CANCER

Appetite suppressors

Many people with cancer experience a prolonged loss of appetite and weight loss, and it is thought that this cancer-induced anorexia results from the effects of tumour-derived signals and/or cancer-associated inflammation on feeding-related neural circuits. However, it is unclear exactly which neurons mediate the suppression of appetite in this context. Now, Campos *et al.* show in mice that calcitonin gene-related peptide-expressing (CGRP⁺) neurons in the external parabrachial nucleus (PBN) can drive cancer-induced anorexia and related behaviours.

Previous studies showed that activation of CGRP⁺ PBN neurons can suppress appetite and that these cells lie downstream of agouti-related peptide-expressing neurons in the hypothalamus, which have been previously linked to cancer-induced anorexia. Here, the authors examined how altering the activity of CGRP⁺ PBN neurons affected feeding in two mouse models of cancer.

First, they subcutaneously implanted Lewis lung carcinoma (LLC) cells — which induce anorexia and weight loss in mice — into transgenic animals in which CGRP⁺ PBN neurons were fluorescently labelled. 40% of the CGRP⁺ PBN neurons showed FOS expression — a marker of neural activation — in mice with LLC tumours, whereas

in sham-treated animals only 3% of such neurons showed FOS expression, indicating that the presence of tumours is associated with CGRP⁺ PBN neuronal activity.

Next, the authors virally expressed tetanus toxin light chain (TetTox) in CGRP⁺ PBN neurons in the transgenic mice to permanently inactivate these cells before they implanted the LLC cells. These mice showed a rise in food intake after LLC cell implantation, as opposed to the decrease observed in mice with active CGRP⁺ PBN neurons after the introduction of LLC cells. Moreover, pharmacological inhibition of CGRP⁺ PBN neurons in LLC cell-implanted mice that were already showing anorexia reversed this behaviour. Thus, these data indicate that CGRP⁺ PBN neuronal activity is required to induce anorexia in the LLC cell-implantation mouse model.

The other mice examined by the authors harboured a mutation in the gene encoding adenomatous polyposis coli protein (*Apc*^{min/+} mice). These mice develop intestinal cancer and, although they do not exhibit a loss of appetite, they are unable to up their intake of food in spite of cancer-induced weight loss, which is a feature of cancer-induced anorexia.

The authors found that *Apc*^{min/+} mice that had developed tumours and exhibited weight loss showed an abnormally high level of CGRP⁺

PBN neuronal activity, as revealed by FOS expression. TetTox-mediated inactivation of such neurons before the onset of weight loss in *Apc*^{min/+} mice led to increased food intake and prevented development of the weight-loss phenotype. These data provide further evidence that CGRP⁺ PBN neurons may have a key role in mediating cancer-induced anorexia.

Other 'sickness behaviours', such as lethargy and anxiety, are often found alongside anorexia in people with cancer. Interestingly, the authors found that mice showed decreases in locomotor activity and nest building (used here as a measure of motivation) and an increase in anxiety-like behaviour (as assessed on the elevated plus maze and the open-field test) following LLC cell implantation and that TetTox-mediated inactivation of CGRP⁺ PBN neurons before implantation precluded these behavioural changes. Thus, CGRP⁺ PBN neurons are important in mediating various sickness behaviours in this murine cancer model.

Together, these data suggest that CGRP⁺ PBN neuronal activity may be a key driver of cancer-induced anorexia and its associated behaviours.

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ORIGINAL ARTICLE Campos, C. A. *et al.* Cancer-induced anorexia and malaise are mediated by CGRP neurons in the parabrachial nucleus. *Nat. Neurosci.* <http://dx.doi.org/10.1038/nrn.4574> (2017)