UNIVERSITÉ DE GENÈVE

PRESS RELEASE

Geneva | 3 April 2013

The Metabolic Weather-vane of Cancer

NCI and UNIGE researchers warn against a potential backfiring of certain therapies in development.

Highly expressed in various cancers and known for its cytoprotective properties, TRAP1 protein has been identified as a potential target for antitumor treatments. As a result of the research conducted by Len Neckers, from the National Cancer Institute in Bethesda, USA, and Didier Picard, from the University of Geneva (UNIGE), Switzerland, this outlook is now being called into question. The researchers' findings, published in *PNAS*, describe how TRAP1 disrupts the metabolism of malignant cells, and shows that the quantity of this protein decreases as they progress to a more aggressive stage. The suppression of TRAP1 leads to the transfer from one metabolic pathway to another (more powerful) one, as well as a significant increase in the motility and invasiveness of cells. In some situations, a therapy designed to inhibit TRAP1 could actually stimulate tumor progression to a metastatic state.

The cells of our body consume various nutrients from which they draw energy for their daily needs, with the help of inhaled oxygen. Glucose, for example, has a maximal energetic yield after complete combustion in mitochondria—genuine intracellular power plants. Even without oxygen, this nutrient may still provide some energy after being partially digested in the cell's cytoplasm. "This is the process—similar to fermentation—that is frequently used by tumor cells, allowing them to proliferate rapidly and free themselves, for the most part, of oxygen. They offset low energy output by consuming more glucose", notes Didier Picard, professor at the Department of cell biology of the Faculty of Sciences at UNIGE.

A shield for malignant cells

Some types of tumors are characterized by an excessive expression of TRAP1, a molecule present in mitochondria. This protein, which belongs to the "molecular chaperone" family, plays a role in protecting against cell auto-destruction and the damage done to its DNA in response to free radicals and other types of stress. "The antioxidant and cytoprotective properties of TRAP1, whose malignant cells use as a shield, have designated this protein as a target for antitumor treatments. Furthermore, TRAP1 inhibitors have demonstrated anticancerous activity in preclinical trials," explains Guillaume Mühlebach, first co-author of the article.

Alternate methods of energy production...

Tumor development occurs in several stages, with distinct metabolic needs. In collaboration with teams in the United States and Japan, researchers in Geneva have demonstrated that the expression of TRAP1 is inversely correlated with tumor stage in various types of human

cancers. “In particular, we found that TRAP1 regulates a metabolic ‘switch’ at the level of glucose digestion. When this protein is overexpressed, as is often the case in primary tumors, the cells use fermentation to generate the resources for growth,” explains Didier Picard.

...according to current needs

On the other hand, in a more advanced tumor stage, the expression of TRAP1 decreases and the cells mainly proceed to a complete combustion of nutrients in mitochondria. This metabolic pathway, with high energy output and high oxygen consumption, could provide them the energy necessary to form metastases. “The lack of TRAP1 indeed translates into a dramatic increase in cell motility and invasive power,” says Evangelia Vartholomaiou, another member of the Geneva group.

The anticancerous strategies targeting this protein could therefore have adverse effects on tumors capable of promoting one metabolic pathway over another according to their needs. While simultaneously inhibiting cell proliferation, this type of treatment could actually stimulate progression into a metastatic state.

contact

Didier Picard
+41 22 379 68 13
didier.picard@unige.ch

UNIVERSITÉ DE GENÈVE
Service de communication
24 rue du Général-Dufour
CH-1211 Genève 4

Tél. 022 379 77 17

media@unige.ch
www.unige.ch