# Loss of protein p53 helps cancer cells multiply in 'unfavourable' conditions

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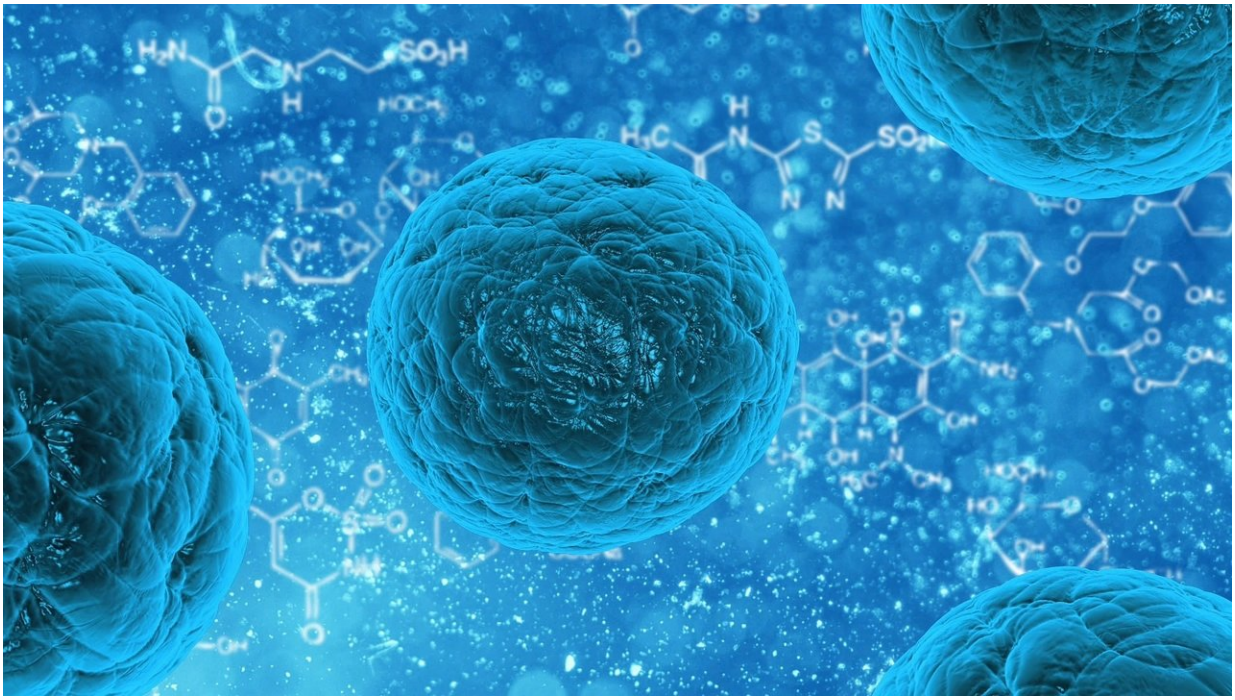

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Researchers have discovered a novel consequence of loss of the tumour protein p53 that promotes cancer development, according to new findings in *eLife*.

The study in mouse and human cells, from the Netherlands Cancer Institute, suggests that multiplication of cancer cells in the absence of

appropriate growth stimuli is supported by the additional loss of p53, which ensures that replication of the genetic material, the DNA, can still take place. This unanticipated discovery paves the way for further investigations of how cancer cells survive and multiply in adverse conditions, and of potential methods for blocking these mechanisms.

When a cell divides, its DNA is replicated and the two copies are equally distributed to two daughter cells. Any problems that arise during this replication process can lead to damaged DNA, which can in turn cause growth arrest or cell death. A healthy cell can therefore only replicate its DNA in favourable conditions, namely where the necessary growth stimuli are present.

"In the absence of growth factors, for example when there is not enough blood supply, a normal cell turns on a 'safety catch' that locks the cell in the first phase of the cell division cycle, the G1 phase, and ensures that no DNA will be replicated," says co-first author Bente Benedict, Ph.D. student at the Netherlands Cancer Institute. "Most cancer cells lack this safety catch, also called the G1 checkpoint, and can therefore start replicating their DNA in conditions without growth stimuli. But a cancer cell pays the high price of DNA damage caused by replication problems, which turns on a second safety catch to impose growth arrest and even cell death. It is not yet fully understood how cancer cells overcome these obstacles to maintain tumour growth."

In addition to loss of the G1 checkpoint, some of the most common mutations found in cancer cells happen in the p53 protein, a central player in the second safety catch. Benedict adds: "It is thought that the loss of p53 helps a cancer cell to survive by circumventing growth arrest and suppressing cell death, but how then do cells deal with the DNA damage?"

Their studies demonstrated that, in the absence of growth stimuli, cells

lacking the G1 checkpoint indeed suffered from severe DNA replication problems. Surprisingly, they also found that the simultaneous absence of p53 reduced the impact of these problems and allowed the cells to multiply anyway. "Rather than merely reducing cell death and cell cycle arrest, loss of p53 reduced the level of DNA damage during DNA replication, allowing cancer cells to multiply in these otherwise unfavorable conditions," says co-first author Tanja van Harn, a graduate student at the Netherlands Cancer Institute at the time the study was carried out. "These findings can explain the frequent loss of p53 in cancer cells that lack the G1 checkpoint."

Although the loss of p53 reduced DNA damage, the cells still experienced severe replication problems. "It is likely that the cells rely on mechanisms that maintain DNA replication to a level that is just sufficient to complete this process without too much damage, thereby constituting an 'Achilles heel' of cancer cells," explains senior author Hein te Riele, Professor and Group Leader at the Netherlands Cancer Institute. "The next step will be to investigate these mechanisms and see whether pharmacological interference might one day provide therapeutic benefit to patients."

**More information:** Bente Benedict et al, Loss of p53 suppresses replication-stress-induced DNA breakage in G1/S checkpoint deficient cells, *eLife* (2018). DOI: 10.7554/eLife.37868

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