Signal may send cancer's cellular factories into overdrive

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A network of signals active in almost all types of cancer sends the protein factories in our cells into overdrive, and may help fuel a tumour's uncontrolled growth, new research suggests.

Scientists at The Institute of Cancer Research, London, identified a molecular trigger responsible for ratcheting up activity of the endoplasmic reticulum (ER) – the cellular factory that makes the building blocks cancer cells need to keep growing.

A protein in the TOR signalling pathway, called SREBP, controls the flow of messages to the endoplasmic reticulum telling it to expand – and could allow cancer cells to produce enough proteins and lipids to fuel their non-stop growth.

The findings may help to explain how cancer cells maintain their high levels of metabolism – and could uncover future targets for cancer treatment.

The study was published in the journal *PLOS ONE*, and funded by the Biotechnology and Biological Sciences Research Council (BBSRC), with additional support from the Wellcome Trust.

Unlike healthy cells, cancer cells are constantly growing, and so need to keep making proteins and lipids - the building blocks of all cells.

In healthy cells constant growth can overwhelm cellular factories like the

ER, leading to cell stress and death, but cancer cells manage to keep their factories running at high capacity to fuel non-stop growth.

Scientists at The Institute of Cancer Research (ICR) used the cells of fruit flies, modified with a fluorescent marker that is activated when the cells are put under stress, to identify the signals responsible for driving up activity of the ER.

They systematically silenced genes thought to be important to the smooth working of the ER and measured the stress signals produced in response.

They found that silencing the TOR signalling pathway - activated in many different types of cancer - increased ER stress in the cells. When they blocked TOR signals, cells took longer to recover from ER stress and the ER factory shrank.

Their findings suggest the TOR signalling pathway promotes cell growth while simultaneously ensuring productivity of the ER matches this growth. And the protein SREBP, which is part of the TOR signalling pathway, appeared to be essential for promoting expansion of the ER, and ensuring it carried out its factory activities effectively.

Lead author Dr Chris Bakal, leader of the Dynamical Cell Systems Team at The Institute of Cancer Research, London, said: "The endoplasmic reticulum is the factory of our cells, creating the proteins and lipids needed for our cells to grow and proliferate. In cancer cells, this factory is active all the time, churning out the building blocks that cancer cells need for their rapid growth.

"We have discovered the key role played by the TOR signalling pathway in driving the expansion of the endoplasmic reticulum, and sending a cell's factories into overdrive. The TOR pathway is active in many types

of cancer, and our study provides new insights into how cancer metabolism works, and suggests that these metabolic signals could be excellent targets for future treatments."

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