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A key genetic safeguard works differently across tissues and individuals

- A study, developed in the context of the LUCIA EU-funded project, and published in *Genome Biology*, suggests that individual variation in mRNA processing influences cancer progression and therapy response.
- The efficiency of the Nonsense-Mediated mRNA Decay (NMD) pathway, a genetic quality control mechanism, differs across human tissues and individuals.

A puzzling question in molecular biology has been why our bodies do not uniformly eliminate faulty genetic information—especially that which could lead to disease. A key mechanism responsible for this removal process is the nonsense-mediated mRNA decay (NMD) pathway, which degrades defective messenger RNA before it can produce malfunctioning proteins.

Although NMD is vital for genetic quality control, we have lacked a clear understanding of how its efficacy varies across different tissues and individuals, and the implications of this variation in the context of diseases like cancer.

Published in the journal *Genome Biology*, a new study led by researchers at IRB Barcelona sheds light on this issue. By analyzing more than 27,000 samples from healthy and tumour tissues provided by international consortia, the team discovered that NMD efficiency varies significantly depending on the type of tissue. In this regard, NMD activity is notably lower in nervous and reproductive tissues and higher in those of the digestive tract.

Importantly, the research team identified substantial inter-individual variability in NMD efficiency. This variation is linked not only to genetic alterations within tumours—such as gains in chromosome 1q, which harbours key NMD-related genes—but also to inherited variants affecting chromatin regulation. These findings suggest that differences in NMD could influence how tumours evolve, impact patient survival, and affect the outcome of immunotherapy treatments.

“We were very interested in studying the NMD quality control pathway, as previous work from the lab showed it to be highly relevant to genetic diseases and cancer, which are often caused by nonsense mutations. The inhibition of NMD is a particularly promising approach, and in another ongoing collaboration, we have observed remarkable antitumour activity by enhancing immunotherapy in a mouse model,” states **Dr. Fran Supek**, author of the paper, professor at the University of Copenhagen, and Group Leader at IRB Barcelona.

By highlighting this variability in NMD activity, the study underscores the importance of personalized approaches to diagnostics and treatment strategies. According to the authors, understanding why NMD efficiency differs—and in whom—could lead to the use of this pathway not only as a biomarker for disease but potentially as a therapeutic target for precision medicine.

“In our study, we showed that NMD, a key RNA control mechanism, operates at different levels across tissues and individuals, helping explain how identical mutations across patients can lead to differences in disease severity and treatment response. This finding is important for precision oncology, as measuring NMD efficiency could guide therapy selection: patients with low NMD efficiency are predicted to respond better to immunotherapy while those with high NMD efficiency might benefit from NMD inhibitor therapy to make cancer cells more visible to the immune system,” explains **Dr. Guillermo Palou Márquez**, first author and postdoctoral researcher at IRB Barcelona.

This research was carried out in the context of the **LUCIA EU-funded** project.

Related article:

Variable efficiency of nonsense-mediated mRNA decay across human tissues, tumors and individuals.

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