

Tissue-trained fibroblasts fuel invasion with lipids

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In this issue of *Nature Metabolism*, Budden et al. show that fibroblasts from distinct anatomical sites release different lipid species, and that fibroblast-derived sphingomyelins and triglycerides activate epithelial-to-mesenchymal transition-linked invasion in cancer cells, providing evidence that stromal cells carry tissue-of-origin programs that actively instruct tumour invasion.

Squamous cell carcinomas (SCCs) arise from disparate anatomical sites and present a clinical paradox^{1,2}. Despite sharing common histological and molecular hallmarks, including epithelial origin, high mutational burden and recurrent alterations in tumour suppressors and oncogenes, their clinical trajectories diverge strikingly. An SCC that originates from the skin rarely spreads; conversely, an SCC from the lung or oral cavity frequently pursues a metastatic and lethal course¹. The prevailing view attributes this discrepancy to tumour aetiology, such as the DNA-damaging effects of UV radiation versus the chemical onslaught of tobacco and alcohol, and the varying epigenetic and immune constraints observed at different anatomical sites³. Spatial and single-cell approaches have reinforced the idea that stromal cells are not a passive bystander but differ systematically across tissues⁴, raising the fundamental question of whether stromal cells can carry tissue-of-origin programs that actively instruct cancer cells, independent of the tumour cell's own origin.

In a new study published in *Nature Metabolism*, Budden et al.⁵ address this question and reveal that SCC aggression may lie in the metabolic 'soil' provided by tissue-resident fibroblasts. Fibroblast metabolism has been largely defined by the transition from quiescence to activation. Resident fibroblasts in healthy tissue are frequently viewed as metabolically 'quiet' cells, mostly dedicated to the maintenance of the extracellular matrix^{6,7}. Only with the onset of malignancy or injury, fibroblasts become 'activated' by factors such as transforming growth factor- β , triggering a dramatic shift towards high-rate glycolysis and glutamine consumption to meet the energy and biosynthetic demands of a reactive stroma⁸. Under this paradigm, in tumours, when fibroblasts transition to an activated state, that is, to cancer-associated fibroblasts (CAFs), they are also metabolically reprogrammed by the tumour to serve its growth⁷. The study by Budden et al., however, challenges this concept by demonstrating that fibroblasts from different tissues are already pre-wired with site-specific metabolic programs that determine tumour behaviour before oncogenic signals are received by cancer cells.

The authors establish this by using an elegant, organotypic three-dimensional co-culture system to uncouple tumour identity

from its environment. By 'cross-planting' SCC cells from the skin, mouth and lung into matrices pre-built by fibroblasts from each of those sites, they found that the origin of the SCC cells mattered less than the origin of the fibroblasts. Dermal fibroblasts remained largely inert, failing to promote invasion regardless of the SCC cell type they hosted. By contrast, lung and oral fibroblasts consistently promoted invasion, implying that the fibroblast tissue of origin can override where the malignant cells themselves arose.

The study's core strength lies in its metabolic granularity, identifying two distinct, site-specific lipid axes (Fig. 1). In the oral cavity, the pro-invasive signal is driven by sphingolipid metabolism. Oral fibroblasts secrete high levels of sphingomyelin, which is processed by the SCC cells into sphingosine-1-phosphate. This signalling lipid acts as a metabolic switch, activating the STAT3 pathway and increasing mitochondrial respiration, and fuels invasion by inducing epithelial-to-mesenchymal transition. The authors demonstrate that inhibiting the conversion of sphingomyelin to sphingosine-1-phosphate, either by pharmacological inhibition of sphingomyelinase or genetic targeting of *SPHK1* in the cancer cells, effectively halts the invasive program both in vitro and in vivo. The lung microenvironment follows a different metabolic blueprint centred on neutral lipids. Lung fibroblasts are rich in triglycerides stored in lipid droplets, which are actively shuttled to SCC cells via the transport protein apolipoprotein E. Once internalized, triglycerides are broken down by adipose triglyceride lipase to provide fatty acids for cholesterol synthesis. This influx of cholesterol fuels the invasive behaviour of SCC cells via epithelial-to-mesenchymal transition, consistent with cholesterol metabolism contributing to tumour invasion⁹. Highlighting the clinical relevance of this discovery, the authors show that statins, which are widely used cholesterol-lowering drugs, blunt lung fibroblast-induced tumour growth and improve survival in mice. This metabolic divergence was further validated using spatial transcriptomics in oral and lung samples from patients with SCC, which confirmed that these specific lipid signatures are spatially anchored to the interaction zones between CAFs and cancer cells. Conversely, sphingosine-1-phosphate signalling and the cholesterol synthesis pathway were absent in the proximity of fibroblasts and CAFs in cutaneous samples from patients with SCC, consistent with its relative indolence.

These findings suggest that the tissue of origin imprints lipid metabolic programs in fibroblasts that persist through the transitions to CAFs. Notably, these site-specific metabolic states are consistent with epigenetic differences described across fibroblasts from distinct anatomical sites¹⁰ and with lipids helping to define fibroblast states¹¹. However, the direction of causality remains unclear, because lipid metabolism may be both a consequence of a given fibroblast state and a mechanism that stabilizes it. For example, triglyceride turnover could influence acetyl-CoA-dependent histone acetylation or DNA methylation¹², whereas epigenetic programming could in turn support expression of lipid transport and secretion that shape the tumour niche.

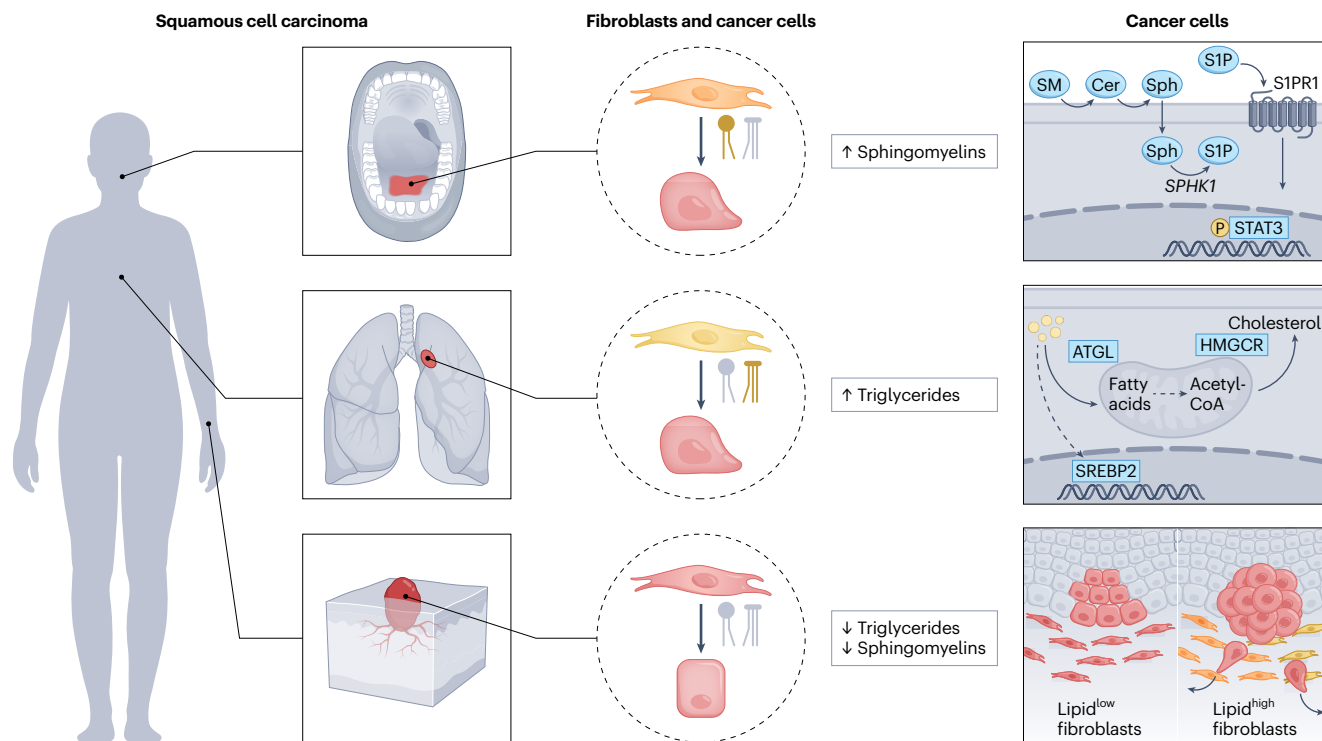


Fig. 1 | Tissue-specific fibroblast-derived lipids regulate SCC cell invasion.

In SCC, tissue-resident fibroblasts produce and secrete distinct lipids that are used by neighbouring cancer cells to activate metabolic pathways and signalling programs that promote cancer cell invasion via epithelial-to-mesenchymal transition. Oral fibroblasts secrete abundant sphingomyelins that activate the sphingomyelin–ceramide–sphingosine-1-phosphate–STAT3 signalling pathway in oral SCC cells to promote invasion. Lung fibroblasts secrete elevated levels of triglycerides that lung SCC cells hydrolyze to fatty acids via adipose

triglyceride lipase (ATGL) for cholesterol synthesis, with possible involvement of the transcription factor SREBP2, to fuel cancer cell invasion. By contrast, dermal fibroblasts are lipid-poor, with reduced triglycerides and sphingomyelins, and do not promote invasion. These tissue-specific stromal lipid environments create metabolic niches that differentially influence tumour growth and metastasis. Cer, ceramide; HMGCR, 3-hydroxy-3-methylglutaryl-coA reductase; SM, sphingomyelin; Sph, sphingosine; S1P, sphingosine-1-phosphate; S1PR1, sphingosine 1-phosphate receptor 1.

The persistence of these programs into CAFs also suggests that initial stromal lipid states may constrain how CAF metabolism subsequently evolves under tumour-imposed conditions, including hypoxia, nutrient availability and inflammation. Given growing evidence that CAF metabolism supports tumour-promoting functions, defining when and how these tissue-encoded programs are retained may reveal tractable windows to disrupt pro-invasive stromal support, particularly at early stages of the disease. A key next step will be to determine how general this principle is across organs and tumour types. For example, whether additional tissues harbour distinct fibroblast metabolic programs that create permissive metabolic niches, and whether these niches help explain organ-specific patterns of progression and metastasis. Ultimately, defining the stability and plasticity of stromal metabolic identity may provide a framework for developing anatomically informed strategies to limit tumour progression and metastasis.

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Competing interests

The authors declare no competing interests.