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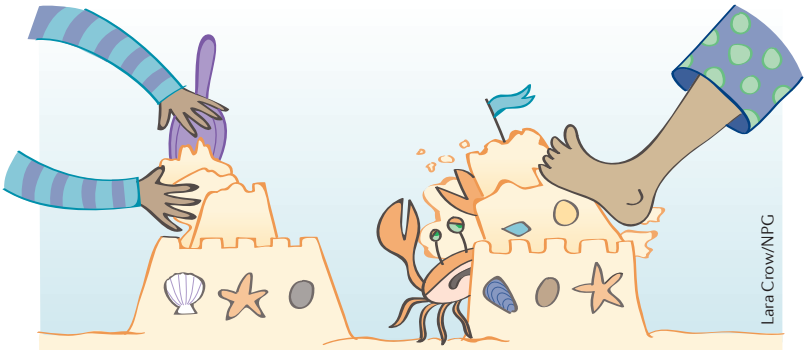


TUMOUR METABOLISM

# Building up and breaking down fatty acids

> how FA metabolic pathways can be targeted will likely depend on whether a tumour is dependent on FA oxidation and its genetic context

Both fatty acid (FA) synthesis and FA breakdown can support cancer cell growth. Tumours require lipid building blocks to proliferate, but some cancers also use FA oxidation as an energy source. Each process is controlled in part by a different acetyl-CoA carboxylase (ACC) isoform: ACC1 predominantly promotes FA synthesis in the cytoplasm, whereas ACC2 prevents transport of FAs into mitochondria (the site of FA oxidation). Two studies have looked at the roles of these processes, and their therapeutic potential, in cancer.

Svensson *et al.* found high *ACC1* and low to undetectable *ACC2* expression in several non-small-cell lung cancer (NSCLC) cell lines. CRISPR–Cas9-mediated *ACC1* deletion prevented *de novo* FA synthesis, and decreased cell growth and survival. Deletion of *ACC1* also prevented growth of subcutaneous xenograft tumours in mice. This suggests that ACC1 might be a valid therapeutic target in NSCLC.

The authors had previously described a series of ACC inhibitors, including ND-646, which prevents ACC dimerization (required for enzyme activity). ND-646 inhibited FA synthesis, growth and survival of NSCLC cells *in vitro*, mimicking the *ACC1* deletion results. ND-646 also inhibited FA synthesis and reduced the growth of established NSCLC subcutaneous xenografts, of xenograft tumours formed within the lungs following intravenous NSCLC cell injection, and of established tumours in two genetically engineered mouse models (GEMMs) of NSCLC. Notably, the treatment was tolerable and was more effective than standard-of-care carboplatin treatment in the intravenous lung tumour model. Furthermore, combined carboplatin and ND-646 was more effective than either monotherapy in both GEMMs. Although ND-646 inhibits both ACC1 and ACC2, as ACC2 expression was low and unable to compensate for ACC1 in the cell line deletion studies, the authors conclude that the effects of ND-646 are due to ACC1 inhibition.

German *et al.* discovered that ACC2, but not ACC1, is hydroxylated by prolyl hydroxylase domain-containing protein 3 (PHD3) and that PHD3-mediated hydroxylation of P450 on ACC2 was necessary for optimal ATP binding. Furthermore, as ACC2 prevents FA oxidation, the authors hypothesized that PHD3 would also prevent FA oxidation. Indeed, knockdown of PHD3 in 293T and HepG2 cell lines increased FA oxidation, and overexpression of an ACC2-P450A mutant could not repress FA oxidation, indicating that hydroxylation is crucial for ACC2 to inhibit FA oxidation.

The authors then investigated whether cancers that have low *PHD3* expression might depend on FA oxidation for growth. They found that many primary human acute myeloid leukaemias (AMLs) had low *PHD3* gene expression, and AML cell lines also had low *PHD3* expression, as well as reduced ACC2 hydroxylation and increased FA oxidation. These cells were sensitive to FA oxidation inhibitors, whereas leukaemia cells with high *PHD3* expression were not. In addition, overexpression of PHD3 in AML cells repressed FA oxidation and cell proliferation, but not when ACC2 expression was silenced. Proliferation was also suppressed following overexpression of PHD3 in primary AML cells and cells derived from an AML mouse model, and mice injected with PHD3-overexpressing AML cells survived longer than those injected with cells expressing low levels of PHD3. These data suggest that low *PHD3* expression might be a biomarker for leukaemias that would be sensitive to FA oxidation inhibitors.

These two papers suggest that how FA metabolic pathways can be targeted will likely depend on whether a tumour is dependent on FA oxidation and its genetic context (for example, high expression of *ACC1* or low expression of *PHD3*).

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**ORIGINAL ARTICLES** Svensson, R. U. *et al.* Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. *Nat. Med.* http://dx.doi.org/10.1038/nm.4181 (2016) | German, N. J. *et al.* PHD3 loss in cancer enables metabolic reliance on fatty acid oxidation via deactivation of ACC2. *Mol. Cell* **63**, 1006–1020 (2016)