A 'weak spot' discovered that potentially makes multi-drug resistant tumors vulnerable

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One of the greatest challenges facing cancer researchers is to understand why some patients don't respond to treatments. In some cases, tumors

exhibit what is known as multidrug resistance (MDR), which significantly limits the therapeutic options for patients. Researchers at the Spanish National Cancer Research Centre (CNIO) have discovered one of the causes of MDR, and a potential strategy to combat it. The work, which is mainly based on cell lines and is therefore still a long way from clinical use, is published in *EMBO Molecular Medicine*.

Our findings "explain why many of the available therapies don't work in certain tumors, and at the same time identify the weak point of these resistant cancers," explains Oscar Fernandez-Capetillo, head of the CNIO's Genomic Instability Group and lead author of this research. "We now know that this vulnerability can be exploited using drugs that already exist."

As the study shows, mutations that inactivate the function of a particular gene, FBXW7, "reduce the sensitivity to the vast majority of available therapies," the authors write, but at the same time render tumor cells vulnerable to the action of a particular type of drug: those that activate the "integrated stress response" (ISR).

A very common mutation in human cancers

"FBXW7 is one of the 10 most frequently mutated genes in human cancers," and is associated with "poor survival across all human cancers," the authors add.

The study began by using the CRISPR technology in mouse stem cells to search for mutations that generate resistance to anti-tumoral agents such as cisplatin, rigosertib or ultraviolet light. Mutations in the FBXW7 gene emerged early on, suggesting that this mutation could confer MDR. Bioinformatic analysis of databases such as the Cancer Cell Line Encyclopedia (CCLE), with information on the response of more than a thousand human cancer cell lines to thousands of compounds, confirmed

that FBXW7 mutant cells are resistant to most of the drugs available in this dataset.

Regardless of mutations, further analyses in the Cancer Therapeutics Response Portal (CTRP) revealed that reduced levels of FBXW7 expression were also associated with a worse response to chemotherapy. In fact, the authors suggest using FBXW7 levels as a biomarker to predict patient response to drugs.

Without FBXW7, mitochondria are stressed

Having established the link between FBXW7 deficiency and multi-resistance, the researchers looked for its cause. They found it in the mitochondria, the cell organelles involved in metabolism and cellular respiration.

FBXW7-deficient cells showed an excess of mitochondrial proteins, which has previously been found to be associated with drug resistance. Nevertheless, a detailed analysis of these organelles further revealed that the mitochondria of these multi-resistant cells appeared to be under a lot of stress.

An antibiotic effective against tumor cells

The discovery of this mitochondrial stress would be key to identifying strategies to overcome drug resistance in cells with FBXW7 mutations. Mitochondria are the remnants of ancient bacteria that fused with primitive eukaryotic cells billions of years ago; therefore, if antibiotics attack bacteria, could an antibiotic kill a cancer cell too rich in mitochondria?

In fact, anti-tumoral properties of certain antibiotics have been identified in the past, but these were isolated cases and therefore

potentially attributable to unknown individual mutations in patients. Fernandez-Capetillo and his group have shown that the antibiotic tigecycline is indeed toxic to FBXW7-deficient cells, opening up a new avenue of research to tackle multi-resistance.

Drugs that act by hyperactivating stress responses

But probably even more important is the discovery of why this antibiotic has anti-tumor properties. The authors of the just-published paper show that tigecycline kills cells by hyperactivating the integrated stress response (ISR), and further demonstrate that other drugs capable of activating the ISR are also toxic to cells with FBXW7 mutations.

It is worth noting that many of these ISR-activating drugs are oncological therapies in common clinical use today, and that until now it was assumed that they worked by other mechanisms. However, the present study reveals that part of their anti-tumor efficacy is due to their effect in activating the ISR.

"Our study, together with other recent works, indicate that activating the ISR could be a way to overcome chemotherapy resistance. However, much work remains to be done. Which drugs activate the ISR best and most strongly? Which patients would benefit most from this strategy? Attempting to answer these questions is what we aim to do in the immediate future," says Fernandez-Capetillo.

More information: Laura Sanchez-Burgos et al, Activation of the integrated stress response is a vulnerability for multidrug-resistant FBXW7 -deficient cells, *EMBO Molecular Medicine* (2022). DOI: 10.15252/emmm.202215855