Abstract

RNA splicing is a process by which introns are removed from a pre-mRNA (precursor messenger RNA) and exons are joined to produce a mature mRNA. RNA splicing is performed by spliceosome, a large macromolecular complex that contains five small nuclear ribonuclear proteins (snRNPs) and more than 150 associated proteins. Recent structural studies showed that the U5 snRNP plays a central role in the spliceosome function and particularly the highly conserved U5 protein Prpf8 (pre-mRNA processing factor) that lies in the catalytic core of spliceosome.

Mutations in Prpf8 protein were connected to the disease known as retinitis pigmentosa (RP), which is one of the most common causes of retinal degeneration affecting 1 out of 4000 people worldwide. The major clinical manifestations of a typical RP are night blindness and tunnel vision. As the disease progresses, the peripheral visual field is further reduced, and patients lose central vision usually by the age of 60 years.

In this thesis we try to understand the mechanism underlying the pathogenesis of RP caused by mutations in Prpf8 protein.

Based on the data from literature, in which the authors present evidence that DNA damage triggers specific profound changes in late-stage spliceosome organization, we tested our hypothesis that the Prpf8 protein is involved in cellular response to DNA damage. We also used stable cell lines carrying RP mutations in Prpf8 protein to investigate the effect of these mutations on cellular DNA damage response.

Key words: RNA splicing, Prpf8 protein, retinitis pigmentosa, DNA damage response pathway