other brain regions[12]. The pancreas, fat tissues and intestine — all of which are involved in glucose metabolism — also express TCF7L2. The possible contribution of these structures to nicotine-induced dysregulation of glucose metabolism needs to be considered and evaluated.

Furthermore, nicotine is a strong activator of the hypothalamus–pituitary–adrenal (HPA) axis — a network that promotes the release of stress hormones[13]. The function of the mHb is altered by stress, and stress hormones induce changes in blood glucose[13]. As such, it is conceivable that the some of the effects reported by the authors reflect not only the direct effect of nicotine on the mHb, but also an indirect effect through HPA-axis activation.

An interesting question is whether the effect of nicotine on the mHb–pancreas axis is different in males and females. In support of this idea, more men than women smoke, and the risk of female smokers developing diabetes is much greater than the risk for male smokers, compared with their non-smoking counterparts[4]. Furthermore, nicotine withdrawal induces greater weight gain in women than in men[14].

More broadly, further investigation is needed to confirm the role of the mHb–pancreas circuit in humans. Tobacco addiction in humans involves the interplay of pharmacological, genetic, social and environmental factors. Therefore, the full picture of nicotine's role in diabetes is likely to involve much more than a single regulatory circuit. Finally, this work raises the question of whether and how TCF7L2 could be targeted to combat tobacco dependency and diabetes. The feasibility of this tantalizing idea will require much more investigation in both mice and humans. ■

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CANCER

Brain tumours reset their clocks

The body's circadian clock ensures the rhythmic expression of some genes across the day. The catalogue of genes under circadian control changes in an aggressive brain cancer — a discovery that might open up a new avenue for treatment.

GUIOMAR SOLANAS & SALVADOR A. BENITAH

All organisms have an internal circadian clock, which ensures that physiological functions occur at the right time of day — for instance, that the intestine, pancreas and liver are ready to metabolize food when you eat rather than when you are sleeping. Writing in *Cancer Discovery*, Dong *et al.*[1] report that the cells responsible for initiating a specific type of aggressive brain tumour, glioblastoma, rely on an altered circadian clock to grow. What's more, drug-based inhibition of the cells' molecular clock can kill them.

Glioblastomas are the most prevalent and aggressive tumour of the central nervous system. Fewer than 6% of patients survive for five years after diagnosis[2]. Cells in a glioblastoma often have varied gene-expression profiles. This, coupled with the fact that glioblastoma-initiating stem cells (GSCs) act to maintain the tumour, means that glioblastomas can rapidly develop resistance to conventional therapies[3]. New treatments are therefore urgently needed.

Disruption of the circadian clock, either because of lifestyle choices or because of mutations in core clock genes, is associated with a higher incidence of tumours[4]. In some tissues, clock genes can be co-opted to promote cancer (they are said to act as oncogenes), whereas in others they act as tumour suppressors[5–7]. The origin of such differences is an open question that, when answered, will help researchers to identify the mechanisms by which tumour cells hijack the molecular clock machinery to increase their chances of survival.

Dong and colleagues show that two key clock genes, *BMAL1* and *CLOCK*, are co-opted to act as oncogenes in glioblastoma. The authors first observed that the genes are essential for the survival and proliferation of GSCs *in vitro*. By contrast, neither differentiated glioblastoma cells nor normal neural stem cells (from which GSCs arise[8]) seem to depend on the genes in this way. The authors validated these findings by showing a strong correlation

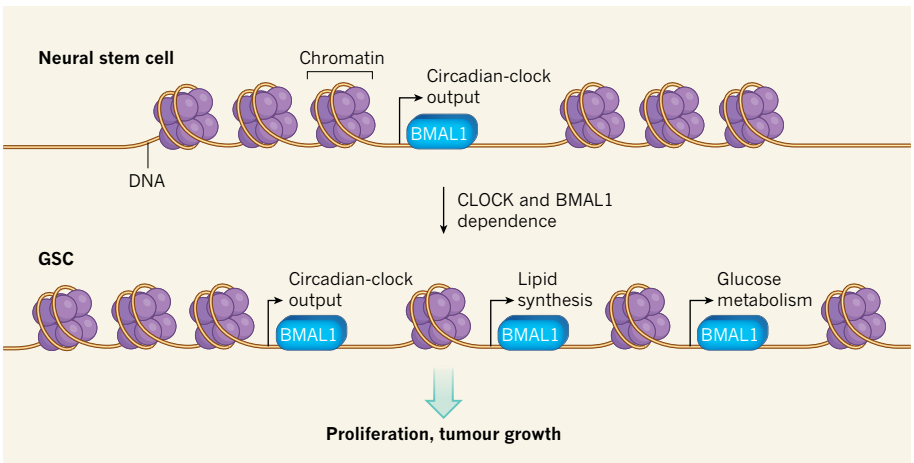

Figure 1 | Circadian reprogramming in cancer stem cells. The proteins BMAL1 and CLOCK are core components of the body's circadian clock. In neural stem cells, the proteins bind to specific regions of DNA (which is packaged around proteins as chromatin) to promote expression of the circadian-clock output — a collection of genes that are expressed in oscillating rhythms across the day (only BMAL1 is shown here). Dong *et al.*[1] report that, when neural stem cells become cancerous glioblastoma-initiating stem cells (GSCs), they become dependent on BMAL1 and CLOCK for survival. Changes in chromatin packaging enable BMAL1 and CLOCK to bind to more sites across DNA, promoting the expression of genes involved in lipid synthesis and glucose metabolism. Activation of these two metabolic pathways promotes GSC proliferation and so tumour growth.

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