Tumour biology

Learning the metabolic language of cancer

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The conversion of dietary sugar to the molecule lactate is a hallmark of many cancers. The discovery of a new binding partner of lactate provides insight into how cells link nutrient metabolism to the decision to divide. See p.790

Lactate is a molecule formed by metabolism of the sugar glucose, and is made in high amounts by tumours and oxygen-deprived tissues, such as muscle cells during exercise. Outside cells, lactate circulating in the bloodstream can serve as a fuel source for many tissues[1]. Inside cells, an open question is whether lactate is mainly a waste product destined for excretion, or whether it can 'speak' directly to processes involved in cellular physiology and disease. On page 790, Liu *et al.*[2] identify a way in which lactate aids cell proliferation: by inhibiting a type of enzyme, called a protease, that is involved in cell-cycle regulation.

In addition to providing energy and cellular building blocks, metabolites can bind directly to proteins and nucleic acids to alter their function. This process is important for biochemical regulation across the tree of life, and resembles how small-molecule drugs work. To investigate whether lactate has regulatory functions that have not been described previously, Liu and colleagues exploited a method called thermal proteome profiling, which is commonly used to study drugs[3]. This technique monitors the ability of a molecule (a ligand) to bind to a protein and prevent the protein from falling apart when heated — analogous to using an extra support pole to stop a tent collapsing during a storm. Using this method to monitor lactate's effect on thermal stability across many proteins, the authors identified the enzyme UBE2C as a protein that is uniquely stabilized by lactate.

UBE2C is a component of a protein complex called APC/C, and it controls progression through the final stage of the cell cycle (termed mitosis). On the assumption that molecules as small as lactate rarely function to increase thermal stability, Liu and colleagues gathered evidence that lactate stabilizes UBE2C by helping it to bind to the large APC/C complex. This is a provocative finding because interaction between APC/C and UBE2C is required for mitosis, a process that occurs when lactate levels in the cell are at their highest.

How might lactate promote UBE2C's interaction with APC/C? The authors surmised that it might be causing a protein modification that 'glues' these proteins together. Lactate itself can modify proteins directly[4,5], but, surprisingly, this was not observed. Instead, the authors found that lactate has the effect of strongly inducing a modification known as SUMOylation (the attachment of a member of the SUMO family of proteins) at two amino-acid residues on the protein APC4, which is a subunit of APC/C. Furthermore, when these APC4 residues are mutated, lactate no longer stimulates the binding of APC/C to either its substrate the protein cyclin B1 or to UBE2C.

To understand the biochemical mechanism underlying metabolite-induced APC/C activation, the authors investigated lactate's ability to inhibit enzymes involved in 'erasing' the SUMO modification. Previous work implicated the protease SENP1 in the removal of SUMO from APC4 during mitosis. Inhibition of SENP1 by lactate could explain lactate-induced SUMOylation of APC/C and thus UBE2C binding (Fig. 1). Liu and colleagues decided to closely analyse the structure of SENP1. This revealed a site of interest — a potential 'coordination pocket' for zinc ions to bind to, near the enzyme's active site. Because lactate is known to bind to zinc ions, the authors propose that high concentrations of lactate inhibit SENP1 by interacting with this zinc, and Liu *et al.* present substantial biochemical and structural evidence to support the plausibility of this mechanism.

Another key question the authors sought to address is whether the newly identified connection between lactate and APC/C is physiologically relevant. Liu *et al.* used biochemical quantification, in combination with careful measurements of cell volume, to confirm that levels of lactate indeed peak at mitosis. The proposed relationship between lactate and the cell cycle was then manipulated by altering cellular lactate levels using multiple methods in wild-type and APC4-mutant cell lines. Several hallmarks of mitotic progression,

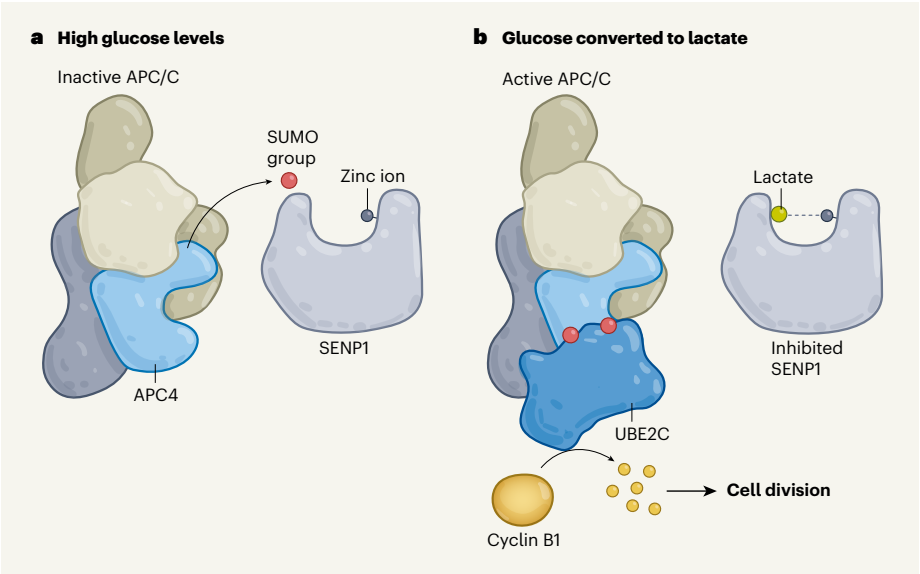

Figure 1 | A 'waste product' of the metabolism of sugar facilitates cell division. a, In a human cell that is not dividing, glucose (not shown) is present and a protein complex required for division, called APC/C, is inactive and lacks one of its components, the protein UBE2C. UBE2C is unable to bind to APC/C because the protein APC4 does not have a modification called SUMOylation — the addition of protein groups from the SUMO family. The enzyme SENP1, which contains a zinc ion bound in a pocket near the enzyme's active site, can remove SUMO groups from APC4. **b**, The metabolism of glucose can generate the molecule lactate, the concentration of which peaks as cells prepare to divide. Liu *et al.*[2] provide evidence that high concentrations of lactate can inhibit SENP1. The authors propose that lactate forms a complex with zinc in SENP1's active site that inhibits the enzyme. This results in the SUMOylation of APC4, triggering structural remodelling of the APC/C that enables UBE2C to bind. The assembled functional APC/C degrades the protein cyclin B1 to aid progression of the cell cycle.

including APC/C-substrate degradation and the ability of drugs to induce mitotic arrest, were highly dependent on lactate in wild-type cells but not in mutant cells. These findings are consistent with the existence of a functional link between lactate, SENP1 and APC4 in cells. A further implication of this finding is that inhibitors of lactate production might help to overcome resistance to antimitotic chemotherapy drugs, although this remains to be shown.

"Cancer cells convert glucose to lactate even when oxygen is available."

It is fitting that the identification of another function for lactate coincides with the 100th anniversary of the report by Otto Warburg that cancer cells convert glucose to lactate even when oxygen is available[6]. Warburg also proposed that this faulty process of respiration is a root cause of cancer. Although that theory has been largely superseded, Liu and colleagues' work emphasizes that such 'Warburg' metabolites have functions in the cell, and raises the possibility that more remain to be discovered.

The study also provides clues about how to find new 'words' in the emerging language that metabolites use to talk to proteins. In addition to using drug–target engagement strategies such as thermal proteome profiling to address this, the authors demonstrate that the interaction between lactate and SENP1 is stereoselective (it has a 'handedness', in a similar way to how a left hand fits only into a left-handed glove), which is a hallmark of many authentic ligand–receptor interactions[7]. Liu and colleagues used a genetically encoded bacterial enzyme to deplete lactate[8] as part of their cellular validation, an approach that could be potentially developed further to manipulate metabolite–protein interactions in specific organelles.

A subtle idea arising from the study is that protein regulation by small metabolites such as lactate might be necessarily cooperative. In this case, SENP1 inhibition requires two stimuli: lactate accumulation and the presence of zinc. This calls to mind other metabolic mechanisms that are cooperative (such as proton-promoted fumarate electrophilicity[9] and sensing of the ratio of the metabolites 2-oxoglutarate and succinate by iron- and oxygen-dependent enzymes called dioxygenases[10]). Designing experiments to capture these types of multipartite interaction will require creativity and rigorous validation, but, as Liu and colleagues' work demonstrates, this has the potential to reveal fresh chapters in metabolite signalling.

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