Cancer is a p53 protein aggregation disease

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Protein aggregation, generally associated with Alzheimer's and mad cow disease, turns out to play a significant role in cancer. In a paper published in *Nature Chemical Biology*, Frederic Rousseau and Joost Schymkowitz of VIB, K.U.Leuven and Vrije Universiteit Brussel (Belgium) describe that certain mutations of p53, an important tumor suppressor, cause the protein to misfold in a way that the proteins start to aggregate. This not only disrupts the protective function of normal p53, but of other related proteins as well.

In the study, the focus was on the p53 protein which plays a key role in protecting the body against cancer. If p53 works normally, it controls cell division. If p53 control ceases - e.g. when there is a mutation in the protein - the cells start to divide in an uncontrolled manner and this may result in a tumor. Mutations in p53 are observed in about half of cancer cases, making the protein an important target in the development of new cancer therapies.

"We have revealed a new mechanism for the action of mutant p53," Joost Schymkowitz and Frederic Rousseau of VIB, Vrije Universiteit Brussel and K.U. Leuven say. "Mutations in p53 cause the protein to lose its protective function. The proteins change in shape, hook into each other and begin to aggregate. The active p53 disappears from the cell and can no longer carry out its control function properly." The mechanism has been encountered in about one third of p53 mutations.

Moreover, the mutations cause p53 to assume a completely different character. From being a protective factor, the mutated p53 changes into

a substance which in fact speeds up tumor growth. It seems to form aggregates with control substances (p63 and p73) in the cell, causing them to lose their function as well.

Even though the underlying principle – protein aggregation - occurs similarly in particular cancers, Alzheimer and systemic amyloidosis, the diseases are otherwise totally unconnected with each other. In cancer, the clustering of p53 protein leads to uncontrolled cell growth. In Alzheimer, clustering of the beta-amyloid protein causes brain cells to die off.

More information: Jie Xu et al, Gain of function of mutant p53 by coaggregation with multiple tumor suppressors, *Nature Chemical Biology*.

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