News & views

Ageing

Molecules in old blood promote cancer spread

Hai Wang & Xiang H.-F. Zhang

A molecule produced by the metabolism of proteins and fats has been found to accumulate in the blood of older people, and to endow cancer cells with the ability to spread from one site in the body to others. **See p.283**

As we get older, the risk that we will develop cancer increases, because we accumulate genetic mutations and are continually exposed to cancer-causing substances[1]. Most cancer-causing agents are found in the environment, but some are produced by our own bodies. Gomes *et al.*[2] report on page 283 that methylmalonic acid (MMA) — a by-product of protein and fat digestion — can accumulate in the blood with age, and might promote the spread of tumours.

Methylmalonic acid is produced in cells in very small amounts[3]. Usually, it becomes linked to the molecule coenzyme A to form methylmalonyl-CoA, and is converted to succinyl-CoA in a reaction that involves vitamin B_{12} as a cofactor. Succinyl-CoA subsequently enters the TCA cycle — a series of chemical reactions that are a key part of energy production in the cell.

In some diseases, the body fails to metabolize MMA efficiently, leading to its toxic accumulation in the blood. For instance, the metabolic disorder methylmalonic acidaemia is characterized by the failed conversion of methylmalonyl-CoA to succinyl-CoA, owing to genetic defects in key enzymes (such as methylmalonyl-CoA mutase) or to vitamin B_{12} deficiency[1].

Gomes *et al.* report that MMA levels are significantly higher in the blood of healthy people over the age of 60 than in those under 30. The elevated level of MMA had not caused ill health in the individuals studied. However, the authors found that treating human cancer cells with serum from the blood of the older group, or with high concentrations of MMA, led them to adopt characteristics of metastatic cancer cells — those that can spread from a primary tumour to seed cancers elsewhere in the body. These characteristics include a loss of cell–cell attachment and an increase in mobility. When injected into mice, the cells formed metastatic tumours in the lungs.

The researchers demonstrated that the presence of large lipid structures in 'old' blood serum was also key to its ability to induce metastatic characteristics in cells. Removing these structures from blood prevented MMA from entering cells, indicating that MMA is in complex with a large lipid. The identity of this lipid structure, and the mechanism by which it helps MMA to enter cells, remains to be determined.

> **"The authors' results should stimulate more interest in the relationship between protein intake and age-associated cancer risks."**

Gomes and colleagues next asked what molecular changes MMA triggers in cells. The authors examined the gene-expression profiles of cells treated with MMA, and compared them with those of untreated cells. One of the genes most highly upregulated in response to MMA was *SOX4*, which encodes a transcription factor involved in the regulation of embryonic development and cancer progression[4]. The authors demonstrated that repressing *SOX4* expression blocked the cancer-cell response to MMA, and prevented the formation of metastatic tumours in mice that received injections of cancer cells treated with old serum. Thus, MMA indirectly induces an increase in the expression of *SOX4*, which in turn elicits broad reprogramming of gene expression and subsequent transformation of cells into a metastatic state (Fig. 1).

Gomes and colleagues' work implies that lipids have dual roles in MMA-driven metastases: first, in the form of the fatty acids from which MMA derives; and second, as large lipids that help MMA to cross cell membranes. Levels of the lipid cholesterol increase between puberty and the age of 50 or 60 (ref. 5) — overlapping with the rise in MMA levels in the blood. It is possible that the lipidic structures observed in the current study involve cholesterol. If so, anti-cholesterol treatments might reduce levels of MMA and slow its entry into cells.

Why does MMA increase with age? Levels of vitamin B_{12} decrease with age, and deficiency in that vitamin is linked to an accumulation of MMA. However, the authors found no reverse correlation between levels of these two molecules in their study participants. Therefore, B_{12} deficiency is unlikely to be the main reason for MMA accumulation. Another potential culprit is protein. A low-protein diet can reduce the substrates for MMA formation[6], and might

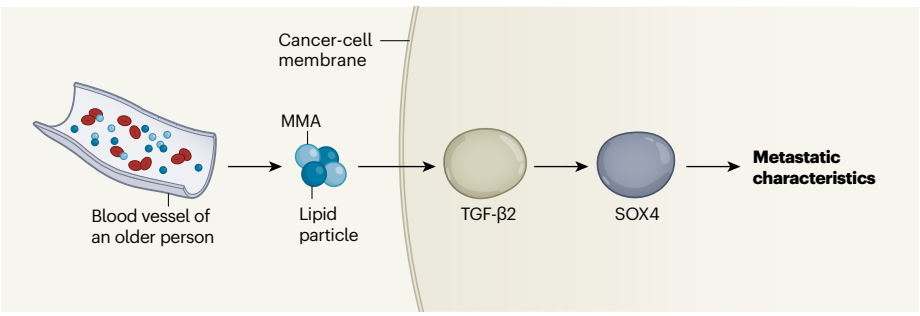

Figure 1 | Methylmalonic acid (MMA) and cancer. MMA is produced during digestion of proteins and fats. Gomes *et al.*[2] report that levels of MMA are elevated in the blood of people over the age of 60, compared with those under 30. The group provides evidence that large lipid structures help MMA to enter cancer cells from older blood vessels. Through unknown pathways, MMA promotes expression of the proteins TGF-β2 and SOX4. In turn, SOX4 drives global gene-expression changes that enable cells to take on the characteristics of metastatic cells, which spread cancer around the body.

enhance anticancer immune responses[7]. In addition, high protein intake significantly increases the risk of death from cancer in people aged 50 to 65 (although the opposite correlation is seen in people over 65)[8]. Given these previous observations, Gomes and colleagues' work should stimulate more interest in the relationship between protein intake and age-associated cancer risks.

All the people in this study who had high plasma levels of MMA seemed to be cancer-free, suggesting that the effects of MMA are specific to cancer spread in the body, rather than to initial cancer formation. Cancer initiation and spread are distinct processes that involve different molecular mechanisms[9]. If future studies can confirm that MMA specifically affects metastasis in humans in the same way that Gomes *et al.* have demonstrated it does *in vitro* and in mice, this molecule will stand apart from many previously known ageing-related causes of cancer, including environmental factors and genetic mutations. Further investigation into the timing of MMA's effects could then inform the optimal timing for therapeutic use of MMA-blocking agents, if they become available.

A final question is how MMA stimulates gene-expression changes associated with metastasis at a molecular level. The authors hypothesized that MMA activates transcription of the gene *TGF-β2*; this gene is part of a TGF-β signalling pathway that, in turn, promotes *SOX4* expression. But how MMA enhances the transcription of *TGF-β2* remains to be seen.

Answers to these questions will further our understanding of metabolic changes and their roles in cancer development. Regardless of the answers, Gomes and colleagues' study has broadened our view of cancer risk factors, by drawing attention to the role of metabolism in ageing-associated cancer progression.

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1. Anisimov, V. N. *Crit. Rev. Oncol. Hematol.* **45**, 277–304 (2003).
2. Gomes, A. P. *et al. Nature* **585**, 283–287 (2020).
3. Chandler, R. J. & Venditti, C. P. *Mol. Genet. Metab.* **86**, 34–43 (2005).
4. Lourenço, A. R. & Coffer, P. J. *Trends Cancer* **3**, 571–582 (2017).
5. Félix-Redondo, F. J., Grau, M. & Fernández-Bergés, D. *Aging Dis.* **4**, 154–169 (2013).
6. Baumgartner, M. R. *et al. Orphanet J. Rare Dis.* **9**, 130 (2014).
7. Rubio-Patiño, C. *et al. Cell Metab.* **27**, 828–842.e7 (2018).
8. Levine, M. E. *et al. Cell Metab.* **19**, 407–417 (2014).
9. Hanahan, D. & Weinberg, R. A. *Cell* **144**, 646–674 (2011).

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Electrical engineering

A cool design for hot microchips

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Miniaturized electronic devices generate a lot of heat, which must be dissipated to maintain performance. A microfluidic system designed to be an integral part of a microchip demonstrates exceptional cooling performance. **See p.211**

An energy-efficient way to improve the performance of electronics systems would be to integrate microfluidic cooling channels into chips, to prevent overheating. However, state-of-the-art microfluidic cooling systems have previously been designed and constructed separately from electronic chips, preventing the channels from being integrated into circuits to provide direct cooling at hotspots. Because such integration greatly increases the complexity of chip fabrication, it would potentially increase the cost. On page 211, van Erp *et al.*[1] report an electronic device designed to have an integrated microfluidic cooling system that closely aligns with the electronic components, and which is constructed using a single, low-cost process.

Power electronics are solid-state electronic devices that convert electrical power into different forms, and are used in a vast array of daily applications[2] — from computers to battery chargers, air conditioners to hybrid electric vehicles, and even satellites. The rising demand for increasingly efficient and smaller power electronics means that the amount of power converted per unit volume of these devices has increased dramatically. This, in turn, has increased the heat flux of the devices — the amount of heat produced per unit area. The heat generated in this way is becoming a big problem: data centres in the United States consume the same amount of energy and water to cool their computer technology as does the city of Philadelphia for its residential needs[1].

Microfluidic cooling systems have great potential for lowering the temperature of electronic devices, because of the efficiency with which heat can be transferred to these systems. In general, three microfluidic cooling designs have been developed. The first is used to cool chips that are covered by a protective lid. Heat is transferred from the chip, through the lid, to a cold plate that contains microfluidic channels through which a liquid coolant flows[3]. Two layers of a thermal interface material (TIM) are used to aid the transfer of heat from the lid to the cold plate: one between the lid and the plate, and the other between the lid and the die (the wafer of semiconductor from which the chip is made).

In the second design, the chip has no lid, and so heat is transferred directly from the back of the chip through a single TIM layer to a microfluidically cooled plate[3]. The main drawback of these two approaches is the need for TIM layers — even though TIMs are designed to transfer heat effectively[4], resistance to heat flow still arises at the interfaces between the TIM layers and the die, lid and cold plate.

An efficient way to overcome this problem is to bring the coolant into direct contact with the chip — this is the third general design. For example, bare-die direct jet cooling is a valuable technique in which a liquid coolant is ejected from nozzles in microchannels directly onto the back of the chip[5–7]. This approach cools highly efficiently because there is no TIM layer, and no changes are needed in the process used to make the chip. However, manufacturing the microfluidics device is generally expensive. Low-cost, polymer-based techniques[8] have been developed, but are not compatible with the existing production and assembly processes for electronic devices.

Another approach that brings coolant into direct contact with the back of the chip is embedded liquid cooling[9,10], in which a cold liquid is pumped through straight, parallel microchannels (SPMCs) etched directly in the semiconductor device. This effectively turns the back of the chip into a heat sink, and offers great cooling performance. However, the die needs extra processing, compared with the other methods. A major drawback of SPMCs is that the pressure in the channels rises considerably as the fluid passes through, which means that a high-power pump is needed. This increases energy consumption and costs, and generates potentially damaging mechanical stress on the semiconductor device. Another big disadvantage is that a high temperature gradient is produced across the chip, which can induce thermo-mechanical stress and