MedicalXpress

Diabetes drug points the way to overcoming drug resistance in melanoma

June 11 2013

Advanced metastatic melanoma is a disease that has proven difficult to eradicate. Despite the success of melanoma-targeting drugs, tumors inevitably become drug resistant and return, more aggressive than before. In the current issue of the journal *Cancer Cell*, however, researchers at The Wistar Institute describe how they increase the effectiveness of anti-melanoma drugs by combining anticancer therapies with diabetes drugs.

Their studies, conducted in cell and animal models of melanoma, demonstrate that the combined therapy could destroy a subset of drug-resistant cells within a tumor.

"We have found that the individual cells within melanoma tumors are not all identical, and tumors contain a sub-population of cells that are inherently drug resistant, which accounts for the fact that advanced melanoma tumors return no matter how much the tumor is depleted," said Meenhard Herlyn, D.V.M., D.Sc., professor and director of Wistar's Melanoma Research Center. "We found that these slow-growing, drug-resistant cells are marked by a high rate of metabolism, which makes them susceptible to diabetes therapeutics."

"Our findings suggest a simple strategy to kill metastatic melanoma —regardless of cell type within the tumor—by combining anticancer drugs with diabetes drug," Herlyn said. "The diabetes drug puts the brakes on the cells that would otherwise repopulate the tumor, thus allowing the anticancer drug to be more effective."

In the *Cancer Cell* article, the researchers describe how various anticancer drugs, including cisplatin and the targeted therapy vemurafenib, which targets melanomas with the BRAF mutation, become more effective when co-delivered with phenformin. According to Herlyn, the researchers used the diabetes drug phenformin in their studies, but they are now working with colleagues to develop a clinical trial using a drug with less toxic side effects.

Melanoma is the deadliest, most aggressive form of skin cancer. Melanoma rates continue to remain on the rise, and the average patient age continues to decrease. While surgical treatment of early melanoma leads to 90 percent cure rates, advanced melanoma is notoriously resistant to chemotherapy and has a tendency to metastasize, or spread, throughout the body. Nearly half of all melanomas contain BRAF mutations, which led to the successful creation and approval of new BRAF-targeting drugs.

In 2010, Herlyn and his colleagues published findings that changed the way scientists look at tumor cells. Melanoma tumors were, as they described, heterogeneous. That is, they contained multiple populations of cells, including the so-called JARID1B cells, which their research suggested was responsible for allowing tumors to survive drug therapy. According to Herlyn, these slow-growing JARID1B cells represent only one to five percent of the cells in a tumor, yet readily divide into the fast-growing cells that are the hallmark of advanced melanoma.

Amazingly, these cells were remarkably resistant to drug therapies. "JARIRD1B cells shrug off chemotherapies and targeted drug inhibitors, regardless of their mode of action," Herlyn said.

"These are not dormant cells—they divide once every six or seven weeks as opposed to every other day like the rest of the melanoma cells," Herlyn explained. "These slow-growing cells are apparently kept in

check by the rest of the tumor, somehow—indeed, if you remove them from a tumor, they grow like crazy."

Working with Wistar's Proteomics Facility, the Herlyn laboratory surveyed JARID1B's proteome (that is, the sum total of all the proteins these cells produce), and found that these cells were on metabolic overdrive. Despite the fact that they hardly seemed to grow and divide, they were continually synthesizing glucose, which is then used to produce chemical energy.

Fortunately, an entire field of study has been created to combat cells that produce glucose—diabetes. Using phenformin, a drug first created nearly a half century ago, the researchers demonstrated it was possible to deprive melanoma tumors of the metabolic dynamos that allow melanoma to survive therapy.

According to Herlyn, Wistar's Melanoma Research Center is working with their clinical partners to develop a clinical trial to apply their research findings to patients with advanced melanoma.

Provided by The Wistar Institute