

Exploiting Translational Readthrough to Rescue p53 Expression in TP53 Nonsense Mutation-Driven Cancer Model

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Nonsense mutations are gene mutations characterized by the substitution of a single nucleotide in the coding sequence of a gene, which causes the onset of a premature stop codon (PTC) within the reading frame of the mRNA, resulting in the formation of a truncated and non-functional protein. This type of mutation accounts for approximately 11% of genetic diseases, including conditions such as Cystic Fibrosis, Duchenne Muscular Dystrophy, and certain types of cancers involving mutations in tumor suppressor genes. For example, 10% of TP53 gene mutations are stop mutations [1]. TP53 encodes a protein of 393 amino acid residues called p53, which acts mainly as a transcription factor, regulating numerous pathways such as cell cycle arrest, DNA damage repair, apoptosis, autophagy, and metabolism when cells are under certain stress conditions. Mutations of TP53 can lead to the formation of tumors due to loss of function, dominant-negative repression, or gain of oncogenic function [2]. Today, there is no therapy for the pathologies caused by this type of mutation, but an approach that has proven to be particularly effective is represented by molecules with readthrough activity (TRIDs; Translational Readthrough Inducing Drugs), which intervene on the ribosome, allowing the overcoming of the PTC and the restoration of the synthesis and subsequent functionality of the protein [3]. In this work, we investigate the effects of TRID compounds in tumor cells that harbor the PTC R213X, the most common TP53 stop mutation, which generates a truncated and non-functional protein. We analyzed the cellular localization of p53, the rescue of the protein, and the regulation of its gene targets, after treatment and induction of DNA damage. We also focused attention on the effect on the cell cycle and proliferation of the cells. We observed the rescue of p53 after treatment with an increase in the transcript of its gene target and an effect on phase G1 of the cells, demonstrating a preliminary functional role of the

protein. This study represents a promising path for developing targeted cancer therapies against nonsense mutations and tumor proliferation, but also a valid alternative for therapies used against other rare genetic diseases.

References:

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