عنوان مقاله:

Restoration of correct splicing in IVSI-۱۱۰ mutation of β-globin gene with antisense oligonucleotides: implications and applications in functional assay development

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خلاصه مقاله:

Objective(s): The use of antisense oligonucleotides (AOs) to restore normal splicing by blocking the recognition of aberrant splice sites by the spliceosome represents an innovative means of potentially controlling certain inherited disorders affected by aberrant splicing. Selection of the appropriate target site is essential in the success of an AO therapy. In this study, in search for a splice model system to facilitate the evaluation of AOs to redirect defective splicing of IVSI-۱۱۰ β-globin intron, an EGFP-based IVSI-۱۱۰ specific cellular reporter assay system has been developed and a number of AOs were tested in this cellular splicing assay. Materials and Methods: A recombinant plasmid (pEGFP/I-۱۱۰) carrying the EGFP gene interrupted by a mutated human β-globin intron ۱ (IVSI-۱۱۰) was developed and transfected into K۵۶۲ cells. A number of AOs with a ۲'-O-methyl oligoribonucleotide (۲'-O-Me) backbone system were systematically tested in this cellular splicing assay. Results: The mutation in the intron causes aberrant splicing of EGFP pre-mRNA, preventing translation of EGFP; however, treatment of the cells with specific concentration of a sequence specific ۲'-O-Me AO targeted to the aberrant splice site induced correct splicing and resulted in restoring of EGFP activity. Conclusion: This cellular splicing assay provides a novel functional assay system in assessing the .cellular delivery efficiency of AOs and therapeutic effect of AOs in restoration of aberrant splicing

کلمات کلیدی:

Antisense, Beta-Thalassemia, Gene Therapy, Oligonucleotides, Splicing