IN BRIEF

CANCER

Targeting the epitranscriptome in AML

Fat-mass and obesity-associated protein (FTO) is a major mRNA N^6-methyladenosine demethylase, which is overexpressed in certain subtypes of AML and can promote leukaemogenesis. Using structure-based rational design, Huang et al. identify a potent and selective small molecule FTO inhibitor, FB23-2, which suppressed proliferation and promoted differentiation of AML cells. In a patient-derived AML mouse model, intraperitoneal administration of FB23-2 delayed disease progression and prolonged survival.

ORIGINAL ARTICLE Huang, Y. et al. Small-molecule targeting of oncogenic FTO demethylase in acute myeloid leukemia. *Cancer Cell* **35**, 677–691 (2019)

INFECTIOUS DISEASE

Selectively targeting antibiotic-resistant bacteria

Targeted antimicrobials, capable of killing antibiotic-resistant bacteria (ABR), are urgently needed. To target ABR *Vibrio cholerae*, López-Igual et al. designed a conjugative antimicrobial plasmid containing a type II bacterial gyrase toxin, split by an intein (to control toxin production and avoid toxicity), which can only be activated by ToxR (a transcriptional activator in *V. cholerae*). Specific killing of ABR was mediated by inclusion of the antitoxin in the plasmid, which is not produced if the bacteria express antibiotic resistance genes. The antimicrobial selectively killed pathogenic ABR *V. cholerae* in a mixed population of bacteria and in zebrafish and crustacean larvae.

ORIGINAL ARTICLE López-Igual, R. et al. Engineered toxin–intein antimicrobials can selectively target and kill antibiotic-resistant bacteria in mixed populations. *Nat. Biotech.* https://doi.org/10.1038/s41587-019-0105-3 (2019)

CANCER

Improving safety and efficacy of immunotherapeutics

Immune checkpoint inhibitors (CPIs) and interleukin-2 (IL-2) have demonstrated clinical efficacy in cancer, but can cause severe off-target adverse events. Ishihara et al. exploit the leakiness of the tumour vasculature and the high presence of collagen in the tumour stroma to target CPI and IL-2 directly to the tumour, through the respective conjugation or fusion to the collagen binding domain (CBD) of the blood protein von Willebrand factor. In mouse models, the CBD-modified agents accumulated in the tumour, increased tumour-infiltrating $CD8^+$ T cells and exerted greater suppression of tumour growth compared with their unmodified forms, without toxicity.

ORIGINAL ARTICLE Ishihara, J. et al. Targeted antibody and cytokine cancer immunotherapies through collagen affinity. *Sci. Transl Med.* **11**, eaau3259 (2019)

METABOLIC DISORDERS

Reversing obesity and diabetes

The fat mass and obesity-associated gene (*FTO*) has been implicated in metabolic disorders, but precisely how FTO is involved in metabolic regulation remains unknown. Through a structure-based virtual screen of FDA-approved drugs, Peng et al. identify the Parkinson's disease treatment, entacapone, as a potent FTO inhibitor. In mouse models of obesity and diabetes, entacapone reduced body weight and fasting blood glucose levels. Mechanistically, FTO demethylated m6A sites on forkhead box protein O1 mRNA to up-regulate expression, thereby modulating gluconeogenesis and thermogenesis.

ORIGINAL ARTICLE Peng, R. et al. Identification of entacapone as a chemical inhibitor of FTO mediating metabolic regulation through FOXO1. *Sci. Transl Med.* **11**, eaau7116 (2019)

REGENERATIVE MEDICINE

Epigenetic route to recovery for spinal cord injury

Damage to the spinal cord typically results in permanent neurological impairments. Writing in *Science Translational Medicine*, Di Giovanni, Courtine and colleagues report that a small-molecule activator of CREB-binding protein (CBP) promotes axon regeneration in rodent models of spinal cord injury (SCI), enabling recovery of sensory and motor functions.

Modulation of neuronal activity with electrical stimulation and rehabilitative training can augment neuroplasticity and recovery in animal models and humans after SCI, but the underlying mechanisms remain poorly understood. To investigate this further, Di Giovanni, Courtine and colleagues used environmental enrichment (EE) — stimulation of the brain by its physical and social surroundings, mimicking an active lifestyle — as a means to physiologically increase neuronal activity in mice.

First, the authors observed that sciatic dorsal root ganglion (DRG) neurons cultured from mice exposed to EE for 10 days showed enhanced neurite outgrowth, which was maintained when the mice were returned to standard housing. Furthermore, pre-exposure of mice to EE before an SCI promoted nerve regeneration, leading to increased conduction through the lesion site. Further studies specifically implicated proprioceptive DRG neurons in EE-dependent regenerative growth.

RNA sequencing and proteomics analyses revealed that EE induced signalling pathways involved in neuronal activity, calcium mobilization and the regenerative programme in proprioceptive DRG neurons.

Analysis of markers of histone acetylation and methylation, which are important in the regulation of gene expression, revealed that EE enhanced the acetylation of two specific histones (H3K27 and H4K8) in DRG neurons. The acetylation of these two histones can be mediated by CBP: EE increased phosphorylated CREB and active acetylated CBP in DRG neurons in mice. Furthermore, deletion of CBP in DRG neurons in mice abolished the EE-dependent increase in neurite outgrowth, suggesting that CBP specifically contributes to the increased regenerative potential of DRG neurons after EE exposure.

Credit: SCIEPRO/Science Photo Library/GettyLimited

Next, the authors investigated the therapeutic potential of a small-molecule activator of CBP — TTK21, conjugated to glucose-derived carbon nanospheres (CSPs; to enable crossing of the blood–brain barrier).

In cultured DRG neurons, CSP-TTK21 increased neurite outgrowth and H4K8 acetylation and reduced neurite branching. In mice subjected to an SCI, weekly intraperitoneal administration of CSP-TTK21 for 6 weeks, beginning 4 hours after injury, increased H4K8 acetylation within DRG neurons and promoted sensory axon regeneration and sensorimotor recovery. Similarly, CSP-TTK21 treatment beginning 6 hours after SCI in rats enhanced sprouting of both descending motor and ascending sensory axons, leading to functional recovery.

These findings reveal an epigenetic-based mechanism underlying activity-dependent neuronal plasticity and highlight CBP activation as a promising novel approach to enhance recovery after SCI. The authors hope to next study the combined effect of CSP-TTK21 and neurorehabilitation on recovery from SCI, as well as assess the drug in non-human primates.

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ORIGINAL ARTICLE Hutson, T. H. et al. Cbp-dependent histone acetylation mediates axon regeneration induced by environmental enrichment in rodent spinal cord injury models. *Sci. Transl Med.* **11**, eaaw2064 (2019)