1847, 957–967 (2015).
4. Liu, H., Li, A., Rochaix, J.-D. & Liu, Z. *Nature* **615**, 349–357 (2023).
5. Jin, Z. *et al. Cell* **185**, 4788–4800 (2022).
6. Ganesan, I., Shi, L.-X, Labs, M. & Theg, S. M. *Plant Cell* **30**, 2161–2173 (2018).
7. Kikuchi, S. *et al. Plant Cell* **30**, 2677–2703 (2018).
8. Chen, Y.-L. *et al. Nature* **564**, 125–129 (2018).
9. Ramundo, S. *et al. Proc. Natl Acad. Sci. USA* **117**, 32739–32749 (2020).

The authors declare no competing interests.
This article was published online on 28 February 2023.

Cancer

Fatty acids prime the lung as a site for tumour spread

Laura V. Pinheiro & Kathryn E. Wellen

The mechanisms that enable the deadly spread of cancer are not fully understood. It emerges that tumours can signal to the lung to manipulate lipids and so prime the organ to support tumour cells that subsequently spread there.

Cancer cells require nutrients such as glucose, amino acids and fatty acids to grow and proliferate. They also require nutrients to disperse and grow in organs distant from the initial (primary) tumour site — a spreading process called metastasis. The nutritional environment affects whether cancer cells can thrive in a new location. Tumour cells are known to secrete factors that act on distant sites ahead of their arrival, to prepare a favourable environment, termed a pre-metastatic niche[1]. However, nutritional aspects of the pre-metastatic niche are poorly understood. Writing in *Nature Cancer*, Altea-Manzano *et al.*[2] reveal how breast cancer cells program the metabolic environment in the lung before colonization, to support metastatic growth.

Fatty acids are a class of nutrient implicated in supporting metastasis, and high-fat diets promote metastasis in mice[3,4]. However, the factors that affect fatty-acid availability at sites of metastasis are not well known. Altea-Manzano *et al.* find that two fatty acids in particular, palmitate and oleate, are highly abundant in the extracellular fluid of the healthy lung and liver — common sites of metastasis. Feeding mice a high-fat diet further increases the fatty-acid abundance in these tissues, and coincides with increased metastatic growth in a breast cancer model.

The authors then considered a crucial question. Could tumour-derived signals remodel the metabolic environment of distant tissues to improve the ability of cancer cells to grow there? The researchers tested this by injecting mice with factors secreted by tumours *in vitro*. Remarkably, this treatment resulted in a rise in palmitate in the lung extracellular fluid, indicating that signals from a distant tumour can change the nutritional environment in the lung. Lung extracellular fluid collected post-mortem from people with breast cancer had higher levels of palmitate than that of individuals who had not had cancer, supporting the relevance of these findings for humans.

A cell type called a lung-resident alveolar type II (AT2) cell was identified as the source of palmitate-containing lipids (Fig. 1a). AT2 cells produce lung surfactant, a complex of phospholipids and proteins that functions to reduce surface tension at the air–liquid interface in the lung's alveolar structures, preventing their collapse. Surfactant is rich in lipids, suggesting that tumours might exploit the normal metabolic function of the AT2 cells.

To understand how palmitate gives metastasizing cancer cells an advantage, Altea-Manzano *et al.* used an experimental system to model features of tumours *in vivo* and to mimic 3D tumour growth. The set-up consisted of a culture system in which cells aggregate and grow into sphere-like structures[5]. Palmitate, but no other fatty acids tested, increased spheroid growth in a manner that required lipid breakdown to generate the metabolic intermediate acetyl coenzyme A (acetyl-CoA). Acetyl-CoA is needed for a protein modification called acetylation, which can regulate protein function, and the abundance of acetyl-CoA can affect the acetylation of certain proteins, including some that are involved in regulating gene expression[6].

Altea-Manzano and colleagues found that acetyl-CoA derived from palmitate is used by an enzyme called KAT2A to acetylate subunit p65 of the transcription-factor protein NF-κB. This acetylation leads to increased expression of genes that promote metastasis. Although several nutrient sources can supply acetyl-CoA, palmitate, but no other nutrients tested, increased the expression of KAT2A, possibly accounting for the role of palmitate, but not other fatty acids, in this setting.

Targeting various components of this pathway in the cancer cells, including palmitate breakdown and KAT2A, potently suppressed spheroid growth in culture and tumour metastasis in mice. These findings delineate a mechanism whereby signals from the tumour instruct AT2 cells to produce and secrete lipids, increasing palmitate abundance in the pre-metastatic niche (Fig. 1b). Palmitate is then taken up by the metastasizing cancer

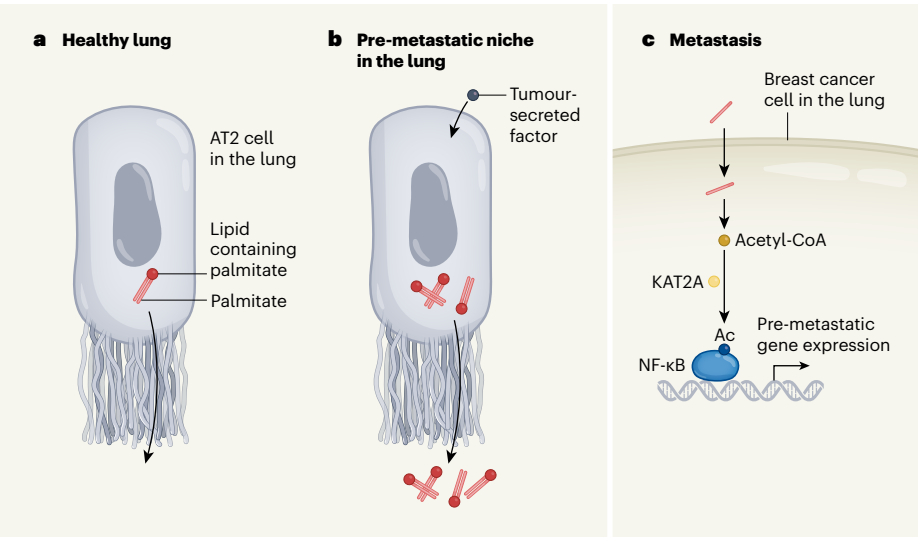

Figure 1 | Tumours manipulate lipids to create a favourable environment for tumour spread. Altea-Manzano *et al.*[2] investigated how breast cancer cells spread to the lungs in mice. **a**, AT2 cells in the lungs synthesize and secrete lipid molecules that contain the fatty acid palmitate. **b**, The authors report that unknown tumour-secreted factors boost palmitate production. This creates a favourable site for tumour spread (termed a pre-metastatic niche). **c**, When breast cancer cells themselves reach the lungs (through a process called metastasis), they take up palmitate and convert it to acetyl-CoA. This molecule is used by the enzyme KAT2A to add an acetyl group (Ac) to the transcription-factor protein NF-κB. NF-κB regulates gene expression to support tumour growth.

cells and used to activate a gene-expression program that allows successful growth in the lung (Fig. 1c).

Several intriguing questions arise from this work. In terms of understanding the mechanism involved, a key unknown is the identity of the tumour-cell signal that acts on AT2 cells. Identifying this signal and discovering how it increases the secretion of palmitate-containing lipids in AT2 cells would elucidate key details of how tumour cells nutritionally prime the pre-metastatic niche, and potentially present opportunities for therapeutic intervention.

Lung surfactant consists mainly of phospholipids, a major component of which is the molecule dipalmitoylphosphatidylcholine, which contains two acyl chains derived from palmitate[7]. Indeed, palmitate in the extracellular fluid is mainly a component of larger lipid molecules. Whether the cancer cells selectively take up specific lipids from the lung environment, and if so, how, remains to be determined. In addition, it will be worth investigating the mechanism by which palmitate specifically regulates KAT2A expression.

Another avenue of research prompted by this work is the interplay between dietary fat, lipids in the pre-metastatic niche and metastasis. The authors found that feeding mice a high-fat diet increases the number of AT2 cells; thus, diet might increase palmitate in the pre-metastatic niche through mechanisms beyond simply providing the fatty acid. With that in mind, it would be interesting to test whether this effect is also specific to palmitate, or whether other fatty acids can similarly modulate the number of AT2 cells. Notably, another study found that dietary palmitate, but not the fatty acids oleate or linoleate, boosts the initiation of metastasis through a reprogramming mechanism (an epigenetic modification) that acts on the complex of DNA and protein called chromatin[8]. It is appealing to imagine future strategies that combine dietary interventions with targeted therapies to suppress metastatic growth.

Finally, because the mechanisms described in Altea-Manzano and colleagues' study use the surfactant-producing function of AT2 cells and thus are specific to the lung environment, it will be important to discover whether distinct mechanisms enable metabolic adaptations for metastasis to other sites. Breast cancer metastasis to the brain requires increased palmitate synthesis by cancer cells there, consistent with the idea that different sites require distinct adaptations[9]. Given the common requirement for palmitate for metastasis to both lung and brain, the data raise the question of whether targeting fatty-acid synthesis throughout the body would decrease metastasis to multiple sites. Inhibitors of fatty-acid synthesis are currently being tested in clinical trials for the treatment of primary tumours and some metastatic cancers[10].

Altea-Manzano and colleagues' work reveals key aspects of how tumour cells facilitate colonization of the lung. The pathway identified might offer new molecular targets for suppressing metastasis — a major challenge for the treatment of cancer.

Laura V. Pinheiro and **Kathryn E. Wellen** are in the Department of Cancer Biology and at the Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.
e-mail: wellenk@upenn.edu

1. Peinado, H. *et al. Nature Rev. Cancer* **17**, 302–317 (2017).
2. Altea-Manzano, P. *et al. Nature Cancer* https://doi.org/10.1038/s43018-023-00513-2 (2023).
3. Broadfield, L. A., Pane, A. A., Talebi, A., Swinnen, J. V. & Fendt. S.-M. *Dev. Cell* **56**, 1363–1393 (2021).
4. Martin-Perez, M., Urdiroz-Urricelqui, U., Bigas, C. & Benitah, S. A. *Cell Metab.* **34**, 1675–1699 (2022).
5. Elia, I. *et al. Nature* **568**, 117–121 (2019).
6. Sivanand, S., Viney, I. & Wellen, K. E. *Trends Biochem. Sci.* **43**, 61–74 (2018).
7. Agudelo, C. W., Samaha, G. & Garcia-Arcos, I. *Lipids Health Dis.* **19**, 122 (2020).
8. Pascual, G. *et al. Nature* **599**, 485–490 (2021).
9. Ferraro, G. B. *et al. Nature Cancer* **2**, 414–428 (2021).
10. Batchuluun, B., Pinkosky, S. L. & Steinberg, G. R. *Nature Rev. Drug Discov.* **21**, 283–305 (2022).

The authors declare no competing interests.
This article was published online on 28 February 2023.