Singapore scientists exploit knowledge of p53 for increasing specificity of cancer treatments

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Researchers from the p53 Laboratory of Singapore's Agency for Science, Technology and Research (A*STAR), have made a finding that makes feasible a unique method of cancer treatment. Their work, published online in the leading journal *Cell Death and Differentiation* today , offers new insight on how to tap on the properties of p53, the 'guardian of the genome' , to more effectively kill cancer cells while sparing normal cells.

The researchers, led by Dr Cheok Chit Fang and Prof David Lane, the co-discoverer of the p53 gene in 1979, achieved this by exploiting one of the key functions of p53 - the control of the cell cycle.

Activating p53 halts the cell cycle and prevents endoreduplication, a process by which a cell accumulates excess genetic material by duplicating its existing genetic material without actually dividing. If endoreduplication happens in human cells, they die. Deliberately inducing endoreduplication in cancer cells through chemical means has been explored as a means of killing off cancer cells. However, as the drugs used are not highly specific to cancer cells, many normal cells are also killed in the process.

Fortunately, in many cancers, the cancer cells lack working copies of p53. By using a drug that activates p53 in healthy cells and temporarily induces the cells to stop the production of genetic material,

endoreduplication is prevented. Cancer cells which lack working copies of p53 are thus left susceptible to a second drug that induces endoreduplication, resulting in tumour-specific killing. The activation of p53 is reversible and the normal cells resume their function once the cancer cells have been killed.

Said Prof David Lane, Director of the p53 Laboratory and A*STAR's Chief Scientist, "We are proposing a unique combination of drugs which may have therapeutic benefits and could potentially alleviate the side effects of currently available cancer treatments. The clinical approval of nutlin or nutlin-like drugs will allow such exciting concepts to be tested in the clinic. We hope that this work encourages further breakthroughs in p53 research and brings more efficient and cost-effective treatments for the millions of cancer patients worldwide."

Dr Cheok said, "One the most difficult problems in treating cancer is ensuring that normal, healthy cells are not killed over the course of treatment. Many of the currently available methods of treatment, such as chemotherapy and radiation therapy, damage normal cells in the process of killing cancer cells. We are using our knowledge of p53 to overcome this difficulty."

Dr Cheok was among the first few Singaporeans to embark on a PhD scholarship from A*STAR in 2001 . After receiving her PhD from the University of Oxford, she began her post-doctoral training under the tutelage of Prof Lane in 2006. She is also an Assistant Professor and a Senior Research Fellow at the Department of Biochemistry at the Yong Loo Lin School of Medicine, NUS.

Prof Lane added, "We are proud of Chit Fang for having made this significant finding so early in her scientific career. It gives me great pleasure to have her as part of my team working on deepening our understanding of how to use basic science findings to develop new

therapies."

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