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Thought on the Present Molecular Genetics

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The working of molecular genetics is involved in finding out the genetic components, their structures, mechanism, dynamics and pathologic alterations in the disease. The final aim is to rectify to normal for the health of human being.

The components are the genetic flows that start from the DNA, which manifests the storage site of all the genes, replication, transcription and translation. Extensive work on DNA sequencing reached the milestone of completing 3×10^9 nucleotide sequences in human and complete genomic sequences from many species. General mechanisms of replication by DNA polymerases and involved factors have been elegantly defined. The structure of four RNA polymerases (pol I, II, III and mitochondrial RNA polymerases) are well characterized. Hundreds offactors are known for co-transcriptional and post transcriptional processing, modifications and splicing.

To understand the progresses made so far, the present is a good time to define some specificity of factors involved in specific gene expression. For example, in replication, how the replication origins are recognized and what may be disturbed in cancer and other diseases. The RNA involvement in replication origin is different from the Okazaki RNA fragment and has not been well characterized. It is interesting to note that the changes in nucleolar transcription system during carcinogenesis is fascinating. But we still don't know enough what specific aberrations may occur. Replication origins are interdigitated in rRNA genes. In human the rRNA genes are in 5 acrocentric chromosomes (chromosomes 13–15, 21 and 22) which place the rRNA genes in close proximity to centromeres and telomeres. The nucleolus is the site where rRNA is synthesized by RNA polymerase I but have been demonstrated that some of RNA polymerase II activity has effect on nucleolar RNA polymerase I activity such as aluRNA [2].

In the tumor cells, pre-rRNA is accumulating in the nucleolus which may be due to transcriptional hyperactivity but may be also involved in some mutations in the processing factors.

In the system of mRNA transcription, many diseases have been reported caused by altered transcription factors which include general transcription factors as well as specific transcription factors. The promoter mutations also causes the diseases.

The modifications of mRNA are also involved in processing as well as its translational activity.

More importantly, the splicing mechanisms of pre-mRNA are extensively worked out and found that > 300 different proteins may be involved.

Are the splicing mechanisms are universally same throughout the different pre-mRNAs or are there specific factors involved in for specific pre-mRNA splicing? The spliceosomes, EJC complex and other protein involved in mRNA maturation have been well characterized structurally.

It is interesting to note that the order of splicing is not always from 5' to 3' direction and one of well characterized splicing order is in the ovomucoid pre-mRNA maturation. The order of splicing sites are from first to last to be in order of 5/6→7/4→2/1→3 (or 5/6→7/4→2→3/1) [5, 7]. Efficient splicing is involved splicing code (GU, branch site, AG), enhancers, suppressors, RNA sequences, secondary structure and tertiary structures. It was interesting to find that SF2/ASF are more abundant in early spliced site at the splice sites 5/6 and SC35 is enriched in late splice site 3 in ovomucoid pre-mRNA.

	SF2/ASF	SC35	SRp40	SRp55	hnRNP A1
1	8.3	6.7	3.3	6.7	3.3
2	6.0	6.0	2.0	4.0	5.3
3	0.4	10.0	4.0	8.0	3.3
4	6.7	3.3	5.0	5.0	4.2
5	13.3	8.3	5.0	5.0	6.7
6	6.7	5.0	8.3	6.7	6.7
7	10.0	3.3	10.0	5.0	3.3

Motifs are analyzes 60 nucleotide at the splice sites (total 120 nucleotide by adding 5' splice site and 3' splice site). Due to short exon 2 (20 nucleotides) the 3' splice site 1 and 5' splice site 2 are 50 nucleotides each). The above values are expressed in number of motifs per 100 nucleotides.

(ESE are screened by ESE finder 3 CSHL and hnRNP A1 is screened by HSF3; Human Splicing Factor finder 3)

Balance between enhancers and suppressors show impact on splicing but how these regulators are distributed in the genes are not well characterized. For example, although, hnRNP A1 has been reported to be suppressor of splicing, it may also confer some RNA structural stability in the complexes.

Although some people stress that RNA transcription is taking place near the nuclear membrane and exit to the cytoplasm, it is well known that chromosomal domains in the nuclear geography are not all at the nuclear membrane. Transcription sites in different chromosomes are located throughout within dynamic nucleoplasm [3, 6, 1]. The location of pre-mRNP maturation stays not as the static site but it is mobile in dynamic movement. The co-transcriptional splicing progresses when pre-mRNP is still attached to the transcription complex, and post transcriptional splicing is taking place after detachment from the transcription complex on the way out to the cytoplasm. The splicing regulators are also dynamic, moving from the storage site to the transcription site [8]. On the other hand, the dynamic pre-mRNP movement after detachment from the transcription site may encounter the splicing factor storage sites where additional splicing and maturation may take place. In the course of dynamic movement of mRNP from the transcription site, it is interesting that SF2/ASF sites are more abundant in early transcription region, and next followed by SC35 and other factors such as SRp40 and SRp55.

SF2/ASF and SC35 are binding not only to RNA but also to DNA and are there intronic active TSS are present?

Research on the stem-cell therapy, gene therapy, gene editing, antisense oligonucleotide therapy are very active with FDA approved nusinersen (Spinraza) for SMA and Exondys 51 for DMD and more to come.

Recent development on targeted protein degradation by small molecules may have future for the specific degradation of proteins with dominant negative mutations [4].

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