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IN BRIEF

ALZHEIMER DISEASE

Antimicrobial role of amyloid-β

The accumulation of amyloid-β (Aβ) in the brain is believed to have a pivotal role in Alzheimer disease (AD) pathology. Kumar *et al.* now provide *in vivo* evidence that Aβ may also perform a protective antimicrobial function. Genetically modified AD mouse models expressing Aβ were protected from *Salmonella enterica* subsp. *enterica* serovar Typhimurium meningitis infection, with mice exhibiting rapid seeding and accelerated Aβ deposition following exposure. Aβ expression in nematodes and cultured mammalian cells similarly increased host resistance to *Candida albicans* infection. The protective effects of Aβ appeared to be mediated by agglutination and entrapment of microbes by Aβ fibrils.

ORIGINAL ARTICLE Kumar, D. *et al.* Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. *Sci. Transl Med.* **8**, 340ra72 (2016)

DEPRESSION

Understanding ketamine action

(*RS*)-ketamine exerts rapid and robust antidepressant efficacy in patients, believed to be mediated by glutaminergic NMDA receptor antagonism. However, its potential for widespread clinical use is limited by its abuse liability and potential side effects. Here, Zanos *et al.* report that metabolism of (*RS*)-ketamine to (2*R*,6*R*)-hydroxynorketamine (HNK) is necessary and sufficient to exert antidepressant actions in mice. These antidepressant effects are NMDA receptor-independent but involve early and sustained activation of AMPA receptors. Importantly, (2*R*,6*R*)-HNK was not associated with ketamine-related side effects in mice.

ORIGINAL ARTICLE Zanos, P. *et al.* NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* **533**, 481–486 (2016)

DRUG DESIGN

Eliminating adverse effects of oestrogen therapy

Oestrogen replacement therapy can provide metabolic and vascular protection in postmenopausal women, but it can have deleterious actions in promoting breast and uterine cancers. Madak-Erdogan *et al.* have now developed structurally novel oestrogens termed 'pathway preferential oestrogens' (PaPEs), which interact with oestrogen receptors to activate the extranuclear-initiated signalling pathway preferentially over the nuclear-initiated pathway. In ovariectomized mice, PaPEs reduced body weight gain, decreased fat accumulation and accelerated repair of endothelial damage, without exhibiting stimulatory activity in reproductive tissues.

ORIGINAL ARTICLE Madak-Erdogan, Z. *et al.* Design of pathway preferential estrogens that provide beneficial metabolic and vascular effects without stimulating reproductive tissues. *Sci. Signal.* **9**, 429ra53 (2016)

AUTOIMMUNE DISEASE

Reversing systemic lupus erythematosus

The molecular mechanisms underlying the autoimmune disorder systemic lupus erythematosus (SLE) remain unknown. Here, Wang *et. al.* report that SH2 domain-containing protein tyrosine phosphatase (SHP2) activity is increased in lupus-prone MRL-*lpr* mouse spleen isolates and in peripheral blood mononuclear cells isolated from lupus patients. In MRL-*lpr* mice, SHP2 inhibition using the hydroxyindole carboxylic acid-based inhibitor 11a-1 increased life span, improved kidney function, reduced splenomegaly, diminished skin lesions, and also decreased T cell proliferation and production of SLE-associated cytokines. Moreover, 11a-1 reduced proliferation and cytokine production of cultured human lupus T cells.

ORIGINAL ARTICLE Wang, J. *et al.* Inhibition of SHP2 ameliorates the pathogenesis of systemic lupus erythematosus. *J. Clin. Inves.* **126**, 2077–2092 (2016)