UNIVERSITÉ DE GENÈVE

PRESS RELEASE

Geneva | 16 December 2014

WARNING: embargoed until December 18th, 6pm, CMT

A CHANGE OF DIET TO UNMASK CANCER VULNERABILITIES AND REDUCE CANCER RISK

Cell stress caused by a change of diet can help hinder tumour growth

Many recent studies showed that calorie restrictions reduce the incidence of cancer, whereas high-calorie diets cause obesity and diabetes, both of which increase the risk of developing cancers. However, tumor biology still hides complex mechanisms, as revealed by researchers from the Faculty of Medicine of the University of Geneva (UNIGE), Switzerland. In a study published in *Cell Metabolism*, scientists not only found the unexpected benefit that a change of diet had on certain types of lung cancer, they also deciphered the molecular mechanism underlying this dietary effect and showed how this cancer vulnerability could be exploited in targeted treatment strategies with limited side effects.

Unlike tumors caused by other oncogenes, KRAS-driven tumors, an oncogenic mutation common in lung, pancreas and colon cancers, are known to be sensitive to dietary restrictions. Although the effect of calorie restriction on these tumors is widely studied, Professor Roberto Coppari and his team from the Department of Cell Physiology and Metabolism at UNIGE's Faculty of Medicine, with colleagues from the University of Texas Southwestern Medical Center and from the Ancona University, decided to explore what would the outcomes of a change of diet be (from low to high-calorie diet). Surprisingly, they discovered that a high-calorie diet could have a potent anti-tumor action if the switch of diet took place before the tumor onset. Conversely, a high-calorie diet started after the tumor onset fueled tumor growth and worsened prognosis. The fact that the moment of dietary change is crucial indicates that this effect is not due to the diet per se but to the metabolic changes it engenders. "Our study does not show that, by eating junk food, people would be protected from lung cancer. But the high-calorie diet helped us discover a very specific molecular mechanism required for lung tumor cells to proliferate that could pave the way for new therapeutic approaches", underlines Giorgio Ramadori, the study's co-first author with Georgia Konstantinidou.

A matter of thresholds

In normally functioning cells, a particular kind of molecules – called chaperones - helps proteins to fold and function properly. However, in case of protein overload, chaperone expression increases, with the goal of reducing the likelihood of proteins being unable to function correctly. In the endoplasmic reticulum (the part of the cells that allows proteins to be properly sorted), when protein overload is achieved, endoplasmic reticulum stress (ER stress) occurs, which involves an increased chaperone expression. When this stress is too high, however, cells cannot cope with it and die. In tumors, the ER stress threshold is different and, in some cases, it seems higher, which constitutes a possible explanation for the fact that they do not die, but can proliferate abnormally even in these circumstances.

The scientists discovered that the dietary change was actually a way to trigger a raise in the ER stress. Indeed, if the ER stress threshold is raised before the tumor onset, the sick cells do not have the ability to trigger an effective response and tumor progression is hampered. However, if the change took

place after the tumor appeared, tumor cells already resolved a good part of ER stress and the additional stress may actually fuel the proliferation phenomenon.

A potential cancer treatment with limited side effects

Reducing side effects is a major goal for achieving improved cancer therapy, as quite often treatment kills indiscriminately sick and healthy cells alike. By undertaking transcriptome analyses of lung tumors from the different dietary groups, the scientists identified a specific chaperone protein, FKBP10, of which expression was greatly reduced by a switch to a high-calorie diet. This protein was expressed in human lung cancer cells but not in the healthy ones. Very interestingly, this same protein is usually expressed during the embryonic development and early age, but not in adults (in mice and most likely in human beings). When the embryo is developing, it induces an important ER stress, which is resolved, in part, by these chaperones. After the development phase, the ER stress diminishes greatly. Hence, several chaperones, including FKBP10, are not needed any longer and stop being expressed; tumors, however, reactivate the expression of the FKBP10 protein, probably to cope with their ER stress. An inhibitor to FKBP10 would therefore act as a therapeutic agent able to selectively hinder cancer cell proliferation while sparing healthy lung.

"FKBP10 was not previously thought to be important for cancerous cells. In this study we show that knock-down of FKBP10 leads to reduced cancer growth. Human lung cancer cells express FKBP10 while the nearby healthy lung tissue does not; this is very interesting and appealing to eventually translate these findings to the clinical arena. Hence, if we manage to identify the right inhibitor, we may open the door to new therapeutic strategies that will be able to hinder cancer cells proliferation without damaging the healthy cells. The inhibition of this protein is predicted to have minimal side effects as it is not expressed in healthy tissues, at least in adulthood," concludes Roberto Coppari, who estimates that, if preclinical data support such expectation, clinical trials could start in a few years' time.

contact

Roberto Coppari
+41 22 379 55 39
roberto.coppari@unige.ch

Giorgio Ramadori
+41 22 379 52 17
giorgio.ramadori@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