Trash talk: molecular conversations trigger cell suicide in yeast

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For cells, like people, relationships are based on good communication. In yeast cells, however, scientists have shown that communication between certain molecules involved in gene regulation can trigger the cell's suicide program, suggesting that molecular "crosstalk" may be an important mechanism by which cells respond to adverse events like cancer.

Scientists in C. David Allis's laboratory at Rockefeller University study what happens to genes when DNA-packaging proteins called histones are chemically modified. These modifications, which involve the addition or removal of specific chemical groups to individual amino acids in the histones, can activate or silence genes. Over the last decade, Allis and his colleagues have provided much of the evidence for the "histone code" hypothesis, which suggests that patterns or combinations of these histone marks represent another layer of gene regulation that takes place away from DNA itself.

The effects of individual modifications on gene expression have been well established, but emerging evidence suggests that these chemical marks also communicate with each other, engaging in crosstalk that regulates important signaling events within the cell. One of these events is a type of programmed cell death called apoptosis. All animal cells use apoptosis to maintain the balance with cell growth required to ensure proper development and survival.

To better understand how crosstalk works in gene regulation, Sung Hee Ahn, a graduate student in the Laboratory of Chromatin Biology and Epigenetics, focused on budding yeast, a simple organism with only one histone, known as H2B (mammalian cells typically contain thousands of histone proteins). Previous research by Ahn and her colleagues showed that when hydrogen peroxide was used to induce cell death in yeast, a kinase called Ste20 phosphorylated (i.e., attached a phosphate chemical group to) the amino acid serine 10. The scientists also observed that an acetyl chemical group is attached to an adjacent amino acid, lysine 11, on H2B in growing yeast. They asked the question, do these two histone modifications in H2B "talk" to each other?

The answer, it turns out, is yes, and in a very specific order that is deadly to the yeast cell.

In a study published recently in *Molecular Cell*, Ahn and her colleagues show that the acetyl mark on lysine 11 blocks the ability of Ste20 to phosphorylate serine 10. The researchers also found that an enzyme known as Hos3 removes the acetyl group from lysine 11 when the cells are exposed to hydrogen peroxide. This in turn sets in motion Ste20, which phosphorylates serine 10 and launches the suicide program in the yeast cell.

"Based upon these findings, we propose a model for regulated crosstalk in H2B, wherein Hos3 directly catalyzes the deacetylation of lysine 11, which then mediates the phosphorylation of serine 10 by Ste20 in a unidirectional fashion during hydrogen peroxide-induced yeast cell death," says Ahn.

"These studies underscore a concerted series of enzyme reactions governing histone modifications that promote a switch from cell proliferation to cell death," says Allis, who is the Joy and Jack Fishman Professor and head of the Laboratory of Chromatin Biology and Epigenetics.

Because H2B also occurs in the cells of mammals, including humans, the results may have implications for human diseases that occur when the cell death pathway fails to function, including cancer and some developmental conditions.

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