A missing protein promotes genetic instability in patients with Mulibrey syndrome

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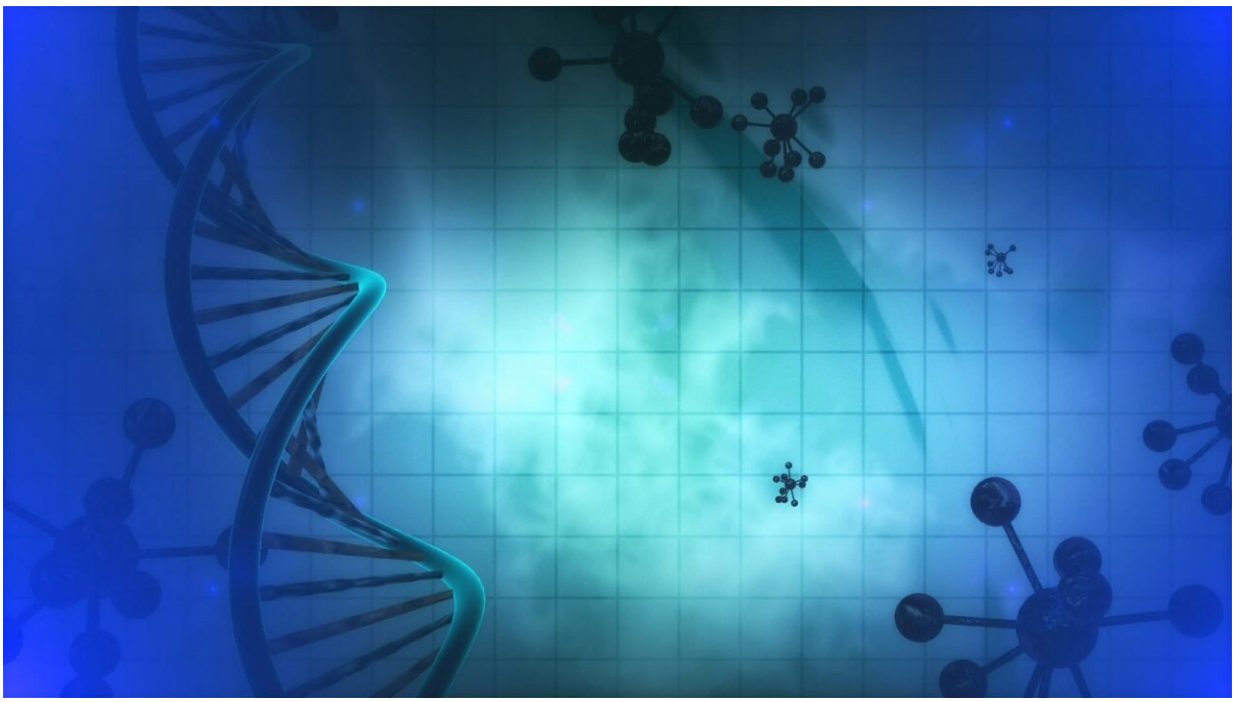

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Researchers from the Andalusian Centre for Molecular Biology and Regenerative Medicine (CABIMER), in collaboration with the Swiss Institute for Experimental Cancer Research (ISREC) have studied the mechanisms behind the greater tendency of people with Mulibrey

syndrome to develop tumors. Their results point to the important role of the TRIM37 protein, whose absence explains the appearance of tumor cells.

Mulibrey syndrome is a so-called rare disease as it occurs in less than 5 out of every 10,000 people. Some of these diseases usually have a very definite genetic basis. Consequently, studying the molecular functions of the altered genes in patients with these diseases, in addition to contributing to the search for new methods of diagnosis and treatment, helps us to understand the basic mechanisms necessary for the individual's proper development.

The disease is characterized by growth retardation, heart failure problems and liver pathologies. In addition, patients have a greater tendency to develop certain types of tumors. The scientific literature shows that development of this disease is associated with the lack of function of a gene known as TRIM37. However, the molecular role that this protein plays and how its lack of function leads to disease remains unresolved. This research focused specifically on how the gene's lack of function may contribute to tumor development in patients affected by Mulibrey syndrome.

TRIM37 is a ubiquitin ligase; a protein that is able to modify other target proteins by adding a small third protein called ubiquitin. This modification can have several effects on the target protein: from stabilizing and promoting its function to abruptly triggering its degradation. This study, led by Dr. Fernando Romero Balestra (Cabimer/US) in collaboration with a group from the Swiss Institute for Experimental Cancer Research (ISREC), with the participation of other researchers from the Andalusian Centre for Molecular Biology and Regenerative Medicine (Cabimer), including Dr. Pablo Huertas (Cabimer/US), Andrés Domínguez Calvo (Cabimer/US), and CSIC researcher Dr. Rosa M. Ríos (Cabimer/CSIC), has discovered that cells

isolated from patients with Mulibrey syndrome are unable to control the number of small cell organelles called centrosomes. Centrosomes are involved in the nucleation and organization of the microtubules necessary for the formation of the mitotic spindle and the correct segregation of genetic material during cell division. Healthy cells have two centrosomes which, after cell division, are distributed between the two daughter cells, thus inheriting one centrosome each. Each daughter cell, before entering the next mitosis, has to "build" a new centrosome by a complicated and highly regulated molecular process that guarantees the formation of a single new centrosome and ensures the correct segregation of chromosomes in the next mitosis. This present study describes how cells from Mulibrey syndrome patients, by having a higher number of centrosomes, during cell divisions form abnormal mitotic spindles that frequently make mistakes and generate cells with an incorrect number of chromosomes.

Interestingly, this dysregulation of centrosome number and the associated chromosome segregation problems is a feature present in many tumor types. Therefore, the researchers suggest that the role of TRIM37 as a regulator of centrosome number may be key in tumor formation in Mulibrey syndrome patients. But what are the molecular mechanisms connecting TRIM37 with the formation of new centrosomes? To answer this question the study turns to molecular biology and cell biology techniques. To characterize the mechanisms by which these new centrosomes are formed without control in cells lacking TRIM37, the researchers used human cell lines that can be easily grown in the laboratory and, in turn, can be modified with Crispr/Cas9 genomic editing techniques or with RNA interference (RPE-1 and HeLa cells).

The use of these techniques has revealed how the absence of TRIM37 activates centrosome formation through a hitherto undescribed pathway of centrosome formation that depends on the proteins Centrobin, PLK4, HsSAS-6 and PLK1. The lack of TRIM37 induces the formation of

Centrobin and PLK4 structures that serve as a platform for uncontrolled centrosome production.

The results of this study contribute to a better understanding of the molecular mechanisms involved in Mulibrey syndrome and open the door to the search for personalized treatments for Mulibrey syndrome patients who develop tumor pathologies. In the future, the authors plan to investigate whether the molecular mechanism involved in extra centrosome formation plays a key role in other tumor types.

More information: Fernando R Balestra et al, TRIM37 prevents formation of centriolar protein assemblies by regulating Centrobin, *eLife* (2021). DOI: 10.7554/eLife.62640

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