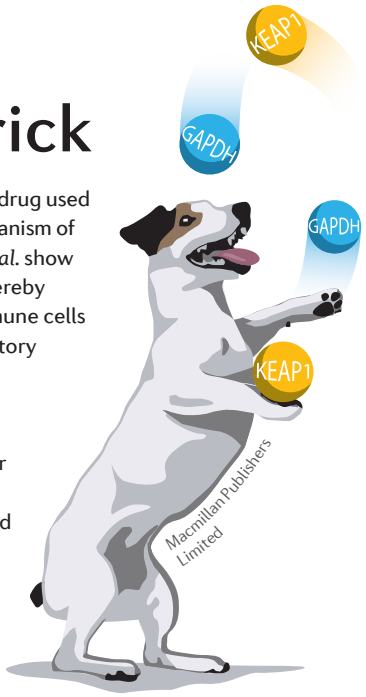
Nature Reviews Immunology | Published online 16 Apr 2018; doi:10.1038/nri.2018.29

IMMUNOMETABOLISM

Old drug, new trick

> an existing immuno-modulatory drug acts by inhibiting glycolysis



Dimethyl fumarate (DMF) is an immunomodulatory drug used to treat psoriasis and multiple sclerosis, but its mechanism of action is unclear. Reporting in *Science*, Kornberg *et al.* show that DMF blocks the glycolytic enzyme GAPDH, thereby downregulating aerobic glycolysis in activated immune cells and favouring their acquisition of an anti-inflammatory phenotype.

DMF is a derivative of the TCA cycle intermediate fumarate and is known to promote activation of the anti-oxidant transcription factor NRF2 (nuclear factor erythroid 2-related factor 2) through succination of cysteine residues in KEAP1 (kelch-like ECH-associated protein 1). However, activation of NRF2 alone does not account for all of the effects of DMF, prompting Kornberg *et al.* to explore other potential mechanisms of action. Endogenous fumarate can inactivate GAPDH by succinating a cysteine in the active site of the enzyme; therefore, the authors examined whether DMF and its major metabolite monomethyl fumarate (MMF) also target GAPDH. They found that MMF promoted monomethyl succination of the active site cysteine and two other cysteines in recombinant human GAPDH, whereas DMF induced a combination of dimethyl and monomethyl succination at the same three cysteine residues. Succination of the active site cysteine of GAPDH was also seen in mice treated with DMF and in peripheral blood mononuclear cells from patients with multiple sclerosis who had been treated with DMF.

This DMF-induced modification of the active site cysteine irreversibly inactivated GAPDH. However, DMF only impaired glycolysis significantly in activated macrophages and T cells, and not in resting cells. By contrast, DMF increased oxidative phosphorylation in both resting and activated macrophages. In agreement with previous work, inhibition of glycolysis by DMF inhibited pro-inflammatory cytokine production by activated macrophages and was associated with the acquisition of an 'M2-like' macrophage phenotype. Furthermore, in experiments where mouse $CD4^+$ T cells were polarized *in vitro*, DMF and MMF inhibited T helper 1 (T_H1) and T_H17 cell responses and promoted the differentiation of regulatory T cells. Finally, the authors showed that treatment with heptelidic acid (which inhibits GAPDH by binding to and covalently modifying its catalytic cysteine) replicated the anti-inflammatory effects of DMF on activated macrophages and T cells *in vitro*, and attenuated disease in a mouse model of experimental autoimmune encephalomyelitis.

There is currently much interest in developing new drugs to target immunometabolic pathways in inflammatory diseases; these findings are important as they show that an existing immunomodulatory drug acts by inhibiting glycolysis. The authors suggest that fumarate-mediated inactivation of GAPDH may represent a physiological negative feedback pathway that DMF, being more cell-permeable and electrophilic, is able to exploit.

Yvonne Bordon

ORIGINAL ARTICLE Kornberg, M. D. *et al.* Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity. *Science* https://doi.org/10.1126/science.aan4665 (2018)