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Strategies to mimic fasting during chemotherapy enhance anticancer T cell activity in mice

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Fasting is known to increase positive outcomes during cancer treatment, and now two independent studies in mice show that fasting, either through diet or drugs, during chemotherapy helps increase the presence of cancer-killing T cells. The research teams show that rodents that received caloric restriction mimetics alone or chemotherapy combined with a fasting-mimicking diet had smaller tumor masses over time than those that received only chemotherapy. Both studies appear July 11 in *Cancer Cell*.

While the two papers demonstrate strategies to exploit the weakness of tumor cells to caloric restriction and enhance immune-mediated cancer cell death, further study will be needed to find out whether mimicking fasting can improve outcomes for all kinds of cancer treatments (especially emerging immunotherapies) as well as whether these results can be replicated in humans. For now, the research provides proof of concept for two potentially safe approaches to enhance chemotherapy.

Valter Longo, Stefano Di Biase, and Changhan Lee of the University of Southern California led the effort to use a fasting-mimicking diet to confer the benefits of starvation without the negative side effects. Mice with breast or skin cancers were given a low sugar, low protein, high fat, low calorie diet and were observed for 6 weeks while receiving doxorubicin, cyclophosphamide, or no chemotherapeutic drugs. All of the mice receiving the diet-drug combination saw their tumors shrink to

half the volume of the tumors in mice that received chemotherapy alone.

"Our main finding is that the T cells are essential for the toxicity of the fasting plus chemotherapy to cancer cells," says Longo, a gerontologist and cell biologist also of the University of Southern California Longevity Institute and FIRC Institute of Molecular Oncology in Italy. "The biggest factor exposing cancer cells to the T cells is the effect on the enzyme heme oxygenase-1, which is normally at high levels in cancer cells. Fasting reduces oxygenase levels and gives rise to a number of changes that included the increase of tumor-killing cytotoxic T cells."

Guido Kroemer, Federico Pietrocola, and Jonathan Pol of INSERM and the Centre de Recherche des Cordeliers in France led a separate effort using caloric restriction mimetics—drugs that selectively trigger some of the biochemical cascades that result from starvation but without the weight loss—that instigated the same chemo-sensitizing effects from T cells. The researchers used a mimetic, hydroxycitrate, in mice with transplanted lung and breast cancers to reduce tumor numbers and size. They observed the T cells responding to the pharmacological starvation of the cancer cells, which changed the tumor microenvironment to increase the formation of new white blood cells.

"My theory is that when you cause some cancer cell death, you stimulate the release of factors that enhances the recruitment of cell types that can fight against the tumor and reduce the immunosuppressive cells," says Kroemer, a cell biologist and cancer researcher, who also practices medicine at Hôpital Européen Georges-Pompidou. "But we haven't excluded that the death of immune cells themselves would also contribute to the effect of caloric restriction mimetics in reaction to chemotherapy."

Longo is more convinced of the immune cell-driven explanation. He speculates that fasting, which would have been very common for our

ancestors, was a tool to reboot the immune system and prevent the circulation of cancer cells. "This coordinated multifaceted effect seems too good to be true," he says. "It may not be a coincidence, but a very precisely evolved process that is meant to get rid of bad cells."

Both Kroemer and Longo agree that their papers are complementary to one another, with similar findings using different approaches to mimic fasting in a way that would be safe for all cancer patients, not just those who can afford the most expensive treatments.

The researchers will next need to conduct long-term studies to demonstrate that their strategies can be effective in humans. Longo has already tested the safety of a fasting-mimicking diet in cancer patients (DOI: 10.1186/s12885-016-2370-6) and is now working with multiple hospitals to test how the diet helps cancer patients respond to treatment. Kroemer is next exploring which immune cells have the most anticancer properties and will be testing how caloric restriction mimetics impact survival of patients with breast cancer.

More information: *Cancer Cell*, Di Biase and Lee et al: "Fasting-Mimicking Diet Reduces HO-1 to Promote T Cell-Mediated Tumor Cytotoxicity" www.cell.com/cancer-cell/fullt … 1535-6108(16)30265-3 , DOI: 10.1016/j.ccell.2016.06.005

Cancer Cell, Pietrocola and Pol et al: "Caloric restriction mimetics enhance anticancer immunosurveillance" www.cell.com/cancer-cell/fullt … 1535-6108(16)30221-5 , DOI: 10.1016/j.ccell.2016.05.016

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