CIC bioGUNE
Biozientzietako Ikerkuntza Kooperatiboko Zentroa
Centro de Investigación Cooperativa en Biociencias

PRESS RELEASE

Research published in 'Cancer Cell'

Discovery of a protein that alters the nutrition of breast cancer cells

- *The project was led by Dr. Marcia Haigis, from Harvard Medical School in the US, and Dr. Arkaitz Carracedo, researcher in CIC bioGUNE, participated in it.*

- *It defends the hypothesis that tumour cells benefit from the elimination of a protein, namely SIRT3, which acts as a "guardian" of metabolism.*

(Bilbao, xxxx March).- A study published in the prestigious journal Cancer Cell in March gives us a better understanding of the causes underlying the development of cancer, especially breast cancer, by revealing that the lack or loss of a cell protein known as SIRT3 is involved in the pathogenesis of the disease, thus meaning that this protein could be a potential therapeutic target for the development of effective anti-cancer therapies.

The project was led by Dr. Marcia Haigis from the Harvard Medical School, and Dr. Arkaitz Carracedo, a researcher in the Proteomics unit of the Center for Cooperative Research in Biosciences (CIC bioGUNE), participated in it.

Cancer is generated by the successive accumulation of errors in the genome (which would correspond to the "instruction manual" for our cells), thus implying that it is a disease that emanates from our own organism. In this sense, one of the key goals of the scientific community is precisely to identify characteristics that differentiate normal cells from cancerous ones, to develop therapies targeting the tumour cells whilst leaving normal cells unaffected, a task that is far less complex in case of infections caused by external organisms such as bacteria, etc.

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PRESS RELEASE

Some 100 years ago, a researcher called Otto Warburg noted that cancer cells "fed" in a unique manner: instead using nutrients to produce energy, they appeared to waste some of this "food" as a result of a less efficient metabolism. Warburg proposed the hypothesis that tumour cells have a dysfunctional metabolism, which he attributed to mitochondrial defects in these cells. They were not using the nutrients to generate energy (ATP) but to generate biomass and construct more cells, divide, proliferate, etc.

"In recent years we have begun to understand this phenomenon much better. Paradoxically, cancer cells obtain enough energy (equivalent to the electricity that runs a house) from nutrients, whereas the limiting factor for these cells is material to build more cells (or to bricks to build more houses)", explains Dr. Arkaitz Carracedo.

"For that reason they have reprogrammed their metabolism to create more 'bricks' (cell membranes, DNA, proteins...). This alteration of the metabolic behaviour in a tumour cells is known as the 'Warburg Effect' in honour of the aforementioned researcher", states Carracedo.

In light of this notion, it becomes apparent that if we understand how the metabolism of tumour cells is reprogrammed, it should be possible to design more powerful and specific therapies. Indeed, this was the goal proposed by a group from Harvard Medical School (USA) led by Dr. Marcia Haigis, in collaboration with the Beth Israel Deaconess Medical Center, which also forms part of the Harvard Medical School and where Carracedo worked for three years until September last year, to try to understand better this aspect of tumour biology.

Dr. Haigis' group concentrated on a group of proteins, known as sirtuins, which regulate cell metabolism. They found that if a protein from the sirtuin family (SIRT3) was eliminated from the cells, there was an apparent change in their nutrients uptake and metabolism, showing a surprising resemblance to cancer cells.

"We found that loss of SIRT3 induced the 'Warburg Effect'. SIRT3 acts as a 'guardian' in the cell, ensuring that the metabolic processes proceed correctly. However, upon loss of SIRT3, another very important protein which needs to be strictly controlled, known as *HIF1*α, runs wild and reroutes the metabolism", states Dr. Carracedo.

According to this hypothesis, a tumour cell would benefit from the elimination of SIRT3, which acts as a "guardian" of the metabolism. "We checked this idea after noting that SIRT3-deficient cells generated cancers that developed faster in mice", notes Carracedo.

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PRESS RELEASE

“These proteins are continually competing. When SIRT3 levels are reduced, HIF1α protein level increases, which promotes tumour growth”, concludes Carracedo.

In order to perform the most important test, namely extrapolation of the findings to humans, they included both pathologists and biocomputing specialists in this project, and together they indeed confirmed that many cancers, particularly breast cancer, showed reduced levels of SIRT3, along with signs of an altered metabolism. This allowed them to reach the conclusion that SIRT3 is a ‘guardian’ of metabolism and that the design of drugs which promote its activation could be of interest for the treatment of cancer.

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