

Study identifies an Achilles heel of many types of cancer

August 22 2019



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A Ludwig Cancer Research study has uncovered a novel vulnerability in tumors that are driven by a common cancer gene known as MYC. Such cancers, it found, are highly dependent on the cell's machinery for

making fats and other lipids.

Led by Chi Van Dang, scientific director of the Ludwig Institute for Cancer Research, and Stanford University researchers Dean Felsher and Richard Zare, the study also identifies a lipid signature associated with MYC-driven cancers. Further, it demonstrates that the [cancer](#) cell's predilection for manufacturing lipids rather than importing them as nutrients may be exploited for the development of new therapies for a broad spectrum of malignancies. The paper appears in the current issue of *Cell Metabolism*.

"Cells that are not growing bring in nutrients from the blood and make some of the other metabolic molecules they need," explains Dang. "But if you're a rapidly replicating cancer cell, you need a much larger supply of the building blocks of [cells](#) in order to continue proliferating."

Dang's laboratory previously discovered that MYC's dysregulation in cancer alters cellular metabolism and detailed how this master regulator of [gene expression](#) cranks up production of the molecular building blocks of cells, including the components of proteins and DNA. But how precisely oncogenic MYC alters gene expression to drive [lipid synthesis](#) was unknown. Lipids are critical constituents of cells: they build the cell's membranes and play an important role in protein function, metabolic reactions and molecular signaling.

In normal cells, a membrane-bound protein named SREBP1 monitors and controls lipid production. When it senses low cholesterol levels in the cell's membranes, SREBP1 moves into the nucleus and activates the expression of [genes](#) involved in lipid synthesis.

Postdoctoral researcher Arvin Gouw—who was previously in Dang's lab and is now in Felsher's—and colleagues found that the MYC protein boosts the expression of SREBP1. "What MYC does is put SREBP into

overdrive and SREBP jumps onto the genes involved in lipid synthesis," Dang explains. "But we also found that MYC then binds to the same genes as SREBP1, and the two collaborate to push lipid synthesis to even higher levels." The researchers show that MYC controls the gene expression required for almost every stage of lipid synthesis, from the generation of precursor molecules to putting the finishing touches on large, complex lipids.

To further examine the phenomenon, postdoctoral researcher Katy Margulis and colleagues used DESI-MSI—a technology for profiling metabolites in intact tissues developed by Zare's lab—to map how oncogenic MYC alters the lipid content of tumors. Those studies revealed that a species of lipids known as glycerophosphoglycerols is particularly abundant in MYC-driven [cancer cells](#). The researchers even identified a lipid signature associated with such tumors that could be used as a diagnostic marker.

Studies on mice engineered by Felsher's lab to generate, on demand, MYC-driven cancers of the blood, lungs, kidneys and liver revealed that such tumors are highly dependent on fatty acid synthesis. Inhibiting an early step of that process led to the regression of the induced tumors and of MYC-driven human tumors implanted in mice. Together with the identification of a lipid signature and the genes activated by oncogenic MYC, these data provide concrete information for the development of new drugs to treat a broad range of cancers.

"A very diverse expertise was essential to this study," Dang observes. "Bringing these various technologies and knowhow together enabled a deep understanding of something we didn't have great ideas about before, and it illustrates the power of interdisciplinary collaboration."

The findings are particularly notable because MYC is the third most amplified gene in human cancers. Even tumors that are primarily driven

by other oncogenes, the researchers show, are susceptible to the inhibition of fatty acid production if they indirectly activate MYC.

Dang, for his part, is now interested in unraveling how cancer cells sense which lipids need to be made and how that information shapes MYC's activation of [lipid](#) synthesis.

This study was supported by Ludwig Cancer Research, the U.S. National Institutes of Health and the Stanford Center of Molecular Analysis and Design.

More information: Arvin M. Gouw et al, The MYC Oncogene Cooperates with Sterol-Regulated Element-Binding Protein to Regulate Lipogenesis Essential for Neoplastic Growth, *Cell Metabolism* (2019). [DOI: 10.1016/j.cmet.2019.07.012](https://doi.org/10.1016/j.cmet.2019.07.012)

Provided by Ludwig Institute for Cancer Research

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