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Researchers studying model to learn why certain cancers become resistant to drugs

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Resistance to chemotherapy treatments can be the worst news a cancer patient ever receives. A pair of researchers at the University of Missouri-Columbia is working steadfastly to learn why some tumors eventually build a tolerance to the common chemotherapy drug cisplatin, in hopes of identifying the particular genes that can be manipulated to make treatment as effective as possible.

In a paper published in the latest edition of *Proceedings of the National Academy of Sciences*, Hannah and Stephen Alexander, professors of biological sciences in MU's College of Arts and Science, in collaboration with Gad Shaulsky and Adam Kuspa, professors at the Baylor School of Medicine, demonstrate that a model organism called "Dictyostelium discoideum" is useful for studying mechanisms of cisplatin drug sensitivity.

Dictyostelium discoideum cells share many genes and biochemistry with human cells – there are more than 30,000 genes in one human cell compared with 15,000 in Dictyostelium discoideum – which simplifies the process of isolating and studying particular genes. The current study identified 400 genes that have the potential for use in improving cisplatin therapy.

"The basic issue is that many types of cancer are treated with cisplatin," Stephen Alexander said. "In some cases it's the best drug, and in some cases it's the only drug. Nevertheless, lots of cancers are either resistant to it or become resistant during treatment. There's a lot of work being

done in developing new drugs as cancer therapies, but not many of them have come on the market yet. Since cisplatin is effective and has already been approved, why not try to make it better""

During more than eight years of research, the Alexanders have examined why tumors become resistant to cisplatin and what, if any, biochemical pathways can be used to improve the drug's efficiency. They identified genes for sphingolipid metabolism as key to whether a tumor cell lives or dies after treatment with cisplatin. The current collaboration with the Baylor team has greatly expanded these studies.

Shaulsky and Kuspa have developed microarray technologies to determine the patterns of gene expression in Dictyostelium discoideum and detect the effects of treatments. Together, the teams of researchers embarked to find the global response to cisplatin and how mutants in sphingolipid metabolism resistant to cisplatin affected the response. The study established that the cause of resistance is not simply that cells do not take up the drug or that the drug is neutralized, but that a specific set of genes responds uniquely to the treatment. Finding ways to use those genes to increase sensitivity to cisplatin could lead to more effective therapy.

"We used genetics to find genes that are involved, and we discovered several completely novel pathways that no one had ever thought was involved with this," Stephen Alexander said. "Ultimately, we're looking for a way to make cisplatin more effective, and the idea is to find out what's going on in the cell that determines whether cells are sensitive or not, and to boost some pathway to make it better."

Source: University of Missouri-Columbia