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BIOCHEMISTRY

A toxin that fuels metabolism

Formaldehyde, a DNA-damaging agent formed in cells, has now been shown to support metabolic processes that involve molecular units containing a single carbon atom — linking metabolism to a DNA-protection mechanism.

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Metabolism is the set of biochemical reactions that processes nutrients to achieve specific goals that benefit cellular or organismal fitness[1]. The outcomes include the production of biomolecules such as nucleic acids, and the maintenance of a specific cellular redox state that can mitigate the effects of oxidative stress. The one-carbon metabolic pathway achieves many of these outcomes by processing nutrient-derived molecular units that contain a single carbon atom[2–5]. The ways in which different carbon sources are used to fuel this pathway aren't completely understood. In a paper published online in *Nature*, Burgos-Barragan *et al.*[6] report that formaldehyde (CH_2O), a genotoxic agent that is removed from cells to protect DNA, can also support mammalian one-carbon metabolism.

The amino acids serine and glycine are thought to be the major sources of the single-carbon units used in one-carbon metabolism. These can be obtained from the diet[7] or synthesized from glucose through the serine-synthesis pathway[2]. The overall network of biochemical reactions, known as serine, glycine and one-carbon (SGOC) metabolism, is the target of some of the most successful cancer chemotherapies[8] — underscoring its crucial role in cell proliferation and genome maintenance.

SGOC metabolism is compartmentalized in two locations in cells: one part of the pathway is contained in mitochondria (organelles that act as metabolic hubs) and the other is in the cytosol and nucleus[9]. Formate ions (HCO_2^-), another fundamental component of one-carbon metabolism, provide a link between these compartments[9]. Formate is generated by the oxidation of folate molecules in the mitochondria, and is released into the cytosol, where it provides one-carbon units for use by other folates in metabolic reactions (Fig. 1). Indeed, proliferation defects in cells cultured in the absence of serine[10] can be rescued when formate is added to the culture medium.

Burgos-Barragan *et al.* now use a combination of genetic approaches (including CRISPR–Cas9 gene-editing technology) and biochemical analyses to show that formate can also be generated from formaldehyde produced in mammalian cells, in sufficient quantities to sustain one-carbon metabolism. The authors first observed a spontaneous decomposition of folates in cells that causes genotoxic stress. Further investigation revealed that this stress seems to be due to formaldehyde production and the generation of covalent crosslinks between different sites in DNA; such crosslinks are known to form when formaldehyde reacts with DNA.

The authors showed that the ability of cells to survive this stress depends on the availability of an enzyme called alcohol dehydrogenase 5 (ADH5) that converts formaldehyde into formate, and on proteins of the Fanconi anaemia pathway, which repairs DNA crosslinks[11] generated by formaldehyde. These observations support the idea that the genotoxic stress is caused by formaldehyde production. The researchers also generated a series of genetically engineered cells unable to express different enzymes involved in one-carbon metabolism, and found that these cells required ADH5 for proliferation. Combined deletion of *ADH5* and of genes that encode enzymes in one-carbon metabolism decreased proliferation.

The study therefore establishes a genetic interaction between the activity of one-carbon metabolism and formaldehyde detoxification. This is perhaps to be expected, because there is substantial evidence indicating that deficiencies in one-carbon metabolism and in folate levels lead to DNA damage and thus create a higher demand for DNA repair[5]. However, Burgos-Barragan *et al.* also report a surprising mechanism that underlies this genetic interaction. In a set of experiments using isotopically labelled nutrients, they show that formaldehyde can directly generate one-carbon units and fuel the folate cycle through ADH5 activity and formate production, thus coupling the detoxification of formaldehyde to the ability to sustain activity in the SGOC pathway. This allows nucleotides — particularly purines, the biosynthesis of which requires one-carbon units — to be synthesized directly from formaldehyde.

Taken together, these findings greatly expand our knowledge of one-carbon metabolism, and show that one-carbon units can derive from formaldehyde formed endogenously (within cells), in addition to dietary and endogenous sources derived from glucose. It also provides a mechanism whereby genotoxic stress is coupled to the activity of the SGOC pathway, which notably generates nucleotides and reducing power[3], both of which can function to counter DNA damage[5].

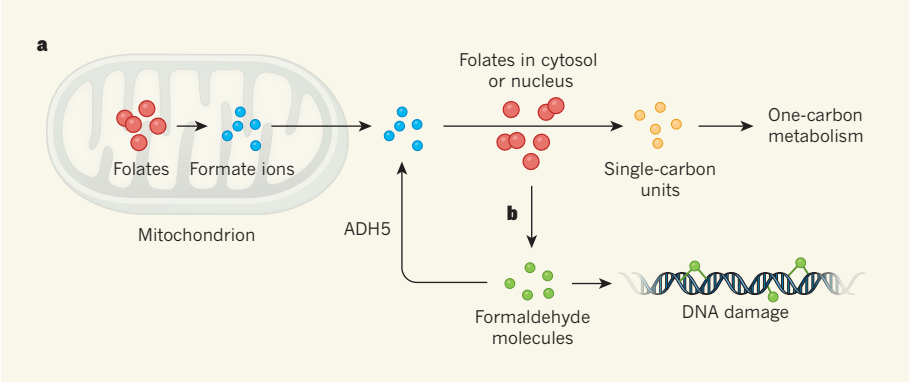

Figure 1 | Formaldehyde fuels one-carbon metabolism. A biological pathway called one-carbon metabolism incorporates molecular units that contain a single carbon atom into metabolic products, such as nucleotides. **a**, In this pathway, folate molecules in organelles called mitochondria are oxidized to produce formate (HCO_2^-), which is released into the cell cytosol. The formate then reacts with other folate molecules in the cytosol and cell nucleus, forming single-carbon units that are used in one-carbon metabolism. **b**, Burgos-Barragan *et al.*[6] show that folates can decompose spontaneously to generate formaldehyde (CH_2O), which can damage DNA. Remarkably, this formaldehyde can be metabolized by the enzyme alcohol dehydrogenase 5 (ADH5) to make formate that is used in one-carbon metabolism.

As with all landmark findings, questions remain. The authors identify folates as a source of formaldehyde, but other sources are present in mammalian cells. The relative contribution made by each source to one-carbon metabolism, the biological contexts that determine their use, and the interactions between formaldehyde production and the production or uptake of other single-carbon donors, such as serine, are still to be determined. The mechanism used by formaldehyde-mediated one-carbon metabolism for regulatory functions is also unknown, but there are many possibilities. For example, SGOC metabolism might act as a buffer or provide negative feedback against genotoxins that generate formaldehyde.

Furthermore, formate is generated in excess of biological requirements when nutrients are readily available[12], suggesting that formaldehyde detoxification could produce a reservoir of formate that could be stored and used to fuel SGOC metabolism under certain conditions — perhaps in a multicellular context such as a tumour microenvironment that is deficient in the amino acids needed for one-carbon metabolism[13]. Burgos-Barragan and colleagues' study therefore opens up several avenues for further enquiry. Given the undoubted relevance of the findings to cancer aetiology, and that technologies are available to probe the biochemical network involved, rapid advances are anticipated. ■

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