News & views

Molecular biology

Alcohol-derived DNA damage fixed in two ways

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A by-product of alcohol metabolism can damage the genome by crosslinking opposing DNA strands. The discovery of a safe mechanism that reverses such damage might open up avenues of research for drug discovery. **See p.603**

Aldehydes are highly reactive molecules that can enter the body from the environment, and can be produced by cellular metabolic processes. One aldehyde relevant to human health is acetaldehyde, which is produced when cells process ingested alcohol. If acetaldehyde accumulates in cells, it reacts with DNA and can link two strands together, generating an extremely harmful form of damage known as a DNA interstrand crosslink[1] (ICL). ICLs are also produced by many anticancer drugs, to kill tumour cells. On page 603, Hodskinson *et al.*[2] report the discovery of a mechanism for repairing acetaldehyde-induced ICLs that is safer than the commonly used route.

An inability to repair ICLs is linked to the rare genetic disease Fanconi anaemia (FA). This condition is caused by mutations in any one of 22 *FANC* genes, which encode proteins that participate in ICL repair[3]. People who have FA experience genomic instability, bone-marrow failure and premature ageing, and have a high risk of developing cancer. Since the 1970s, scientists have known that the cells of people who have FA are exquisitely sensitive to ICL-inducing drugs[4], but it was not until 2011 that researchers found genetic evidence[5] suggesting that acetaldehyde-derived DNA damage is a driving force of FA. How this damage is repaired was unknown.

The need to clear acetaldehyde from cells to prevent DNA damage (lesions) became evident after the *in vivo* identification of a two-tier system in mice that protects against this highly reactive molecule[5]. The first tier of protection involves the enzyme aldehyde dehydrogenase 2 (ALDH2), which converts acetaldehyde to harmless acetate molecules (Fig. 1). Inactivation of this enzyme is common in members of Asian populations, and is associated with a higher incidence of alcohol-derived cancers[6]. The second tier is repair of the DNA damage generated by acetaldehyde.

Because the combined inactivation of *FANC* and *ALDH2* genes recapitulates the characteristics of FA in mice, it is suspected that ICLs are the cytotoxic (cell-killing) lesions generated by acetaldehyde[5]. Consistent with this view is the observation that FA severity correlates[7] with the presence of an *ALDH2* mutation in Japanese people who have FA. However, direct investigation of these crosslinks is not possible in cellular or *in vivo* systems using available technologies. Hence, whether acetaldehyde-induced ICLs accumulate in people who have FA remains a crucial unanswered question.

A previously reported cell-free *in vitro* system derived from frog eggs[8] has been widely used to study the mechanisms underlying repair of ICLs induced by other agents, including the anticancer drug cisplatin[9]. This system allows DNA molecules that contain a single, site-specific DNA lesion to be analysed. In the case of cisplatin-induced ICLs, the cell-free system revealed a sophisticated repair mechanism that depends on FANC proteins[9,10]. This mode of repair requires DNA replication and cuts DNA strands to 'unhook' and remove the ICL (Fig. 1).

In their work, Hodskinson *et al.* undertook the enormous challenge of synthesizing a DNA molecule containing a single, site-specific acetaldehyde ICL, and then investigated how the lesion is repaired in the cell-free system. They found that this repair process requires an active FA pathway (a mechanism that involves

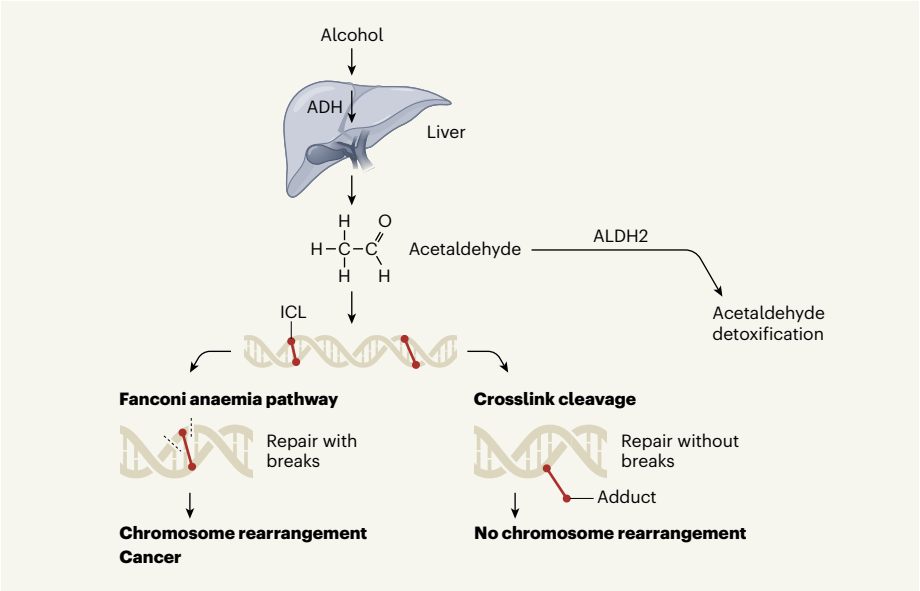

Figure 1 | Cellular defences against acetaldehyde. When humans ingest alcohol, it is converted in the liver to toxic acetaldehyde by the enzyme alcohol dehydrogenase (ADH). Acetaldehyde can also be formed by other metabolic processes, or come from the environment (not shown). The compound is detoxified by another enzyme, aldehyde dehydrogenase 2 (ALDH2), but still sometimes accumulates in cells, in which it forms interstrand crosslinks (ICLs) between bases in DNA molecules. This damage can be repaired by the Fanconi anaemia pathway, in a process that involves the formation of DNA breaks either side of the ICL. However, DNA breaks are potentially dangerous, and can lead to harmful chromosome rearrangements and cancer. Hodskinson *et al.*[2] report a second pathway for ICL repair in which the crosslink, rather than a DNA strand, is cut. This completely restores one of the bases that was crosslinked, and leaves an adduct on the other. This repair process prevents chromosomal rearrangements.

FANC proteins). This is consistent with genetic evidence that FANC proteins are required in the two-tier system that protects against acetaldehyde damage. However, the authors unexpectedly discovered that about half of the crosslinks are fixed by a second, faster mechanism. Further investigation revealed that this second route also involves DNA replication, but is independent of the FA pathway.

Surprisingly, in the fast repair route, no cuts are made to the DNA strands; instead, the ICL is probably cut within the crosslink. This mode of repair results in the reversion of the crosslink to an undamaged base on one of the DNA strands, but leaves an adduct on the other strand (Fig. 1), which specialized DNA-replication enzymes can bypass to complete repair. This mechanism is reminiscent of the one that fixes ICLs generated by the drug psoralen[11], but involves different enzymes. By avoiding DNA breaks — which are associated with genomic rearrangements, one of the hallmarks of cancer and ageing — the fast repair mechanism has an important advantage over the FA pathway. Taken together, Hodskinson and colleagues' findings provide a holistic glimpse of how acetaldehyde-derived crosslinks are cleared from DNA, and support the idea that these lesions contribute to FA.

The authors do not identify a protein that cleaves the crosslinks in the newly described repair route. One can therefore only speculate as to whether cleavage occurs spontaneously as a consequence of mechanical forces generated during replication as the DNA unwinds, or is the result of enzymatic activity. If it is indeed an enzymatic process, identifying the components of the pathway will be a challenge, but could open up opportunities for therapies: stimulation of the pathway might alleviate the symptoms of FA, or reduce the incidence of alcohol-derived cancers.

The identification of the protein(s) involved in the crosslink cleavage would also allow *in vivo* experiments to test whether impairment of the alternative repair route increases acetaldehyde toxicity, especially under conditions in which this molecule is not detoxified by metabolism. Furthermore, mutations in the genes encoding proteins involved in this pathway might reveal the existence of a new group of people who have an FA-like disorder. In the meantime, Hodskinson and colleagues' study underlines the need to develop better assays to study ICLs and other types of DNA damage in cells. By studying the repair of specific DNA lesions induced by compounds such as acetaldehyde, or other mutagens that arise in the body, we are likely to uncover other cellular defence mechanisms against cytotoxic DNA damage.

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Atmospheric science

Jet stream stops shifting as ozone layer recovers

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The Antarctic ozone hole shifted the jet stream in the Southern Hemisphere poleward, leading to hemisphere-wide climatic changes. But the Montreal Protocol, which banned ozone-depleting substances, has halted the shift. **See p.544**

The discovery[1] of a hole in the springtime atmospheric ozone layer over the Antarctic in the mid-1980s revealed the threat posed by human-made ozone-depleting substances (ODSs): the damage caused by these compounds exposes people and Earth's ecosystems to harmful ultraviolet radiation. A related, unexpected effect was revealed in the early 2000s, when studies[2,3] showed that the Antarctic ozone hole, which resides at altitudes of around 10–20 kilometres, has affected atmospheric circulation all the way down to the surface in the Southern Hemisphere — most notably, by shifting the summertime jet stream poleward. The production and use of ODSs was banned by the Montreal Protocol of 1987 and its subsequent amendments. Atmospheric ODS concentrations are therefore decreasing, and the first signs of ozone-layer recovery have emerged[4,5]. On page 544, Banerjee *et al.*[6] report that the hole-associated circulation effects have paused since ozone recovery started.

Stratospheric ozone absorbs ultraviolet solar radiation, and the absorbed energy heats the stratosphere, the atmosphere's second-lowest layer. Consequently, ozone depletion and the related lack of heating cool the stratosphere — indeed, the Antarctic springtime stratosphere cooled by about 7 °C between the late 1960s and late 1990s as a result of the ozone hole[2]. This cooling increased the north–south temperature gradient between the southern mid-latitudes and the Antarctic, which strengthened the stratospheric westerly winds in the Southern Hemisphere and, in turn, caused a poleward shift of the jet stream in the troposphere (the lowest layer of the atmosphere).

It is not obvious why changes to stratospheric winds affect circulation in the underlying troposphere. The stratosphere represents only about 15% of the atmospheric mass, and therefore, when in motion, has much less momentum than the troposphere. Yet observations and computational modelling confirm that the tropospheric jet stream is sensitive to changes in stratospheric winds at monthly, seasonal and decadal timescales, and that the cooling of the polar stratosphere is associated with a poleward shift of the tropospheric jet stream[7].

By the end of the twentieth century, the summertime tropospheric jet stream had shifted by about 2° of latitude, altering the transport of atmospheric heat and moisture. This contributed to warming of the Antarctic Peninsula, Patagonia and New Zealand, and to drying of western Tasmania and western New Zealand, and affected the circulation, temperature and salinity of the Southern Ocean[8,9]. A cessation of the tropospheric-circulation trends since the beginning of the twenty-first century has previously been noted[10], but Banerjee and colleagues are the first to formally attribute it to the effects of the Montreal Protocol.

The authors had to overcome several difficulties to demonstrate that the poleward shift has paused, and to attribute the pause to changes in stratospheric ozone levels. First, the natural year-to-year variability of atmospheric circulation in the mid- and polar latitudes is large, which makes it challenging to detect atmospheric-circulation trends in those regions[11]. Therefore, even though no