

Dr O V Makarova - Splicing and Disease

The process of gene expression in eukaryotes requires the removal of introns from the final mRNA. This process, dubbed splicing, is highly regulated and can be upset/derailed by a single nucleotide change in the primary transcript, leading sometimes to a catastrophe for the cell. There are two projects currently available to study mechanisms of splicing. The first is focused on splicing of the PRPF31 gene, which was linked to the disease Retinitis Pigmentosa (RP11). Many mutations have been mapped that lead to age-related loss of rod cells in retina and subsequent blindness. The effect of these mutations on the formation of mature mRNA will be analysed, using cell culture models, and the underlying mechanism will be dissected by determining the factors involved in the recognition of introns and the formation of spliceosomes. The second project studies splicing of a gene coding for acetylcholinesterase (ACHE), which altered processing is associated with diseases like Alzheimer's, Parkinson's or myasthenia gravis. ACHE's pre-mRNA is differentially processed in different cell types. Moreover, physiological stress causes one small intron to be retained rather than spliced out, which affect AChE activity and exacerbate the problem. The mechanisms responsible for ACHE differential processing will be investigated. The knowledge of disease-related splicing regulators will have a pharmaceutical application as these proteins or their interacting partners can be targeted in drug design to discover new remedies.

References

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