Simultaneous glucose fasting and autophagy inhibition enhances chemotherapy treatment

If you could cut your risk of developing cancer, diabetes, and heart disease, rejuvenate your immune system, and potentially live longer – would you do it? What if the answer to potentially save your life is as simple as the amount of calories you intake each day? Fasting has become a hot topic in popular press, but also in the scientific world. Short-term fasting for 72-96 hours prior to chemotherapy has been shown to increase efficacy of the treatment in mice as well as decrease of side effects for human patients.

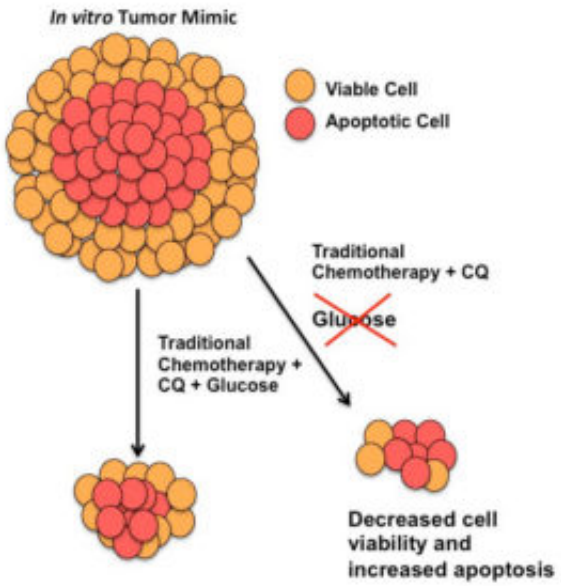

Fig. 1.

The use of short-term fasting is a potential cancer treatment that could be used in tandem with current cancer regimes to increase their potency. The only caveat to glucose restriction is that when a cell is deprived of glucose it begins to activate a stress response pathway known as autophagy. The autophagy pathway is the process by which cells maintain cellular metabolism by recycling their cellular components, thereby acting as a last ditch effort to stay alive. We hypothesized using a colorectal cancer model system that simultaneous glucose restriction and autophagy inhibition prior to chemotherapy would increase the efficacy of the chemotherapy treatment. We were able to show just that. Our results revealed that the supplement of glucose restriction to autophagy inhibition, with the antimalarial drug chloroquine, caused an increase in programmed cell death after chemotherapy treatment. Additionally, cells grown after glucose

restriction, chloroquine, and chemotherapy were unable to grow as prolific as they did prior to treatment.

We set out to understand the molecular mechanisms behind these results with the use quantitative proteomics. Quantitative proteomics is a tool to survey all of the proteins in a cell and their relative abundance between biological conditions. Using this technology, the results indicate that adding glucose restriction and autophagy inhibition to treatment regimes for colorectal cancer caused many molecular changes in the cell. The downstream effect of this action is an increase in abundance of tumor suppressor proteins. For example, when looking at the proteins differentially regulated by both treatment conditions, there is only discrepancy in one. When glucose is restricted, circadian clock protein Per2 is up regulated. Per2 is a known tumor suppressor gene and is the primary circadian pacemaker in the mammalian brain.

An increase in the abundance of tumor suppressor proteins can lead to a decrease of viability and proliferation and an increase of programmed cell death. The cellular processes of autophagy and glucose metabolism through glycolysis allow for cancer cells in solid tumors to survive chemotherapy. Our study shows that targeting these cellular processes prior to chemotherapy treatment weakens cancer cells making them more susceptible to treatment.

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Publication

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