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Understanding 'master regulator' genes could lead to better cancer treatments

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A pair of genes work together as "master regulators" in cell division to keep the correct number of chromosomes in each daughter cell. Ipl1 and Mps1 work to hook and unhook chromosomes for proper DNA separation. The discovery could lead to better anti-cancer therapies.

Cell division is serious business. Cells that divide incorrectly can lead to birth defects or set the stage for cancer. A new discovery from the Oklahoma Medical Research Foundation has identified how two genes work together to make sure chromosomes are distributed properly when cells divide, providing new insights that could contribute to the future development of cancer treatments.

In a paper published in the new issue of the journal *Science*, OMRF researchers Dean Dawson, Ph.D., and Regis Meyer, Ph.D., reveal how two genes—known as Ipl1 and Mps1—are integral to the correct division of cells and life itself. If these "master regulator" genes can be controlled, it could help physicians target and destroy pre-cancerous cells or prevent birth defects.

"The human body begins as a single cell. Through the process of cell division, we come to be composed of trillions of cells. And every one of those divisions must be perfect so that each new cell inherits a correct set of chromosomes," said Dawson, the senior author of the new study. "Given the sheer number of cell divisions involved, it's amazing there aren't more mistakes. My laboratory is interested in dissecting the machine that does this so well and understanding why it fails in some

rare cases."

"When cells divide, they first duplicate the DNA, which is carried on the chromosomes," he said. "Think of the cell kind of like a factory. First it duplicates the chromosomes—so that each one becomes a pair, then it lines them up so the pairs can be pulled apart—with one copy going to each daughter cell. This way, one perfect set goes to each new daughter cell, ensuring that the two new cells that come from the division have full sets of the DNA."

To do that properly, each chromosome is attached to a kind of cellular winch, he said. Just before the cells divide, the winches drag the chromosomes into the new daughter cells. In the laboratory, Dawson used high-powered microscopes to observe the process of cell division in yeast cells. But as he watched the cells dividing, Meyer and Dawson observed something unexpected: The cells kept making mistakes as they attached the chromosomes to the winches.

"About 80 percent of the time, chromosomes would get hooked to the wrong winch, and the cell would begin pulling both copies off to the same side instead of pulling one towards each new daughter cell," he said. "If the cell divided like that, you'd have all sorts of problems. The cells that fail to receive a chromosome will probably die. The cell that receives too many is likely in trouble. Inappropriate chromosome numbers is a leading cause of birth defects and is a common feature of tumor cells."

However, with further study, Dawson discovered that the Ipl1 and Mps1 genes act as quality controllers. When a chromosome gets pulled to the wrong side, one gene disconnects the winch, then the other gene connects to a new winch. "These genes are master regulators. If they're removed, the entire process goes haywire," Dawson said.

While the genes are responsible for correcting the mistakes that could lead to cancer, researchers have found that cancer cells with abnormal numbers of chromosomes are even more dependent on Ipl1 and Mps1 than normal cells, Dawson said. Several groups are investigating ways to target the genes as a potential anti-cancer treatment.

"We think this research is going to be useful in designing those compounds," he said. "When you understand exactly how the process works, you know how to better craft a treatment."

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