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Herding cancer cells to their death

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An advanced tumor is a complex ecosystem. Though derived from a single cell, it evolves as it grows until it contains several subspecies of cells that vary dramatically in their genetic traits and behaviors. This cellular heterogeneity is what makes advanced tumors so difficult to treat. Publishing their findings in today's online issue of *Cancer Cell*, an international team of scientists led jointly by Professors Colin Goding from the Ludwig Institute for Cancer Research who is based at the University of Oxford and José Neptuno Rodriguez-López from the University of Murcia, Spain describe a therapeutic strategy that manipulates a mechanism driving that heterogeneity to treat advanced melanoma. Their preclinical studies show that the strategy, which employs a new drug-like molecule in combination with an existing chemotherapy, is highly specific to melanoma cells and effective against tumors that resist all other therapies.

If caught early, melanoma is relatively easy to treat. But in its late stages, it is a stubborn and deadly cancer. Until about a decade ago, patients survived only about seven months after starting treatment. Since then, therapies, such as vemurafenib, that specifically target signaling proteins essential to the proliferation and survival of melanoma cells have extended the lives of some patients. But only about half respond to these targeted therapies, and even in those patients the cancer begins to resist the targeted therapy within six to nine months.

To bypass such resistance, the researchers developed a strategy that essentially pushes subtypes of melanoma cells that are not dividing—and are therefore not susceptible to chemotherapy—to become vulnerable to

a shrewdly targeted drug.

To develop their therapy, the scientists first screened a variety of molecules to find one that boosts the expression of MITF, a master gene that, at high levels, pushes melanoma cells to proliferate and to express a protein known as Tyrosinase that fuels pigment production. The scientists found that methotrexate—a drug currently used to treat autoimmune diseases and some other cancers, though not melanoma—had precisely that effect. The Spanish team then synthesized a novel molecule called TMECG that is lethal only when it is chemically modified by Tyrosinase. When activated by Tyrosinase, TMECG disrupts the protein machinery of cell division and so poisons cells that are multiplying rapidly.

"The beauty of the therapy," says Professor José Neptuno Rodriguez-López, PhD, leader of the Spanish team at the University of Murcia, is that "TMECG is activated by a process that is specific to pigmented cells but not other cells. So, first the methotrexate sensitizes melanoma cells to the effects of TMECG. Then that molecule gets processed and activated by Tyrosinase to form an active compound that kills rapidly dividing cells. Even better, the methotrexate then delivers a second blow to melanoma cells by prompting them to commit suicide through a very specific mechanism."

The researchers found that the combined treatment efficiently destroyed melanoma cells in culture, even those derived from patient tumors resistant to vemurafenib and other targeted melanoma therapies. It also significantly suppressed tumors in one mouse model and diminished metastases in another.

In mice, the treatment combination does not appear to injure other pigmented cells, such as healthy cells of the skin, or those of the iris or the retina, probably because those cells are not rapidly proliferating. The

researchers are now refining their new drug to improve its pharmacologic profile and figure out how to deliver it to the right places in the body.

"Think about what you ideally want from a cancer therapy," says Professor Colin Goding, PhD, Member of the Ludwig Institute for Cancer Research who is based at the University of Oxford. "You want a therapy that addresses cancer cell heterogeneity, that eradicates the tendency of cancer cells to become invasive, that works on cells that are resistant to other therapies and that targets only the cancer cells and not any others. I think we've ticked all those boxes."

"By inducing melanoma to differentiate using an old chemotherapy drug, Saez-Ayala and colleagues took advantage of a protein expressed at high levels as a consequence of that differentiation to turn a molecule they have designed into a prolific melanoma killer," said Antoni Ribas, MD, PhD, Professor of Medicine at the University of California Los Angeles and the Jonsson Comprehensive Cancer Center in Los Angeles. "Based on their preclinical data, I believe that this two-step approach may have promise for treating melanoma."

Still, Goding notes, cancer cells are so mutable that some melanoma cells will inevitably develop resistance to the novel therapy. So he expects that, aside from showing that the strategy works in patients, future research will have to show that it can be combined with other cancer therapies to get around such resistance. "That's how we should be thinking about cancer therapy," he says. "The complexity of the disease is such that any one therapy probably won't work on its own. But if you give complementary therapies that work in completely different ways, then I think you have a chance against this disease."

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