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RESEARCH NEWS STORY

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Understanding Why Some Tumors Survive Heat Shock Treatment

Researchers discover cholesterol protects cancer cells from heat damage, paving the way to understand and develop more effective hyperthermia treatments

Hyperthermia, a cancer treatment using controlled heat to kill tumor cells, shows promise but faces limitations due to some tumor cells' unexpected heat resistance. Researchers from Japan have now discovered that high cholesterol levels in cancer cell membranes act as a protective barrier, shielding against heat-induced membrane breakdown. When cholesterol was depleted using drugs, previously heat-resistant tumors became vulnerable to hyperthermia treatment, opening new possibilities for personalized cancer therapy targeting cholesterol levels to improve outcomes.

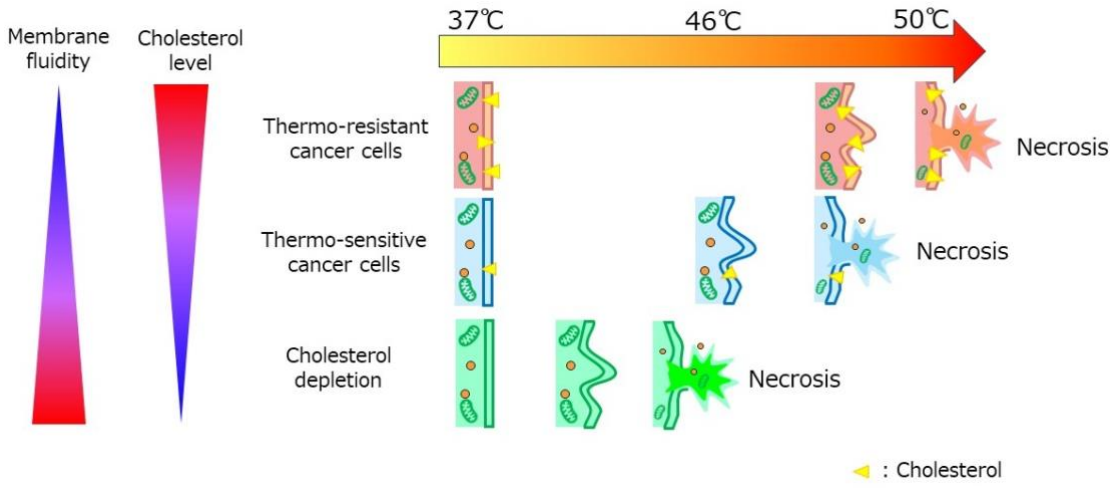

Image title: Establishing a link between cholesterol levels and resistance to heat treatment in cancer cells
Image caption: Heat-induced increase of membrane fluidity is suppressed by cholesterol, preventing membrane disruption. Thus, cholesterol-rich cells are resistant to heat-induced necrosis, and cholesterol depletion converts heat-resistant cells into heat-sensitive cells.
Image credit: Professor Hiroto Hatakeyama from Chiba University, Japan
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Since the time of the ancient Greek physician Hippocrates, cancer has been recognized as being sensitive to heat. Today, this principle forms the basis of hyperthermia treatment—a promising cancer therapy that uses controlled heat to kill tumor cells while sparing healthy ones. Unlike chemotherapy or radiation, hyperthermia works by heating cancerous tissue to temperatures around 50 °C, causing cancer cell death while simultaneously activating the body's immune system against the tumor. This approach holds particular promise when combined with immunotherapy, as heat-killed cancer cells can trigger a stronger anti-tumor immune response.

However, a few major challenges have limited hyperthermia's clinical success. One of the main hurdles is the limited understanding of the biological mechanisms behind heat sensitivity in cancer cells. Researchers have discovered that some cancer cells—even those from the same organ—react differently to heat shock, with some surprisingly more heat-resistant than others. This resistance involves two distinct cell death types: necrosis, which occurs rapidly through direct physical damage to cell membranes, and apoptosis, a slower, programmed cell death that happens hours later. In particular, how heat-resistant cancer cells regulate **necrosis** has received little scientific attention, limiting hyperthermia's potential as a standard cancer treatment.

To tackle this knowledge gap, a research team led by Professor Hiroto Hatakeyama from the Graduate School of Pharmaceutical Sciences, Chiba University, Japan, investigated the molecular mechanisms behind heat resistance in cancer cells. Their study, published in Volume 15 of the journal *Scientific Reports* on March 24, 2025, was co-authored by Dr. Taisei Kanamori and Mr. Shogo Yasuda from Chiba University and Dr. Takuro Niidome from Kumamoto University. "*Despite the general belief that cancer cells are heat-sensitive, I was surprised to find heat-resistant cancer cells in one of my previous studies*," shared Prof. Hatakeyama, "*Since then, I have been interested in how these cancer cells acquire heat resistance and how physical heat affects the biological processes of cells and cancer*."

Through a series of experiments in mice and cell cultures, the researchers compared the characteristics and behaviors of heat-sensitive cancer cells with heat-resistant ones. They discovered that **cholesterol** could act as a protective shield for cancer cells during heat treatment. Heat-resistant cancer cells contained significantly higher levels of cholesterol than heat-sensitive ones. This, in turn, helped maintain the stability of cell membranes when exposed to heat, preventing the rapid membrane breakdown that leads to necrosis. Notably, when researchers artificially removed cholesterol from cancer cells using a cholesterol-depleting drug, even the most heat-resistant cells became vulnerable to hyperthermia treatment.

This breakthrough came through a detailed analysis of cell membrane behavior during heat exposure. Using advanced imaging techniques, the researchers observed that heat treatment causes cell membranes to become more fluid (increased membrane fluidity). In cells with high cholesterol levels, this increase in membrane fluidity was suppressed, thereby protecting the cells from heat damage. However, when cholesterol was removed, membrane fluidity increased, making the cells much more susceptible to heat-induced damage, leading to rapid cell death through necrosis.

Testing their findings across multiple human and mouse cancer cell lines confirmed that cholesterol levels were consistently related to heat resistance. The researchers further validated their discovery in living mice with implanted tumors, using gold nanoparticles and near-infrared light to create localized heating. Tumors treated with both cholesterol depletion and hyperthermia showed dramatic shrinkage, with most tumors completely disappearing—a far superior result compared to heat treatment alone.

This research suggests that measuring cholesterol levels in tumors could help doctors identify which patients are most likely to benefit from hyperthermia treatment. More importantly, the combination of cholesterol-depleting drugs with localized heat therapy could transform hyperthermia from an inconsistent treatment into a powerful weapon against cancer. Since cholesterol depletion primarily triggers necrosis, this approach may also enhance the immune system's ability to recognize and attack the remaining cancer cells. "*Previous studies reported that cancer cells killed by hyperthermia can activate anti-tumor immunity*," explains Prof. Hatakeyama. "*If hyperthermia therapy can be appropriately incorporated into cancer treatment, it could help improve the response rate of cancer immunotherapy, which currently helps only 10–20% of patients.*"

Overall, these findings open new possibilities for personalized cancer treatment, paving the way for new tools to fight many forms of this dreaded disease.

About Professor Hiroto Hatakeyama

Dr. Hiroto Hatakeyama joined Chiba University in 2016 as an Assistant Professor after working at Hokkaido University and the University of Texas MD Anderson Cancer Center. He currently serves as a full-time Professor at the Graduate School of Pharmaceutical Sciences of Chiba University. He specializes in cancer therapy, drug delivery systems, and cellular and molecular biology. He has published over 100 articles with more than 6,000 citations. He has been an honorable awardee of multiple accolades, including the Incentive Award 2017 from The Pharmaceutical Society of Japan and the Young Investigator Award from The Japan Society of Drug Delivery System.

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Reference:

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