

Targeting TP53 nonsense mutations by Translational Readthrough: functional rescue of p53 and enhanced chemotherapy sensitivity

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Nonsense mutations generate premature termination codons (PTCs), leading to the synthesis of truncated proteins that are frequently unstable and functionally inactive. This type of mutation accounts for 11% of genetic diseases, including hereditary cancers [1]. Today, there is no therapy for these mutations; however, an approach is represented by TRIDs (Translational Readthrough Inducing Drugs), which allow overcoming the PTC and restoring the protein [2]. In our study, we investigated the effects of TRIDs on tumor cells with an R213X nonsense mutation in TP53 by evaluating protein localization, rescue, and functionality, as well as their effects on the cell cycle after DNA damage induction and treatment. We observed the rescue of p53 expression and an increase in transcripts of its target genes, thereby demonstrating a functional rescue of the protein. This study provides promising evidence that translational readthrough approaches can restore the expression and function of tumor suppressors carrying nonsense mutations, thereby enhancing the sensitivity of tumor cells to chemotherapeutic agents.

References

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