MedicalXpress

Scientists find the "missing link" in important tumour suppression mechanism

November 12 2013

Novel discovery relating to the function of RUNX3 gene provides new insights on human defence mechanism against early stages of lung cancer development

RUNX3, a gene that is intensively studied for its function as a tumour suppressor, is likely to be a key and critical component of the body's first line of defence against lung cancer development, according to a recent study by scientists from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS), together with their collaborators from Chungbuk National University in Korea.

The team, led by Professor Yoshiaki Ito of CSI Singapore, showed that RUNX3 is a major component in a well-established tumour suppression mechanism involving p53, a tumour suppressor protein that regulates cell proliferation and prevent cancer. In addition, the research team also demonstrated that RUNX3 plays a pivotal role in preventing early tumour formation.

Although the current study focused on lung cancer, the results help to explain the development of other types of human cancers.

These novel findings were published in leading scientific journal *Cancer Cell* on 11 November 2013.

Implications on early cancer detection and prevention

Mutations of the p53 gene occur in 50 per cent of virtually all cancer types, indicating that p53 inactivation constitutes one of the main drivers of cancer development. p53 has since been shown to exert multiple effects – be it enhancing DNA repair, arresting cell proliferation or promoting cell death – to inhibit cancer growth.

"This study uncovered an important missing component of the tumour suppressor pathway that regulates p53 function. The identification of RUNX3 as the key component throws light on why RUNX3 gene inactivation, particularly via epigenetic mechanisms, is so prevalent in cancer," Prof Ito explained.

"From a clinical viewpoint, this finding has applications in early cancer detection and prevention. Cancer-specific epigenetic inactivation of RUNX3 is marked by DNA methylation, which can be readily screened for early detection or prognosis of a wide variety of cancer. It also suggests the exciting possibility that RUNX3 inactivation, if reversed by therapeutic means, may restrain cancer growth. It is therefore likely that many new approaches of cancer treatment or prevention will be generated," he added.

Role of RUNX3 in suppressing tumour formation

Lung cancer is the most frequently occurring cancer worldwide, and it is also the No. 1 killer cancer for both men and women in Asia-Pacific and Singapore. The prevalent type of lung cancer, called adenocarcinoma, is frequently observed to harbour genetic alterations in the oncogene K-Ras.

In normal cells, K-Ras is activated by a short-lived signal to promote cell growth and then rapidly deactivated. However, in lung cancer, a mutated version of K-Ras gene - K-Ras^{G12D} - is expressed. Instead of responding to the growth signal, the mutant K-Ras^{G12D} constantly stimulates cell

growth, causing the uncontrolled and rapid growth of the cancer cells. Confronted with the activation of such oncogenes, normal cells would turn on tumour suppressor pathways to stop cell growth or kill abnormal cells.

Currently, the best studied tumour suppressor is p53, which is frequently inactivated in various human cancers. The activity of p53 is tightly regulated by a gene called MDM2 (which acts to limit the p53 growth-suppressive function) and its inhibitor $p14^{ARF}$. While scientists have found that $p14^{ARF}$ inhibits MDM2 and thus promotes p53 activity, it is unclear how $p14^{ARF}$ is induced.

To fill this gap in knowledge, the research team studied the molecular mechanism underlying K-Ras-induced lung adenocarcinoma. They found that $p14^{ARF}$ is induced by the RUNX3 in collaboration with another protein called BRD2, in response to $K\text{-}Ras^{G12D}$. This suggests that RUNX3 is one of the major components of the well-established tumour suppressor pathway involving p53.

The discovery of the link between RUNX3 and BRD2 will also initiate new directions in studies on complex mechanisms that regulate gene expression, the impairment of which is often associated with cancer development.

RUNX3 as first line of defence against cancer formation

Another important breakthrough achieved by Prof Ito and the team was the discovery of different roles of RUNX3 and p53 in tumour suppression.

Since 2010, it has been known that while p53 can effectively destroy

well-developed cancer cells, but it cannot respond to low levels of oncogenic stimuli and prevent the early stages of cancer development.

The research team showed that the sole inactivation of RUNX3 results in the rapid development of pre-cancerous adenoma (a benign tumour that may become malignant over time) in less than four months. On the other hand, inactivation of p53 alone has not been shown to induce adenoma. By showing that RUNX3 prevents adenoma formation, the team contributes to a better understanding of an important aspect of tumour suppression mechanism.

Commenting on the findings, Prof Ito said, "It is very likely that our body is protected by two lines of defence mechanisms against lung cancer development - RUNX3 forms the first line which protects against adenoma formation while p53 forms the second line in protecting against adenocarcinoma formation. It will be important to examine whether other types of cancer also show two lines of defence mechanisms, since p53 is frequently inactivated in various cancer types."

The next step

p53 is often mutated and it is practically impossible to revert this mutation for the purpose of treatment. By contrast, RUNX3 is inactivated by DNA methylation (ie. epigenetic inactivation), a chemical event that silences the gene without altering its coding information.

"Clinical trials have shown that reactivation of epigenetically inactivated genes is feasible. Indeed, RUNX3 gene can be reactivated by chemicals in cancer cells in laboratory. Therefore, the team's immediate task is to find a way to effectively re-ignite RUNX3 gene activity. Since RUNX3 functions at early stages of cancer, reversal of RUNX3 inactivation could halt cancer development by timely prevention of permanent neoplastic changes," said Prof Ito.

Provided by National University of Singapore