The Transcript

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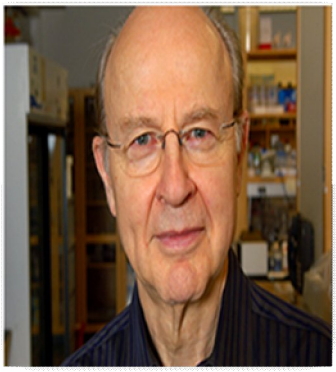

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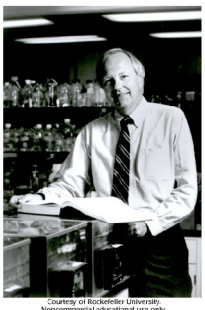
All these people contributed to our understanding of genetic control of life processes.

The central dogma of the last century is DNA ⟶ RNA ⟶ Proteins. These scientists gave a detailed understanding of the first part of this process DNA⟶ RNA, also known as 'Transcription'. How are different types of RNA molecules formed inside the nucleus of a cell?

They elaborated how this process is regulated by associated factors called 'transcription factors'. Different cell types have diverse sets of transcription factors. This information leads to an understanding of the basic process and its alteration in diseased condition.



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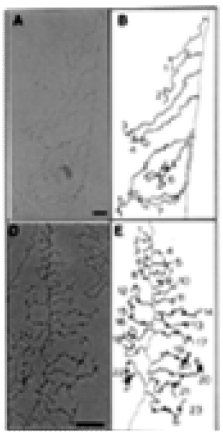


James E. Darnell, Jr He studied streptococci, penicillin and viruses. Working at Pasteur Institute, Paris, along with his first postdoctoral fellow, he developed the method called 'hot phenol plus sodium dodecyl sulphate' to extract complete RNA from cells. He also discovered pre-ribosomal and pre-tRNA using a labeling and sucrose gradient separation method that he invented. He also conducted versatile experiments on identification of cell specific m-RNAs.

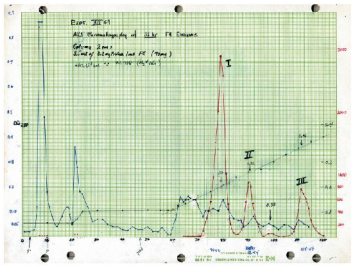
To understand the process of RNA editing, he carried out hybridization of m-RNA specific to SV 40 virus with RNA obtained from SV40 DNA from the nucleus of cells infected with this virus. And he found significant difference in the nucleotide lengths.

So, there must be some editing after transcription and before translation. He called it 'carpentry'. Nowadays it is known as 'splicing' of the transcript. He also asked 'what are the signals cells use to express particular genes?

He recognized that signals outside the nucleus control transcription in the nucleus. Using interferon's IFN approach, he showed that signals outside the nucleus control transcription; Interferon's are molecules formed by the cell during virus infection. From this, a new term emerged: signal transducers and activators of transcription (STAT's).These are protein signals that enter the nucleus, bind to DNA and activate transcription.STAT3 and STAT4 were discovered by two graduate students from his lab.

His research showed that STAT3 is the culprit in many cancers. Molecules that block STAT3 signaling are possible therapeutics for cancers.

Robert Roeder collecting sea urchins in the frigid waters of the Strait of Juan de Fuca (1968).



Robert Roeder is currently Arnold and Mabel Beckman Professor, Rockefeller University, USA. He obtained his PhD in biochemistry from University of Washington, Seattle.
He received prestigious General Motors Cancer Research Foundation's Alfred P. Sloan Prize and Albert Lasker Basic Medical Research Award.

He pioneered the use of cell free system to understand the fundamental process of transcription regulation in a simple system such as a test tube. The "Eureka moment of his life was his discovery of all three types of RNA polymerases" i.e. RNA Polymerase I, II, III from sea urchin embryos using chromatographic separation.

The function of these polymerases is carried out using α-amanitin from mushroom sensitive to each stage of transcription. It was found that

1) RNA Polymerase I - Synthesis of r-RNA
2) RNA Polymerase II - Synthesis of pre m-RNA
3) RNA Polymerase III – Synthesis of cellular 5s and t-RNA

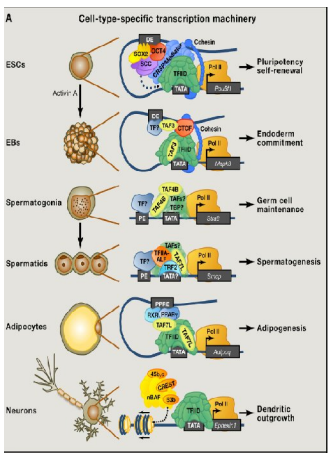
RNA polymerase II is actively involved in transcription of protein coding genes. For any gene expression specific regulation of promoter is required. Other factors like initiation factors form a pre initiation complex. They sit on the promoter in a specific order for effective transcription.

The DNA sequence commonly present at initiation starts with TATA and is called the TATA box. Roeder's current work includes studies on cofactors such as multisubunit histone acetyltransferase, methyltransferase and ubiquitination complexes. These include co-activators and co-repressors involved in normal homeostasis and also in malignancies, DNA damage responses etc. He is currently working on the relationship between cofactors and co-activators that determine cell fate.

Robert Tjian is currently Professor of Biochemistry, Biophysics, and Structural Biology, Department of Molecular and Cell Biology, UCB and President, HHMI, Chevy Chase, MD USA. He obtained his Ph.D. from Harvard University and postdoctoral fellowship at the Cold Spring Harbor Laboratory (CSHL) with James Watson.

He received the prestigious General Motors Cancer Research Foundation's Alfred P. Sloan Prize. He was the director of the Berkeley Stem Cell Center. He also co-founded a biotech company 'Tularik', which was sold to 'Amgen'. His interest led him to study biochemistry of gene transcription. He used special approaches such as 'in vitro biochemistry and in vivo genetics'.

We know that only three percent of the human genome is coding and the rest is non-coding.
But three percent of the human genome is very huge and contains a large number of genes.
During transcription, RNA polymerase cannot discriminate between coding and non-coding genes. He discovered the genes that code for transcription factors.



He further gave us a glimpse of the process in which transcription factors regulate gene expression in a cell type specific manner (e.g. embryonic stem cell (ESCs) differentiation).Alteration of transcription factor assembly results in a diseased condition.

He showed that different types of transcription factor sets are necessary for each process that occurs inside our body, in simple terms cell specific transcription machinery. He further demonstrated the relationship between regulation of gene expression and organism complexity by using whole genome sequencing tool. He also classified cellular identity based on promoters, enhancers and transcription factors placed in a particular arrangement.

Darnell, Roeder and Tjian contributed largely to the basic understandings of gene expression. This will lead to the applications in the vital areas such as cancer, metabolic disorders, Inflammation and many more.

Article written by *Gaurav Gunjal* freelance writer based in Pune,Maharashtra,India.