pathways[9] are needed — and needed now. The hope is that this evidence will soon raise global recognition of the fact that unprecedented hazards require unprecedented adaptation.

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Biochemistry

Cancer metabolism pumped up by Akt protein

Philipp Poeller & Almut Schulze

Mutated forms of the protein Akt can be central drivers of cancer metabolism. A mechanism by which Akt promotes synthesis of the metabolic molecule coenzyme A broadens our understanding of the protein's activity. **See p.192**

The protein Akt is part of a signalling cascade that is frequently activated in human cancer[1]. In healthy cells, Akt regulates many metabolic processes, including glucose metabolism and the synthesis of fatty acids[2]. These metabolic programs are enhanced in cancer to support rapid cell division, and so the role of Akt activation in these cancer-related changes is of great interest. Dibble *et al.*[3] show on page 192 that Akt targets a central point of cellular metabolism, by inducing the synthesis of the metabolic molecule coenzyme A.

Coenzymes are small molecules that assist in chemical reactions and that have to be regenerated after the reaction has taken place. Coenzyme A (CoA) facilitates the coupling of acyl groups to other molecules and participates in multiple metabolic pathways, including the metabolism of glucose, amino acids and lipids[4]. In its most prominent form, as acetyl-CoA, it provides essential building blocks for lipid assembly. In addition, acetyl-CoA regulates protein function, for example by providing substrates for a process called histone acetylation, which modulates gene expression[5]. Rapidly dividing cancer cells need to replenish their CoA pool constantly to keep up with the metabolic demands of rapid cell division, which requires high levels of biomass production.

Dibble *et al.* activated Akt in cells by stimulating them with insulin, and investigated the resulting metabolic changes using mass spectrometry. This revealed a marked increase in the synthesis of CoA from its precursor, pantothenate (vitamin B_5), through a multi-step process. The authors then carried out a series of experiments to show that increased CoA synthesis is indeed mediated directly by Akt and not by other downstream effectors of the insulin pathway.

Akt is a protein kinase — an enzyme that adds a phosphate group to other proteins to modulate their function, acting at a specific recognition site in the target protein. The authors therefore searched for such a site in the proteins linked to CoA biosynthesis and identified several pantothenate kinase (PANK) enzymes as potential Akt targets. Further experiments confirmed that Akt phosphorylates PANK2 and PANK4.

PANK2 catalyses the initial step of CoA synthesis (the conversion of pantothenate

From the archive

A scientific society in Renaissance Italy, and concern about attempts to forge fingerprints.

50 years ago

The Experimenters: a Study of the Accademia del Cimento.
By W. E. Middleton — The Accademia del Cimento of Florence has always fascinated scientists. It existed for very little more than ten years (1657–1667, approximately), and during that period rumours of its devotion to experiment combined with some news of the experiments it performed caused the learned world to await with great eagerness its research report, published in 1667 under the title *Saggi di Naturali Esperienze* ... [T]he enterprise remains of interest, for the Accademia del Cimento was a fascinating blend of currents. The patron and, as it were, President of the Academy was Prince Leopold de' Medici, brother of Grand Duke Ferdinand of Tuscany ... Prince Leopold was energetic in designing experiments on freezing — a subject of perpetual fascination to Italians.
From *Nature* 4 August 1972

100 years ago

It is disconcerting to learn from an article ... in ... the new publication, *Dactylography,* that the practice of forging finger-prints is increasing and will soon become a problem for New Scotland Yard. The criminal must first obtain specimens of the prints of the dupe on whom he intends that suspicion should fall. This he does by arranging that the dupe leaves his prints on a glass, or on a polished piece of furniture, after which the prints are photographed. One method of forging involves the use of a rubber stamp, where a facsimile of the original is reproduced on the rubber by means of transfer paper, and the surrounding rubber deftly pared away with a sharp knife. The second method is to take a negative cast of the finger to be forged by pressing it into a mould of soft wax, plaster of Paris, clay, or even bread. A third process involves photographing a photograph of the prints to be forged on a reversed plate.
From *Nature* 5 August 1922

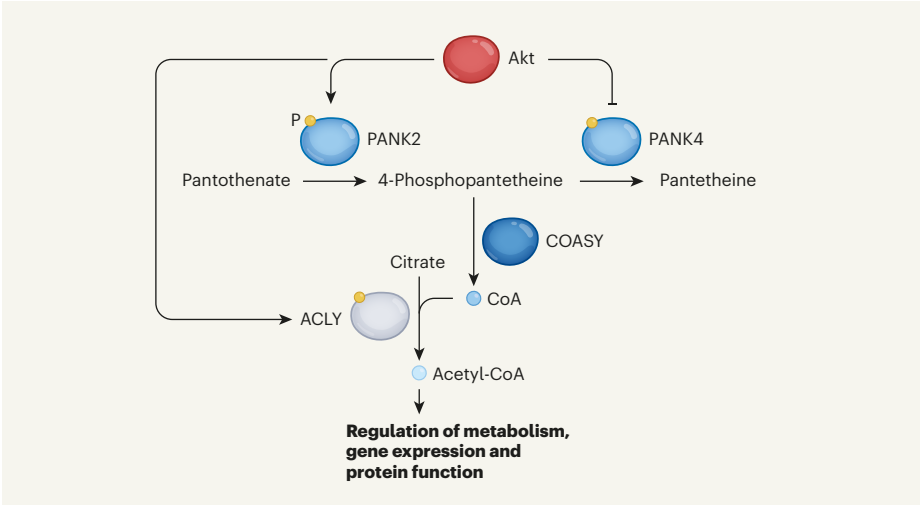

Figure 1 | Regulation of acetyl-CoA synthesis. Dibble *et al.*[3] report that the protein Akt, which is frequently activated in cancer, controls production of coenzyme A (CoA) molecules by modulating the activity of two PANK proteins. First, Akt activates PANK2 through the addition of a phosphate group (P). Activated PANK2 catalyses the first of three steps required to convert pantothenate molecules to 4-phosphopantetheine (second and third steps not shown). 4-Phosphopantetheine can then be converted to CoA by the enzyme COASY. Second, Akt-mediated phosphorylation inhibits PANK4. Active PANK4 converts 4-phosphopantetheine to pantetheine and so acts to prevent CoA synthesis. CoA is used by the enzyme ATP-citrate lyase (ACLY; itself also activated by Akt-mediated phosphorylation) to convert citrate to acetyl-CoA, which is a central intermediate in metabolism, gene expression and protein function.

molecules to 4-phosphopantothenate, which is in turn undergoes a two-step process to be converted to 4-phosphopantetheine, a precursor of CoA). Dibble and colleagues therefore suspected that phosphorylation by Akt was activating PANK2, and so activating CoA synthesis. However, although a drug that blocks PANK activity abolished CoA synthesis, genetic deletion of PANK2 from cells did not clearly do so. The researchers therefore turned their attention to the less-studied PANK4.

PANK4 differs from other PANK enzymes because its predicted kinase domain is inactive but is linked to a phosphatase domain that removes phosphate groups from metabolite molecules. Surprisingly, Dibble and colleagues found that expression of PANK4 decreased CoA synthesis, and that this effect was abolished when they prevented phosphorylation of PANK4 by Akt. Further experiments revealed that PANK4 uses its phosphatase domain to remove further intermediates from the CoA synthesis pathway by converting 4-phosphopantetheine to pantetheine. Thus, phosphorylation of PANK4 by Akt inhibits PANK4 activity, redirecting 4-phosphopantetheine towards CoA production (Fig. 1).

Dibble *et al.* further investigated the effect of PANK4 expression on the metabolism of cells expressing activated Akt. They found that wild-type PANK4, but not a version in which the phosphatase domain had been inactivated, lowered cellular oxygen consumption, reduced histone acetylation and led to changes in the abundance of numerous metabolites and lipids. The phosphatase domain of PANK4 was also essential for the ability of the protein to decrease cell proliferation and reduce tumour growth in a mouse model of breast cancer, suggesting that targeting this domain or inhibiting CoA synthesis in other ways could be of therapeutic value.

These results add to our understanding of how acetyl-CoA – a key link between cancer signalling and metabolism – is regulated. Several mechanisms by which Akt stimulates acetyl-CoA production were already known. One such mechanism is Akt-mediated activation of an enzyme called ATP-citrate lyase[6], which produces acetyl-CoA from citrate, a major intermediate of glucose metabolism. Another is the production of acetyl-CoA from acetate, which is triggered when Akt indirectly activates expression of the protein ACSS2 (ref. 7). The finding that Akt also increases the production of CoA itself now adds a missing piece to the puzzle.

By inhibiting PANK4, Akt effectively shuts an overflow valve for CoA synthesis, rather than just opening the tap. This mode of regulation raises interesting questions. Why are intermediates constantly drained from the CoA synthesis pathway? Perhaps this makes the pathway more responsive to acute changes in metabolic demand and ensures that intermediates do not accumulate to toxic levels. Indeed, the authors acknowledge that PANK4 might help to remove oxidized derivatives of 4-phosphopantetheine from cells. It will be interesting to investigate whether PANK4 could have further functions, for example in controlling levels of harmful molecules called reactive oxygen species.

Because CoA acts as a central node in metabolism, targeting its synthesis is likely to affect numerous processes that are important for cancer cells. For example, CoA plays a part in the mevalonate pathway, which drives biosynthesis of the lipid cholesterol and produces molecules needed to target key signalling proteins, such as Ras, to their correct locations in the cell[8]. Moreover, 4-phosphopantetheine is an essential part of the enzyme fatty-acid synthase[9] and so acts as a coenzyme for the biosynthesis of fatty acids, which are part of complex lipids. Akt-mediated inhibition of PANK4 could therefore support lipid synthesis through multiple pathways. CoA also regulates proteins, either through enabling addition of acyl groups to histone proteins associated with DNA[10] (which can lead to changes in gene expression) or through direct binding of other proteins (which protects them from oxidative damage)[11]. Going forward, researchers should investigate how inhibition of CoA synthesis by PANK4 contributes to Akt-dependent changes in lipid synthesis, gene expression and the oxidative-stress response – and how this affects the growth of cancer cells.

That said, targeting CoA synthesis therapeutically might be challenging, because activating the PANK4 phosphatase domain or preventing the enzyme's phosphorylation by Akt is difficult to achieve with small molecules. Furthermore, systemic targeting of CoA synthesis is likely to have major side effects, meaning that the benefits of treatment might have to be weighed carefully against potential damage. Further work will be required to define the effects of interfering with CoA synthesis in normal and diseased cells. Nevertheless, Dibble and colleagues' study provides much-needed insight into a key role for Akt in the metabolic regulation of cancer.

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