Good indicator of cancer prognosis turned on its head by new research

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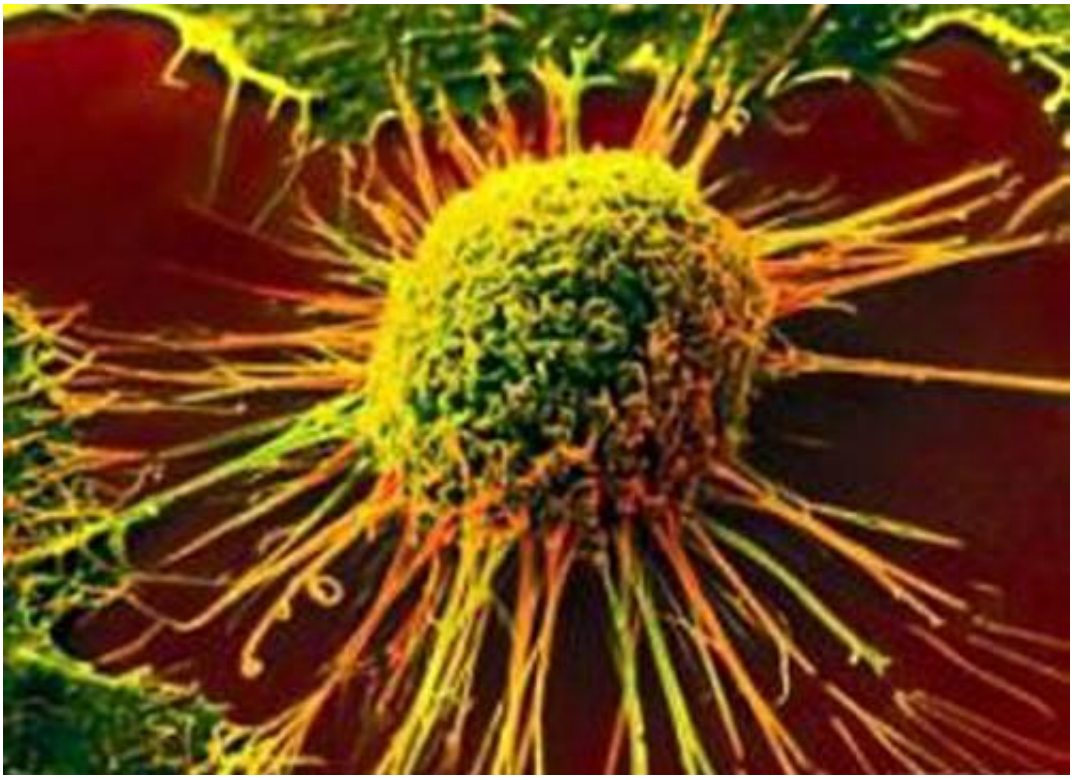

A molecule which, for the last 20 years has been believed to be an indicator of good prognosis in tumours has been shown to have a dark side by new research from The Universities of Manchester, Athens and collaborators, recently published in *Nature Cell Biology*.

The molecule p21WAF1/Cip1 (or p21 for short) is often found in association with a so-called 'master tumour-suppressor' p53. This has traditionally given doctors an indication that there is a good prognosis for cancer – the presence of p21 indicating that the p53 tumour suppressor will lead to a less aggressive tumour.

However, the new study has presented evidence that turns this assumption on its head. Scientists at The University of Manchester, part of the Manchester Cancer Research Centre, alongside international collaborators, especially at the University of Athens, have shown that in tumours where the p53 molecule is deficient, p21 dramatically increases the ability of tumours to grow and spread throughout the body.

Professor Paul Townsend, one of the lead authors, along with senior author, Professor Vassilis Gorgoulis, Honorary Professor in Manchester, and Professor-Director, University of Athens, have said: "Years ago, being exposed to a lot of sunshine was thought to be one of the best ways of being healthy before we realised the harmful effects of too much could have.

"This protein has a similar effect. When the activity of wild type p53 is lost, excess production of p21 is far from a good thing. This protein which was previously thought benign turns out to have a dark side."

The findings are a result of five years' of study into p21, originally with a view to developing treatments, which increase its presence and supress tumours. While conducting this investigation the international research team noticed that in p53-deficient tumours increased p21 was actually correlating aggressive behaviour. This led them to suspect a different possibility for how the molecule was working in tumours.

In reality, p21works by deregulating the DNA replication machinery and triggering what's called replication stress. This causes genomic

instability, a key hallmark of cancer.

The new findings open up the possibility of treatments being developed which counter p21, an avenue of research which has not been previously explored.

Professors Townsend added: "We now know that p21, when unleashed from p53 control, is a factor in causing the danger signs of cell replication found in aggressive tumours. Although this goes against what we have known to date, it offers the hope of developing new treatments for cancer in the years ahead."

More information: Panagiotis Galanos et al. Chronic p53-independent p21 expression causes genomic instability by deregulating replication licensing, *Nature Cell Biology* (2016). DOI: 10.1038/ncb3378

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