Existing anti-obesity drugs may be effective against flu, hepatitis and HIV

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Viruses dramatically increase cellular metabolism, and existing anti-obesity drugs may represent a new way to block these metabolic changes and inhibit viral infection, according to a study published today in the journal *Nature Biotechnology*.

Metabolism refers to all the reactions by which living things break down nutrients to produce energy, along with those by which they rebuild broken-down nutrients into complex molecules (e.g. DNA). A significant example is the breakdown of blood sugar (e.g. glucose) and its conversation via chain reactions into adenosine triphosphate, the energy-storing currency of cellular life. As an important offshoot of that process, glucose can also be converted into fatty acids, the lipid building blocks of human hormones and cell membranes. Many viruses, including influenza, HIV and hepatitis, use those same fatty acids to build instead their viral envelopes, outer coatings that help them penetrate human cells. Going into the study, little was known about the mechanisms through which viruses hijack metabolic building blocks from their cellular hosts, with older techniques providing a limited picture.

In the current study, a team of researchers from the University of Rochester Medical Center and Princeton University created a new technique to clarify these mechanisms, and found that the technique could identify anti-viral therapeutic targets. Researchers combined drug discovery technologies to capture for the first time the exact concentrations and turnover, in other words, the fluxes, of interchangeable molecules within the metabolic chain reactions that

convert sugars into fatty acids. The fields of metabolomics and fluxomics have emerged to measure these patterns, and to provide insight into diseases with a metabolic component, from diabetes to infectious diseases to cancer.

"Using new fluxomic techniques, our study reveals that viral infection takes control of cellular metabolism and drives, among other things, marked increases in fatty acid synthesis," said Joshua Munger, Ph.D., assistant professor of Biochemistry and Biophysics at the University of Rochester Medical Center, and a study author. "We also found that if you target these increases in fatty acid metabolism using existing anti-obesity and anti-metabolism drugs, you inhibit viral replication."

A Thousand-fold Reduction in Viral Replication

In their experiments, Munger and colleagues developed a technique to measure changes in metabolic flux in human cells as they become infected by human cytomegalovirus (HCMV), an enveloped virus of the b-herpes family that infects most human adults and that causes severe disease in those with weakened immune systems. Researchers chose cytomegalovirus for experiments because it serves as an excellent model for processes at play in many enveloped viral infections and in cancers. HCMV replicates in a variety of human cell types, including fibroblasts, the cell type used in the study.

To study metabolic flux, Munger and his team created a stable, isotope-labeled version of glucose, which when "fed" to cells, was metabolized in a similar fashion as unlabeled glucose. Liquid chromatography and mass spectrometry were then employed to track the isotope label as it spread, or permeated, through the metabolic network. The impact of viral infection on cellular metabolism could be measured by the speed at which the labeled version spread, and then compared to uninfected cells. Given the complexity of interconnections within the metabolic network,

the team also developed a novel computer model of metabolic function to analyze the data and guide further experimentation.

Many metabolic processes are essential to the survival of human cells, and so are not candidates for research efforts that would shut them down in the attempt to stop viral replication. For that reason, Munger and colleagues chose to look at whether interfering with glucose-to-fatty acid metabolism could stop viral replication, because fatty acid biosynthesis is not essential in adult humans. It does appear, however, to be essential to the ability of viruses to build their envelopes, reproduce and spread.

Thus, the team next used drugs known to inhibit enzymes that build fatty acids, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), used in the treatment of obesity and high cholesterol, to determine whether HCMV-induced fatty acid production was necessary for enveloped viruses to make copies of themselves. Indeed, treatment (10 mg ml-1) with 5-tetradecyloxy-2-furoic acid (TOFA), an ACC inhibitor, resulted in a more than thousand-fold reduction in HCMV replication. C75 (trans-4-carboxy-5-octyl-3-methylene-butyrolactone), an inhibitor of FAS, resulted in a more than 100-fold effect at the same dose.

To investigate whether this requirement extended to other enveloped viruses, the team measured influenza A replication in the presence of the same TOFA and FAS inhibitors, and found similar reductions in replication. Influenza A has little in common with HCMV except for its lipid envelope.

Extensive clinical testing would be needed to draw conclusions about the safety of TOFA and C75, or similar compounds, as antiviral treatment. That said, the team took an early look at toxicity, exposing uninfected fibroblasts to C75 or TOFA for 96 hours. They found that the drugs blocked HCMV replication without causing cell toxicity or self-destruction (apoptosis).

Along with Munger, Jessica McArdle of the Department of Biochemistry and Biophysics contributed to the work. Bryson Bennett also worked on the project from the Lewis-Sigler Institute for Integrative Genomics in the Carl Icahn Laboratory at Princeton University. Leading the effort from the Princeton side was the corresponding author, Joshua Rabinowitz, who worked with Anuraag Parikh, Thomas Shenk in the Department of Molecular Biology, and Xiao-Jiang Feng and Herschel Rabitz at the Frick Laboratory. The work was supported by the National Institutes of Health (NIH) Metabolomics Roadmap initiative, the National Science Foundation, the Beckman Foundation, the American Heart Association, the National Science Foundation and the American Cancer Society.

"Recent studies have shown that fatty acid biosynthesis is important for the replication of diverse enveloped viruses," Munger said. "The replication of both hepatitis C and HIV, for example, has been linked recently with lipid synthesis, reinforcing our approach and its importance. Lastly, viral infection also clearly upregulates glycolysis, a marker for tumor growth, which is just the latest in the longstanding connection between viruses and cancer. Hopefully, our work will at some point provide insight into the metabolic manipulations seen in cancer as well."

Source: University of Rochester