locomotion is mediated by the modulation of known circuits that control behaviour and not through previously unknown regulatory mechanisms.

Why does *L. brevis* make xylose isomerase? It should not be assumed that this is a specific adaptation to life in a *D. melanogaster* host. This bacterium is not specialized to exist only in the fruit fly gut. It maintains substantial free-living populations[6] and is neither universally present nor abundant in *D. melanogaster* populations in the natural environment[7]. Xylose isomerase probably functions to increase the diversity of the carbon sources that *L. brevis* can exploit, as is the case for the many other bacteria that produce this enzyme. It would be interesting to learn the outcome of experiments comparing the abundance in *D. melanogaster* of resident wild-type *L. brevis* and of *L. brevis* mutants lacking xylose isomerase, to determine whether this enzyme enhances the fitness of the bacterium and whether any fitness effects depend on fly locomotor activity.

The most important question to ask next is whether the effect of *L. brevis* and xylose isomerase on the locomotor activity of *D. melanogaster* is relevant to animal behaviour in general, including that of humans and other mammals. As with many other discoveries first made in *D. melanogaster*[8], perfect correspondence with mammalian systems is unlikely. Schretter and colleagues' study does, however, alert microbiologists and those studying animal behaviour to pay attention to the enzymes of gut bacteria and their possible effects on sugar metabolism and on the neuronal circuits regulating walking activity. ■

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1. Mohajeri, M. H., La Fata, G., Steinert, R. E. & Weber, P. *Nutr. Rev.* **76**, 481–496 (2018).
2. Schretter, C. E. *et al. Nature* **563**, 402–406 (2018).
3. Cryan, J. F. & Dinan, T. G. *Nature Rev. Neurosci.* **13**, 701–712 (2012).
4. Sharon, G. *et al. Cell Metab.* **20**, 719–730 (2014).
5. Roeder, T. *Annu. Rev. Entomol.* **50**, 447–477 (2005).
6. Duar, R. M. *et al. FEMS Microbiol. Rev.* **41**, S27–S48 (2017).
7. Bost, A. *et al. Mol. Ecol.* **27**, 1848–1859 (2018).
8. Letsou, A. & Bohmann, D. *Dev. Dyn.* **232**, 526–528 (2005).

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METABOLISM

A back door to improved health

The coenzyme NAD$^+$ can be produced from the amino acid tryptophan. It emerges that inhibiting an enzyme that degrades an intermediate in this pathway can help to combat kidney and liver diseases in mouse models. SEE ARTICLE P.354

SAMIR M. PARIKH

Throughout the history of life on Earth, there has been a requirement for small molecules called nucleotides. Long chains of nucleotides make up the genetic code, and single nucleotides transduce signals or transfer energy. In addition, a dimeric form of nucleotide called nicotinamide adenine dinucleotide (NAD$^+$) serves at least two pivotal cellular functions. The first is to shuttle high-energy electrons to enzymatic complexes found in organelles called mitochondria, where their energy can be efficiently harvested; the second is as a substrate for enzymes such as sirtuins, which regulate many cellular behaviours. On page 354, Katsyuba *et al.*[1] shed light on a fundamental mechanism by which the correct levels of NAD$^+$ are maintained in cells, and demonstrate how augmenting this pathway can affect disease.

In simple terms, the available pool of NAD$^+$ in a cell is governed by the balance between its generation and its consumption. The predominant pathway by which NAD$^+$ is generated in rodents relies on the recycling of a molecule called nicotinamide (Nam) that is either ingested or released by enzymes that consume NAD$^+$ (Fig. 1). There are several other routes of NAD$^+$ production, including a *de novo* synthesis pathway that starts with the essential amino acid tryptophan (Trp)[2]. Mutations that disrupt the enzymes responsible for converting Trp to NAD$^+$ result in multi-system developmental alterations in humans[3], demonstrating the importance of this *de novo* pathway.

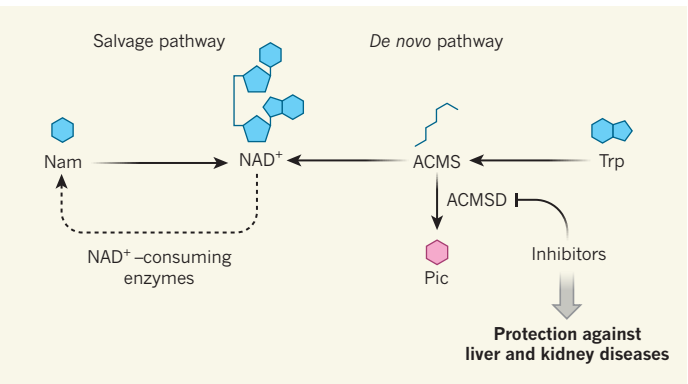

Figure 1 | NAD$^+$ biosynthesis in disease. When the coenzyme nicotinamide adenine dinucleotide (NAD$^+$) is consumed by enzymes, nicotinamide (Nam) is generated as a reaction product. Through a recycling mechanism called the salvage pathway, NAD$^+$ can then be regenerated. Nam salvage is considered the predominant mechanism for NAD$^+$ biosynthesis, but NAD$^+$ can also be generated through multiple other routes. One of these is the *de novo* pathway, whereby the amino acid tryptophan (Trp) is converted to NAD$^+$ through several intermediates, including α-amino-β-carboxymuconate-ε-semialdehyde (ACMS). This pathway can be depleted by the enzyme ACMS decarboxylase (ACMSD), which degrades ACMS to picolinic acid (Pic). Katsyuba *et al.*[1] report that chemical inhibition of ACMSD raises NAD$^+$ levels in mice and nematode worms, and improves outcomes in mouse models of liver and kidney diseases.

Katsyuba *et al.* set out to study α-amino-β-carboxymuconate-ε-semialdehyde (ACMS), an unstable and little-studied intermediate of the Trp pathway. ACMS can either spontaneously convert to the next intermediate on the path to NAD$^+$, or can be degraded by a train of enzymes, starting with ACMS decarboxylase (ACMSD). As such, ACMSD would be predicted to limit the amount of NAD$^+$ produced through *de novo* synthesis. ACMSD is evolutionarily conserved from the nematode worm *C. elegans* to mice[4] — an observation that is striking because, until recently, nematodes were not thought to synthesize NAD$^+$ *de novo*.

The authors inhibited the *acsd-1* gene, which encodes the equivalent of ACMSD in nematodes. This inhibition did increase NAD$^+$ levels. Increasing NAD$^+$ is well known to extend lifespan in worms, and the authors found that lifespan was longer in the worms in which *acsd-1* expression was completely blocked. Moreover, preventing *acsd-1* expression led to molecular responses that have been linked to defence against ageing[5,6]: increased activation of the sirtuin enzyme sir-2.1; enhanced mitochondrial function; and a protective mitochondrial stress response.

In mice and humans, ACMSD is most highly expressed in the liver and kidney[7], and a recent study indicates that these are the main organs for Trp-dependent NAD$^+$ generation[8]. Katsyuba *et al.* found that inhibition of the *Acmsd* gene increased NAD$^+$

levels and mitochondrial function in cultured mouse liver cells. The authors therefore developed chemical inhibitors of ACMSD, and tested whether these inhibitors could improve outcomes in mouse models of two ageing-related diseases: diet-induced fatty liver disease and acute kidney injury.

Earlier work had already described a beneficial effect of augmenting NAD^+ in each of these settings[9,10]. Katsyuba and colleagues' data confirmed the potential for therapeutic NAD^+ augmentation — treatment with their inhibitors protected against disease in these models. The results also suggest that increases in the *de novo* NAD^+ synthesis pathway alone are sufficiently robust to ameliorate liver and kidney diseases associated with low NAD^+ levels. However, proving this will require a demonstration that the benefit of ACMSD inhibition derives from the increase in NAD^+, rather than from another mechanism such as depletion of the molecule picolinic acid, which is produced by ACMSD-mediated degradation of ACMS. If proved, this finding would be consistent with a study[11] that identified a different enzyme in the Trp pathway, quinolinate phosphoribosyltransferase, as a determinant of susceptibility to acute kidney injury.

Several basic questions merit further consideration. For instance, what evolutionary pressures could have led to the conservation of multiple biosynthetic routes to NAD^+? And why is the *de novo* pathway most active in organs involved in detoxification of the body in mammals? One attractive possibility is that the liver and kidney are more exposed than other organs to toxic stressors that stimulate NAD^+ consumption. The fact that these organs export Nam to the rest of the body[8] might explain some aspects of inter-organ metabolic relationships in health and disease — for example, why people with chronic liver disease often develop impaired brain and heart function.

The ACMSD inhibitors developed by Katsyuba *et al.* are indicative of the interest in harnessing NAD^+ augmentation in the clinic. It has been nearly 20 years since NAD^+ was first proposed to be a determinant of lifespan[12]. But because ageing is so complex, a clinically testable definition has been lacking. Trials to examine the relationship between NAD^+ augmentation and human lifespan would take too long to be financially feasible. If, instead, a definition of ageing incorporated waning resistance to acute stressors such as infections, trauma or surgery, then clinical testing of NAD^+ modulators could become more viable. Another study has recently applied this logic, reporting a trial of orally administered Nam among people undergoing cardiac bypass surgery — an invasive procedure often performed on older individuals and associated with post-operative kidney injury[11]. The beneficial effect of NAD^+ augmentation on acute kidney injury observed in that work, although preliminary, illuminates a translational track for NAD^+ manipulation.

However, oral consumption of NAD^+ precursors might not be an efficient way to increase NAD^+ levels[8], so there is a need to consider more-targeted pharmacological approaches. The ACMSD inhibitors developed by Katsyuba and colleagues are therefore a valuable proof of concept. Given the enrichment of enzymes of the *de novo* pathway in the kidney and liver, this particular strategy also raises the intriguing possibility of tissue-specific NAD^+ manipulation.

The list of conditions potentially amenable to NAD^+ augmentation is varied and growing, from glaucoma[13] to neurodegenerative conditions[14] and metabolic syndrome[15]. A confluence of work using distinct approaches — human genetics[3], radiochemistry[8], comparative phylogeny[1] and clinical studies[11] — now indicates that the Trp pathway is both a major gatekeeper of NAD^+ levels and a target for medical exploration. ■

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1. Katsyuba, E. *et al. Nature* **563**, 354–359 (2018).
2. Krehl, W. A., Teply, L. J., Sarma, P. S. & Elvehjem, C. A. *Science* **101**, 489–490 (1945).
3. Shi, H. *et al. N. Engl. J. Med.* **377**, 544–552 (2017).
4. Fukoka, S.-I. *et al. J. Biol. Chem.* **277**, 35162–35167 (2002).
5. Mouchiroud, L. *et al. Cell* **154**, 430–441 (2013).
6. Gomes, A. P. *et al. Cell* **155**, 1624–1638 (2013).
7. Pucci, L., Perozzi, S., Cimadamore, F., Orsomando, G. & Raffaelli, N. *FEBS J.* **274**, 827–840 (2007).
8. Liu, L. *et al. Cell Metab.* **27**, 1067–1080 (2018).
9. Tran, M. T. *et al. Nature* **531**, 528–532 (2016).
10. Gariani, K. *et al. Hepatology* **63**, 1190–1204 (2016).
11. Poyan Mehr, A. *et al. Nature Med.* **24**, 1351–1359 (2018).
12. Lin, S.-J., Defossez, P.-A. & Guarente, L. *Science* **289**, 2126–2128 (2000).
13. Williams, P. A. *et al. Science* **355**, 756–760 (2017).
14. Wang, G. *et al. Cell* **158**, 1324–1334 (2014).
15. Cantó, C. *et al. Nature* **458**, 1056–1060 (2009).

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MEDICAL RESEARCH

HIV rebound prevented in monkeys

Antiviral drugs prevent HIV from replicating, but the virus can hide in the cells of infected individuals in a non-replicating, latent form. A two-pronged approach to target this latent virus shows promise in monkeys. SEE ARTICLE P.360

SHARON R. LEWIN

Advances in the management of HIV over the past three decades have been spectacular, thanks to the development of antiretroviral drugs that prevent the virus from replicating. These drugs have very few side effects, prolong life and block sexual transmission. However, the virus is never eliminated — instead, it hides in immune cells called $CD4^+$ T cells in a non-replicating, latent form. If treatment is stopped, the virus rapidly re-emerges from this latent reservoir[1]. Given the cost of antiretroviral drugs, the need for ongoing engagement in care and the persisting stigma for people living with HIV, there is intense focus on finding a way to target the latent virus so that treatment can be safely stopped without viral re-emergence. On page 360, Borducchi *et al.*[2] report remarkable findings that may have achieved just that in a monkey model of HIV.

Disappointingly, no intervention has so far managed to eliminate the latent HIV reservoir in people[3]. Borducchi and colleagues set out to investigate whether a combination of two treatments could do so in monkeys. The first treatment, GS-9620 (vesatolimod), is an oral drug that activates the Toll-like receptor 7 (TLR7) protein. TLR7, in turn, activates immune cells — not only $CD4^+$ T cells, but also $CD8^+$ T cells and natural killer (NK) cells, both of which can h unt out and destroy virus-infected cells[4]. Activation of latent HIV contained in $CD4^+$ T cells is thought to render them more susceptible to destruction by other immune cells[5]. The second treatment, PGT121, is an antibody, one end of which recognizes and binds to key HIV proteins on the surface of infected cells, with the opposite end triggering other immune cells to destroy the target cell[6].

Borducchi and colleagues infected 44 monkeys with a hybrid of HIV and the simian immunodeficiency virus. Seven days later, they began to treat the animals with a potent combination of antiretrovirals, similar to that used in humans. HIV rapidly disappeared from the blood of all monkeys, as expected. After 96 weeks, the authors split the monkeys into 4 randomized groups of 11 — one group received no intervention, a second was given GS-9620, a third was injected with PGT121, and a fourth received both GS-9620 and PGT121. The monkeys received these treatments until week 114, then continued to