Exploiting cancer cells' weaknesses

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Professor of Biology Angelika Amon. Photo: Donna Coveney

When designing new cancer drugs, biologists often target specific gene mutations found only in cancer cells, or in a subset of cancer cells. A team of MIT biologists is now taking a slightly different approach, targeting a trait shared by nearly all cancer cells -- they have too many chromosomes.

MIT biology professor Angelika Amon has been studying this peculiarity, known as aneuploidy, for several years. In developing fetuses, aneuploidy causes death or birth defects. However, in cancer cells, aneuploidy appears to confer a survival advantage.

“We’re interested in this because the vast majority of human cancers are aneuploid,” says Amon, a member of the David H. Koch Institute for

Integrative Cancer Research. “The question arises, can we exploit the fact that all tumor cells are aneuploid for treatment? Compounds that selectively kill aneuploid cells would be effective against a broad spectrum of human tumors.”

In a study published Feb. 18 in the journal Cell, Amon and her colleagues identified three such compounds, and they are now running a large-scale screen of thousands of compounds, with researchers from Harvard, to identify even more drug candidates. Lead author of the paper is Yun-Chi Tang, a postdoctoral fellow at the Koch Institute.

Cell stress

Amon has previously shown that aneuploid cells divide very slowly and grow too large. Aneuploidy also puts significant stress on cells: It takes a lot of energy to replicate all of that extra genetic material, and to produce the proteins encoded by those extra genes. Furthermore, the cells then have to break down all those proteins, since they’re not needed. “Cells have a limited number of tools available to deal with extra proteins,” Amon says. “These pathways get stressed and they can’t keep up.”

In the Cell study, Amon selected about 20 potential drug compounds that might exploit those weaknesses. “We said, maybe we can enhance those stresses and induce lethality. The hope is to enhance it to a level that does not affect normal cells but would affect aneuploid cells more,” she says.

The researchers tested the compounds in mouse embryonic fibroblasts that have an extra chromosome, and then in human cancer cells. They identified three compounds that preferentially targeted the aneuploid cells (both human and mouse): chloroquine, a drug commonly used to treat malaria, and two other compounds called AICAR and 17-AAG.

AICAR stresses cells by activating an enzyme called AMPK, which cranks up cellular metabolism. 17-AAG inhibits the production of a protein involved in stabilizing other proteins that cancer cells need to grow. Chloroquine acts by blocking a cancer cell's ability to rid itself of damaged proteins and cell structures.

Amon says she believes the drugs are exaggerating the stresses of aneuploidy, but more experiments are needed to show that.

All three compounds induce human cancer cells to kill themselves, but they work much better when two are used together. 17-AAG is already in clinical trials for leukemia, but these new data suggest that it would be better used in combination with other drugs, Amon says.

AICAR is not approved for human use, but a similar drug called metformin is used to treat diabetes. However, metformin did not perform as well in this study as AICAR.

Pumin Zhang, professor of molecular physiology at Baylor College of Medicine, says the results represent a significant step toward finding drugs that specifically target cancer cells, unlike most of the chemotherapy drugs now available. "It shows there is a clear difference between normal cells and aneuploid cancer cells, and we can exploit that difference," says Zhang, who was not involved in this research.

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