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A new discovered mutation can hold the key to treat a large number of different cancers

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Scientists have discovered a mutation responsible for cancer progression, a finding with potential implications for the development of treatment against not one, but a series of cancer types since this mutation can be linked to an abnormality recently discovered to exist in all malignancies. The discovery has just been published in the journal *Nature Genetics.*

Sonia Melo from the Spanish National Cancer Research Centre in Madrid and the Institute of Molecular Pathology and Immunology in Porto, Portugal and colleagues from laboratories in Spain, Portugal, Finland, Japan and US, in the study now published, worked with MicroRNAs (or miRNAs), which are tinny pieces of RNA that regulate gene expression by aberrantly binding to other RNAs blocking the formation of their corresponding protein (as normally the information in the DNA is translated into RNA, which then go to serve as “blueprint” for protein formation).

Some miRNAs have also been suggested to suppress tumour formation and, very interestingly, recent reports found that abnormal levels of these molecules exist on all cancers suggesting that these changes could be a new form of cancer predisposition. If true, this also meant that therapy capable of reversing miRNA abnormal levels could be used to treat more than one type of cancer in what might be an important breakthrough in the treatment of the disease.

It is in light of these last new results that Sonia Melo, Manel Esteller the head of the team and colleagues decided to analyse cells from twelve

different cancers looking for mutations in the genes of a eight-protein pathway responsible for miRNA formation, since disruption in any of these proteins would inevitably result in changes in the quantities of the molecule. And in fact, one of its genes - called TARP2 - that produces a protein from the pathway called TRBP was found mutated in two of the cancers analysed. Not only that, but the mutations were associated with low quantities of miRNA, that, nevertheless, quickly returned to normal when functional TARBP2 genes were successfully inserted into the cancer cells by the researchers.

Even more interesting was the fact that most of the reinstated miRNA (so those with quantities affected by the mutation and restored by the normal TARBP2) has been previously suggested to have tumour suppressor capabilities. And in fact, when Melo and colleagues analysed the levels of expression of several oncoproteins - that are known to promote cancer when abnormally activated - it was found that these levels were aberrant in TARBP2-mutated cells but returned to normal when functional TARBP2 was introduced (and normal miRNA quantities re-established).

To substantiate this observation the next step was to compare the carcinogenicity (capacity to originate cancer) of the cells with functional or mutated TARBP2. In here again restoration of normal TARBP2 into previously mutated cancer cells strongly reduced their carcinogenic capabilities: they started dying and were less capable of forming tumours (cancer cells are characterised by abnormal growing and immortality).

To confirm that these results reflected what happens in living organisms Melo and colleagues then injected mice with no immune system (so to be able to clearly see the cells' effect) with the new TARBP2 restored cells or, alternatively, with the old TARBP2-mutated cancer cells and compared the results. Again, while the latter formed tumours very rapidly, the first showed much less capacity to do so, further confirming

that aberrant TARBP2, by reducing miRNA levels, promotes the appearance and development of cancer.

In conclusion, Melo and colleagues' work, not only proves that miRNA can in fact act as tumour suppressors, but also identifies a mutation responsible for their deregulation (and so their capability to promote cancer) as well as a potential treatment to solve the problem. The fact that TARBP2 mutations affect the machinery producing every miRNA in the body, together with the finding that aberrant levels of these molecules seem to be a characteristic of all cancers just highlights the potential breakthrough importance that the therapy described by Melo and colleagues to efficiently revert TARBP2, might have in the combat against cancer.

Supporting that idea when the researchers looked into TARBP2 status in 282 different human primary tumours the gene was mutated in as many as 26% of them, including in cancers as distinct as family and sporadic colorectal cancer or gastric malignancies.

Sonia Melo a Portuguese PhD student and the first author of the work believes that what is most interesting about the study is the fact it reveals such a wide-ranging regulatory system - "with this work we were able to find an error in the production of these molecules, but once the mutated gene is reconstituted the cells are again capable of produce normal levels of miRNA to regulate the expression of several genes, including quite a few oncogenes that should not be active during normal conditions."

More information: *Nature Genetics* - February 2009 Advance Online Publication "A TARBP2 mutation in human cancer impairs microRNA processing and DICER1 function," www.nature.com/ng/journal/vaop … rent/abs/ng.317.html

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