that were increased or suppressed by prolonged hyperosmolarity (saline ingestion) in mice. miR-7b, which showed increased expression, was found to have potential binding sites in the 3′ untranslated region of *Fos* mRNA. The team confirmed that *Fos* was indeed a target of miR-7b, showing that the induction of FOS in cultured cells was largely inhibited in the presence of miR-7b and that this was due to inhibition of translation rather than of mRNA transcription.

The team identified a number of hypothalamic miRNAs that are both up- and downregulated in the body's reaction to hyperosmolarity. It will therefore be interesting to determine whether these could also be involved in the fine-tuning of osmolarity control by the hypothalamus and what their potential targets might be.

Ruth Williams

ORIGINAL RESEARCH PAPER Lee, H.-J. *et al.* miR-7b, a microRNA up-regulated in the hypothalamus after chronic hyperosmolar stimulation, inhibits Fos translation. *Proc. Natl Acad. Sci. USA* **103**, 15669–15674 (2006)

mice. Furthermore, in *Per2* mutants, expression of the clock-controlled genes *Dbp* and *Avp* in the SCN was greatly reduced.

Although these results indicated that *Per1* and *Per2* have a role in the resetting of the central body clock by nutritional cues, peripheral food-entrainable oscillators did not require *Per1* and *Per2*. Using quantitative PCR, the researchers showed that food restriction caused phase shifts in the expression of clock genes *Bmal1* and *Rev-Erbα* and the clock-controlled gene *Dbp* in the liver and kidney that were similar in *Per1* and *Per2* mutants and in wild-type mice.

This study provides evidence that that *Per1* and *Per2* are involved in the mechanism by which nutritional cues entrain the central, but not peripheral clocks and shows for the first time that *Per2* is crucial for the ability to anticipate circadian cycles of food availability.

Leonie Welberg

ORIGINAL RESEARCH PAPER Feillet, C. A. *et al.* Lack of food anticipation in *Per2* mutant mice. *Curr. Biol.* **16**, 2016–2022 (2006)

CANCER

Rooting out resistance

Glioblastomas are aggressive brain tumours that rapidly become resistant to radiotherapy. Jeremy Rich and colleagues now show that glioma stem cells are the root of this problem.

Glioblastomas present as diffuse tumours that invade normal brain tissue, and patients who are diagnosed with this disease have a median survival of less than 12 months. Glioblastomas recur after treatment with radiation, but often as focal masses, suggesting that only a small proportion of cells are responsible for recurrence. Both normal brain stem cells and brain tumour stem cells have recently been characterized, and cells that express prominin 1 (also known as CD133) often show stem-cell-like characteristics.

Rich and colleagues asked whether the glioma subpopulation of $CD133^+$ cells is involved in the development of radioresistance. A fourfold enrichment of the $CD133^+$ cell population from human explants is evident after treatment with ionizing radiation *in vitro*, and the authors showed that radiation does not induce CD133 expression in $CD133^-$ cells. In addition, increasing the percentage of $CD133^+$ cells in a defined number of glioblastoma tumour cells decreases the time taken for the tumours to grow in the frontal lobes of immuno-compromised mice, indicating the enrichment of tumorigenic stem cells.

So, are $CD133^+$ glioma stem cells more resistant to radiotherapy? *In vitro* colony-formation assays after the irradiation of either $CD133^-$ or $CD133^+$ cells from the same patient or xenograft confirmed that more $CD133^+$ cells survive this treatment. Moreover, viable $CD133^+$ cells from irradiated xenografts formed secondary tumours in mice with the same kinetics as $CD133^+$ cells that had not been irradiated, indicating that 2 Gy of radiation does not reduce the tumour-forming capacity of these cells.

Why can these cells survive radiation treatment? The authors analysed DNA-damage checkpoints in both the $CD133^-$ and $CD133^+$ cell populations, and found that $CD133^+$ cells show greater activation (levels of phosphorylation) of DNA-damage checkpoint proteins such as ataxia telangiectasia mutated (ATM) and RAD17. Although both cell populations sustain the same level of DNA damage (shown by analysing DNA double-strand breaks using the comet assay) in response to irradiation, the repair of these breaks occurs 4–9 times more rapidly in $CD133^+$ cells. The pre-treatment of $CD133^+$ cells with an inhibitor of the DNA-damage checkpoint kinases CHK1 and CHK2 reduced the survival of these cells after irradiation *in vitro*.

> “Drugs that target the DNA-damage checkpoint are in pre-clinical and clinical trials … their use might improve the outcome for patients…”

Drugs that target the DNA-damage checkpoint are in pre-clinical and clinical trials, and these results suggest that their use might improve the outcome for patients with glioblastoma and potentially other solid tumours.

Nicola McCarthy, Senior Editor,
Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Bao, S. *et al.* Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 18 October 2006 (doi:10.1038/nature05236)