lymphoma cells. Mice that received bone marrow but no T cells died as a result of uncontrolled tumour growth, whereas mice that received wild-type T cells along with bone marrow controlled tumour growth but died from severe GVHD. Strikingly, mice transplanted with bone marrow and *Csf2*$^{-/-}$ T cells controlled the lymphoma and were also protected from GVHD. Antibodies against GM-CSF had a similar effect in preventing GVHD without loss of the GVL response. Finally, the expression of GM-CSF and frequencies of GM-CSF-producing T cells were found to be increased in intestinal biopsies from patients who developed acute GVHD after HCT.

Although further work in humans is necessary, these findings suggest that GM-CSF could be targeted during allo-HCT to prevent potentially fatal GVHD while preserving the GVL response.

Yvonne Bordon

ORIGINAL ARTICLE Tugues, S. et al. Graft-versus-host disease, but not graft-versus-leukemia immunity, is mediated by GM-CSF-licensed myeloid cells. *Sci. Transl Med.* **10**, eaat8410 (2018)

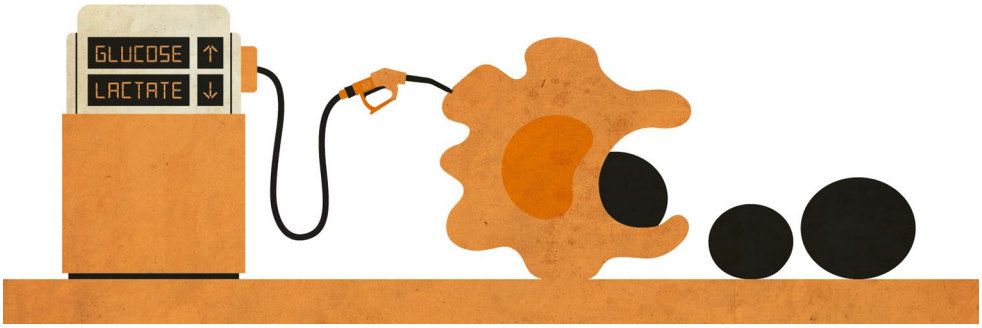
The central role of WNT10b production by CD8$^+$ T cells was further confirmed in T cell-deficient mice reconstituted with wild-type CD4$^+$ T cells and *Wnt10b*$^{-/-}$ CD8$^+$ T cells. In these mice, LGG or butyrate supplementation increased numbers of T_{reg} cells, but did not increase bone formation.

Co-culture experiments showed that T_{reg} cells can directly activate *Wnt10b* expression in CD8$^+$ T cells by producing TGFβ, which promotes the association of the transcription factor NFAT with SMAD3, a TGFβ signalling protein, in CD8$^+$ T cells. The authors showed that the NFAT–SMAD3 complex binds to the promoter region of *Wnt10b* and is critical for its transcription.

This study suggests that boosting T_{reg} cells with butyrate-enhancing probiotics may be a therapeutic strategy for conditions of bone loss, such as osteoporosis.

Alexandra Flemming

ORIGINAL ARTICLE Tyagi, A. M. et al. The microbial metabolite butyrate stimulates bone formation via T regulatory cell-mediated regulation of WNT10B expression. *Immunity* **49**, 1–16 (2018)



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PHAGOCYTES

Transporters help clear cell corpses

To ensure normal development and tissue homeostasis, dead cells must be removed by phagocytes through a process known as efferocytosis. This is a highly energetic process, requiring extensive actin polymerization to engulf large apoptotic cell corpses. A new study shows that efferocytosis is associated with a coordinated programme of expression of membrane transport proteins of the solute carrier (SLC) family, which mediate glucose uptake for enhanced glycolysis and lactate release for establishment of an anti-inflammatory environment.

RNA sequencing of phagocytes undergoing efferocytosis identified numerous changes in multiple transcriptional programmes. As expected, there was decreased expression of pro-inflammatory genes, increased expression of actin rearrangement genes and increased expression of anti-inflammatory genes, but there was also upregulation of glycolysis-associated genes and downregulation of genes required for oxidative phosphorylation (OXPHOS), fatty acid oxidation (FAO) and cholesterol synthesis. A notable change was in 33 genes encoding SLC proteins; 19 SLCs were upregulated (such as those involved in carbohydrate metabolism) and 14 SLCs were downregulated (such as those involved in OXPHOS and FAO). By contrast, macrophages undergoing antibody-mediated phagocytosis did not show expression changes in the same SLCs.

One SLC family member that was strongly upregulated during efferocytosis was SLC2A1 (also known as GLUT1), which mediates the transport of glucose into cells from the extracellular space. Treatment with an SLC2A1 inhibitor or knockdown of *Slc2a1* expression reduced corpse uptake by phagocytes in vitro and in vivo. In a mouse model of atherosclerosis (*Ldlr*$^{-/-}$ mice), mice with a myeloid cell-specific *Slc2a1* deletion showed a build-up of necrotic material in aortic roots when fed a high-fat diet, suggesting defective corpse clearance.

The role of SLC2A1 as a glucose transporter was shown to be required for efferocytosis, as switching cells to a glucose-free medium or pre-treating phagocytes with the non-metabolizable glucose analogue 2-deoxyglucose decreased efferocytosis. Consistent with the gene expression data, Seahorse analysis of cell metabolism showed increased aerobic glycolysis and concurrent suppression of OXPHOS in efferocytic phagocytes. Importantly, SLC2A1-mediated glucose uptake and induction of glycolysis was shown to contribute to actin polymerization during efferocytosis.

Efferocytosis involves three stages: 'smell', when factors released by apoptotic cells are sensed; 'taste', when phagocyte–apoptotic cell contact is established; and 'ingestion', when corpses are engulfed and processed. Morioka et al. showed that distinct steps of SLC2A1-dependent aerobic glycolysis were regulated by these different stages of efferocytosis. Apoptotic cell supernatant induced upregulation of *Sgk1* (which phosphorylates and promotes SLC2A1 plasma membrane expression); the find-me signal ATP also upregulated *Sgk1*; and the binding (without internalization) of apoptotic targets or phosphatidylserine liposomes to phagocytes induced *Slc2a1* expression.

Following corpse ingestion by phagocytes, there was an increase in expression of *Slc16a1*, which is a transporter for the glycolytic by-products lactate and pyruvate. Knockdown of *Slc16a1* expression or treatment with an SLC16A1 inhibitor reduced apoptotic cell uptake, with a concomitant reduction in lactate release and an accumulation of intracellular lactate. This reduction in lactate release was associated with an impaired ability to promote an anti-inflammatory M2-like macrophage phenotype.

So, coordinated regulation of select SLCs during efferocytosis provides the necessary metabolic programme for anti-inflammatory corpse clearance.

Lucy Bird

ORIGINAL ARTICLE Morioka, S. et al. Efferocytosis induces a novel SLC program to promote glucose uptake and lactate release. *Nature* **563**, 714–718 (2018)
FURTHER READING Poon, I. K. H. et al. Apoptotic cell clearance: basic biology and therapeutic potential. *Nat. Rev. Immunol.* **14**, 166–180 (2014)