

Finding therapeutic vulnerabilities in tumour cells that exhibit hyperactive MYC could improve cancer treatment as MYC is altered — and is functionally important — in many cancer types.

To identify mechanisms by which tumour cells are able to tolerate hyperactive MYC, Westbrook and colleagues had previously carried out a genome-wide short hairpin RNA (shRNA) screen in human mammary epithelial cells (HMECs) that inducibly express MYC. MYC expression and knockdown of BUD31 consistently resulted in synthetic lethality in HMECs, which underwent apoptosis, and reduced clonogenic proliferation compared with controls.

To find out more about the role of BUD31 in supporting the survival of cells with hyperactive MYC, the authors undertook immunoprecipitation of tagged BUD31 and found that several spliceosome subcomplexes were bound to it. In fact, 79 of 134 core spliceosome components were bound by BUD31, indicating that BUD31 is involved in several stages of RNA splicing. They also showed that BUD31 knockdown significantly inhibited pre-mRNA splicing *in vitro* and abrogated early spliceosome assembly.

To assess whether the role of BUD31 in splicing was responsible for the survival of MYC-expressing HMECs the authors carried out an *in vitro* competition assay and showed that the reduced proliferation of MYC-expressing breast cancer cells in which BUD31 was knocked down was not rescued by the expression of mutant BUD31 that is unable to bind spliceosome factors.

In addition, knockdown of several splicing factors, such as SF3B1 and U2AF, in MYC-overexpressing cells also reduced proliferation and increased apoptosis, indicating that MYC hyperactivation results in a reliance on RNA splicing for survival and proliferation.

Spliceosome perturbation in HMECs with hyperactive MYC increased intron retention in 42% of the genes analysed. Because MYC has been shown to promote pre-mRNA synthesis, the authors hypothesized that increased cellular pre-mRNA heightens the reliance on spliceosome activity for mRNA maturation. However, when BUD31 (or other spliceosome components) are knocked down — and thus their expression is reduced to a hypomorphic state — these cells are unable to maintain mRNA homeostasis. Indeed, spliceosome inhibition in MYC-hyperactive cells led to defective pre-mRNA maturation and stability, consistent with the idea that mRNAs with retained introns are unlikely to mature. Many of these genes for which corresponding RNAs had increased intron retention were involved in essential cellular processes. This dysregulation of essential cellular processes may account for the loss of viability of MYC-expressing cells in which BUD31 is knocked down.

Can RNA splicing be therapeutically targeted? A genome-wide RNA interference (RNAi) screen in 72 breast cancer cell lines revealed that those cell lines that were sensitive to MYC knockdown were also significantly sensitive to knockdown of spliceosome components. Using the MYC-dependent breast cancer cell line MDA-MB-231-LM2, the authors carried out pooled competition assays *in vivo* by injecting cells expressing inducible shRNAs into the flanks of nude mice. Cells expressing MYC shRNA or cells in which spliceosome components (including BUD31 and SF3B1) were knocked down were not retained in primary tumours or lung metastases. Moreover, treatment of mice bearing MDA-MB-231-LM2 xenografts with SD6 (a small-molecule inhibitor of SF3B1) restrained tumour growth without causing toxicity, and SD6 treatment also reduced lung metastasis from tail vein injection of MDA-MB-231-LM2 cells.

These experiments were carried out with RNAi and so the spliceosome is not eliminated, which is expected to be lethal for all cell types. Therefore, the authors have identified a selective hypersensitivity of tumour cells that have a dependency on MYC for proliferation and survival.

Gemma K. Alderton

“the authors have identified a selective hyper-sensitivity of tumour cells that have a dependency on MYC”

ORIGINAL RESEARCH PAPER Hsu, T. Y.-T. *et al.* The spliceosome is a therapeutic vulnerability in MYC-driven cancer. *Nature* http://dx.doi.org/10.1038/nature14985 (2015)

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