Research team clarifies mechanics of first new cell cycle to be described in more than 20 years

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An international team of researchers led by investigators in the U.S. and Germany has shed light on the inner workings of the endocycle, a common cell cycle that fuels growth in plants, animals and some human tissues and is responsible for generating up to half of the Earth's biomass. This discovery, led by a geneticist at Fred Hutchinson Cancer Research Center and reported Oct. 30 in *Nature*, leads to a new understanding of how cells grow and how rates of cell growth might be increased or decreased, which has important implications in both agriculture and medicine.

"It can be argued that this is the first completely novel cell cycle to be elucidated in more than a two decades," said Bruce Edgar, Ph.D., corresponding author of the paper and a member of the Basic Sciences Division at the Hutchinson Center, referring to the groundbreaking description of the mitotic cell cycle in the same journal in the late 1980s.

Mitosis is the division of a mother cell into two daughter cells that contain identical sets of chromosomes. Endocycling, in contrast, is a special type of cell cycle that skips mitosis. The cell replicates its DNA over and over again without ever dividing into two cells. Endocycles play a crucial role in nature because they generate very large cells in invertebrate animals and plants, as well as some human tissues, such as liver and muscle. Most cells in plants and invertebrate animals such as insects, crustaceans (such as shrimp), mollusks (such as clams, oysters

and snails) grow by endocycling.

"When a cell goes through an endocycle, it doubles its DNA, and typically also doubles its size and protein content," said Edgar, also a professor at the Center for Molecular Biology and the German Cancer Research Center in Heidelberg, Germany. "Because of this, one could imagine that promoting just one extra endocycle in the cells of a crop plant or farmed shellfish might double the agricultural yield from that crop," he said. "Similarly, suppressing endocycling in an insect pest would be expected to dramatically slow the growth and reproduction of that pest."

For the research, Edgar and colleagues used genetic approaches to study a model organism – the fruit fly – which has many endocycling cells. The researchers primarily studied the saliva glands, as the cells in these glands endoreplicate about 10 times during the fly's life cycle, which increases the amount of DNA – and the corresponding size of each cell – more than 1,000-fold.

The researchers studied genetic transcription factors and enzymes that drive endocycling and DNA replication through a series of choreographed pulses. Specifically, they found that a transcription factor called E2F is temporarily destroyed during DNA replication by an enzyme called CRL4. Function of E2F is then restored after DNA replication and the cycle repeats itself.

"Together, E2F and CRL4 function a molecular oscillator," Edgar said. "An analogy might be a water wheel, which is driven by the filling and emptying of its buckets. E2F would be analogous to the water, which first accumulates in a bucket, and then DNA replication would be analogous to the rotation of the wheel. CRL4 destroys the accumulated E2F, which is analogous to the bucket emptying so the process can repeat," Edgar said.

Edgar and colleagues also found that the rate of cell growth controls the rate of E2F accumulation and thereby controls how rapidly cells can replicate and re-replicate their DNA. "In the water wheel analogy, the more water that flows into the wheel the faster it rotates. Similarly, in the endocycle, the faster E2F is produced, the faster the endocycle spins and the bigger the cell gets. We think this property probably applies to all growing cells," he said.

Although humans don't have many cells that endocycle, several important examples that do include trophoblast giant cells in the placenta, which support fetal development. "If they don't endocycle, no baby," Edgar said. Heart muscle cells also grow by endocycling, as do certain types of blood cells. Some diseases that arise from a malfunction of these cells could involve defects in endocycling, and such diseases might be treated by drugs that target the proteins that comprise the endocycle oscillator.

"Generally, the gene products and principles used by the endocycle oscillator are employed to control DNA replication in virtually all cells," Edgar said. "Because of this, our findings are potentially relevant to many diseases that involve abnormal cell proliferation. These include all cancers and some degenerative diseases."

In addition to researchers at the Hutchinson Center and the German Cancer Research Center, collaborators included researchers from the University of Heidelberg, University of Washington, University of North Carolina at Chapel Hill, University of Zurich and University of Calgary.

More information: “Control of Drosophilia endocycles by E2F and CRL4,” doi:10.1038/nature10579

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