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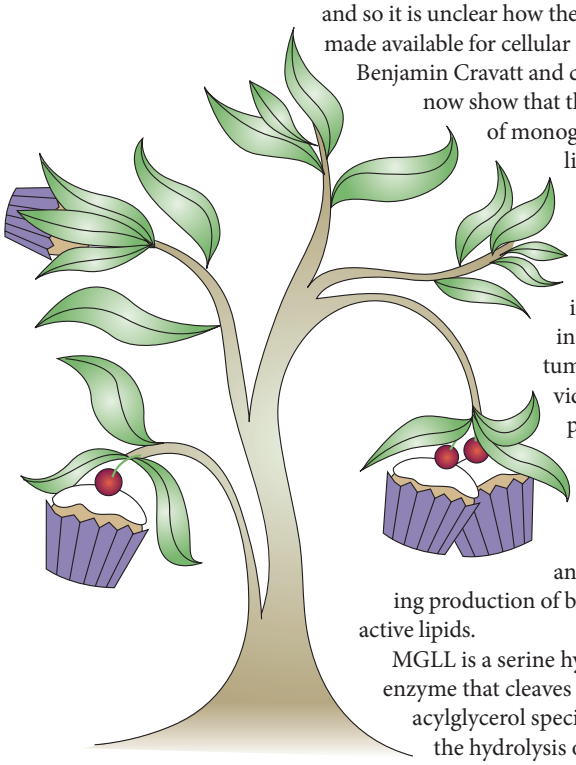
LIPIDOMICS

Growing on a free-fat diet

Heightened lipogenesis, a common metabolic signature of malignant cells, is thought to promote pathology by generating substrates for energy production and membrane synthesis, as well as signalling lipids that trigger pro-tumorigenic cascades. However, newly synthesized fatty acids are quickly incorporated into lipid stores and so it is unclear how they are made available for cellular functions.



Benjamin Cravatt and colleagues now show that the activity of monoglyceride lipase (MGLL; also know as MAGL) is increased in aggressive tumours, providing the principal source of free fatty acids (FFAs) and increasing production of biologically active lipids.

MGLL is a serine hydrolase enzyme that cleaves monoacylglycerol species during the hydrolysis of fat stores, liberating FFAs and glycerol. It has no established role in cancer and does not control the levels of FFAs in most normal tissues. Probing serine hydrolase activities across a panel of cancer cell lines, the authors found that MGLL activity is consistently increased in cells derived from aggressive tumours, including ovarian cancer (SKOV3), melanoma (C8161 and MUM2B) and breast cancer (231MFP) cell lines. Higher basal levels of FFAs were eliminated by inhibiting the enzyme, indicating that it is the principal regulator of FFA levels in these cells.

To investigate the effect of MGLL expression on cancer pathogenicity, the authors stably blocked its expression in the malignant cells, and overexpressed it in non-aggressive ovarian (OVCAR3) and melanoma (MUM2C) cell lines. Growth, survival and migration of the cells were all promoted by MGLL expression, as was the growth of xenografts in immune-deficient mice. The impaired pathogenicity of MGLL-disrupted cells was rescued by treatment with exogenous fatty acids, and a high-fat diet had the same effect on the growth of MGLL-disrupted xenografts in mice.

To determine which lipid networks are modulated by the increase in FFAs, the authors profiled cellular lipids using a standard lipidomics approach that involves liquid chromatography coupled with mass spectrometry; they identified a common profile of lipid metabolites regulated by MGLL. These metabolites included lysophosphatidic acid and prostaglandin E2: treatment with either rescued the impaired migration of MGLL-disrupted cells.

These data show that MGLL–FFA regulates a lipid network in aggressive cancer cells, and demonstrate how increased lipogenesis can be paired with lipolysis to promote malignancy. Pharmacological inhibition of MGLL might be a viable cancer therapy. Furthermore, as the high-fat diet compensated for disrupted MGLL activity, dietary fat might promote malignancy by mimicking the effects of increased MGLL expression.

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ORIGINAL RESEARCH PAPER Nomura, D. K. *et al.* Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. *Cell* **140**, 49–61 (2010)

FURTHER READING Menendez, J. A. & Lupu, R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nature Rev. Cancer* **7**, 763–777 (2007)