How Cells Fix Their Own Defects

For decades, geneticists have been intrigued by a paradox: some individuals carry severe mutations in essential genes yet show no signs of disease. This unexpected resilience is often explained by transcriptional adaptation (TA). When a gene is mutated, the cell does not simply lose the corresponding protein. Instead, it actively degrades the defective messenger RNA (mRNA). Somehow, this degradation triggers the activation of related genes, or paralogs, which can compensate for the missing function. Until recently, the mechanism linking RNA decay to gene activation in the nucleus was unclear.
El-Brolosy et al. (1) have identified the missing link in this cellular backup system. The crucial signal is not the mutation itself, but the specific mRNA decay products, small fragments generated from the defective transcript. These fragments act as signaling molecules. A key player is the protein ILF3, which binds these RNA fragments in the cytoplasm and transports them into the nucleus. There, the ILF3-bound fragments help locate and activate compensatory genes with similar sequences.

This mechanism is most effective for mutations that produce a faulty mRNA, such as nonsense mutations. In these cases, the destruction of the abnormal mRNA is what initiates the compensatory response. By contrast, if a gene is completely deleted, no mRNA is produced. Without mRNA to degrade, no signal fragments are generated, and the backup system remains silent.

1. https://www.science.org/doi/10.1126/science.aea1272