MedicalXpress

Singapore scientists discover widely sought molecular key to understanding p53 tumor suppressor gene

October 13 2009

Scientists at the Singapore Immunology Network (SIgN) have determined how the master gene regulator p53 could switch a gene in a cell "on" or "off" by recognizing specific sequences of nucleotides in the gene's DNA.

Their findings provide a missing piece about p53 gene repression that has eluded researchers investigating the master regulator, which undergoes mutations or deletions in over 50 percent of all cancers.

"The precise interaction of p53 with its response elements has been studied for some 20 years, and while we have a good understanding of how p53 turns on genes, no clear answer as to the equally important question of how p53 turns off or 'represses' genes has emerged," said Sir David Lane, Ph.D., a co-discoverer of p53 and now Chief Scientist at Singapore's A*STAR (Agency for Science, Technology and Research), which oversees SIgN.

"The SIgN group's identification of a bona fide 'repressive' response element has provided the missing piece which has eluded p53 researchers for a long time, as well as a definitive key with which to perform future studies," Dr. Lane added.

The findings, highlighted in the Oct. issue of *Nature Reviews Cancer* and published in the Proceedings of the National Academy of Sciences in

August, may allow scientists to confirm the many genes involved in the complex pathways of p53 and, potentially, to uncover new p53 pathways.

The findings also clarify scientists' understanding about the cellular pathways damaged by p53 mutations and may point to areas in the pathways where new cancer targets might be discovered.

The specific sequences of nucleotides, known as response elements, that are recognized by p53 have been very difficult to decipher because they could total over one million possible combinations. In fact, predicting whether p53 actually switched a gene "on" or "off" had been an elusive goal until this recent discovery.

"The findings are truly intriguing," added Dr. Lane, who attributed the SIgN group's success to a combination of sound thinking and the right opportunities. "I expect their findings to have very positive and significant impact on the progress of biomedical research and to help define this vital tumor-fighting pathway."

By applying a systematic approach to analyzing known p53 response elements, the Singapore scientists succeeded in identifying a simpler two-nucleotide core sequence that was sufficient to provide an accurate prediction.

Interestingly, the discovery was made by a SIgN research group, led by Ren Ee Chee, Ph.D., that focuses on immunology rather than molecular biology or genetics.

"We had been studying a metastasis gene which is upregulated in liver cancer called Lasp-15," said Dr. Ren. "As it happened to be under the control of p53, we wanted to determine in detail the role of p53. However we quickly realized that the existing literature was not helpful enough as there were ambiguities over how p53 exerts control over

specific genes."

This led to the SIgN researchers' identification of the definitive two-nucleotide sequence, and subsequent establishment of a general set of rules to predict the roles of nucleotides within a response element, which enabled them to correct those of 20 response elements (out of 162 assessed).

Dr. Ren added, "Our findings illustrate how exciting science can be, when innovative discoveries can arise from unexpected sources. They are also proof that frequently in nature, what may seem very complicated at first eventually turns out to be simple and elegant."

Praising the group's efforts, SIgN Scientific Director Paola Castagnoli, Ph.D., said, "This study has significant and far-reaching implications. It will allow for the confirmation of many genes involved in the complex pathways of p53 and, potentially, uncover new p53 pathways. It also clarifies our understanding of which cellular pathways are damaged by p53 mutations and points to areas where new cancer targets might be discovered. I am proud of the group's achievements thus far, and look forward to more exciting findings from them."

Source: Agency for Science, Technology and Research (A*STAR)