

New research on the 'guardian of the genome'

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(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.

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