RESEARCH HIGHLIGHTS

IN BRIEF

INFLAMMATION

Gasdermin D inhibitor protects against sepsis

Gasdermin D (GSDMD) is the final common effector of inflammasome activation, forming membrane pores to enable pro-inflammatory cytokine release and pyroptosis. Inhibiting GSDMD, therefore, represents a promising approach to treat inflammatory disorders. Through a high-throughput screen, Hu et al. identify disulfiram (used to treat alcohol addiction) as a potent inhibitor of GSDMD pore formation. In cells, disulfiram inhibited cytokine release and prevented pyroptosis. In mice, the drug protected from lethal lipopolysaccharide-induced septic shock. Mechanistically, disulfiram covalently modified Cys191 of human GSDMD to block pore formation.

ORIGINAL ARTICLE Hu, J. J. et al. FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation. *Nat. Immunol.* https://doi.org/10.1038/s41590-020-0669-6 (2020)

CIRCADIAN RHYTHM

Shortening jet lag recovery

Regulation of the circadian clock is essential to sleep and health and involves a core set of clock genes that regulate large gene transcription networks. Here, Ju et al. identify the adenosine analogue cordycepin as a circadian phase shifter. Cordycepin targeted RuvB-like ATPase 2 to disrupt its interaction with the core clock component BMAL1 and caused disassembly of a circadian regulatory super-complex, which enabled transcription of E-box-containing clock genes. Cordycepin induced a rapid 12 hour clock phase shift in human cells, mouse tissues and mice. In a mouse jet lag model, cordycepin penetrated the BBB and accelerated recovery.

ORIGINAL ARTICLE Ju, D. et al. Chemical perturbations reveal that RUVBL2 regulates the circadian phase in mammals. *Sci. Transl Med.* **12**, eaba0769 (2020)

🔁 MUSCULAR DYSTROPHY

Targeting CDK12 to treat DM1

In myotonic dystrophy type 1 (DM1), the causal CTG repeat sequence in the 3' untranslated region of the dystrophia myotonic protein kinase gene results in mutant repeat expansion transcripts, which form pathological nuclear foci. Using DM1 cells, Ketley et al. identify a group of compounds targeting cyclin-dependent kinases (CDKs) that reduce nuclear foci. In a mouse model of DM1, injection of the CDK inhibitor dinaciclib decreased mutant repeat transcripts and the number of cells containing nuclear foci, resulting in improved myotonia. These beneficial effects were due to inhibition of CDK12, which is elevated in muscle biopsies from patients with DM1.

ORIGINAL ARTICLE Ketley, A. et al. CDK12 inhibition reduces abnormalities in cells from patients with myotonic dystrophy and in a mouse model. *Sci. Transl. Med.* **12**, eaaz2415 (2020)

CARDIOVASCULAR DISORDERS

TRAIL blockade improves heart function

The expression of death receptor 5 (DR5) and its ligand TRAIL is elevated in patients with myocardial infarction (MI) and correlates with disease severity and outcome. However, the roles of DR5 and TRAIL in MI remain unknown. Here, Wang et al. demonstrate that DR5 is upregulated in the hearts of rats, minipigs and rhesus monkeys after ischaemia and reperfusion (I/R). Blocking TRAIL with a soluble DR5 immunoglobulin fusion protein in models of MI and I/R in these species improved cardiac function and decreased inflammation through prevention of TRAIL-induced cardiomyocyte death and cardiac myeloid cell recruitment.

ORIGINAL ARTICLE Wang Y. et al. Blocking the death checkpoint protein TRAIL improves cardiac function after myocardial infarction in monkeys, pigs, and rats. *Sci. Transl Med.* **12**, eaaw3172 (2020)



CANCER IMMUNOTHERAPY

Tumours use NETs as physical shields

An expansion of neutrophils in patients with cancer is usually associated with a poor prognosis. This is thought to be due to the ability of neutrophils to induce angiogenesis and mediate immunosuppression. Reporting in *Immunity*, Teijeira et al. now show that cancer cells can also subvert neutrophil functions by inducing the extrusion of neutrophil extracellular traps (NETs), which wrap around the tumour cells and protect them from T cell- or natural killer (NK) cell-mediated toxicity.

NETosis is a peculiar form of cell death that is unique to neutrophils and results in the extrusion of DNA-protein complexes. It is induced by various stimuli, including chemotactic cues. The authors show that chemokines that are secreted by tumour cells induce NETosis in human neutrophils. This was dependent on the chemokine receptors CXCR1 and CXCR2, as inhibitors of these receptors, such as reparixin and pertussis toxin or blocking antibodies against CXCR1, prevented NETosis induction.

To investigate the effects of NETs on tumour cells the authors created tumour spheroids from a colon carcinoma cell line and filmed their interactions with healthy donor allogeneic neutrophils. The spheroids induced NETosis, which was inhibited in the presence of reparixin. When tumour cell-targeted cytotoxic lymphocytes (CTLs) and/or NK cells were added, tumour cell spheroids with NETs showed much better survival than spheroids that had been stripped of their NETs with DNAse I.

In mice that received xenografted human tumour cell lines and human neutrophils, abundant NETs were detected in the tumours; however, these were reduced if the animals were treated with reparixin or pertussis toxin. Credit: S. Bradbrook/ Springer Nature Limited

The in vivo relevance of the protective role of NETs in tumours was demonstrated in mouse models of breast cancer (4T1) metastasis, where treatment of the animals with DNAse I or the PAD4 inhibitor GSK484, an inhibitor of NETosis, reduced the number of micrometastases. However, the treatment did not have any effect in mice that lacked both T cells and NK cells, confirming that NETs provide protection from these cells. In mice with established 4T1 tumours, treatment with GSK484 showed a synergistic effect with dual checkpoint inhibition (anti-PD1 and anti-CTLA4), and this was dependent on the presence of CTLs.

Further in vitro experiments, as well as intravital microscopy in mice injected with Lewis lung carcinoma (LLC) cells, demonstrated that NETs reduce the physical contact between tumour cells and cytotoxic lymphocytes.

This study shows that tumours induce the formation of NETs, which coat and thereby shield tumour cells against NK cell- and T cell-mediated cytotoxicity. Moreover, it indicates that inhibitors of NETosis may be of value in combination with checkpoint inhibitors.

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ORIGINAL ARTICLE Teijeira, A. et al. CXCR1 and CXCR2 chemokine receptor agonists produced by tumors induce neutrophil extracellular traps that interfere with immune cytotoxicity. *Immunity* https://doi.org/10.1016/j.immuni.2020.03.001 (2020)

FURTHER READING Németh, T., Sperandio, M. & Mócsai, A. Neutrophils as emerging therapeutic targets. Nat. Rev. Drug Discov. **19**, 253–275 (2020)