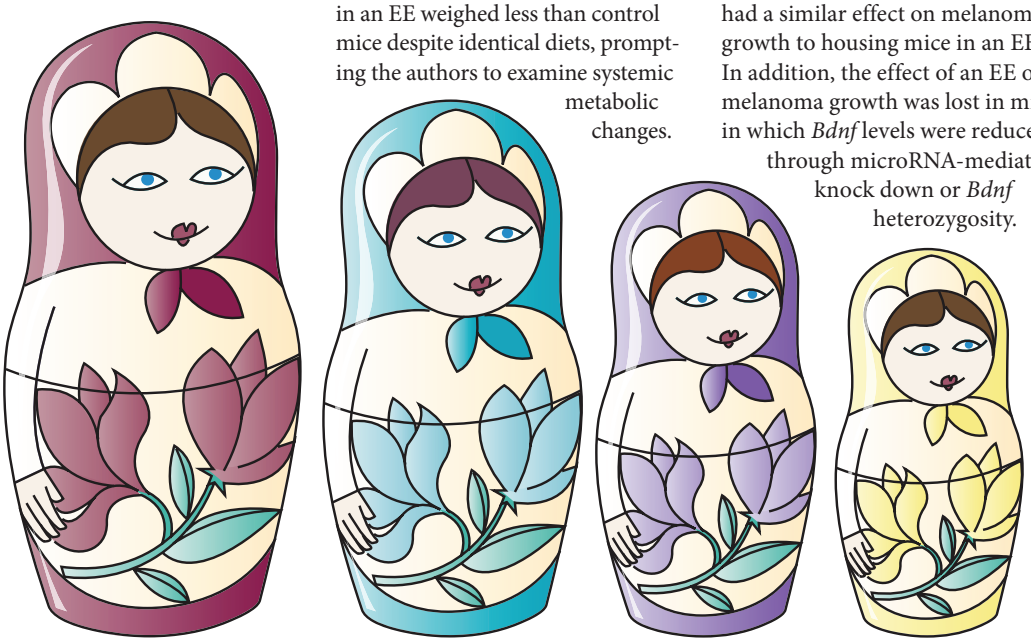
MACROENVIRONMENT

Stimulating resistance

A link between a positive environment and a better outcome for cancer patients has long been inferred, but it has been difficult to prove in the absence of concrete molecular pathways to underpin such an effect. A paper recently published in *Cell* may go some way to addressing this, as it found that mice living in an enriched environment (EE) are more resistant to tumour growth through a pathway involving brain-derived neurotrophic factor (BDNF), leptin and adiponectin.

An EE for mice consists of complex housing that contains sensory, cognitive, motor and social stimulation, as opposed to a standard cage. Lei Cao and colleagues found that the growth rate of transplanted malignant melanoma cells in mice housed in an EE was significantly reduced compared with mice housed in standard (control) conditions. Mice in an EE weighed less than control mice despite identical diets, prompting the authors to examine systemic metabolic changes. Levels of insulin-like growth factor 1 and leptin were reduced in mice housed in EE cages, and serum from these mice reduced the growth of melanoma cells *in vitro*. Increased levels of both of these factors have been associated with an increased risk of cancer development and progression, as they can stimulate the growth of cancer cells. Conversely, levels of adiponectin were increased.

Leptin is a hormone that relays information back to the hypothalamus, which is involved in regulating energy balance along with the production of neuroendocrine factors and the regulation of the immune system through the hypothalamic–pituitary–adrenal axis. Expression of BDNF by the hypothalamus was increased early on when mice were placed in an EE. Overexpression of BDNF through the infection of mice with viruses expressing this gene had a similar effect on melanoma growth to housing mice in an EE. In addition, the effect of an EE on melanoma growth was lost in mice in which *Bdnf* levels were reduced through microRNA-mediated knock down or *Bdnf* heterozygosity.



How does BDNF influence the levels of leptin and adiponectin? Both leptin and adiponectin are predominantly synthesized by white adipose tissue, and suppression of leptin expression is thought to be influenced by the baseline activity of the sympathetic nervous system affecting the expression of β-adrenergic receptors (β-ARs). The expression of β-ARs and one of their ligands, noradrenaline, was increased in white adipose tissue from mice housed in EE cages. Use of a β-blocker prevented the EE-mediated changes in leptin and adiponectin levels as well as the reduced growth of the transplanted melanoma cells. Moreover, leptin-deficient (*ob/ob*) mice did not show reduced melanoma growth when housed in an EE.

These results were not restricted to melanoma; injection of mice with colon cancer cells, or transgenic mice that spontaneously develop colon cancer ($Apc^{Min/+}$ mice), had reduced tumour burden in an EE compared with mice housed in control conditions. Moreover, exposure of mice with established tumours to an EE led to prolonged survival.

Overall, these data indicate that exposure to an EE induces increased expression of BDNF in the hypothalamus, which induces activation of the sympathetic nervous system resulting in the production of noradrenaline and increased expression of β-ARs in white adipose tissue, which suppresses leptin and increases adiponectin levels. This, combined with an increase in the immune response in mice housed in an EE, suggests that exposure to 'positive stress' reduces the growth of tumours in mice.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Cao, L. *et al.* Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis causes cancer remission and inhibition. *Cell* **142**, 52–64 (2010)