Institut Hospital del Mar d'Investigacions Mèdiques

Press release

Mechanism determined for treating the most aggressive tumours

- ***Researchers from the Hospital del Mar Medical Research Institute have been able to prevent the growth of tumours and eliminate them using a treatment that combines chemotherapy with a protein inhibitor to prevent the repair of damaged DNA in cancer cells***
- ***The feasibility of this approach has been tested in mice, studying the evolution of metastatic colon tumours from human patients***
- ***The use of this drug combination will now be studied in human patients. The research has been published in the journal Molecular Cell***

Barcelona, 9 July, 2019. A study led by researchers from the Hospital del Mar Medical Research Institute (IMIM), has determined, for the first time, the importance of a cell mechanism that may be key to treating metastatic tumours. The work has demonstrated the role a protein, **kinase IKKα**, plays in the ability of tumour cells to repair themselves. This is a key factor in **treatment resistance** and tumour spread. The research has been published in the journal *Molecular Cell*.
The researchers analysed the role of this protein, activated by mutations of the **BRAF and KRAS oncogenes**, present in the majority of the most aggressive tumours. The function of this protein is to facilitate DNA-repair in tumour cells after they have been damaged by chemotherapy, making them more resistant to the action of these drugs. This is key for the treatment approach, since this new study demonstrates, conclusively, that combining a BRAF oncogene inhibitor with chemotherapy deactivates and kills the tumour.
"These same oncogenes, in addition to converting normal cells into tumours, make them better able to repair the damage caused by chemotherapy agents or radiation, and make them more resistant. In other words, they play a double role, facilitating tumour transformation and protecting the tumour from the damage caused by chemotherapy and radiation", explains one of the principal authors of the study, Dr. Lluís Espinosa, director of the Molecular Mechanisms of Cancer and Stemness research group at the IMIM and CIBER of Cancer (CIBERONC) researcher. ***"The presence of these mutations makes treatment very difficult"***, he explains, ***"but this is also an advantage, because if, thanks to these mutations, the tumour cell is more resistant to damage, eliminating their activity with drugs that are currently used in clinical practice will make the tumour even more sensitive to the treatments. And that's what we've demonstrated."***
The study included researchers from the IMIM Stem Cell and Cancer Group, as well as doctors from the Medical Oncology and Pathological Anatomy services at Hospital del Mar, and researchers from the Catalan Institute of Oncology (ICO)-Institut d'Investigació Biomèdica de Bellvitge (IDIBELL) and the CIBERONC. Members of the Proteomics Unit of the Centre for Genomic Regulation (CRG), in Barcelona, and The Francis Crick Institute, in London, also participated.

Analysis with tumours from human patients
The researchers verified the role of the protein IKKα and its importance as a therapeutic target, implanting colon tumours, from human patients who had developed metastasis and treatment resistance, into mice. The study results showed that animals which received no treatment, or were treated only with either BRAF inhibitors or chemotherapy, died. But those that received a treatment combining these inhibitors with chemotherapy survived. What is more, the tumour cells were found to have died. This was confirmed with *in vitro* samples.
The researchers behind the study now want to start a clinical trial in cancer patients, taking advantage of the fact that the drugs employed in the study already exist and are used in clinical

practice. Firstly, their usefulness for treating colon and rectal cancer will be analysed, but the researchers have not ruled out the possibility that they may be effective for any kind of tumour involving BRAF and KRAS oncogenes, such as pancreatic cancer and melanoma. One of the authors of the work, Dr. Clara Montagut, head of the Digestive Oncology section in the Hospital del Mar Medical Oncology Service and IMIM and CIBERONC researcher, points out that ***"the results of the study are new and promising, and open new avenues for cancer treatment. But before this reaches patients, we must first conduct a clinical trial to confirm the efficacy and characterise any side effects in humans.***

Reference article

Carlota Colomer, Pol Margalef, Alberto Villanueva, Anna Vert, Irene Pecharroman, Laura Solé, Mónica González-Farré, Josune Alonso, Clara Montagut, Maria Martinez-Iniesta, Joan Bertran, Eva Borràs, Mar Iglesias, Eduard Sabidó, Anna Bigas, Simon J. Boulton & Lluís Espinosa. *IKKα kinase regulates the DNA damage response and drives chemo-resistance in Cancer*. Mol Cell 2019

Further information

IMIM/Hospital del Mar Communications Service: Marta Calsina 93 3160680 mcalsina@imim.es, Rosa Manaut, 618509885 rmanaut@imim.es, David Collantes 600402785 dcollantes@hospitaldelmar.cat