IN BRIEF

CANCER

Overcoming chemoresistance

Mutagenic translesion synthesis (TLS) contributes to the development of chemoresistance and represents an attractive therapeutic target for improving chemotherapeutics. Using a small-molecule screen, Wojtaszek et al. identify a 1,4-dihydroquinolin-4-one derivative, JH-RE-06, as a potent inhibitor of TLS. JH-RE-06 induces dimerization of the mutagenic DNA polymerase REV1, thereby blocking recruitment of the mutagenic DNA polymerase ζ. JH-RE-06 sensitized mouse and human cell lines to cisplatin, and its combination with cisplatin suppressed tumour growth of xenograft human melanomas in mice and increased survival.

ORIGINAL ARTICLE Wojtaszek, J. L. et al. A small molecule targeting mutagenic translesion synthesis improves chemotherapy. *Cell* https://doi.org/10.1016/j.cell.2019.05.028 (2019)

FIBROSIS

Blocking hyaluronan synthesis

The extracellular matrix glycosaminoglycan hyaluronan (HA) is a biomarker for cirrhosis, but its role in the development of liver fibrosis is undefined. Yang et al. report that HA and HA synthase 2 (HAS2) are overexpressed in hepatic stellate cells (HSCs) in human and mouse fibrotic livers. In mice, deletion of HAS2 in HSCs reduced HA production and liver fibrosis, whereas HAS2 overexpression promoted liver fibrosis. Investigation of downstream effectors of HAS2 identified NOTCH1 as a mediator of HSC activation and liver fibrosis. Inhibiting HA production with oral 4-methylumbelliferone treatment reduced HSC activation and liver fibrosis in mice.

ORIGINAL ARTICLE Yang, Y. M. et al. Hyaluronan synthase 2-mediated hyaluronan production mediates Notch1 activation and liver fibrosis. *Sci. Transl Med.* **11**, eaat9284 (2019)

DRUG SCREENING

Body-on-a-chip for anticancer drug testing

Recent advances in biomedical engineering have led to the development of body-on-a-chip multi-organ systems. McAleer et al. have designed a reconfigurable five-chamber multi-organ system — which uses recirculating serum-free medium to mimic blood circulation and functional biological micro-electromechanical systems for monitoring drug effects — to simultaneously investigate anticancer drug efficacy and off-target toxicity. In two models incorporating an array of cancer and healthy human cell types, the system provided insight into the efficacy and toxicity of diclofenac, imatinib and tamoxifen.

ORIGINAL ARTICLE McAleer, C. W. et al. Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics. *Sci. Transl Med.* **11**, eaav1386 (2019)

RARE DISEASES

Epigenetic mechanism of systemic sclerosis

The pathogenic mechanism of systemic sclerosis (SSc), an autoimmune disease that results in progressive fibrosis of connective tissue, remains unknown. Here, Shin et al. report that constitutive epigenetic activation of a novel enhancer of transforming growth factor-β2, which regulates collagen synthesis and deposition in the extracellular matrix, locks lesional fibroblasts from patients with SSc in a profibrotic state, through a BRD4 and NF-κB-dependent mechanism. Treatment of SSc patient-derived skin explants with the bromodomain inhibitor JQ1 repressed collagen synthesis and reversed fibrosis.

ORIGINAL ARTICLE Shin, J. Y. et al. Epigenetic activation and memory at a TGFB2 enhancer in systemic sclerosis. *Sci. Transl Med.* **11**, eaaw0790 (2019)

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CANCER

PROTAC moves in on lymphoma

For patients with diffuse large B cell lymphoma (DLBCL) that becomes refractory to standard therapy, outcomes are poor. Jain and colleagues analysed DNA copy number and gene expression, and found that transcription factor 4 (TCF4) drives the hyperactive signalling in activated B cell (ABC)-like DLBCL. Reducing TCF4 levels by targeting TCF4-inducing proteins, using small molecules or a proteolysis-targeting chimaera (PROTAC), reduced DLBCL tumour growth and prolonged survival in mice.

To pinpoint genetic alterations in ABC-like DLBCL, Jain and colleagues integrated multiple data sets and found that copy number gains at 18q21.2 and 18q22.1 are the most frequent genetic alterations. Gene expression profile data from tumours suggested that *TCF4* and *BCL2* are the most frequently amplified and overexpressed genes in these aberrations.

The authors then investigated which targets of TCF4 contribute to oncogenesis. Primary ABC-like DLBCL tumours with an increase in *TCF4* copy number showed higher expression of the immunoglobulin μ (IgM) heavy chain locus compared with tumours without *TCF4* amplification, and TCF4 occupied regions in the immediate vicinity of the *IGHM* locus. ABC-like DLBCL cells are known to have constitutively active signalling from the B cell receptor (BCR), likely because of increased levels of IgM, which forms part of the BCR.

Inducible overexpression of TCF4 increased the levels of IgM transcripts and protein. When BCR was stimulated with a cross-linking antibody, TCF-induced IgM expression increased downstream BCR signalling events in DLBCL cell lines. Dominant-negative TCF4 constructs, which interfere with TCF4-mediated transcription, decreased IgM expression and reduced the capacity of DLBCL cell lines to compete with parental strains.

TCF4 is itself subject to transcriptional control. *TCF4* was loaded with bromodomain-containing 4 (BRD4), and knockdown of BRD4 reduced TCF4 expression. The authors used two strategies to alter BRD4 levels: the small-molecule inhibitors JQ1 and OTX015, which inhibit BRD4 and the other bromodomain and extra-terminal motif (BET) family members, and ARV-771, a BRD4-directed PROTAC. Both approaches reduced TCF4 and IgM levels in DLBCL cell lines; ARV-771 also induced apoptosis.

Importantly, in mouse xenograft models using two DLBCL cell lines with *TCF4* copy number gain, daily subcutaneous injections of ARV-771 reduced tumour growth and increased survival.

BET inhibitors have been investigated for their therapeutic potential but most have adverse effects in preclinical studies, possibly because they target multiple proteins. Using a TCF4-specific PROTAC or developing a TCF4-specific small molecule may overcome this issue and lead to a therapy for patients with refractory DLBCL. The first PROTAC to enter the clinic, which targets the androgen receptor, began a phase I trial earlier this year.

Megan Cully

ORIGINAL ARTICLE Jain, N. et al. Targetable genetic alterations of TCF4 (E2-2) drive immunoglobulin expression in diffuse large B cell lymphoma. *Sci. Transl Med.* **11**, eaav5599 (2019)

FURTHER READING Mullard, A. First targeted protein degrader hits the clinic. *Nat. Rev. Drug Discov.* **18**, 237–239 (2019) | Lai, A. C. & Crews, C. M. Induced protein degradation: an emerging drug discovery paradigm. *Nat. Rev. Drug Discov.* **16**, 101–114 (2017)