between the expression of some of the core clock components and patient outcomes.

The researchers went on to show that a process called circadian reprogramming might explain why GSCs depend on the circadian clock. Circadian reprogramming involves changes in the circadian-clock output — that is, in the collection of genes in a given cell or tissue that are under the control of the clock, and so are expressed in oscillating rhythms across the day. Dong *et al.* demonstrated that the circadian-clock output of GSCs includes genes involved in glucose metabolism and lipid synthesis, whereas the circadian-clock output of normal neural stem cells does not. Changes in glucose metabolism and lipid synthesis have been previously shown to aid cancer progression[9].

In addition, Dong and colleagues observed that the metabolic capacity of GSCs changed in the absence of *BMAL1* and *CLOCK*. The group showed that circadian reprogramming in GSCs is mediated by changes in chromatin — the DNA–protein complex in which DNA is packaged. More regions of chromatin are open in GSCs than in normal neural stem cells, allowing the BMAL1 and CLOCK proteins to bind to and activate different genes. The authors then linked these data by showing that BMAL1 and CLOCK regulate the expression of genes involved in lipid metabolism in GSCs, indicating that the oncogenic activity of the clock genes might involve metabolic pathways (Fig. 1).

Previous reports have described circadian reprogramming in response to various stimuli, such as changes in diet, physiological ageing or exercise[10–13]. In all these cases, circadian reprogramming is a fast and effective way to respond to changing external demands. Circadian reprogramming has also been observed between organs — for instance, reprogramming in the livers of mice that have developed lung cancer probably ensures that the liver provides sufficient energy for the tumour cells to grow efficiently[14]. The picture that is emerging is of circadian reprogramming as a common mechanism to help cells, tissues and whole organisms adapt to change, whether they are healthy or cancerous.

In a final set of experiments, Dong *et al.* showed that small molecules that repress *BMAL1*, either directly or indirectly, strongly inhibit the self-renewing potential of GSCs. Mice that carried GSCs from patients survived longer if they were treated with one of these molecules than they did without treatment.

Caution is needed when considering translating these findings to humans, because the small molecules used by Dong and colleagues also affect the activity of the clock machinery systemically, potentially perturbing normal physiological processes in healthy tissues — this might induce damage accumulation and signs of premature ageing[15]. A better alternative might be to target the factors that induce circadian reprogramming in GSCs. Such an approach should block circadian-related changes in gene expression in cancer cells without perturbing the clock in the rest of the organism.

What might these factors be? There is likely to be a mixture, some intrinsic to the cells, others extrinsic, probably acting synergistically. For example, as in the current study, a change in energy requirements when a cell becomes cancerous can lead to changes in the metabolic products generated in that cell; this, in turn, can affect chromatin remodelling, changing the catalogue of genes available to be activated and thereby altering the rhythmic transcription of genes[16]. Outside the cell, signalling pathways involving the hormone insulin and the neurotransmitter molecule adrenaline are both altered in tumours, and can re-entrain the cancer-cell clock, thus integrating whole-body information into the cell's circadian output[15].

These systemic pathways might represent therapeutic targets to treat cancer. However, the complex effect of these pathways on circadian reprogramming in cancer cells is still poorly understood. Nonetheless, Dong *et al.* have opened a new chapter in the search for therapeutic targets for aggressive and incurable glioblastomas. ■

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AGEING

Neural excitation moderates lifespan

Signals emanating from the nervous system are potent modulators of longevity. It now seems that overall neural excitation is also a key determinant of lifespan. SEE ARTICLE P.359

NEKTARIOS TAVERNARAKIS

The question of why and how we age — and why only a minority of humans live to become centenarians — has fascinated people for millennia. Over the past few decades, we have learnt that the rate of ageing is highly sensitive to intrinsic and extrinsic cues, and that these cues act, by means of numerous genetic pathways, to regulate the cellular and systemic processes that ultimately influence ageing[1].

On page 359, Zullo and colleagues[2] uncover a new twist in the saga: an unexpected link between the nervous system and ageing. They show that overall neuronal excitation is a major determinant of lifespan, and that it is higher in short-lived individuals and lower in the long-lived. The authors also characterize some of the molecular players in this effect, and tie it to a well-known regulator of lifespan: signalling by the hormone insulin or by insulin-like growth factor 1 (IGF1).

Ageing affects the nervous system in a complex way that is not yet fully understood[3–5]. Perhaps less intuitively, this relationship also works in the opposite direction: signals from the nervous system can modulate the rate of ageing of the whole organism[6–10]. But although the nervous system is known to influence longevity in species ranging from invertebrates to mammals, the underlying molecular mechanisms have been unclear.

Zullo and colleagues began their investigation by studying brain tissue from aged humans who had shown no cognitive deficits before their death. The authors analysed gene-expression profiles from the frontal cortex, and uncovered an intriguing correlation: genes involved in neural excitation and in the function of the synaptic connections between neurons are downregulated in long-lived individuals, but genes required for inhibitory neurotransmission are not.

How might this occur? The authors found that the downregulated genes are probably targets of the transcriptional regulator protein REST — a general repressor of genes involved

in neuronal excitation and synaptic function[11]. Previous studies[12,13] had implicated REST in preventing hyperexcitation of the neuronal network, maintaining its steady state, resisting oxidative stress and protecting neurons over time. (For instance, deleting the *Rest* gene increases neural activity in the mouse cortex and renders animals vulnerable to blockers of inhibitory neurotransmission, further exacerbating neural excitation and triggering epilepsy.) The new findings directly associate long human lifespan with increased REST activity and reduced neural excitation.

Is this association merely a corollary of the ageing process, or is there a causal relationship? To find out, Zullo and colleagues turned to the nematode worm *Caenorhabditis elegans* — a malleable test bed that has been invaluable in unpicking the mechanisms that modulate lifespan[14]. The authors found that neural activity increases as the worm ages. In addition, interventions that inhibit either overall neural excitation and synaptic neurotransmission or signalling by neuropeptide molecules extend the lifespan of *C. elegans*. In effect, tempering excitatory neurotransmission to reduce overall neural activity is enough to make worms longer-lived. By contrast, suppressing inhibitory neurotransmission increases neural activity and shortens lifespan. Overall neural excitation is, therefore, an important regulator of lifespan in worms and humans.

Digging deeper into this process in worms, the authors focused on the SPR-3 and SPR-4 proteins[15], which are counterparts of mammalian REST. This is where the research began to reveal links with insulin/IGF1 signalling, which is a key part of the cellular response to the presence of nutrients. Low insulin/IGF1 signalling is associated with long lifespan in worms.

Zullo *et al.* found that the longevity conferred by reduced neural activity requires DAF-16, a transcription factor that is also needed for the extended lifespan linked to low insulin/IGF1 signalling in *C. elegans*. Moreover, neuronal SPR-3 and SPR-4 are key to the increase in lifespan seen under conditions of low insulin/IGF1 signalling. Genes required for neuronal excitation are downregulated by low insulin/IGF1 signalling in an SPR-3/4-dependent manner. In addition, worms carrying mutations in the insulin receptor DAF-2 show reduced neural excitation that is instigated by SPR-3 and SPR-4 and is required for activation of DAF-16. Similarly, SPR-3 and SPR-4 are needed to activate DAF-16 under conditions of oxidative stress. Of note, SPR-3/4 depletion restores higher levels of neural excitation in animals carrying DAF-2 mutations, compromising their exceptional longevity.

Collectively, these findings in *C. elegans* indicate that stress and insulin/IGF1 signalling converge on SPR-3 and SPR-4 to modulate neural activity. In turn, this influences DAF-16, another point of convergence that integrates neural excitation and insulin/IGF1 signals to promote stress tolerance and longevity (Fig. 1a). Exactly how DAF-16 is activated by reduced neural excitation remains to be seen.

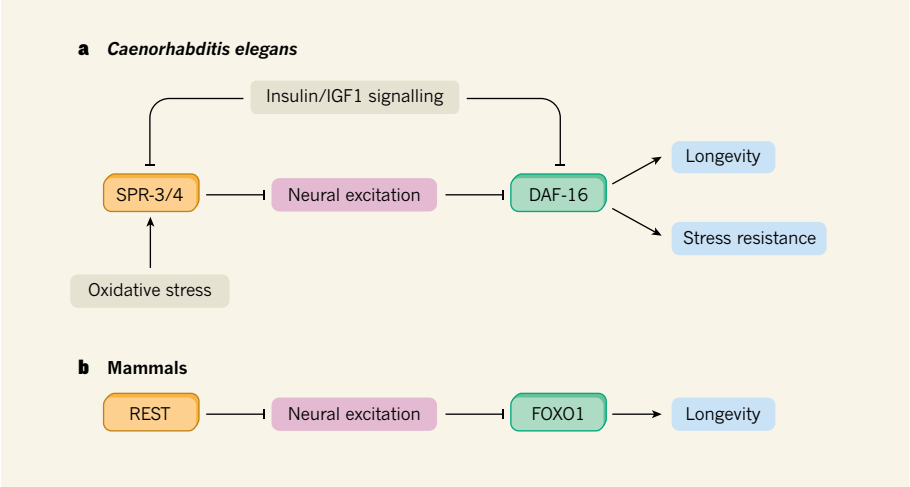

Figure 1 | Lifespan is regulated by neural excitation in worms and mammals. **a**, Zullo and colleagues[2] show that, in the nematode worm *Caenorhabditis elegans*, the proteins SPR-3 and SPR-4 reduce the expression of genes involved in neural excitation and transmission across synapses. SPR-3 and SPR-4 therefore act to quench neural excitation. Subsequent activation of the transcription factor DAF-16 (normally inhibited by neural excitation) promotes longevity and resistance to oxidative stress. Oxidative stress and signalling through insulin or insulin-like growth factor 1 (IGF1) are both known to affect lifespan. The new findings suggest that they do this, in part, through their effects on SPR-3/4 and neural excitation. **b**, The authors also find that, in humans and mice, the SPR-3 and SPR-4 counterpart REST downregulates genes involved in neural excitation in the brain's cortex. The ensuing tempering of neural excitation activates the DAF-16 counterpart FOXO1. REST expression is increased in the cortex of long-lived humans, whereas genes involved in neural excitation are downregulated.

A similar signal-transduction pathway seems to be at work in mammals (Fig. 1b). Zullo *et al.* find that, in humans, the expression and levels of REST in cell nuclei correlate with those of the DAF-16 counterpart FOXO1. Moreover, both REST and FOXO1 are found in neurons in the human prefrontal cortex. The authors showed that repressing neural excitation in mouse cortical neurons grown in culture increases the expression and nuclear levels of FOXO1. And the age-dependent rise in nuclear FOXO1 in mice requires REST. The parallels between nematodes and mammals suggest that the REST–FOXO1 (or the SPR-3/4–DAF-16) axis is a key part of the mechanisms by which nervous system function influences ageing. Moreover, a reduction in overall neural excitation is a major contributor to the lifespan extension caused by low insulin/IGF1 signalling.

"The new findings have revealed a previously unappreciated conduit for integrating neural activity and metabolism."

These findings shine new light on previous work. For example, certain anticonvulsant drugs have been found to promote longevity in *C. elegans*[16] — again implicating overall neural activity in regulating lifespan. However, these compounds act in complex ways, and their anti-ageing effects might not be entirely reliant on the nervous system. Moreover, unlike REST-mediated quenching of neural excitation, some anticonvulsants function independently of DAF-16, and further extend the lifespan of animals with DAF-2 mutations.

Another line of work, again in *C. elegans*, has offered a link between longevity and the inhibition of signalling by the neurotransmitter molecule serotonin, which is involved in the organismal response to nutrients[17]. That research showed that antidepressants that block serotonin receptors extend lifespan, probably by simulating dietary restriction (known to promote longevity universally). Given that dietary restriction is associated with low insulin/IGF1 signalling, which limits overall neural excitation through REST, could REST (or SPR-3/4) also contribute to lifespan extension under nutritional stress? Zullo and colleagues consider this unlikely, because inhibiting neural excitation in *C. elegans* late in adulthood — even after the worms have stopped feeding — still extends lifespan. But some role for this molecular axis is possible, given that cessation of food intake is not always equivalent to a state of perceived calorie restriction.

As well as offering insight into the link between overall neural excitation and ageing, Zullo and colleagues' findings provide a previously unappreciated conduit for integrating neural activity and metabolism, through the insulin/IGF1 pathway. This integration could fine-tune an organism's physiology and orchestrate appropriate behavioural adaptations

towards optimizing fitness and enhancing survival. What is more, by buffering changes in overall neural excitation and maintaining a proper balance in neuronal-network activity, REST might also prevent age-related neurological disorders to boost longevity in humans. Indeed, accumulating evidence couples neural overexcitation to Alzheimer's disease[18–20]. So REST and other molecules that control neural excitability are possible targets for interventions aimed at battling the decline and maladies of old age. ■

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INFECTIOUS DISEASE

Malaria mosquitoes go with the flow

The rapid return of mosquitoes to African semi-desert regions when the dry season ends was an unsolved mystery. A surprising solution to the puzzle is the long-range migration of mosquitoes on high-altitude winds. SEE LETTER P.404

NORA J. BESANSKY

During the long dry season in the semi-desert region of Africa known as the Sahel, malaria transmission ceases because the mosquitoes that can transmit the disease (termed malaria mosquitoes or vectors) disappear, along with the surface water required for the development of the next generation of mosquitoes. Yet with the first rains that end the dry season, adult numbers surge more quickly than can be explained by resumed breeding in newly rain-filled sites. Evidence to explain this adult population boom has remained elusive for decades. On page 404, Huestis *et al.*[1] report high-altitude sampling of malaria vectors in the Sahel, which revealed data consistent with long-range wind-borne migration of mosquitoes.

Insect flight typically occurs close to the ground, in a habitat patch that provides all of the insect's essential resources such as food, shelter, mates and breeding sites. Among malaria vectors, this type of foraging flight rarely exceeds a distance of five kilometres[2]. By contrast, during long-distance migration, insects ascend to altitudes as high as 2–3 km, where fast air currents transport them downwind for hundreds of kilometres in a few hours[3]. This behaviour is beneficial[3] for insects moving in seasonally favourable directions.

The migration of monarch butterflies (*Danaus plexippus*) between North America and Mexico is one of the most widely known insect migrations, but the extent to which other insects engage in long-distance migration is under-appreciated, because these high-altitude flights are undetectable without technology such as radar. The type of radar that can detect larger insects (those heavier than 10 milligrams) had been mainly used to track just a few agricultural pests, until a 2016 study of the southern United Kingdom[4] used such radar to investigate insect migration in general. This study revealed that an estimated 16.5 billion insects migrate annually at high altitude (defined in this case as a height of more than 150 metres) above the 70,000 km^2 study area, indicating that wind-borne insect migration can occur on a strikingly large scale.

Current radar technology does not detect small insects (lighter than 10 mg) such as mosquitoes, which must instead be tracked by sampling using aerial nets. In the UK study[4], such insect capture provided evidence that three trillion small insects undertake high-altitude migrations, a number that substantially exceeds that of the larger radar-tracked insects in the same area. These migrations, termed mass seasonal bioflows[4], involve representatives of all major insect orders[3], including Diptera, to which mosquitoes belong. Seasonal patterns in the direction of high-altitude winds can enable consistent routes for these bioflows (Fig. 1).

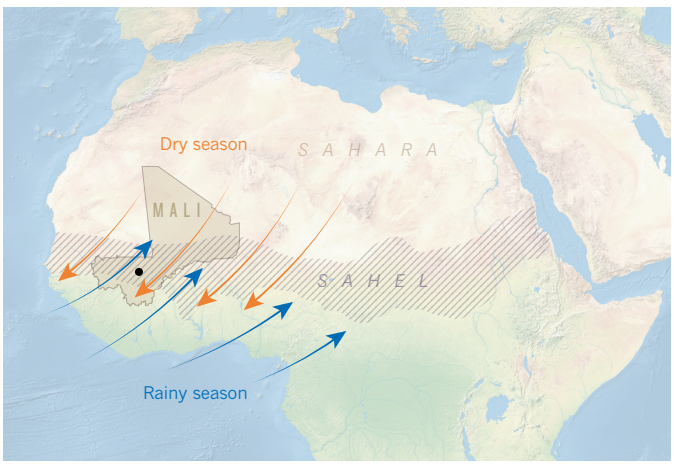

Figure 1 | High-altitude winds enable the seasonal migration of African mosquitoes. Huestis *et al.*[1] report that certain types of mosquito that can transmit malaria undergo long-distance wind-borne journeys. The authors studied sites in Mali (region marked with a black circle) in a semi-desert region of Africa called the Sahel. In the rainy season, there is a sudden rapid rise in the number of mosquitoes in the Sahel. The seasonal patterns of high-altitude wind directions (coloured arrows) are consistent with rainy-season winds transporting mosquitoes into the Sahel from southerly sites, where mosquitoes reside throughout the year. During the dry season, winds from the north blow into the Sahel, which could transport mosquitoes southwards.

Huestis and colleagues studied four villages in the Sahel region of Mali. The possibility that wet-season mosquito populations are re-established there by adults flying from the nearest year-round populations was excluded in a previous study[5] by this team. This is because the distance of more than 150 km to such sites is prohibitively long for self-powered mosquito flight.

A second possibility is that mosquitoes maintain a local presence and survive during the dry season, hidden away in a state of dormancy termed aestivation. Important, albeit indirect, support for this