NOBEL SYMPOSIA

Report from the lecture presented by Joan Steitz

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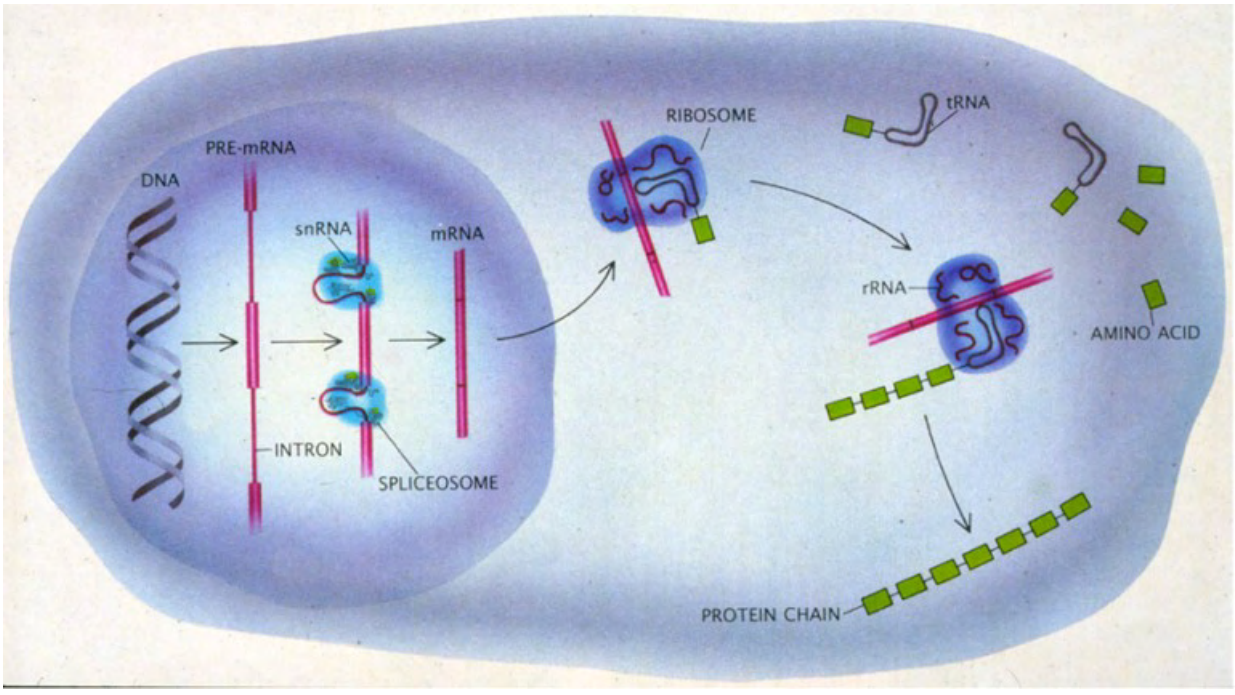
It is well known that our genes (DNA) contain the instructions to make our proteins and that these instructions are carried over to the protein synthesis machinery by messenger RNA (mRNA). However, there is a lot more in it for RNA. Professor Steitz provided an inspiring survey of a thrilling series of discoveries that result from very careful experimental investigations in her own and other laboratories. A first example regarded the discovery of RNA-protein complexes involved in splicing to produce mature mRNA. This is an essential process because the coding regions of our genes are discontinuous (in the form of exons) and interspersed with a number of non-coding regions (introns) that have to be cut out.



The cellular machinery that executes the RNA splicing, the spliceosome, is astounding both as regards its size and fidelity. Its discovery was brought about by identification of the targets of auto-antibodies in one of the auto-immune diseases (Lupus). The spliceosome is found to be even larger than the ribosome, and it is composed of a large number of specific RNA-protein complexes called snRNPs plus additional protein factors. The binding of the snRNPs

to the RNA precursor determines the minimum size of an intron that can be spliced out to produce the mRNA. In addition, the snRNPs provides a mechanism to identify the boundaries of exons and introns to ensure that the correct mRNAs and subsequently the correct proteins are made. For this to work there are some nucleotides in the RNAs of each snRNP that are totally essential and strongly conserved all the way from yeast to man.

Another fascinating aspect of splicing is the way by which we are protected from miss-synthesized proteins through the coordination in time and space of splicing with other events in gene expression. Molecular interactions between a mark deposited by the spliceosome and ribosome components form the basis for a mechanism that degrades any mRNA that by mistake has acquired a premature stop codon. This mechanism is called nonsense-mediated mRNA Decay (NMD). NMD happens because the ribosome stalls for a while at the stop codon and this allows the ribosome to interacts with the mark at a position where an intron used to be. This interaction produces a signal to degrade the mRNA, and thereby the cell is protected from synthesis of erroneously truncated protein. By the same token, it is possible to incorporate an extra intron after the native stop codon to promote degradation of full-length mRNA.

Another intriguing RNA-mediated process is the regulation of cellular function by alternative splicing. This may lead to the production of a series of distinct proteins from the same gene. A beautiful example is that of a potassium channel in cochlea. Alternative splicing results in hundreds of different variants of the channel, with different ones being expressed in every cell. These variants are involved in frequency tuning of the auditory hair cells so that we may appreciate music.

There are many other ways by which RNA regulates gene expression, for example via the microRNAs that have been discovered during recent years. MicroRNAs are small (ca. 20 nucleotides) RNA molecules of specific sequence that interfere with the expression of genes that contain the same sequence.

Professor Steitz also discussed the question of why it is so difficult to crystallize the spliceosome now that we have a structure of the ribosome. snRNPs and proteins components of the spliceosome differ at different events along the splicing pathway and come on and off during the process. It is not straight-forward to produce a homogenous sample for

crystallization unless one finds an ingenious way to lock the spliceosome in one stage along the splicing process. This is one of many great challenges for the future.