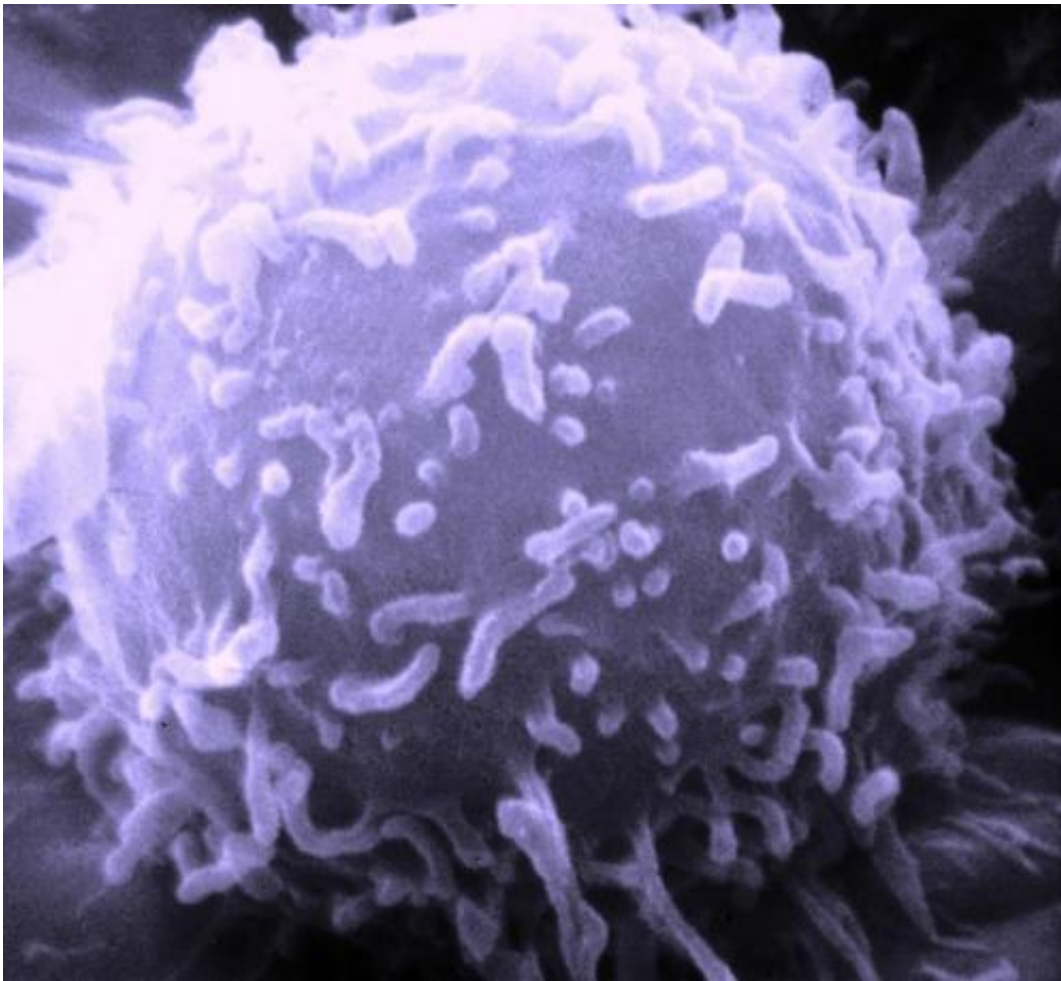


# 'Master switch' helps cancer cells survive stress

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Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Scientists have discovered a 'master switch' within cancer cells that seems to override the normal stress response and allows them to survive conditions that would normally be lethal.

The mechanism could be critical in allowing cancer cells to withstand the huge amounts of stress they come under as they divide rapidly and their metabolism goes into overdrive.

The master switch, which is described today (Thursday) in the prestigious journal *Cell*, appears to play a key role in lung and breast cancer, and could be a promising target for future cancer drugs.

Scientists at The Institute of Cancer Research, London, showed how a molecule called Brf2 acts as a chemical sensor and shuts down gene activity when [normal cells](#) are placed under metabolic stress.

That in turn sends normal cells to their deaths—stopping them from suffering potentially dangerous mutations as a result of the stress they are under.

The researchers think that cancer cells can overcome this trigger for cell death by producing more Brf2, allowing them to survive and accumulate mutations, even when they are under significant stress.

It was already known that cancer cells could withstand higher levels of metabolic or oxidative stress than normal cells, but until now little had been known about how they were able to do this.

The new study was funded by The Institute of Cancer Research (ICR) itself, with additional support from the Biotechnology and Biological Sciences Research Council.

The ICR scientists became interested in Brf2 when research showed that

some cancers, in particular lung and [breast cancer](#), have increased levels of the protein. It was not clear if this was incidental, or if Brf2 was playing a critical role in the development of cancer.

The researchers used X-ray crystallography to scrutinise the three-dimensional structure of Brf-2 when the protein was in the act of recognising specific DNA sequences. This is a key mechanism for activating RNA polymerase III—a piece of cellular machinery that turns on certain essential genes in the cell.

The researchers found that the protein's structure had an unpredicted part used to 'sense' levels of oxidative stress.

Interfering with this part of the structure by mimicking stress stopped Brf2 interacting with other proteins, and prevented the activation of RNA polymerase III. That in turn stopped specific genes becoming active, and triggered cell death.

The researchers found that increasing the amount of Brf2 made cancer cells less likely to die when placed under [oxidative stress](#), while reducing its levels made them more likely to die.

Some cancer cells are much more dependent on Brf2 than normal cells, making it a potential new target for cancer treatments.

Dr Alessandro Vannini, Team Leader in Structural Biology at The Institute of Cancer Research, London, said:

"We were intrigued by the Brf2 protein because it is found at high levels in a number of cancer types, including breast and lung cancer, but no one knew why.

"What we found really surprised us. It turns out that the Brf2 protein is a

sensor of metabolic cell stress, and acts like a [master switch](#) in switching [gene activity](#) on and off, and determining whether cells live or die.

"Cancer cells thrive under stress, and we think that producing more Brf2 protein can protect them and keep them alive. That not only allows cancer cells to keep on dividing but also increases the chance that they will sustain even more cancer-driving mutations."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"This is an important fundamental study, revealing both the structure and function of a fascinating protein which seems to play a critical role in the survival of cancer cells. Some [cancer cells](#) seem to be much more reliant on the Brf2 protein than healthy cells, and that could make it a promising target for cancer treatments of the future."

**More information:** *Cell*, [dx.doi.org/10.1016/j.cell.2015.11.005](https://doi.org/10.1016/j.cell.2015.11.005)

Provided by Institute of Cancer Research

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