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Drug resistance in cancer patients linked to oxygen-bearing molecules in body, study finds

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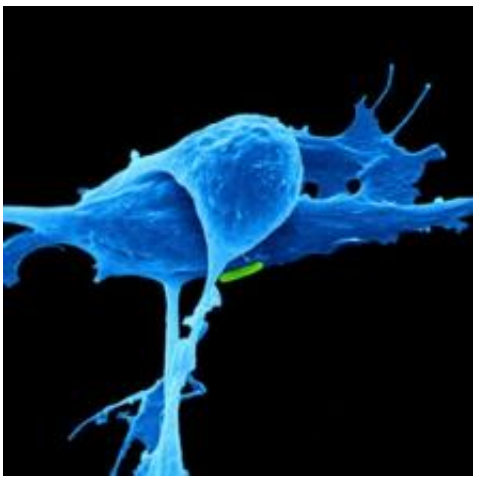

Increased levels of certain chemically reactive, oxygen-containing molecules in the body can cause patients to become resistant to cancer drugs such as chemotherapy, according to researchers at Georgia State University.

The findings, published in a review article in the journal *Pharmacological Research* in August, suggest there is a direct link between cancer drug resistance and reactive oxygen species (ROS) found in mitochondria, the powerhouses of cells that supply cellular energy.

The discovery has important implications for cancer therapy.

The researchers found cancer patients who receive chemotherapy treatment for a sustained period have heightened levels of ROS, which correlates with drug resistance.

"Based on our studies with responsive versus drug-resistant cancer cells, it appears that patients who still respond to therapy typically don't have such high levels of ROS," said Imoh Okon, assistant professor in Georgia State's Center for Molecular and Translational Medicine.

Despite advances in anti-cancer therapies, cancer drug resistance remains a major problem in healthcare because many patients who die from cancer become resistant to previously effective drugs. This review article analyzes recent cancer studies to explain why this happens, Okon said.

Okon and his co-author Dr. Ming-Hui Zou, director of the Center for Molecular and Translational Medicine at Georgia State, propose that physicians need a measure of relative ROS levels under "normal" or basal conditions to help determine if patients are becoming resistant to cancer drugs. They are developing a cancer diagnostic drug resistance test kit that will provide accurate and early detection of drug resistance transition.

ROS, which is regulated by the body's redox system, is beneficial at normal levels in the body and essential to human physiology. However, under disease conditions such as cancer, the regulatory redox balance becomes altered. Conventional anti-cancer treatments, such as chemotherapy and radiation, are designed to destroy cancer cells through ROS-mediated mechanisms. However, heightened and persistent ROS levels can also become detrimental, thereby promoting changes in cells, even causing normal cells to have genetic abnormalities and mutations

over time, Okon said.

"If you know what the relative basal ROS level is, then you can really monitor over time whether it's getting too high based on the specific treatment for that patient," Okon said. "We also recommended having some sort of spacing in between these treatments to allow the cells to recover and ROS levels to come down to normal levels to get the cells going again before you hit cancer cells with another battery of targeted or chemotherapy drugs."

Tumors become unresponsive to cancer drugs because cancer cells adapt to survive and proliferate, usually by altering their metabolism. When mitochondria, which control cellular metabolism, are exposed to external factors such as drug treatments, this triggers adaptations to their normal function, and they begin to play abnormal roles that promote drug resistance.

In their recent study published in *The Journal of Biological Chemistry*, the researchers demonstrated that resistance to gefitinib—a new-generation, target-specific cancer drug—correlates with mitochondrial dysfunction and increased ROS in lung cancer cells.

While there are likely other contributors to cancer drug resistance, ROS plays a key role in metabolic events that may be central to the process, Okon said.

More information: *Pharmacological Research*, www.sciencedirect.com/science/ … ii/S1043661815001279

Provided by Georgia State University