New research on the 'guardian of the genome'

May 12 2009

(PhysOrg.com) -- Protein p53 protects the body against cancer and is knocked out in many cancer tumours. Researchers at Karolinska Institutet have identified two molecules that can restore p53's cancer-killing properties. New results are now presented on the two substances, one of which will undergo clinical tests later this year.

The p53 protein, which exists in all the cells of the body, is commonly called the "guardian of the genome", since it detects harmful DNA changes and prevents them from being transmitted further into the body. p53 activates genetic programmes that arrest the division and growth of damaged cells or trigger their apoptosis. In half of all cancer tumours, the gene for p53 is damaged, and the scientists believe that the protein has been rendered dysfunctional in all cancer tumours.

Researchers at Karolinska Institutet have formerly identified a small molecule, called PRIMA-1, that is able to repair the mutated p53 protein and inhibit tumour growth in mice (1). The first clinical tests designed to reveal if the effect is the same in the human body will be held later in the year.

It is not fully understood how PRIMA-1 goes about reactivating mutated p53, but new results show that PRIMA-1 is transformed into other molecules in the cell (2). According to Professor Klas Wiman, who is leading the research into PRIMA-1, it is likely that these molecules bind to the p53 protein and alter its structure so that it can once again bind to DNA.

"We're just starting to understand what the mechanism looks like, and this makes us better equipped to one day change the molecule and make it even more effective," says Professor Wiman.

Another molecule, RITA, which can also induce the death of tumour cells in mice, has been identified by Galina Selivanova, associate professor at the Department of Microbiology, Tumour and Cell Biology. However, unlike PRIMA, this molecule is active against tumour cells in which p53 is non-mutated. In many tumour cells, p53 is inactivated by being bound to another molecule, HDM-2. RITA blocks the p53/HDM-2 interaction, resulting in an increase in p53 and the eventual death of the tumour cell. Two new studies reveal further details of the mechanisms by which RITA affects the cell (2, 3).

"RITA can kill many different types of cancer cell without causing any damage to normal cells, which is very important," says Dr Selivanova. "We believe that RITA has considerable potential as the basis of a future drug."

According to Dr Selivanova, the results also suggest that PRIMA-1 and RITA are mutually reinforcing when co-active. A combination therapy is therefore a possibility.

"But the two molecules will have to undergo individual clinical tests first," she adds.

References:

1. Bykov, V.J., Issaeva, N., Shilov, A., Hultcrantz, M., Pugacheva, E., Chumakov, P., Bergman, J., Wiman, K.G, and Selivanova, G. "Restoration of the tumor suppressor function to mutant p53 by a low molecular weight compound"
Nature Medicine 8 March 2002

2. Jeremy M.R. Lambert, Petr Gorzov, Dimitry B. Veprintsev, Maja Söderqvist, Dan Segerbäck, Jan Bergman, Alan R. Fersht, Pierre Hainaut, Klas G. Wiman and Vladimir J.N. Bykov
"PRIMA-1 Reactivates Mutant p53 by Covalent Binding to the Core Domain"
Cancer Cell 5 May 2009

3. Enge M, Bao W, Hedström E, Jackson SP, Moumen A, Selivanova G.
"MDM2-dependent downregulation of p21 and hnRNP K provides a switch between apoptosis and growth arrest induced by pharmacologically activated p53"
Cancer Cell 3 March 2009

4. Vera Grinkevich, Fedor Nikulenkov, Yao Shi, Martin Enge, Wenjie Bao, Alena Maljukova, Olle Sangfelt , Angela Gluch, Alexander Kel, and Galina Selivanova
"Ablation of Key Oncogenic Pathways by RITA-Reactivated p53 Is Required for Efficient Apoptosis"
Cancer Cell 5 May 2009

Provided by Karolinska Institutet (news : web)