acids[2,3]. When nutrients are scarce, however, this complex is inactivated, allowing individual cells — and the whole organism — to economize on nutrients by halting cell growth.

Much progress has been made in our understanding of how mTORC1 senses growth signals (Fig. 1). This complex responds to systemic nutrient signals through a biochemical pathway that is initiated at the cell surface by secreted factors. The pathway communicates with a regulatory circuit that involves the protein complex TSC and its target Rheb — an essential activator of mTORC1 (refs 2, 3). In the absence of secreted growth factors, TSC inhibits the ability of Rheb to stimulate mTORC1 activity. As for local nutrients, cells mainly sense intracellular amino-acid levels through a second set of essential mTORC1 activators called Rag proteins[2,3]. Both Rheb and Rag signals are essential, providing a mechanism by which mTORC1 can integrate systemic and local nutrient signals. Consequently, mTORC1 is activated, and so promotes cell growth, only under conditions that are favourable to both the cell and the whole organism.

Bar-Peled *et al.* identify GATOR as a crucial regulator of Rag proteins. They show that this protein complex is required for mTORC1 inhibition in response to amino-acid shortage in the cell — an evolutionarily conserved mechanism for sensing amino acids that is also present in yeast and fly cells[1,4,5]. Just as the TSC complex inhibits Rheb, GATOR seems to inhibit the ability of Rag proteins to activate mTORC1 under conditions of nutrient deprivation (Fig. 1).

Because mTORC1 is a major promoter of cell growth, it is not surprising that it is abnormally activated in most human cancers across nearly all cell lineages[6]. Some of the most frequent genetic changes in cancer lead to persistent activation of this complex, at least in part by permanently activating pathways that inhibit the TSC complex. Furthermore, components of the TSC complex are mutated in some cancers and in the cancer-like syndromes tuberous sclerosis complex and lymphangioleiomyomatosis, which are driven by uncontrolled mTORC1 activity. These genetic changes disconnect mTORC1 signalling from systemic nutrient control by growth factors. Loss of TSC-complex-mediated regulation facilitates cell-autonomous growth in a tumour, rendering it largely independent of organismal nutrient status.

The present study suggests that defects in local nutrient sensing can also contribute to mTORC1 activation and tumour-cell growth. The authors show that on disruption of protein components of GATOR, mTORC1 can no longer sense local amino-acid levels, remaining active irrespective of the cellular availability of these nutrients. Moreover, the genes encoding NPRL2, NPRL3 and DEPDC5 (the core components of GATOR that are involved in Rag inhibition) are tumour suppressors, and their mutation or deletion occur in a variety of human cancers, albeit at low frequency[1,7]. From the cancer-cell perspective, what could be the advantage to tumour development of disrupting local nutrient signals?

Generally, homeostatic pathways that monitor nutrient fluctuations in the cell, and alter cellular physiology accordingly, promote cell survival. Such adaptive responses would seem to be equally, or even more, important in the immediate environment of a growing tumour, where insufficient or immature vasculature might lead to variable delivery of nutrients to the tumour cells. Loss of other nutrient-sensing pathways (including the LKB1–AMPK pathway) that act as tumour suppressors sensitizes tumour cells to nutrient starvation or to drugs that mimic aspects of starvation[8,9]. Therefore, a vulnerability to nutrient deprivation is likely to counterbalance the advantage of a sustained increase in mTORC1 activity after GATOR loss. An explanation for selective loss of this and other nutrient-sensing pathways in tumours could be that removal of these brakes on cell growth provides a growth advantage under suboptimal — but not growth-limiting — nutrient levels that would normally inhibit mTORC1.

Bar-Peled and colleagues' findings could have implications for cancer treatment. They find that, compared with some other cancer cells, GATOR-mutant cells are more sensitive to the mTORC1 inhibitor rapamycin. In addition to targeted therapeutics such as rapamycin, exploiting specific vulnerabilities arising from disruption of inherent adaptive responses to nutrient availability might provide alternative strategies for selectively killing cancer cells. Indeed, cancer cells that lack these adaptive responses might be particularly susceptible to nutrient mimetics, such as amino-acid or glucose analogues; drugs that cause general metabolic stress in cells, including the anti-diabetes drug metformin; or compounds that target the specific metabolic dependencies of tumour cells. These are all active areas of investigation in the field of cancer metabolism. ■

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50 Years Ago

Nowadays, most scientists who reach a fair degree of seniority in their profession are called on at some time … to plan a new laboratory. On the first occasion, they usually tackle this with enthusiasm, pride and little else, other than their own prejudices or knowledge of the deficiencies of the laboratories they have themselves worked in.
From *Nature* 29 June 1963

100 Years Ago

A shameful outrage has just been perpetrated at the Gatty Marine Laboratory of St. Andrews … The laboratory has always been freely open to scientific workers of both sexes … and might therefore have been expected to be immune from attack; yet it has been fired, apparently by militant suffragettes … It appears that on Saturday, June 21, the incendiaries effected an entry by smashing one of the windows … The print of a small shoe, and suffragette literature stuck between the wall and a rain-pipe, were the only traces left. Fortunately the fire was seen by a fisherman, who gave the alarm.
ALSO:
Yorkshire Education Committee has decided to include in the vacation … a laboratory course of experimental science … This course is intended for science teachers in secondary schools, and especially for those who teach the subject to girls and desire to acquaint themselves with methods of correlating it with domestic subjects. It will relate chiefly to the subject of combustion … provide examples of the teaching of science in relationship to the phenomena and appliances of daily life and especially of domestic life; and give a connected account of the modern science of combustion and the chemistry of flame.
From *Nature* 26 June 1913