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Researchers discover mechanism that allows cancer to survive without glucose

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The main goal of a tumour cell is, above all, to survive, even at the cost of damaging the health of the organism to which it belongs. To do this, it is equipped with skills that healthy cells do not have, including the ability to continue surviving when glucose levels are very low. This could be one of the reasons why widely-used anti-angiogenic agents often fail to eliminate cancer, no matter how much they starve it by hindering the development of the blood vessels that provide nutrients in general and glucose in particular. Now, a group of CNIO researchers have identified one of the key biochemical mechanisms that allow cancer cells to survive without glucose.

In particular, they have discovered a group of proteins that actually act as a switch: when food -glucose- is available, tumour cells use a particular biochemical path to survive and continue to proliferate; when there is no glucose, the switch triggers a different path to achieve the same goal, namely the survival of the tumour cells.

As explained by Nabil Djouder, researcher at the CNIO and the intellectual author of the paper published today in *Cancer Cell*, "tumour cells are very smart; when one door that seemed essential for their growth and proliferation closes, they open new ones that allow them to adapt to any stress and survive. This is why they develop highly sophisticated mechanisms and learn to survive, and this is why it is so difficult to cure cancer".

The paper is of a basic nature, far from any clinical application at the

moment. However, its publication in a high impact magazine confirms that the community considers it a highly relevant piece of the puzzle. Researchers have been wondering for some time how tumour cells manage to survive in the interior -in the centre- of a tumour mass, where barely any blood vessels can reach. It is also urgent to understand the resistance to anti-angiogenic agents, one of the most widely-used anticancer drugs in recent years and whose effectiveness is based on preventing the growth of the blood vessels that supply the tumour, thus starving the cancer cells of nutrients.

'Switches' To Detect Glucose And Act Accordingly

Everything that happens in cells -whether they are cancer cells or not- is based on chains of biochemical reactions: a protein is modified through the addition of one or another molecule, and that change induces changes in other proteins. In a very simplified metaphor, it is like a circuit with numerous switches that connect or disconnect. Djouder and his partners have identified the system of switches that allows cells to detect whether or not there is glucose, and to decide, in the light of this, what biochemical path they must follow to achieve their ultimate goal, which is to survive.

This is a sophisticated system composed with three proteins: URI protein (which act as the switch), OGT and c-Myc. c-Myc is a well known oncogene, i.e. it promotes cell proliferation and survival. However, Djouder's group has discovered that c-Myc protein levels matter for cancer cell survival upon nutrient stress.

The sequence of events is as follows: URI controls OGT activity. OGT senses and utilizes the glucose to control c-Myc levels. When glucose is present, OGT uses glucose to stabilize c-MYC levels which fulfils its role as an oncogene. When, on the contrary, cells face a situation of glucose shortage, URI becomes a potent inhibitor of OGT and decreases

OGT activity which reduces its glucose consumption. This leads to c-Myc degradation. c-Myc is thus eliminated. The result is that in the absence of glucose the survival of the cell depends on URI which has oncogenic activities.

Our findings suggest an important glucose-sensing mechanism in which URI acts as a rheostat controlling OGT activity and therefore c-MYC levels, conferring selective traits that allow cancer cells to tolerate severe metabolic stress and survive under selective pressures imposed by environmental challenges".

This mechanism can be of general importance in tumorigenesis and may explain how cancer cells exposed to glucose deficiency can expand instead of regressing".

This finding is still far from having any practical application as one of the obvious strategies, such as hijacking the action of URI is simply not possible to date. URI is a protein whose functions are not yet sufficiently known and, in fact, Nabil Djouder and his group at the CNIO will continue to study it.

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