From the archive

Support from America for natural selection, and the search for a suitable standard.

100 years ago

I note with interest, perhaps I might say amusement, the statement by Mr. Cunningham that Natural Selection is "as extinct as the dodo." It may be in the land of its birth, but it is still very much in evidence in America. Nearly every systematic zoologist whom I know personally believes in it as a factor in evolution ... Prof. E. G. Conklin of Princeton, certainly one of our foremost zoological thinkers, has just completed a course of Lowell Institute lectures in Boston on "The Revolt against Darwinism," in which he has most clearly and emphatically stated his strong conviction, not only that such revolt is unjustifiable, but that Natural Selection is the most important theory that has yet been proposed for helping us to understand adaptation. It surely seems a little rash to call Natural Selection, or anything else, "extinct" because it has disappeared from one's own horizon. Horizons contract with increasing near-sightedness.

From *Nature* 3 February 1923

150 years ago

The material for constructing ... new Standards, for which an alloy of pure platinum with 10 per cent. of iridium has been selected, is obviously a matter of primary importance. Before determining upon this metallic alloy, a series of experiments was made ... A material was needed ... that should as far as possible be unalterable in its composition and molecular structure, in its form and dimensions, from the ordinary action of air, water, fire, or other chemical agents, or from mechanical forces to which it might be subject; that would in fact possess physical properties rendering it invariable with time ... [P]latinum, which was the best pure metal for the purpose, has the disadvantage of being too soft and too weak for a measuring bar. Combined, however, with a proper proportion of iridium, platinum satisfied all the conditions required either for a Standard metre or kilogramme.

From *Nature* 30 January 1873

their rest phase than during their active phase (Fig. 1).

Does this principle apply to humans? Perhaps. The authors observed that human DCs, like their mouse counterparts, display time-of-day-dependent properties, both in CD80 production and in their activation of tumour-specific cytotoxic T cells. However, one difference between humans and mice is that humans are active during the day, whereas mice are active at night.

This raises the question of when might be the right time to vaccinate humans — during our rest phase at night or during our active phase, when mice are normally resting? The authors retrospectively analysed data from a clinical anticancer vaccination trial of ten people with a skin cancer called melanoma, and found an advantage of morning over afternoon vaccination (vaccination at night was not performed in that trial).

Anticancer vaccines in humans are designed to stimulate the immune system to attack tumours that have been developing for months or years. Such tumours are usually not new threats to the body's defences, and have often acquired mechanisms to escape targeting by the immune system[1,6]. Therefore, it will be important to assess whether a favourable time-of-day-dependent effect of vaccination obtained against newly injected tumour cells would also apply to a vaccination aimed at mature and immune-experienced tumours.

Nevertheless, the authors' study adds to a growing body of evidence indicating that the timing of treatment can influence the outcome of therapeutic approaches, as has been suggested for conventional vaccination[7] and cancer immunotherapy using drugs called checkpoint inhibitors[5]. Including treatment timing as a variable in future clinical trials of cancer vaccines might therefore have the potential to improve patient outcomes. In addition, there is a plethora of other circadian-controlled processes waiting to be exploited in the realm of circadian medicine[8]. Clever timing of interventions, such as administering a treatment when it has the strongest effect and the fewest side effects, might improve the effectiveness and safety of already available therapies for a variety of diseases. We should not miss this opportunity.

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Metabolism

Lack of serine causes complications in diabetes

Thorsten Hornemann

Impaired sensory-nerve function is a common complication of diabetes. Evidence in mice indicates that deficiency of the amino acid serine causes these complications — and suggests that supplements could help to treat them. **See p.118**

One of the most common complications of type 2 diabetes is diabetic polyneuropathy (DPN), in which impaired nerve function causes a range of symptoms, including pain and numbness. DPN can lead to skin ulcers and difficulties in wound healing[1] and is a leading cause of limb amputations[2]. There is currently no way to treat the underlying causes of DPN — a mechanism-based therapy is therefore in high demand. On page 118, Handzlik *et al.*[3] demonstrate that changes in the levels of the amino acid serine can impair nerve function, and suggest that the pathway altered could be targeted therapeutically.

DPN is associated with changes in how neurons and neuron-insulating Schwann cells generate energy from glucose and fatty acids. Diabetes causes increases in the levels of these two substrates, which have been proposed to affect neurons detrimentally in several ways. First, high levels of the substrates saturate the pathway that metabolizes fatty acids, leading

to the accumulation of a form of fatty acid called acyl carnitine that is toxic to Schwann cells and certain neurons[4]. Second, an excess substrate load results in the production of reactive oxygen species, leading to failure of organelles called mitochondria, which are responsible for cellular energy production[5]. Third, increased glucose levels lead to the 'glycation' of proteins, forming advanced glycation end products (AGEs), which then interact with an AGE-specific receptor protein. This causes modified gene expression and the release of harmful pro-inflammatory molecules and free radicals[6].

Although all these phenomena occur in type 2 diabetes, none has been successfully targeted to treat DPN. Instead, current approaches to managing DPN in this condition focus on lifestyle modifications and management of neuron-related pain. No mechanism-based treatment has been approved for use in the clinic[7].

Handzlik *et al.* have now identified a different pathway through which a set of metabolic changes can affect neurons in DPN. The authors altered the diets of mice to render them obese and insulin resistant (a hallmark of type 2 diabetes). They found a drop in the concentration of two amino acids, serine and glycine, with levels reduced by 30% or more in the liver and kidneys, compared with in those of control animals.

Serine is required for the synthesis of sphingolipids — bioactive lipids that are essential building blocks of cellular membranes and vesicles. The authors showed that serine deficiency resulted in an altered sphingolipid profile, and the formation of an atypical class of 1-deoxysphingolipid (1-deoxySL), which is toxic to neurons. These side products are formed during sphingolipid synthesis, when the key regulatory enzyme serine palmitoyltransferase (SPT) metabolizes alanine instead of its preferred substrate, serine[8]. The authors showed that the increase in 1-deoxySL in serine-deficient mice led to structural and functional defects in the animals' sensory nerves.

Why are serine levels low in obese animals? Handzlik and colleagues found increased expression of genes that encode several key enzymes in a pathway called one-carbon metabolism in their obese mice, compared with controls. One-carbon metabolism supports many physiological processes, including molecule biosynthesis, maintenance of amino-acid levels and redox-defence systems (which eliminate free radicals). In particular, the authors detected increased expression of the gene encoding the enzyme serine dehydratase, which converts serine to a precursor of alanine, and decreased expression of the gene that encodes phosphoglycerate dehydrogenase, an enzyme involved in serine synthesis from glucose (Fig. 1).

Together, these findings add to growing evidence for the role of serine deficiency in a suite of diseases. The group that conducted the current study has previously shown[9] that 1-deoxySL levels are increased in macular telangiectasia type 2 — a rare retinal disease that is associated with serine deficiency. Abnormally high 1-deoxySL levels are also associated with a neuronal disorder called hereditary sensory and autonomic neuropathy type 1 (HSAN1), which is clinically very similar to DPN. HSAN1 is triggered by mutations in the genes that encode SPT, inducing a permanent shift in SPT's preferred substrate from serine to alanine, resulting in increased 1-deoxySL levels[10].

There is emerging clinical evidence that metabolic disorders, such as non-alcoholic fatty liver disease and metabolic syndrome, are also associated with serine deficiency and increased 1-deoxySL formation[11–13]. The reasons that serine levels are reduced under these atypical metabolic conditions are not yet understood. Handzlik and co-workers' discovery of changes in one-carbon metabolism in obese animals supports one possible explanation, providing a direct link between these metabolic conditions, a reduction in serine and increased 1-deoxySL synthesis by SPT.

An intriguing aspect of Handzlik and colleagues' work is that the underlying serine deficiency in their diabetic animals can be corrected by oral serine supplementation. A clinical trial[14] has shown that giving serine supplements to people with HSAN1 results in significantly lowered 1-deoxySL levels and improved nerve function. Serine supplements also reduce nerve damage in a rat model of diabetes[15]. Together, these data hint at the exciting possibility that serine supplements might be a safe and cost-effective way to reduce 1-deoxySL levels in people who have type 2 diabetes. The next essential step is to test this possibility in human clinical trials.

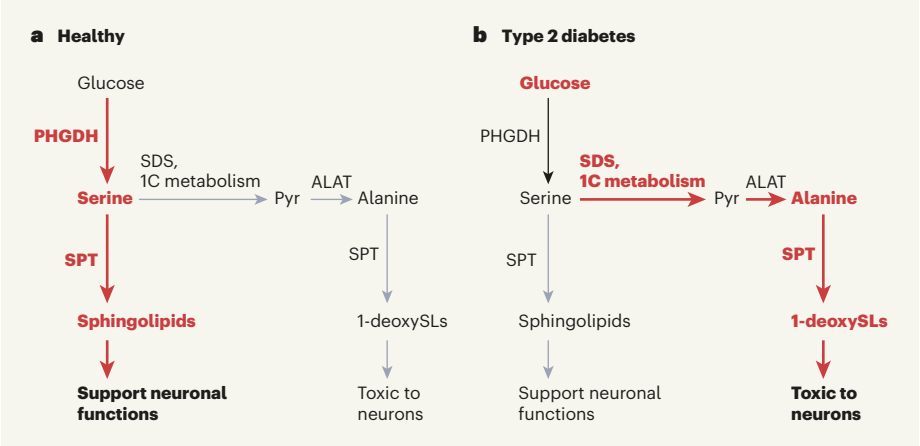

Figure 1 | Abnormal serine metabolism in type 2 diabetes. a, In healthy mice, metabolism of glucose produces the amino acid serine, in a multi-step process that involves the enzyme phosphoglycerate dehydrogenase (PHGDH). Serine is converted by the enzyme serine palmitoyltransferase (SPT) into sphingolipids, which support healthy neuronal functions. Alternatively, serine can be converted to pyruvate (Pyr) by the enzyme serine dehydratase (SDS), as part of the one-carbon (1C) metabolism pathway, and then to another amino acid, alanine, by the enzyme alanine aminotransferase (ALAT). SPT converts alanine into harmful 1-deoxysphingolipids (1-deoxySLs). However, the activity of this pathway is low in healthy neurons (indicated by grey, rather than red, font and arrows). **b**, Handzlik *et al.*[3] report that, in a mouse model of type 2 diabetes, SDS levels are increased and PHGDH levels are low. Together, these factors increase the ratio of alanine to serine.

"These findings add to growing evidence for the role of serine deficiency in a suite of diseases."

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