

Three is the magic number: A chain reaction required to prevent tumor formation

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Protein p53 is known for controlling the life and death of a cell and has a key role in cancer research. P53 is known to be inactive in 50 percent of cancer patients. If researchers succeed in re-establishing the presence of p53 in patients, they may hold the key to a promising avenue of research. However, p53 does not act alone.

The expression of p53 and Mdm2 is closely related. In an article published this week in the *Cancel Cell* review, Robin Fahraeus and his collaborators from Inserm Unit 940 ("Therapeutic Targets for Cancer"), demonstrate that cellular response to DNA damage requires involvement from the protein kinase ATM so that Mdm2 can positively or negatively control [protein p53](#).

Much focus is placed on protein p53 in cancer research. Discovered in 1979, p53 precisely regulates [cell proliferation](#) and triggers cell distribution or programmed natural cell death (apoptosis) in accordance with requirements.

In contrast to "normal" cells, the cell cycle of [tumour cells](#) is out of control, causing the anarchic proliferation of cells, the cause of cancer. The cells become immortal, thus causing significant deregulations in the body. A few years ago, researchers proved that the protein [p53 gene](#) is inactive in half of all human cancers. The p53 coding gene was classified as a tumour-suppressing gene. Scientists suggested a new hypothesis: if this gene were reactivated, this uncontrolled cell activity, responsible for the formation of [cancer tumours](#), could be prevented. However, they

would later discover that p53 is itself regulated by another factor: protein Mdm2. They then thought they had discovered a means to reactivate p53.

Today, Robin Farhaeus and his collaborators have provided a new element in the understanding of carcinogenesis mechanisms: the involvement of protein kinase ATM in the p53 regulation via Mdm2. "Following DNA damage, Mdm2 is required to activate p53 and this may occur through the intervention of the ATM kinase protein" explains Robin Farhaeus, Inserm Research Director.

To complete the demonstration, the researchers highlighted the chain of events that triggers p53 activation. Mdm2 activation is caused by phosphorylation through the ATM kinase protein, which is itself activated in the event of cell stress. This phosphorylation of Mdm2 is crucial for the transition from a negative p53 regulator state to a positive p53 regulator state (thus encouraging its interaction with p53 ARN messenger to cause translation). This leads to an increased quantity of p53 in the cell.

This study improves understanding of how the respective regulation of p53 and [Mdm2](#) are organised in response to damaged DNA. Better understanding of specific molecular mechanisms at work during cell stress may help create new therapeutic approaches to cancer.

More information: The p53 mRNA-Mdm2 interaction controls Mdm2 nuclear trafficking and is required for p53 activation following DNA damage, *Cancer Cell*, December 2011

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