Eggs' quality control mechanism explained

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To protect the health of future generations, body keeps a careful watch on its precious and limited supply of eggs. That's done through a key quality control process in oocytes (the immature eggs), which ensures elimination of damaged cells before they reach maturity. In a new report in the February 18th *Cell*, a Cell Press publication, researchers have made progress in unraveling how a factor called p63 initiates the deathblow.

In fact, p63 is a close relative of the infamous tumor suppressor p53, and both proteins recognize DNA damage. Because of this heritage it was initially assumed that p63 would also function as a tumor suppressor, but various forms of the protein are now known to be important in development. One in particular, called TAp63a, is responsible for killing off damaged oocytes.

But it seems that plenty of TAp63a is always around, whether oocytes are damaged or not, suggesting that there must be a very special way that the protein is kept under wraps lest it kill off perfectly good cells. A team lead by Volker Dötsch of Goethe University has figured out how that works.

The quality control factor normally exists in oocytes in inactive pairs or dimers, he explained. When double strand breaks to the DNA occur, those dimers are chemically modified by an as-yet unidentified enzyme, allowing them to open up and join forces with a second open pair. The result is an active tetramer that can bind DNA more effectively, leading to the death of the damaged cells.

That activation of TAp63a cannot be undone, they show, even if you reverse the chemical modification that enabled the tetramer formation in the first place. That irreversibility stems from an extra helix structure that keeps the tetramer stable.

"It's all or nothing," Dötsch said. "Once activated, the path to cell death is decided."

Dötsch believes that this quality control of the genetic integrity of oocytes likely represents the original function of the p53 family, with cell cycle arrest and tumor suppression arising as later evolutionary developments. That's because p53-like genes are found in invertebrates, including tiny nematode worms.

"Worms live for two weeks," Dötsch said. "They don't need a tumor suppressor, but they do need to worry about the genetic stability of their germ cells." It turns out the worm version of the gene also resembles p63 more closely than it does p53.

The findings also help to explain what happens in young women who undergo chemotherapy that so often leads them to become infertile as a result, Dötsch noted. It may even be possible to devise strategies to counteract the players responsible for activating TAp63a once it is found or others in the pathway, he said. Unfortunately, that might not be such a good idea.

"If oocytes are damaged, there is probably good reason for them to be destroyed," he said.

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