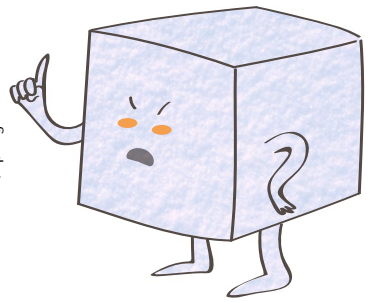


Credit: Lara Crow/Springer Nature Limited

compared with non-diabetic mice. Metformin, an activator of AMPK, reduced the growth of TET2WT tumours in both non-diabetic and diabetic mice, whereas mock tumours were not sensitive to metformin.

This newly identified glucose–AMPK–TET2–5hmC axis provides an additional molecular basis for the anticancer effect of metformin, and potential targeting of this axis in selected patients could be used for cancer prevention.

Ulrike Harjes

ORIGINAL ARTICLE Wu, D. et al. Glucose-regulated phosphorylation of TET2 by AMPK reveals a pathway linking diabetes to cancer. *Nature* **559**, 637–641 (2018)

mirrored in patients with glioblastoma. An inverse relationship between bone marrow T cell counts and T cell surface S1P1 levels was observed in both mice and humans.

Finally, the authors investigated whether stabilizing surface S1P1 might enable T cells to resist sequestration. They utilized a S1P1 knock-in mouse strain in which S1P1 internalization was hindered. Sequestration of T cells was markedly reduced in glioma-bearing knock-in mice, although they showed no improvement in survival. However, stabilization of S1P1 in conjunction with T cell activating therapies, such as 4-1BB agonism and immune checkpoint blockade, proved effective. The authors conclude "reversal of T cell sequestration may serve as a useful therapeutic adjunct", perhaps through the development of pharmacological means for stabilizing S1P1.

Isobel Leake

ORIGINAL ARTICLE Chongsathidkiet, P. et al. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. *Nat. Med.* https://doi.org/10.1038/s41591-018-0135-2 (2018)

METASTASIS

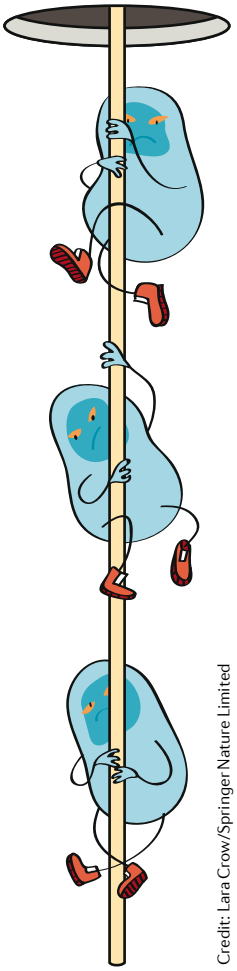
Leukaemic escape routes

Acute lymphoblastic leukaemia (ALL) can be widely metastatic, often invading organs such as the spleen, lymph nodes and central nervous system (CNS). ALL metastasis to the CNS largely involves the leptomeninges, in contrast to the parenchyma, which is the predominant site for brain metastases of solid tumours. Although all subtypes of ALL display a propensity to disseminate to the CNS, a common molecular mechanism for invasion has not been identified. Now, Yao et al. have established that ALL cells, instead of metastasizing within the circulation, can use a neuronal pathfinding mechanism to navigate along the vascular channels that directly bridge the bone marrow to the meninges, leading to CNS disease in mice.

To determine whether ALL cells can metastasize to the CNS via a haematogenous route, the authors intravenously engrafted fluorescently labelled Nalm-6 pre-B ALL cells derived from a patient with CNS relapse into mice and used real time in vivo microscopy to visualize the meningeal and superficial cerebral vasculature through thinned skin windows. This revealed that while Nalm-6 cells could transiently arrest inside microvessels at early time points after engraftment, they did not diapedese across the leptomeningeal blood–brain barrier, despite being present as metastases in leptomeningeal tissue at late disease stages. The choroid plexus vasculature was also eliminated as a potential site of entry, as Nalm-6 cells were seldom found in choroid vessels or choroid tissue. However, shortly after engraftment, Nalm-6 cells had invaded through the bone marrow vasculature.

Early histological studies of patients with ALL in the CNS indicated that lymphoblasts were first detected in the basement membrane of superficial arachnoid veins in the brain. Therefore, the researchers hypothesized that ALL cells could access the CNS by migrating along the extracellular matrix (ECM) of emissary bridging vessels. Contained within bone channels, these small vessels could be identified in healthy mice connecting the vertebral bone marrow to the subarachnoid space. Importantly, ALL cells in the Nalm-6-engrafted mice were observed filling the many openings in the vertebral cortical bone, indicative of ALL cells in transit to the CNS.

The ECM protein laminin is localized to specific regions in the CNS, coating the meninges and a subset of blood vessels. Immunohistochemical staining revealed that the vessels within the bone channels of mice were laminin positive. As neural stem and/or progenitor cells (NSPCs) during embryonic development have been shown to migrate to the olfactory bulb along the ECM of vessels in a manner dependent upon the laminin receptor α6 integrin, the authors reasoned that ALL cells could migrate along the abluminal surface of emissary vessels. Consistent with this idea, ALL cells, including Nalm-6 cells, were positive for surface expression of α6 integrin.



Credit: Lara Crow/Springer Nature Limited

To test whether a molecularly targeted intervention could prevent CNS disease, the authors treated leukaemic mice with a PI3Kδ inhibitor tool compound, GS-649443. The clinical end point for euthanasia of the Nalm-6 mouse model of ALL is CNS complications including paresis and not bone marrow failure. Treatment with GS-649443 switched the clinical end point, with most mice being euthanized instead as a result of bone marrow failure. In addition, PI3Kδ inhibition specifically reduced CNS disease burden by ~50%, decreased the amount of ALL infiltrates in bony channels and prolonged survival of the mice. In vitro, GS-649443 also decreased the membrane expression of α6 integrin on ALL cells.

Additional evidence that ALL invades the CNS via α6 integrin–laminin-based migration came from treating Nalm-6-engrafted mice with α6 integrin-blocking antibodies. Treated mice exhibited a modest increase in survival without incidence of paresis at the point of euthanasia.

As α6 integrin expression on ALL cells from bone marrow biopsy samples of patients was shown to correlate with CNS relapse, this study reasons that clinically available PI3Kδ inhibitors, such as idelalisib could have utility in preventing CNS disease in patients with B cell leukaemias.

Anna Dart

ORIGINAL ARTICLE Yao, H. et al. Leukaemia hijacks a neural mechanism to invade the central nervous system. *Nature* **560**, 55–60 (2018)