Cell death discovery suggests new ways to protect female fertility

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Associate Professor Clare Scott of the Walter and Eliza Hall Institute was one of the researchers leading a study that has suggested new ways to protect female fertility. Credit: Walter and Eliza Hall Institute, Australia

Melbourne researchers have identified a new way of protecting female fertility, offering hope to women whose fertility may be compromised by the side-effects of cancer therapy or by premature menopause.

The researchers, from the Walter and Eliza Hall Institute, Monash University and Prince Henry's Institute of Medical Research, made the discovery while investigating how egg cells die.

They found that two specific proteins, called PUMA and NOXA, cause the death of egg cells in the ovaries. The finding may lead to new strategies that protect women's fertility by blocking the activity of these

two proteins.

Associate Professor Clare Scott from the Walter and Eliza Hall Institute said the research showed that when the DNA of egg cells is damaged following exposure to radiation or chemotherapy, such as that received during some cancer treatments, PUMA and NOXA trigger the death of the damaged eggs. This egg cell death causes many female cancer patients to become infertile.

"PUMA and NOXA can trigger cell death, and have been found to be necessary for the death of many different cell types in response to DNA damage," Associate Professor Scott, who is also an oncologist at The Royal Melbourne and Royal Women's Hospitals, said. "This removal of damaged cells is a natural process that is essential to maintaining health but, for women undergoing cancer treatment, can be devastating when it leads to infertility."

Associate Professor Scott, Dr Ewa Michalak and Professor Andreas Strasser from the Walter and Eliza Hall Institute, together with Associate Professor Jeffrey Kerr from Monash University, and Dr Karla Hutt and Professor Jock Findlay from Prince Henry's Institute of Medical Research, focused their studies on egg cells called primordial follicle oocytes, which provide each woman's lifetime supply of eggs. Low numbers of these egg cells can also be a cause of early menopause. Their findings are published online this week in the journal *Molecular Cell*.

Associate Professor Jeff Kerr said that when these egg-producing cells were missing the PUMA protein, they did not die after being exposed to radiation therapy. "This might ordinarily be cause for concern because you want damaged egg cells to die so as not to produce abnormal offspring," he said. "To our great surprise we found that not only did the cells survive being irradiated, they were able to repair the DNA damage they had sustained and could be ovulated and fertilized, producing

healthy offspring. When the cells were also missing the NOXA protein, there was even better protection against radiation."

"We were very excited to see healthy offspring could be produced from these cells," Associate Professor Scott said. "It means that in the future, medications that block the function of PUMA could be used to stop the death of egg cells in patients undergoing chemotherapy or radiotherapy. Our results suggest that this could maintain the fertility of these patients."

A joint leader of the study, Professor Jock Findlay, head of the Female Reproductive Biology Group at Prince Henry's Institute, said the study could also have implications for delaying menopause. "We know that the timing of menopause is influenced by how many egg cells a female has," he said. "Interventions that slow the loss of egg cells from the ovaries could delay premature menopause. As well as prolonging female fertility, such a treatment could have the potential to reduce menopause-associated health conditions, such as osteoporosis and heart disease."

Provided by Walter and Eliza Hall Institute