Research reveals cancer-suppressing protein 'multitasks'

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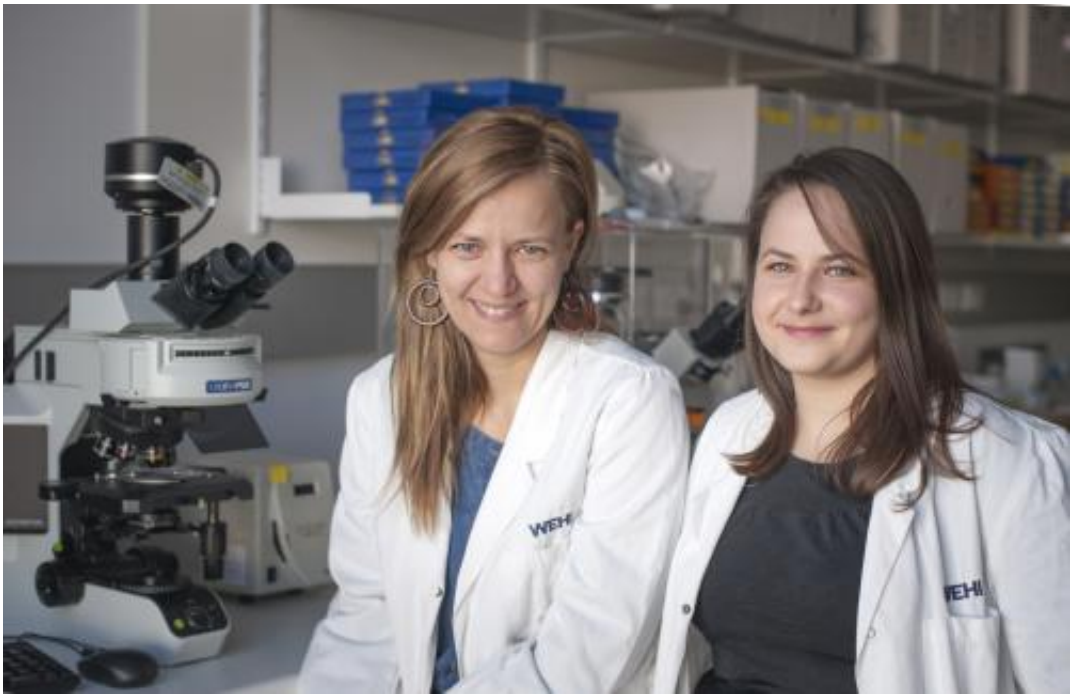

Dr Ana Janic (left) and Ms Liz Valente have upended the understanding of how a powerful protein called p53 protects against cancer development. Credit: Walter and Eliza Hall Institute, Australia

The understanding of how a powerful protein called p53 protects against cancer development has been upended by a discovery by Walter and Eliza Hall Institute researchers.

More than half of human cancers carry defects in the gene for p53, and

almost all other cancers, with a normal p53 gene, carry other defects that somehow impair the function of the p53 protein. Inherited mutations in the p53 gene put people at a very high risk of developing a range of cancers.

The p53 protein's functions are normally stimulated by potentially cancer-causing events, such as DNA damage from ultraviolet radiation (a cause of skin cancer), or the over-activity of cancer-causing genes.

Ms Liz Valente, Dr Ana Janic and Professor Andreas Strasser from the Molecular Genetics of Cancer division at the Walter and Eliza Hall Institute have been dissecting the processes that are controlled by p53, to discover how this protein can suppress cancer development. Their surprising results are published online today in the journal *Cell Reports*.

Dr Janic said many scientists believed that the most important processes activated by p53 to prevent cancer formation were stopping cells with DNA damage from dividing until the DNA could be repaired, and making cells die if they had sustained irreparable genetic damage.

"Changes that make damaged cells become long-lived and divide uncontrollably are key features of cancer formation," Dr Janic said. "Because p53 can control cell survival and cell division, it was assumed that these two processes constituted the critical functions that p53 used to prevent cancer. The purpose of our research was to examine whether this assumption was correct."

Ms Valente said the team compared cells that lacked p53 with cells in which p53 could not regulate cell survival and cell division. "In the past 20 years it has become clear which proteins are activated by p53 to block cell division and promote cell death," Ms Valente said. "We were able to remove all of these proteins (called p21, Puma and Noxa) from cells, to completely disable the ability of p53 to stop cell division and

trigger cell death. To our surprise, p53 could still prevent cancer formation, even without being able to make cells die or stop dividing after DNA damage."

Professor Strasser said the team's discovery had upended the understanding of how p53 functions. "When p53's cancer-suppressing function was first discovered, it was important to understand how this protein functioned," he said. "Many scientists had concluded that regulation of cell death and division were the key roles of p53," he said.

"Our findings have re-opened the question of how p53 functions. My suspicion is that it is not one protein but several with very many critical functions that work together to prevent cancer formation by coordinating the proper repair of damaged DNA, rather than stopping cells from dividing or killing them. Further research to decipher how these processes are integrated will be an important step towards understanding the tumour-suppressing function of p53 function. This knowledge, in turn, may then be exploited to develop improved cancer therapies," Professor Strasser said.

Provided by Walter and Eliza Hall Institute