New insight into exon-skipping approach for Duchene muscular dystrophy treatment

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Abstract

Exon-skipping is one of the most promising tool for Duchenne muscular dystrophy (DMD) treatment. Approximately, 80% of all possible mutations in dystrophin gene are amenable to exone-skipping therapy. The idea of exon-skipping is to the restore reading frame of dystrophin mRNA at the splicing level and get a shortened form of protein with functional N- and C-ends, which are crucial for binding to actin myofibers and membrane protein complex, correspondingly. We created a new mice model of DMD with deletion of exons 8–34 and tested antisense oligonucleotides (AON) for skipping of exons six and seven on primary murine myoblasts derived from 16 day old model mice embryos. Three days after the AONs, addition skipping success has been analized by RT-PCR, following sequencing of products. B009 vivo-morpholino addition resulted in only short deletion instead of full-exon skipping. 36 base upstream of 7th exon-intron junction alternative non-canonical splice site (AT-GC) has been activated. Occasionally or not, 36 base skipping doesn't lead to frameshift and can move to 12 amino acid deletion of translated protein. As soon as sequence of murine of 7th exon is completely identical to the human one, analysis of predicted splice sites was performed. Surprisingly, there was no such variant in the database. So, splicing involving such splice sites can be driven by unknown mechanisms. Presence of unknown intra-exonic splice sites can explain naturally occuring exon-skipping in DMD patients and animal models. Discovery of new splice sites in DMD gene can ease the exon-skipping approach, leading to the treatment of a large number of pateints.

Biography

Tatiana V Egorova has completed a specialization course from the M V Lomonosov Moscow State University. She is Junior Researcher at Institute of Gene Biology, RAS and Researcher at Marlin Biotech LLC. She has published six papers in reputed journals and took a part in six research projects, and attended research schools for young scientists in Russia and Europe.

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