Study reveals new molecular target for melanoma treatment

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A laboratory study led by UNC medical oncologist Stergios Moschos, MD, demonstrates how a new targeted drug, Elesclomol, blocks oxidative phosphorylation, which appears to play essential role in melanoma that has not been well-understood. Elesclomol (Synta Pharmaceuticals, Lexington, MA) was previously shown to have clinical benefit only in patients with normal serum lactate dehydrogenase (LDH), a laboratory test routinely used to assess activity of disease.

For more than 60 years, scientists have known that cancer cells undergo glycolysis, or metabolize glucose, at a much higher rate than normal cells. The observation, called the Warburg effect, demonstrated that the normal energy producing processes in the cell are disrupted in cancer cells, preventing them from using metabolic pathways in the cell's mitochondria (often called the cell's "power plants").

Recently, however, increasing evidence suggests that, in addition to glycolysis, other metabolic pathways may also play a role in cancer, with important therapeutic implications. A promising strategy for targeting cancer cells, while sparing normal cells, is to target these altered metabolic processes with drug therapies. Elesclomol has been shown to trigger cell death in metastatic melanoma cells, primarily by suppressing oxidative phosphorylation – the process that cells use to transform nutrients into energy.

Moschos and his team demonstrated in the lab that metastatic melanoma cells exhibit a higher rate of glycolysis compared to their normal

counterpart cells, termed melanocytes, which would be expected due to the Warburg effect.

"But we also found, surprisingly, that these cells have higher rates of oxidative phosphorylation – they are producing energy through more than one pathway, which explains a lot about how the drug works," says Dr. Moschos.

He notes that this drug has an interesting history. In a 600-patient phase III clinical trial conducted almost 4 years ago, Elesclomol had clinical benefit in the subgroup of patients with normal serum LDH. However, the FDA discontinued the trial, because the Elesclomol in combination with another chemotherapeutic drug may have negative effects in patients with high serum LDH, which is associated with poorer patient outcomes in metastatic melanoma. At the time, very little was known about Elesclomol's mechanism of action – blocking oxidative phosphorylation.

"Our inability to show how Elesclomol worked through measurement of biomarkers was the major driver to conduct this laboratory study," said Moschos, whose team took the clinical trial results back to the lab to try to figure out why the drug worked.

"Our results suggest that targeting oxidative phosphorylation in melanoma is a promising strategy for early metastatic disease, before melanoma cells switch their primary metabolic source to glycolysis, as Otto Warburg showed 60 years ago" said Dr. Moschos.

"Second, we were able to demonstrate a mechanism of resistance to Elesclomol, where long-term exposure to the drug leads to the selection of melanoma cells with high levels of glycolysis. This suggests that a two-pronged strategy aimed at blocking both metabolic pathways may be called for."

The results of the study were published today in the journal *Public Library of Science One*.

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