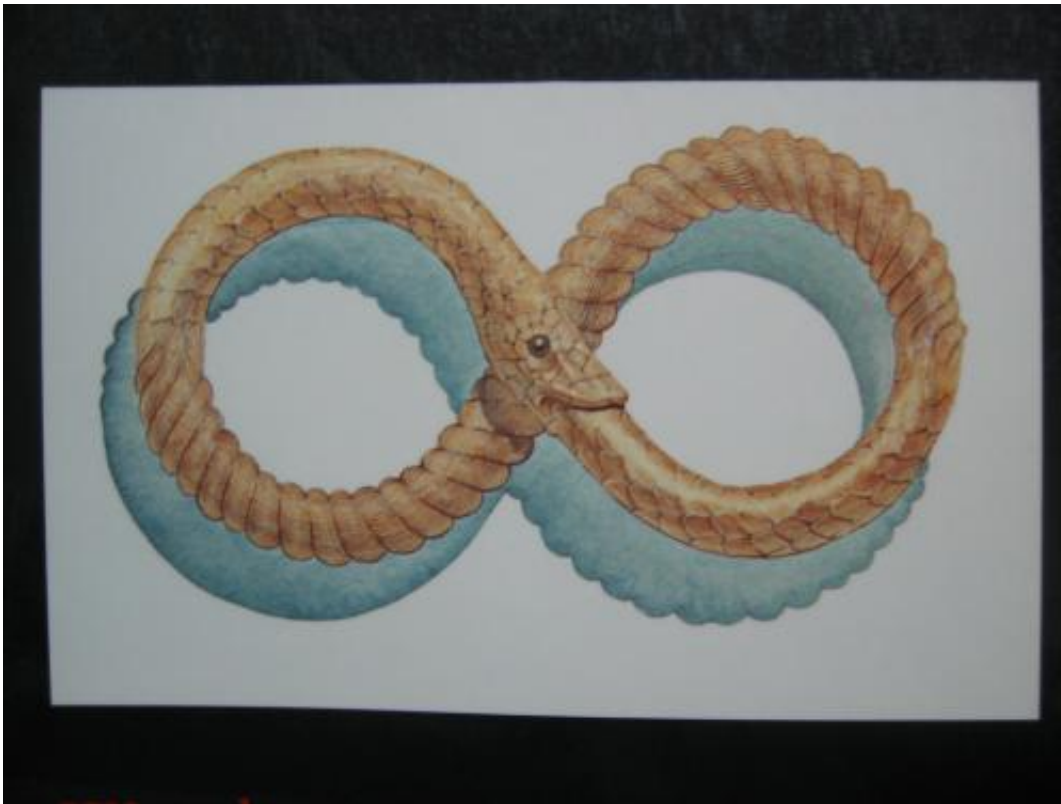


# Autophagy predicts which cancer cells live and die when faced with anti-cancer drugs

January 10 2014, by Garth Sundem

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In the process of autophagy, cells reprocess or “eat” parts of themselves in order to survive times of energy scarcity or other challenges.

(Medical Xpress)—When a tumor is treated with an anti-cancer drug, some cells die and, unfortunately, some cells tend to live. A University of Colorado Cancer Center study published in the journal *Nature Cell Biology* details a possible difference between the susceptible and

resistant cells: the rate at which cells are able to cleanse themselves via the process known as autophagy.

"In these studies, say we treat cells with the IC-50 of a drug - at that dose, 50 percent of cells should live and 50 percent of cells should die. But the fundamental question is why does cell A die whereas cell B lives? What we show is that the difference may be due to random variation in the amount of [autophagy](#) that's going on," says Andrew Thorburn, PhD, deputy director of the CU Cancer Center.

Previous studies show that autophagy promotes cell survival – under conditions of stress or shortage, cells break down non-necessary components to provide energy or use the same strategy to prevent cellular damage by degrading and recycling potentially damaging proteins. And so it seems logical that cancer cells with low autophagy would have high mortality when faced with anti-cancer drugs. However, the current study shows that rates of cell death may increase or decrease depending on levels of autophagy and the specific mechanism of the anti-cancer drug.

"We separated cancer cells into populations with low and high autophagy and then treated them with two drugs, both of which should activate death. Interestingly, when treated with the first drug, cells with high autophagy had the highest mortality. But then when treated with the second drug, cells with low autophagy had the highest mortality. Depending on the drug, the effect of autophagy was opposite," Thorburn says.

Specifically, Thorburn and colleagues including first author Jacob Gump, PhD, treated high- and low-autophagy cell populations with chemicals TRAIL and Fas ligand, which activate cells' death receptors. Cells treated with these chemicals are "told" to die and as the researchers expected, some cells in all populations underwent the programmed cell

death known as apoptosis. However, cells with high autophagy were more sensitive to treatment with Fas ligand, whereas cells with low autophagy were more sensitive to TRAIL. Similar differences were seen across types of cancer cells - in some cancers, autophagy protects against these drugs and in others autophagy makes cells more susceptible.

While the work does not necessarily add to our understanding of how autophagy aids cell survival, the group showed how it creates [cell death](#) in some tumors when confronted with some drugs: a protein known as FAP-1 is present in some but not all [cancer cells](#) where it serves to decrease the ability of Fas ligand to kill the cells. Autophagy degrades this cell-survival protein and this, in turn, makes cells more susceptible to Fas ligand but only in the cells where FAP-1 is normally present.

"If similar variation occurs in other contexts, a cancer cell you're trying to kill could be more or less resistant to whatever you're using to try to kill it depending on its level of autophagy," Thorburn says. Additionally, Thorburn points out that cells in these lab studies tend to be homogenous in their levels of autophagy compared to [cells](#) in natural tumor environments. It is likely, he says, these laboratory results will be magnified in actual tumors, where levels of autophagy tend to vary more widely.

While Fas ligand and TRAIL agonists are used in the lab only at this time, Thorburn says the next step in this line of research is to perform similar experiments with drugs that could be used in people.

**More information:** [www.nature.com/ncb/journal/v16...n1/full/ncb2886.html](http://www.nature.com/ncb/journal/v16...n1/full/ncb2886.html)

Provided by University of Colorado Denver

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