Microreviews in Cell and Molecular Biology

2016

[The basic mechanism of pre-mRNA splicing]

Author: Yecheng Wang
Major: Chemistry
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

Key Words:
Alternative splicing; pre-mRNA

Spliceosome is used to do the splicing of pre-mRNA. It is a protein-directed ribozyme for the delivery of critical RNA molecules into close proximity of one another at the right time for the splicing reaction. There are several explanations for the splicing of pre-mRNA.

Introduction

Splicing of RNA is an important biology process in gene expression of eukaryotic cells. It was discovered in 1997. By this process, many functional m-RNA, which carry code information can be produced. Cell is the basic unit of living organisms and gene expression is the most basic and important activity of life. The gene expression can be divided into three steps: The first step is transcription, which describes the process that the genetic information in DNA transfers into the pre-m-RNA. The second step is splicing, which is the process that pre-m-RNA deletes the introns and arrange exons to be a mutual m-RNA by the effect of spliceosome. The third step is called translation. The mutual m-RNA transfers into protein under the impact of ribosomes. The whole process is central dogma.

Spliceosomes consist of RNA and protein. It looks like a mix of scissor and needle. We take the mRNA as a piece of cloth and then the spliceosomes can cut the cloth and link it. The result is that the introns are deleted and exons arrange to be a mutual m-RNA. This study is aimed to explain the mechanism of its process.

There are several approaches of splicing. It can be divided into intramolecular cissplicing and intermolecular transsplicing. No matter which approach we take, the introns will be abandoned.

Recent Progress

Current research shows that [1]the splicing of pre-m-RNA is connected with heterogeneous nuclear ribonucleo-protein particle and positive and negative regulatory signals of R protein.

Scientists have proposed an algorithm to simulate the splicing of pre-m-RNA in eukaryotic cells, and it was realized by the independent research by the help of E-Cell model Analog-Cell and got the simulation results, which met the principle of biology. [2] Through simulation of the process, the study has found that this algorithm has the capacity to make the introns to form the lariat structure efficiently and accurately, meanwhile to unit the exons selectively. In this way, the Analog-Cell can finish the formation of the mature mRNA.

[3]By the help of cryo-electron microscopy, people have get the structure of a yeast spliceosome at 3.6-angstrom resolution. It gives three dimensional spatial structure of eukaryotic cells spliceosome compound at high resolution. The fission yeast was selected as the experimental object, After the purification of sample, scientists quickly freeze it in the liquid state,

Scientists have improved the traditional Tandem affinity chromatography. The endogenous expression of the yeast splicing complex was successfully extracted. By using the

advanced electron microscope image processing and three dimensional reconstruction method, the high resolution three dimensional structure of the splice is obtained. As can be seen in the structure, the outline of the spliceosome is very asymmetric, and the various proteins are intertwined, forming a complex of molecular weight and volume.

The RNA component of the spliceosome was analyzed in detail, and the pre-m-RNA was set up to be cut and connected to the atom model, and the molecular mechanism of the splicing reaction was expounded. Scientists have found that the yeast spliceosome is composed of 4 RNA molecules. They are U2 snRNA, U5 snRNA, U6 snRNA, and an intron lariat, which have been unambiguously located in the EM density map. During the process of splicing, the spliceosome takes the pre-m-RNA as the center, in accordance with the highly accurate sequence of progressive assembly and the occurrence of large-scale structural reorganization, to complete the splicing.

Assembly of the splicing body is similar to the assembly of the ribosome. It relies on the interaction between protein-protein, RNA-RNA and RNA-protein. The process occurs in the nucleus of the cell. Using a large protein complex and short chain RNA, the spliceosome can identify the beginning and end of the coding segment, which can accurately cut and sew the pieces together.

[4] In the cryo-EM structure of the yeast spliceosome, U5 snRNP acts as a central scaffold onto which U6 and U2 snRNAs are intertwined to form a catalytic center next to Loop I of U5 snRNA. Magnesium ions are coordinated by conserved nucleotides in U6 snRNA. The intron lariat is held in place through base pairing interactions with both U2 and U6 snRNAs, leaving the variable- length middle portion on the solvent-accessible surface of the catalytic center. The protein components of the spliceosome anchor both 5′- and 3′- ends of the U2 and U6 snRNAs away from the active site, direct the RNA sequences, and allow sufficient flexibility between the ends and the catalytic center.

Discussion

What is the meaning of understand the mechanism of spliceosome?

Spliceosome near atomic resolution structure analysis not only is a preliminary answer to the foundation in the field of life science, but also reveals the pathogenesis of diseases, which associated with the spliceosome and provides the structural basis and theoretical guidance.

Does it have a connection with heredopathia?

Many human diseases are due to the error of the gene or the regulation of the splicing. 35% of human genetic disorders are caused by mutations in a single gene: For example, increasing or missing single splicing sites may cause alpha or beta thalassemia. Some alternative splicing balance disorders leading to abnormal expression of exon may result in frontotemporal dementia. Some cancers are also related to the regulation of splicing factors. Structural analysis of spliceosome has been considered as one of the most anticipated structural biology studies for a long time.

When this discovery can be applied into the practice?

The result is a breakthrough in basic research in the field of life science, but there is still a great distance from the practical application to the treatment of diseases. Pharmaceutical and other relative studies also need other scientists and working groups to follow up according to their interest.

References

[1]Yan Jinchun, Chen Yuhua, Song Jindan, Chen Cheng. “Progress in the study of alternative splicing of pre-Mrna”. Chinese Bulletin of Life Sciences. 14 (2002):151-152.

[2]Ouyang Dantong, Wang Jue, Han Xiaosong, Lu Xinhua. “Simulation and Research on Pre-Mrna Splicing in Analog-Cell”. Journal of Software. 9 (2012): 2273-2284.

[3] Chuangye Yan, Jing Hang, Ruixue Wan, Min Huang, Catherine C L Wong, Yigong Shi. “Structure of a yeast spliceosome at 3.6-angstrom resolution”. Science.349(2015):1182-1191.

[4]Jing Hang, Ruixue Wan, Chuangye Yan, Yigong Shi. “Structural basis of pre-mRNA splicing”. Sciencexpress.349(2015):1191-1198.

