

LURING MELANOMA CELLS TO THEIR DEATH

An experimental strategy pushes drug-resistant stem cells into a susceptible state—and kills them

It all began with a white mouse. Ludwig Oxford scientist Colin Goding first heard about the creature in 1992, through the scientific grapevine. The mouse that so piqued his curiosity carried a disruption in a long-sought gene that controlled the production of melanocytes, pigmented cells of the skin.

Goding, who was using cells grown in culture to study the control of cellular pigmentation, had already identified a key DNA sequence pattern he called the M-box. He predicted that this M-box was bound by a master regulator in pigment cells. When he heard about the mutant mouse, he knew immediately that its disrupted gene encoded that missing regulator.

Now, more than 20 years later, Goding's research on the gene, called MITF, is paying off with a potential treatment for melanoma, a skin cancer that is easily treated if caught early but swiftly lethal once it has metastasized. Goding's approach involves a two-drug combination: one drug tweaks tumor cells so they produce the protein encoded by the MITF gene, and the second selectively kills cells expressing high levels of that protein. Last year Goding and his Ludwig colleagues showed that this combination beats back melanoma in mice, and they are now conducting preclinical studies toward its future assessment in patients.

FROM STEM CELL TO DEAD CELL

Melanoma tumors, like those of most cancers, comprise a variety of cells. The bulk of the primary melanoma tumor contains pigmented cells, some of which proliferate rapidly. These cells generally express the MITF gene. But most melanomas also contain some deadly unpigmented cells lacking MITF that tend to be highly resistant to therapy because they do not divide very frequently. Like stem cells, these unpigmented cells can seed new tumors elsewhere in the body.

Metastatic tumors account for the poor prognosis of melanoma. Recent advances in harnessing the immune response to treat melanoma—in which Ludwig has played a leading role—have significantly improved prospects for patients. Still, there remains a serious need for new strategies to control this cancer.

In their new study, Goding and his colleagues reasoned that there might be a way to prompt the stem cell-like components of melanoma tumors to become susceptible to therapy. After testing various agents, the researchers found that methotrexate, a drug that has long been used in the clinic to treat some cancers and autoimmune diseases, prompted those cells to express MITF, produce pigment and proliferate. Methotrexate had this effect on the cells in both laboratory cultures and animal models.



Colin Goding, Ludwig Oxford

Next, the researchers asked how they could selectively disable the MITF-expressing cells. To do this, Goding and his colleagues designed a drug that was activated by a protein whose expression is ramped up in MITF-expressing melanocytes. When activated, the drug, called TMECG, killed tumor cells. “The drug combination works beautifully in mouse models,” says Goding.

MOVING IN ON MELANOMA

This two-step approach has several potential advantages as a therapy. By transforming the stem cell-like cells into proliferating, pigmented cells, the researchers eliminate the source of metastases. And by killing off the tumor with a drug that is activated only in pigmented, MITF-expressing cells, they effectively target the drug to melanoma cells. “This drug combination is very specific to pigmented cells,” says Goding. “You would not expect to see any side effects.”

Moreover, the new combination also works in tumor cells that have become resistant to targeted therapies, such as inhibitors of the protein BRAF.

Goding is now laying the groundwork for potential clinical trials, and he is already working with colleagues to perform toxicology tests on his new drug candidate. The utility of the new strategy will, of course, be proved only through such trials. What requires no further proof is that it pays to keep an ear close to the scientific grapevine.

REFERENCE

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