Scientists find promising way to boost body's immune surveillance via p53

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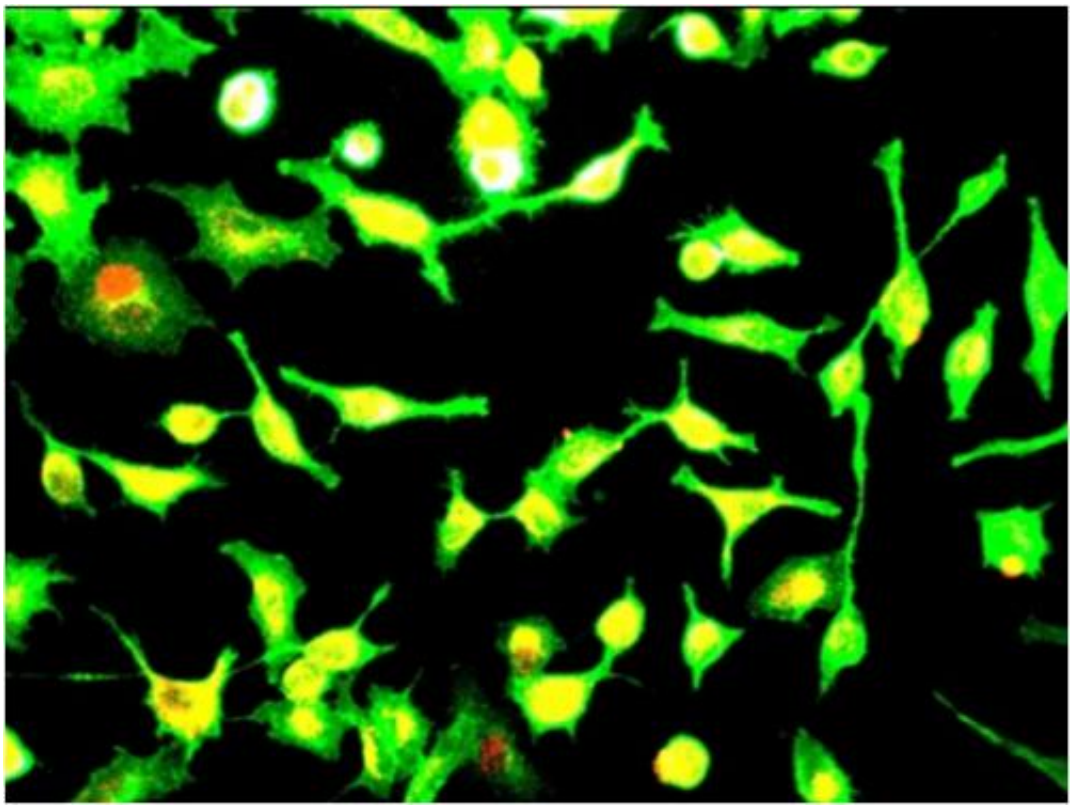

Researchers at A*STAR's Singapore Immunology Network (SIgN) have discovered a new mechanism involving p53, the famous tumour suppressor, to fight against aggressive cancers. This strategy works by sabotaging the ability of the cancer cells to hide from the immune system. Published in the prestigious *Nature Communications* journal, this

research opens a new avenue to improve targeted cancer therapy by harnessing the body's own immune system to control and eliminate cancer cells.

Also known as the "Guardian of the Genome", p53 fights cancer by causing damaged cells to die or by halting the growth of mutant cells before they become cancerous and spread to the rest of the body. Ironically, because of its pivotal role in coordinating a range of cancer-fighting mechanisms in the human body, it is also one of the most important cancer-causing genes when mutated. Studies have shown that more than 50% of all human cancers carry defects in the p53 gene, and almost all other cancers with a normal p53 function carry other defects which indirectly impair the cancer-fighting function of p53.

In this study, the SIgN team discovered for the first time that the integrity of p53 affects the production of a special cell surface protein called Major Histocompatibility Complex (MHC) class I. MHC class I molecules on the cancer cell surface serve as targets for the immune system. Therefore, having less MHC I molecules may allow cancer cells to hide better and escape detection by the immune system.

Using two cancer cell lines differing only in the integrity of p53 gene, the scientists observed that cancer cells with defective p53 had much less MHC class I on the cell surface. Specifically, they discovered that p53 moderates the expression of MHC I by controlling the amount of another protein called ERAP1 in the cells. Interestingly, a number of disease conditions including tumour malignancy, multiple sclerosis and autoimmune disease were recently reported to be associated with ERAP1.

The team leader, Associate Professor Ren Ee Chee from SIgN said, "We were surprised to discover that p53 regulates MHC class I production by acting through ERAP1. This may explain how cancer cells escape

detection by our body's immune system. More importantly, it opens up exciting avenues of research to explore how restoration of p53 with drugs such as those that target ERAP1 can help to harness the immune system to recognise and destroy cancer cells."

Acting Executive Director of SIgN, Associate Professor Laurent Rénia said, "The team has uncovered a new door to manipulate one of the most studied yet enigmatic cancer-associated genes of our times. I am confident that this work will pave the way for more targeted, efficient and cost-effective treatment for the millions of cancer patients globally."

p53 also plays a role in virus infection by increasing MHC I. This is a microscope image of lung cancer cells infected with H1N1 influenza virus. Upon H1N1 viral infection, the cells showed an increase in MHC class I (green) and p53 (red) expression. The co-expression of increased MHC class I and p53 is in yellow. This demonstrates that p53àERAP1àMHC I pathway also occurs in viral infection. It may be interesting to explore the role of p53 in viral infection.

More information: www.nature.com/ncomms/2013/130 … full/ncomms3359.html

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