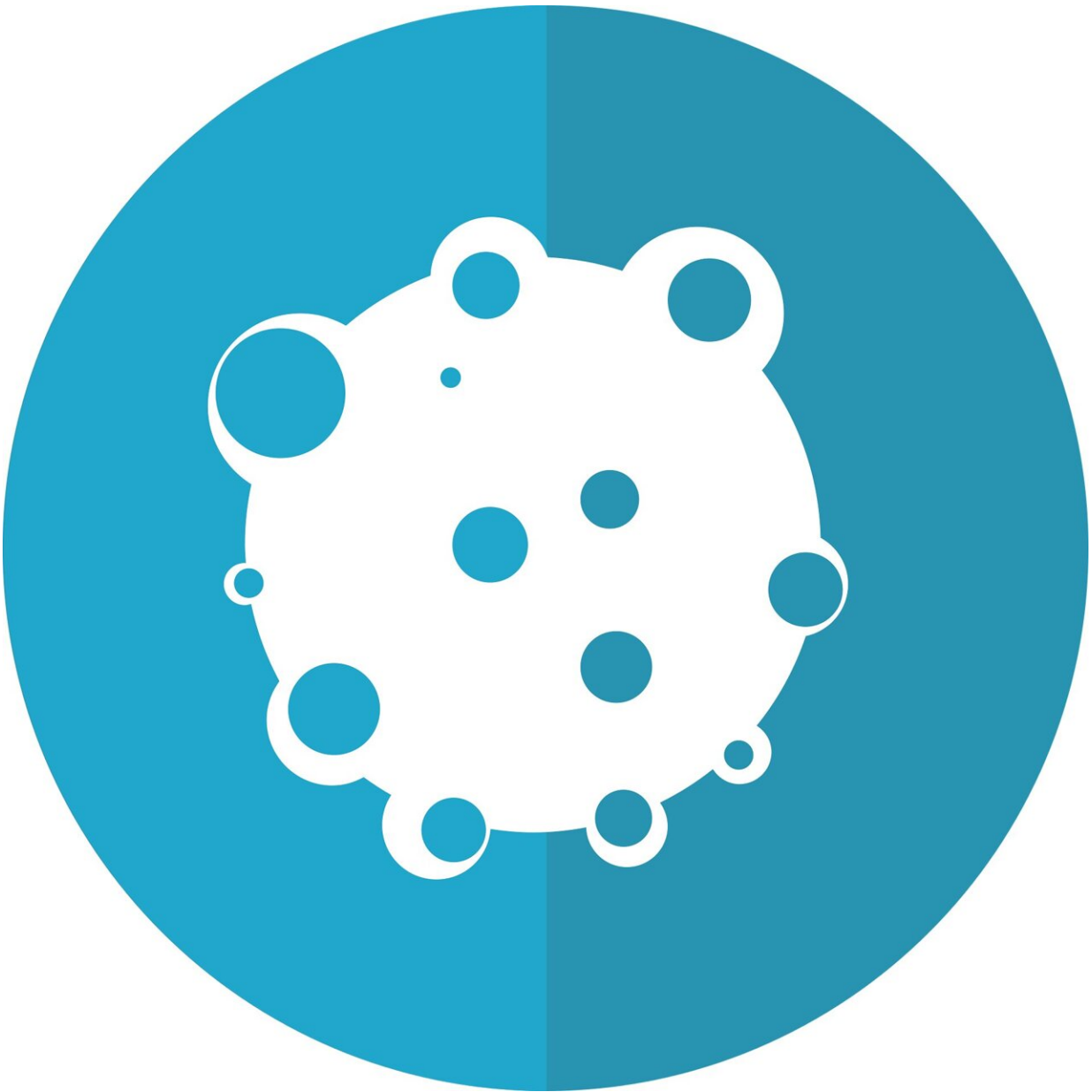


# How cancer cells engineer macrophages to support cancer growth

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A Ludwig Cancer Research study has identified a means by which cancer cells engineer the conversion of immune cells known as macrophages from destroyers of tumors to supporters of their growth and survival. The new research, led by Ludwig Lausanne's Ping-Chih Ho and postdoctoral fellow Giusy Di Conza, reveals that in mouse models of the skin cancer melanoma, this transformation of macrophages within tumors is prompted by a fat molecule, or lipid, released by cancer cells.

The study, published in the current issue of *Nature Immunology*, also identified some of the key events and molecular players that drive this "polarization" of tumor-associated macrophages (TAMs). Ho, Di Conza and colleagues show that the lipid responsible,  $\beta$ -glucosylceramide, binds to a receptor on TAMs, triggering a stress response within a tubular cellular organelle known as the endoplasmic reticulum (ER). This, in turn, sets off at least two signaling cascades within the cell, which drive the expression of genes in macrophages that facilitate their transformation.

"Aside from exposing a previously unknown mechanism by which tumors manipulate the [immune system](#) to their own benefit, our study identifies signaling events that could be pharmaceutically targeted to push macrophages back toward an anti-tumor phenotype for [cancer therapy](#)," said Di Conza, who is first author of the paper.

Ho, Di Conza and colleagues began these studies with the observation that pro-tumor TAMs display two curious traits: a higher than usual lipid content and swelling of their ER. Swelling is usually a sign of ER stress, and the team also detected elevated levels of [stress-response](#) proteins in the pro-tumor TAMs. One such protein—a form of XBP1 recently

linked to suppressing the function of other immune cells—appeared to be necessary for skewing TAMs toward a pro-tumor state, or phenotype.

These observations fit with other emerging evidence that abnormal lipid metabolism in cancer cells causes the accumulation of lipids in the tumor microenvironment that inhibit anti-tumor immunity.

"We know that metabolites in the tumor are important for shaping not only the phenotype of the tumor, but also the immune cells residing in the tumor microenvironment," said Di Conza. "So, we wondered whether there is a metabolic link between cancer cells and macrophages that tells a macrophage to become a bad guy."

The team tested this possibility by removing lipids from the conditioned medium in which the mouse tumor cells were cultured. Doing this prevented TAM conversion into the pro-tumor phenotype.

Next, the team sought to identify the particular lipid triggering TAM polarization. Ironically, they were assisted in this difficult task by the COVID-19 pandemic. Unable to enter the lab during the pandemic lockdown, Di Conza passed some of the time reviewing data on genes involved in lipid recognition and binding. There, she found a new lead.

A lipid receptor found on the surface of macrophages, known as Mincle, was conspicuously active when exposed to the medium in which mouse cancer cells were growing. Mincle can induce ER stress responses and the accumulation of lipids in macrophages—the very traits that Di Conza and her team had observed in pro-tumor TAMs.

When the researchers blocked Mincle activity using an antibody, they observed a marked reduction in TAM polarization toward a pro-tumor state.

Mincle's involvement led the researchers to take a closer look at  $\beta$ -glucosylceramide, a lipid released into the tumor microenvironment that binds to Mincle. Disabling its production by cancer cells resulted in fewer pro-tumor TAMs and slowed tumor growth in mice.

"Based upon the finding, our speculation is that cancer cells upregulate this lipid as a response to stress," said Ho, associate member of the Ludwig Institute for Cancer Research, Lausanne. "The secretion of  $\beta$ -glucosylceramide then informs surrounding cells that those cancer [cells](#) need help. It also helps facilitate the functional skewing of macrophages in the [tumor microenvironment](#) to become pro-tumorigenic."

Subsequent experiments further revealed that XBP1 is activated in pro-tumor TAMs, and removing this gene slowed tumor growth, indicating that XBP1 is not only vital for TAM polarization but also supports cancer cell survival.

Further, XBP1 alone is not sufficient to promote the pro-tumor phenotype. Other experiments indicated that another signaling cascade was coordinating with the one involving XBP1 to induce TAM polarization. This turned out to be a pathway involving a signaling protein and transcription factor named STAT3, which binds DNA and directly regulates the expression of genes.

Now that some of the key events and molecular players in TAM polarization have been identified, it may be possible to target them pharmaceutically to slow or even reverse the process.

**More information:** Giusy Di Conza et al, Tumor-induced reshuffling of lipid composition on the endoplasmic reticulum membrane sustains macrophage survival and pro-tumorigenic activity, *Nature Immunology* (2021). [DOI: 10.1038/s41590-021-01047-4](https://doi.org/10.1038/s41590-021-01047-4)

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