Sweet! -- sugar plays key role in cell division

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Using an elaborate sleuthing system they developed to probe how cells manage their own division, Johns Hopkins scientists have discovered that common but hard-to-see sugar switches are partly in control.

Because these previously unrecognized sugar switches are so abundant and potential targets of manipulation by drugs, the discovery of their role has implications for new treatments for a number of diseases, including cancer, the scientists say.

In the January 12 edition of *Science Signaling*, the team reported that it focused efforts on the apparatus that enables a human cell to split into two, a complicated biochemical machine involving hundreds of proteins. Conventional wisdom was that the job of turning these proteins on and off — thus determining if, how and when a cell divides — fell to phosphates, chemical compounds containing the element phosphorus, which fasten to and unfasten from proteins in a process called phosphorylation.

Instead, the Johns Hopkins scientists say, there is another layer of regulation by a process of sugar-based protein modification called O-GlcNAcylation (pronounced O-glick-NAC-alation). "This sugar-based system seems as influential and ubiquitous a cell-division signaling pathway as its phosphate counterpart and, indeed, even plays a role in regulating phosphorylation itself," says Chad Slawson, Ph.D., an author of the paper and research associate in the Department of Biological Chemistry, Johns Hopkins University School of Medicine.

Because the sugar molecule has some novel qualities — it is small, easily altered, and without an electrical charge — it is virtually imperceptible to researchers using standard physical techniques of detection such as mass spectrometry.

Suspecting that the sugar known as O-GlcNAc might play a role in cell division, the Hopkins team devised a protein-mapping scheme using new mass spectrometric methods. Essentially, they applied a combination of chemical modification and enrichment methods, and new fragmentation technology to proteins that comprise the cell division machinery in order to figure out and analyze their molecular makeup, identifying more than 150 sites where the sugar molecule known as O-GlcNAc was attached. Phosphates were found to be attached at more than 300 sites.

They noticed that when an O-GlcNAc molecule was located near a phosphate site, or at the same site, it prevented the phosphate from attaching. The proteins involved in cell division weren't phosphorylated and activated until O-GlcNAc detached.

"I think of phosphorylation as a micro-switch that regulates the circuitry of cell division, and O-GlcNAcylation as the safety switch that regulates the microswitches," says Gerald Hart, Ph.D., the DeLamar Professor and director of biological chemistry at the Johns Hopkins School of Medicine.

Using a standard human cell line (HeLa cells), the scientists discovered abnormalities when they disrupted the cell division process by adding extra O-GlcNAc. Although the cell's chromosome-containing nuclei divided normally, the cells themselves didn't divide, resulting in too many nuclei per cell — a condition known as polyploidy that's exhibited by many cancer cells.

The researchers not only mapped O-GlcNAc and phosphorylation sites

but also measured changes in the cell division machinery, because, Hart says, the chemical changes act more like "dimmer" switches, than simple on/off ones.

As important as the discovery is to a deeper understanding of cell division, Hart says, this extensive cross talk between O-GlcNAc and phosphorylation is paradigm-shifting in terms of signaling. Signaling is how a cell perceives its environment, and how it regulates its machinery in response to stimuli. The new sugar switches reveal that the cellular circuitry is much more complex than previously thought, he adds.

More information: stke.sciencemag.org/

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