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Singapore scientists discover p53 mutation hinders cancer treatment response

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Scientists from the National Cancer Centre Singapore (NCCS) have discovered the workings of the gene that has been hindering treatment response in cancer patients. This discovery was made after 5 years of studying the mutant form of the p53 gene, the major tumor suppressor in humans, which is generally found mutated in over 50% of all type of human cancers.

The dominant-negative (DN) effect of the mutant p53 gene in cancers was found to affect the outcome of cancer treatment modalities. DN effect is a phenomenon whereby one copy of mutant p53 that exists in cancer cells inhibits the tumor suppressor activity of the other wild-type p53 copy when they co-exist. The result is that a patient may either have poor response or earlier relapse of tumours after their treatment.

The research findings is significant in that it offers hope to improve cancer treatment outcomes by selectively inhibiting mutant p53's DN effect through several methods by generating selective and specific inhibitory molecules specific for some of the common hot-spot p53 point mutations. There are currently no drugs or compounds that can alleviate DN effects of mutant p53.

In order to understand the specific roles of mutant p53 DN properties in regulating acute treatment response and long-term tumourgenesis, a team of five researchers led by NCCS Prof Kanaga Sabapathy, the Principal Investigator in the Laboratory of Carcinogenesis and Head of the Division of Cellular & Molecular Research from NCCS, carried out

experiments by generating genetically engineered knock-in mouse strains expressing varying levels of mutant p53. The results showed that DN effect is observed after acute p53 activation by a variety of chemotherapeutic drugs and irradiation, thereby affecting anti-cancer treatment. This breakthrough came after five years of intensive research.

It was found that mutant p53 have DN effects in a cell-type and dose-dependent manner, especially during acute p53 activation where p53 levels are elevated. Based on the above observations, efforts to generate specific inhibitors for the common hot spot p53 point mutations are underway. The inhibition of mutant p53 expression in cells carrying a wild-type and mutant p53 alleles can improve response to chemotherapeutic drugs.

In a further study, the researchers also questioned the possibility of the mutant p53 acquiring new functions (or Gain of Function) to drive carcinogenesis, transforming normal cells to cancerous cells. Their investigation comparing cells from genetically engineered mouse strains expressing 2 different types of p53 mutations: the R172H mutation versus the R246S mutation, which showed that Gain of Function (GOF) was found only in the former. This showed that GOF of mutated p53 is specifically dependent on mutation-type but not across all kinds of genetic mutations, highlighting diversity in properties of the different types of p53 mutations, thereby indicating that mutations found in human cancers can behave differently, and thus, need to be carefully assessed prior to treatment.

Thus, the existence of mutant p53 certainly has a negative impact on cancer treatment, whether it is through DN effect or GOF. Prof Sabapathy said that the team is now embarking on more research to determine the possibility of targeting mutant p53 without affecting wild-type p53 in human cells, paving way to clinical trials in the future to test the efficacy on cancer therapeutic response.

More information: The study was published by Cell Press in the premier cancer journal *Cancer Cell*, on 10 Dec 2012.

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