Nature Reviews Drug Discovery | Published online 1 Oct 2018

IN BRIEF

METABOLIC DISEASE

Preventing fat uptake

Dietary fats are absorbed by enterocytes and incorporated into chylomicrons, which enter the bloodstream through specialized lymphatic capillaries known as lacteals. However, the molecular mechanisms controlling lacteal chylomicron uptake are unknown. Zhang et al. now demonstrate in mice that loss of the endothelial VEGFA receptors NRP1 and VEGFR1 increases VEGFA–VEGFR2 signalling, which induces lacteal junction zippering, resulting in chylomicron malabsorption. Consequently, the VEGFA receptor-deficient mice were resistant to high-fat diet-induced obesity.

ORIGINAL ARTICLE Zhang, F. et al. Lacteal junction zippering protects against diet-induced obesity. *Science* **361**, 599–603 (2018)

IMMUNOTHERAPY

Blocking T cell sequestration

Lymphopenia can be a side effect of cancer treatment and is particularly severe in patients with glioblastoma (GBM). Here, Chongsathidkie et al. report that T cell lymphopenia also occurs in treatment-naive subjects with GBM and in mouse glioma models, in conjunction with lymphoid organ contraction. The naive T cells were found to be sequestered in the bone marrow of both mice and subjects with GBM, directed by loss of T cell surface receptor S1P1. Hindering S1P1 internalization in mice abrogated T cell sequestration in bone marrow and synergistically increased survival when coupled with a T cell-activating therapy (a 4-1BB agonist antibody).

ORIGINAL ARTICLE Chongsathidkie, P. et al. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. *Nat. Med.* **24**, 1459–1468 (2018)

CANCER

Disrupting energy metabolism

Glioblastoma (GBM) stem cells have been implicated in tumour progression, treatment resistance and tumour recapitulation. Polson et al. therefore investigated the therapeutic effects of KHS101, which has been previously shown to promote neural differentiation. Unexpectedly, KHS101 was found to be cytotoxic in multiple patient-derived GBM cell lines, disrupting GBM cell energy metabolism and mitochondrial dynamics, promoting autophagy and apoptosis. In patient-derived xenograft mouse models of GBM, systemic KHS101 treatment reduced tumour growth and prolonged survival, without adverse effects.

ORIGINAL ARTICLE Polson, E. et al. KHS101 disrupts energy metabolism in human glioblastoma cells and reduces tumor growth in mice. *Sci. Transl Med.* **10**, eaar2718 (2018)

OBESITY

Blocking ceramide formation

Ceramide lipids have been implicated in the regulation of metabolic physiology. In particular, increased levels of the C-18 ceramide in muscle have been associated with impaired insulin action and increased visceral fat. Turner et al. identify the first isoform-selective ceramide synthase (CerS) inhibitor, P053, which specifically and potently targets CerS1 (responsible for C-18 ceramide formation), reducing C-18 ceramide levels in cultured cells and mouse skeletal muscle. In mice fed a high-fat diet, daily oral treatment with P053 promoted skeletal muscle fatty acid oxidation and reduced whole-body fat accumulation, without effects on insulin resistance.

ORIGINAL ARTICLE Turner, N. et al. A selective inhibitor of ceramide synthase 1 reveals a novel role in fat metabolism. *Nat. Commun.* **9**, 3165 (2018)