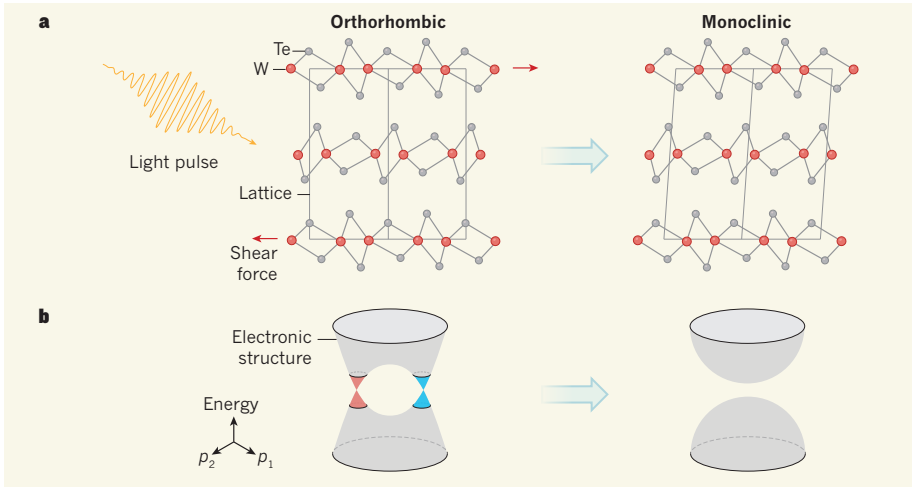

Figure 1 | Switching mechanism in a Weyl semimetal. a, Tungsten ditelluride (WTe_2) is an example of a material known as a Weyl semimetal. Sie *et al.*[3] report a transition in WTe_2 between two crystal structures: orthorhombic and monoclinic. The authors show that terahertz-frequency light pulses can transform the orthorhombic structure into the monoclinic one by altering the material's atomic lattice in a similar way to shear forces — pairs of equal and opposite forces that act on the top and bottom layers of the material. **b**, The dynamics of electrons in a solid can be described by a particular structure in phase space (the space of all possible energy and momentum values). Shown here are highly simplified electronic structures, in which only two components of momentum (p_1 and p_2) are considered. In orthorhombic WTe_2, electrons can behave as massless particles called Weyl fermions that have a chirality (handedness) of −1 (red) or +1 (blue). In monoclinic WTe_2, these states of opposite chirality can annihilate each other.

inversion symmetry is preserved in the monoclinic structure, and the states of opposite chirality can annihilate each other. The two crystal structures have almost the same atomic lattice, except that the monoclinic one is tilted by about 4° with respect to the out-of-plane direction of the orthorhombic one.

Owing to the weak attractive force between the layers of the $MoTe_2$ and WTe_2 compounds, each layer can slide easily, unlike in ordinary materials. As a result, shear forces — pairs of equal and opposite forces that act on the top and bottom layers — can deform the orthorhombic structure into the monoclinic structure, and therefore the Weyl-semimetal phase into a normal phase. Applying such forces in a mechanical way might either permanently alter the atomic lattices or be impossible. A theoretical study suggested that the crystal symmetries of these structures could instead be switched using charge doping, whereby electrons are added to or subtracted from a material[9]. The study indicated that this method might provide a controllable way to switch between the different topological phases.

Sie and colleagues' work is probably the first to demonstrate a dynamic transition between two crystal structures that have distinct topological phases. Previous studies have reported similar topological transitions, but these studies used static mechanical controls that cannot easily switch between the different phases[10,11]. Sie *et al.* found that light pulses at terahertz (THz) frequencies could cause the orthorhombic structure to become unstable by exciting electrons. This could induce the structural transition of WTe_2 from orthorhombic to monoclinic, as if charge doping had been applied to the sample. The authors analysed the crystal structures using a technique known as relativistic ultrafast electron diffraction. They corroborated their measurements using a method called time-resolved second-harmonic generation, which is quite sensitive to the inversion symmetry of crystals.

All the authors' measurements clearly indicate that the crystal structure of WTe_2 has inversion symmetry after the light pulses have been applied, and the switching between structures occurs at THz frequencies — although recovery of the original structure takes much longer. Because the absence of inversion symmetry is a key characteristic of the Weyl-semimetal phase in orthorhombic WTe_2, the observation of this switch of symmetries provides strong indirect evidence of the topological transition. Sie and colleagues have therefore discovered a dynamical way to control the topological properties of Weyl semimetals that could open up many applications, because the existence of Weyl fermions can substantially alter the behaviour of these materials[2].

Further studies are needed to realize the full potential of the authors' switching mechanism. Because the structural transitions in $MoTe_2$ and WTe_2 are closely related to topological changes[9], combined electrical and optical measurements would not only conclusively determine the topological transitions, but also provide a way to study topology-related transport phenomena in these solids[2]. The microscopic description of how THz-frequency light pulses affect the electronic and structural properties of WTe_2 is also required to understand the observed dynamic transitions. These endeavours and others will surely accelerate a fruitful era of topological materials and the control of these materials for applications. ■

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BIOCHEMISTRY

Signalling molecule reprograms metabolism

The signalling molecule nitric oxide protects the kidneys by reprogramming metabolism, and its levels are regulated by a two-component system in mice. These findings identify new targets for drug discovery. SEE LETTER P.96

CHARLES J. LOWENSTEIN

Acute kidney injury can lead to chronic renal failure, which causes fluid and electrolyte imbalances in the blood that require dialysis. Such injuries commonly involve ischaemia–reperfusion events, in which the blood supply to the kidney is temporarily restricted but then restored; this process generates toxic oxygen radicals that can cause renal inflammation and damage. Zhou *et al.*[1] report on page 96 that the signalling molecule nitric oxide[2,3] reprograms a metabolic pathway, and thereby limits ischaemic injury and protects renal function.

Nitric oxide is synthesized by a family of

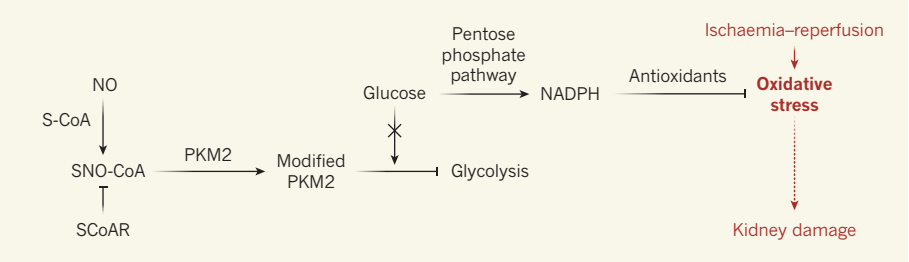

Figure 1 | Nitric oxide reprograms metabolism and limits oxidative stress. Zhou *et al.*[1] report that, in mice, the signalling molecule nitric oxide (NO) attaches to the molecule *S*-coenzyme A (S-CoA) to form *S*-nitroso-coenzyme A (SNO-CoA). This, in turn, delivers nitric oxide to the enzyme pyruvate kinase M2 (PKM2), modifying PKM2 and thereby inhibiting glycolysis — a metabolic pathway that consumes glucose. Glucose therefore enters another metabolic pathway, the pentose phosphate pathway, which generates NADPH, a cofactor used by antioxidants. The antioxidants can inhibit oxidative stress in kidney cells caused by a process called ischaemia–reperfusion, thus limiting damage to the kidneys (dotted arrow indicates damage limitation). The enzyme *S*-nitroso-coenzyme A reductase (SCoAR) removes nitric oxide from SNO-CoA, and so controls how much nitric oxide is available to modify target proteins.

enzymes called nitric oxide synthases (NOS), which fall into three groups: neuronal NOS, inducible NOS and endothelial NOS (eNOS). The molecule signals through several distinct mechanisms[4]. For example, it can interact with transition metals such as those in the haem group of guanylyl cyclase enzymes, which produce cyclic GMP — a messenger molecule involved in many biological processes. It can also combine with oxygen molecules to produce reactive nitrogen oxide species that, in turn, react with cysteine amino-acid residues on target proteins[5], forming modifications called *S*-nitrosothiols. Nitric oxide regulates a variety of physiological processes, including dilation of blood vessels (vasodilation), communication between neurons and the killing of disease-causing agents by the immune system.

Zhou and colleagues now show that nitric oxide protects kidneys from ischaemic damage. In particular, they observed that renal injury after ischaemia and reperfusion was worse in mice genetically engineered to lack eNOS than in wild-type mice. This result is consistent with previous findings that nitric oxide — not only nitric oxide produced in the body, but also that introduced from an external source[6] — can limit ischaemic injury in the kidneys[7], heart[8], brain[9] and other organs. The role of nitric oxide in these protective effects was not fully understood, but it has been proposed to act variously as an antioxidant[10], an anti-inflammatory agent[11] or a vasodilator[7].

The authors of the current study set out to identify the pathways by which nitric oxide protects against ischaemia. Using mass spectrometry, they discovered that one of the proteins most commonly modified by the molecule is pyruvate kinase M2, an enzyme that catalyses glycolysis (the metabolic pathway by which glucose is converted into energy). In a clever set of biochemical studies, they showed that nitric oxide modifies specific cysteine residues of pyruvate kinase M2. These modifications block the assembly of the active form of the enzyme, thereby inhibiting glycolysis. This is one of the key findings of the study: pyruvate kinase M2 is a target of nitric oxide.

Zhou *et al.* next genetically engineered mice so that their kidneys did not produce pyruvate kinase. The authors found that ischaemia causes less damage in these mice than in wild-type mice, consistent with the idea that pyruvate kinase mediates the protective effects of nitric oxide. But how?

The researchers used a technique called metabolic profiling to show that the kidney cells of mice lacking pyruvate kinase have high levels of products of the pentose phosphate pathway[12] — a metabolic pathway parallel to glycolysis that produces sugars called pentoses and the enzyme cofactor NADPH. NADPH acts in antioxidant systems to restore the function of proteins that have been damaged by oxidative stress in ischaemia[13]. The authors therefore conclude that nitric oxide inhibits pyruvate kinase and glycolysis, causing glucose levels to increase. The excess glucose spills over into the pentose phosphate pathway, generating high levels of NADPH, which shores up the antioxidant defences that limit renal injury (Fig. 1). This reprogramming of metabolism represents a major new aspect of nitric oxide biology.

How is nitric oxide conveyed to its renal-protein targets? Workers from the same group as Zhou and colleagues had previously identified[14] a two-component system that controls the availability of nitrosothiol groups in yeast. The first component is *S*-nitroso-coenzyme A, a molecule that donates nitric oxide groups to target proteins. The second component is an enzyme called *S*-nitroso-coenzyme A reductase, which removes nitric oxide from *S*-nitroso-coenzyme A. But does this binary system have any relevance to mammals?

To answer this question, Zhou *et al.* studied the impact of *S*-nitroso-coenzyme A reductase in mice during renal ischaemia and reperfusion. As expected, genetic deletion of the enzyme increased levels of *S*-nitrosylated proteins, protected mice from renal damage and prolonged survival compared with results in wild-type mice. Kidney levels of NADPH were also increased compared with levels of its oxidized form, $NADP^+$, as were levels of the antioxidant glutathione relative to its oxidized form, glutathione disulfide, confirming that protection occurs through the action of antioxidant defences. These exciting results show that *S*-nitroso-coenzyme A reductase acts *in vivo* in mammals to control nitric oxide signalling, which is the third major discovery of the study.

This work highlights important questions for further research. The authors' identification of a two-component system for regulating *S*-nitrosylation levels in renal injury raises the issue of what effect this system has on such regulation in normal physiological processes. How does this system function during other disorders, such as inflammation and cancer, which are also characterized by oxidant stress? And could pyruvate kinase M2 be a target for anti-ischaemic therapies?

Further work is also needed to identify how modification of pyruvate kinase M2 by nitric oxide protects cells — through inhibition of the enzyme's metabolic activity, or by inhibiting its other functions[15] (such as protein kinase activity and transcriptional co-activation)? Finally, Zhou *et al.* show that nitric oxide inhibits glycolysis in the setting of renal ischaemia, but it has previously been shown that it increases glycolysis in other settings[16]. Perhaps the activity of the newly discovered two-component regulatory system can explain previously puzzling aspects of nitric oxide biology, and might open up approaches for treating ischaemic injury in the kidney and other organs. ■

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