RNA Biology
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Lecture - 06
Introduction to RNA Biology and RNA World-Origin of RNA Enzymes

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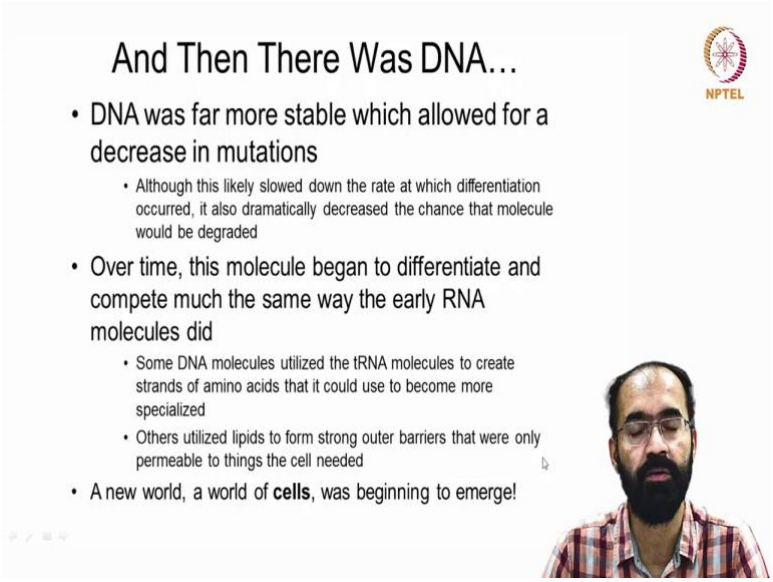

Hello everyone. Welcome back to another session of RNA biology course and today most likely we will conclude the RNA world hypothesis part and we were here in the last class that the characters or the properties that is gained through random events in an RNA is now has to be stored in the form of DNA. So, we should understand the genes make the DNA rather than the concept what we have DNA encodes the gene.

Of course, both are right but in the prebiotic world a quality or a character that is acquired has to be stored in a safe format in the form of DNA. And the prebiotic world the soup the liquid environment that provided ample ingredients for the protection of this genetic material the DNA and that is the emergence of a new world of cells that started appearing.

And of course, for the formation of cell; cell is nothing but a enclosure the genetic material is now enclosed in an envelope and that is coined or that is contributed by lipids, carbohydrates and also the proteins. Of course, they are not encoded by a genetic material at that time it was assembled.

And later on, we can see in the modern-day cells even starting from bacteria the genetic material is capable of producing this carbohydrate, lipids and also the proteins a kind of self sufficiency or self sustenance, but in the prebiotic world it is a random assemblage.

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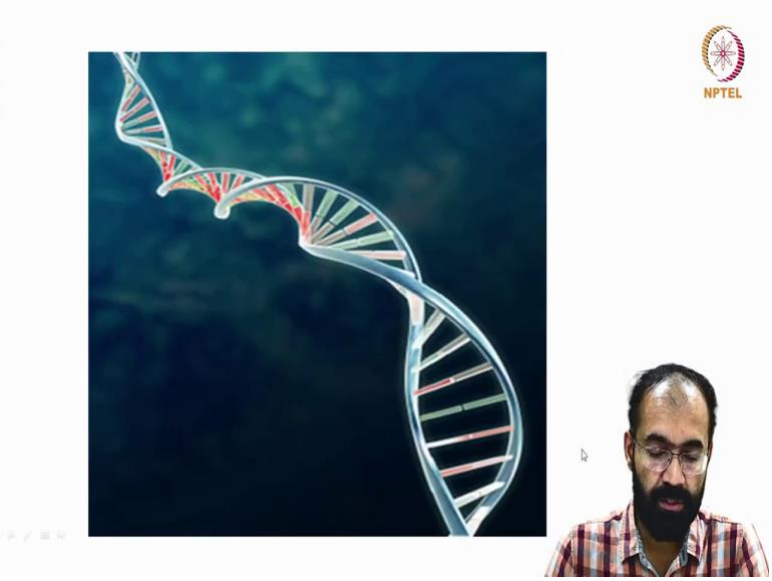

So, this is a secondary structure of the DNA double helix and it kind of shows how stable and how strong and how compact it can be and this is what the DNA looks like when it is completely unwound.

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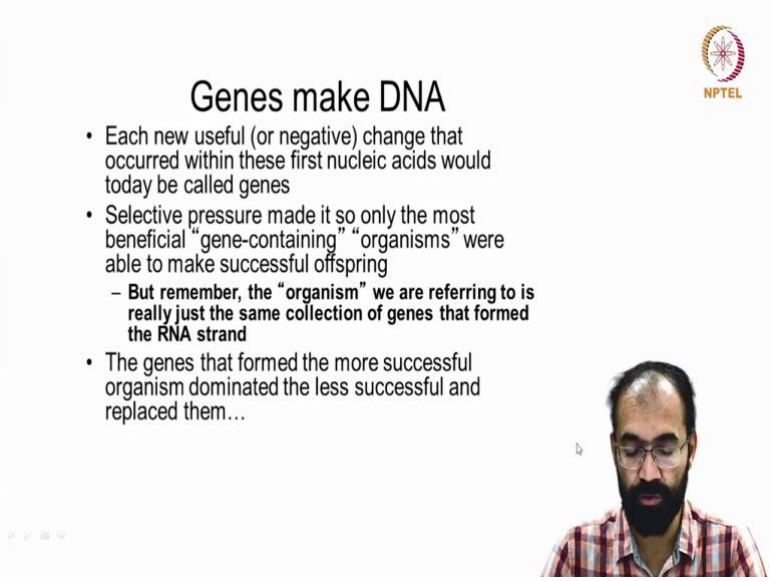

So, like I told you the genes make the DNA and each new useful or non useful we can call it as negative change that occurred within these first nucleic acids would today be called as the genes in the modern world. Because gene is nothing but a character, a property or a quality that is supposed to perform a task.

So, again there is a lot of selective pressure is acting onto the genes and it is so, became eventually that most beneficial genes that is most beneficial genes containing organism or the so, called organism is little bit advanced word to use for those primitive life forms, but those useful gene containing organisms have an upper hand over the remaining not so, useful gene containing organism because it gives some fitness.

And this organism should have lot of qualities and one of the most important quality is the ability to make a copy of itself without which it will just disappear from the that prebiotic soup. But we should also understand the organism what we are referring to here is just a collection of genes or a collection of properties which is now encoded in the form of DNA that is capable of converting it into an RNA strand as and when required. So, that is what we referring to as a organism.

So, the genes that formed the more successful organisms or the more adapted organism they dominated the less successful ones and eventually replaced them because the successful one need raw material like we have already seen if a ribozyme has to make a copy of itself it need raw material. If raw material is not available in the environment it has to chew up a existing nucleotide and or existing nucleic acid and make the monomer and make use of it.

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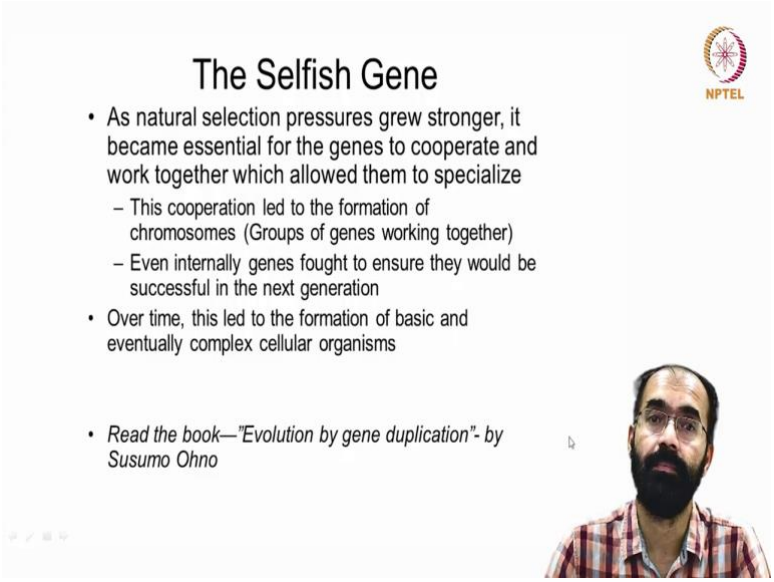

And then we are coining a term called selfish gene. Selfish gene here basically means that a gene that is making useful of the environmental factors that is available and try to sustain itself. This is what you see at organism level or at cellular level or at any level if you are looking every genes property innate property is to make a copy of itself. In as the natural selection pressures grew stronger and stronger it became essential for the genes to cooperate and work together which allowed them to specialize.

So, what we should understand when you have a property 1, property 2 and property 3 if they are able to put to use for doing one common task let us assume a house. In house you need to have a cook, you need to have a maid who is cleaning the house, cook who is making food and you also need to have someone who is bringing the raw material for doing the cooking.

So, one person need not to do all this job of course, one can do it, but at when you are talking about the genes gene 1 does cooking, gene 2 does cleaning the house, gene 3 does bringing the raw material for cooking the food. So, these collaborate and give rise to one common function. So, this is what we should understand when you are referring to as the cooperation of the genes and this eventually leads to the specialization.

So, we should also understand if one gene is doing three functions or ten functions, then it do not have the scope of evolving, but if one gene is doing only one function then it can always explore doing that function little bit better way or can it adapt a novel

character. So, this is also something which you should be keeping in mind that is how genes specialize.

So, this cooperation led to the formation of chromosomes and chromosomes in other words in genetics we use the word linkage group; that means, in bacteria you may have heard about lac operon, tryp operon etcetera which normally for synthesis of tryptophan you need to have five genes and they are located together so, that whenever the cell need a tryptophan these five genes are turned on without any problem.

So, they are clustered together we usually refer to them as operons same way if lactose is available in the medium bacteria want to make use of it then three genes are needed for the utilization of lactose and we refer to them as lac operon. So, in this way genes that are specialized for different functions congregate together in one lockers or in a neighboring place in the genome and they can be turned on and turned off rather easy.

So, even internally the genes fought each other means they were very competitive so, that they would be successful in the next generation. And we can assume a situation where a gene is having property A, it is doing a particular function now if that function is able to evolve into a stage where that function becomes superior over a similar function done by another gene there is another gene which is also performing a function similar to function A.

However, it is not that efficient it is doing, but it takes time in such situation the gene 1 which is having a property A is now able to get an upper hand over gene 2 which is also have a related function. So, this is called competition within the gene which also allows the evolving of the genes within and now we should understand the other gene the gene 2 which was having a property A which was not doing efficiently it lost the battle to the gene 1.

But the gene 2 will have the freedom and the opportunity to acquire a new function and the gene 2 now will evolve and start performing a better function which is unrelated to the gene 1. So, this is how there are many examples even in human where an ancient gene 1 classic example is human growth hormone, prolactin and placental lactogen they have originated from one common gene but they diversified eventually and they became three different function.

So, over time this led to the formation of basic and eventually complex cellular organisms and those who are interested can read the book Evolution by gene duplication by the Japanese scientist Susumo Ohno. So, it is a very interesting book those who are interested to know more in depth can read that book.

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And you can also see the reference the antiquity of RNA based evolution it's from the book 'RNA worlds' and also you can read 'the origins of RNA world' and this is a quite interesting article. So, you can read.

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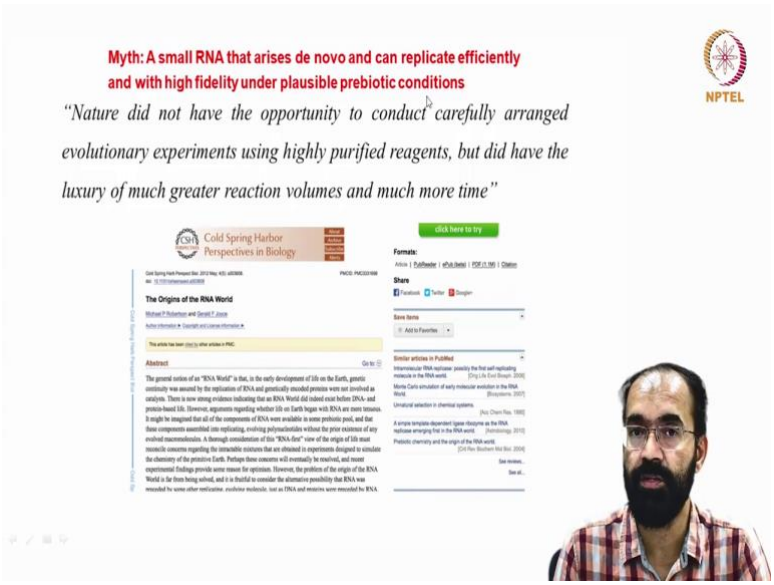

So, we should understand nature did not have the opportunity to conduct carefully arranged evolutionary experiments using highly purified reagents. But it did have the luxury of much greater reaction volumes and much more time you are talking about a long evolutionary time scale and large volume which is equivalent to the size of the planet earth itself. So, this allowed the evolution of life much much possible in planet earth.

So, coming back to the myth what we have been discussing earlier that a small RNA that arises de novo and that can replicate efficiently and with the high fidelity under plausible prebiotic conditions is very much possible without which the life could not have originated. So, that is no longer a myth it should have happened without which the modern life forms could not have existed.

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So, let us look into some of the key discoveries in the RNA biology and their impact.

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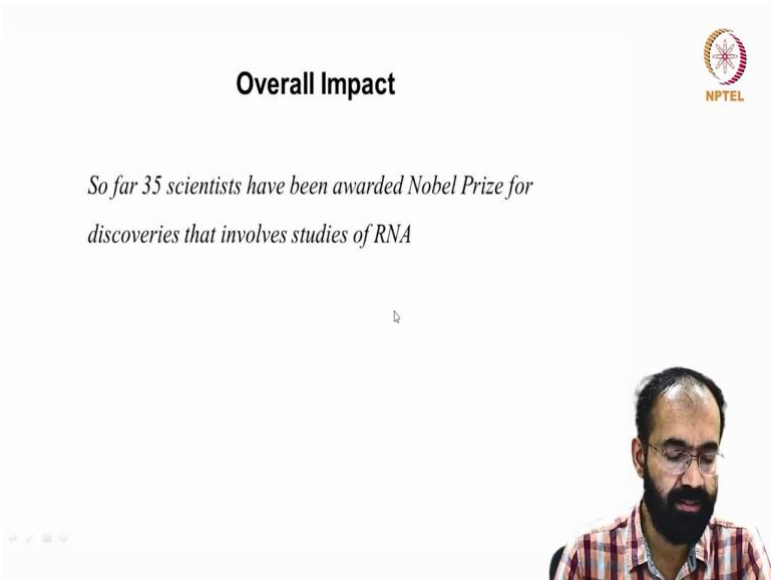

So, more than 30-35 scientists have got the Nobel Prize for RNA related discoveries one of the latest or the one of the recent ones being recent means maybe a decade ago was for one of the Indian scientists you may have heard about his name his name is Venki Ramakrishna who discovered the structure of the ribosomes. So, he was quite instrumental in decoding the crystal structure and that is nothing but an RNA related discovery.

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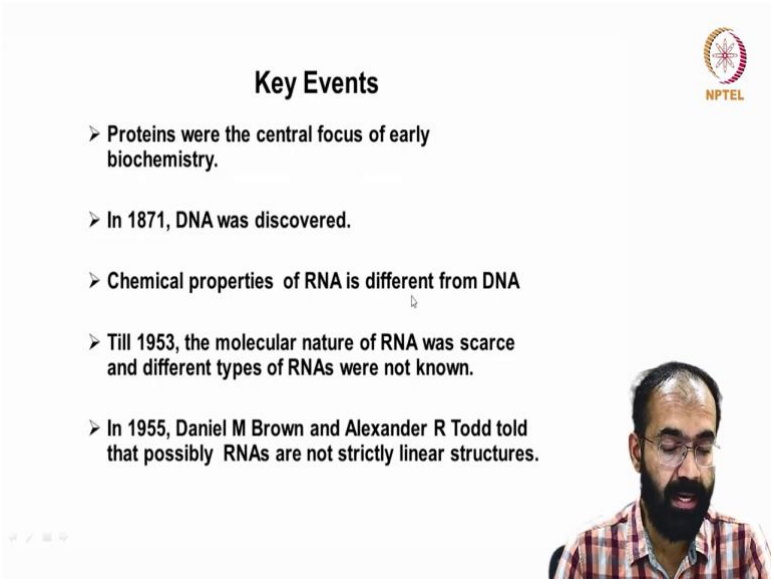

And we should understand that the proteins were one of the central focus of the earlier research earlier biology research we can call them as biochemistry that time the molecular biology of RNA and DNA was kind of sideline because of lack of evidences, lack of adequate tools whereas, the chemistry was quite strong and growing quite good.

So, lot of discoveries happened in biochemistry and the molecular world was revealed much much later. In 1871 DNA's existence was discovered, but we never knew its structure until almost 80 years 70 80 years down the line. Chemical properties of RNA is different from that of DNA was also known and till 1953, the molecular nature of RNA was scarce and different types of RNA were not known until 1953.

In 1955, Daniel Brown and Alexander Todd told that the possibility of RNA is not strictly linear structure means they can adopt secondary and tertiary structure which was a big revelation in the RNA biology.

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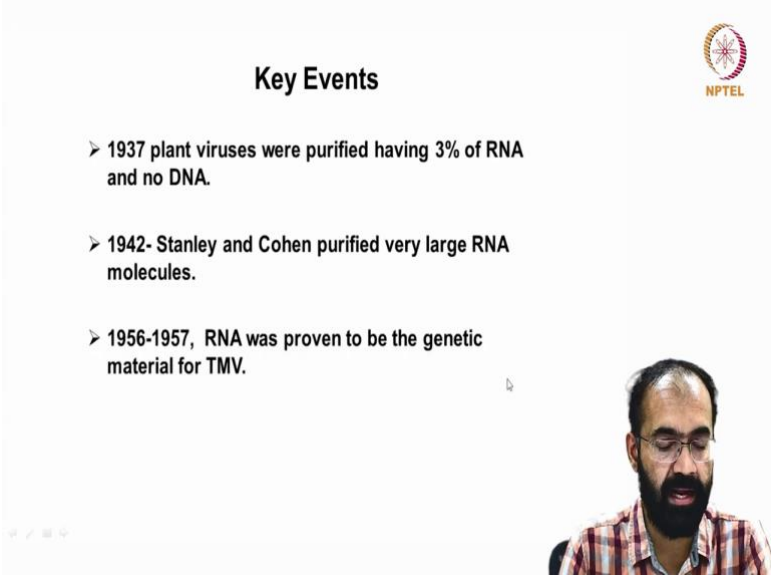

In 1937 plant viruses were purified and they were known to have 3 percent of the RNA and contain no DNA because majority of the plant viruses even modern world they are RNA viruses similar to that of COVID or influenza virus. 1942, Stanley and Cohen purified a large RNA molecules and in year 1956-57 RNA was proven to be the genetic material for Tobacco Mosaic Virus abbreviated as TMV.

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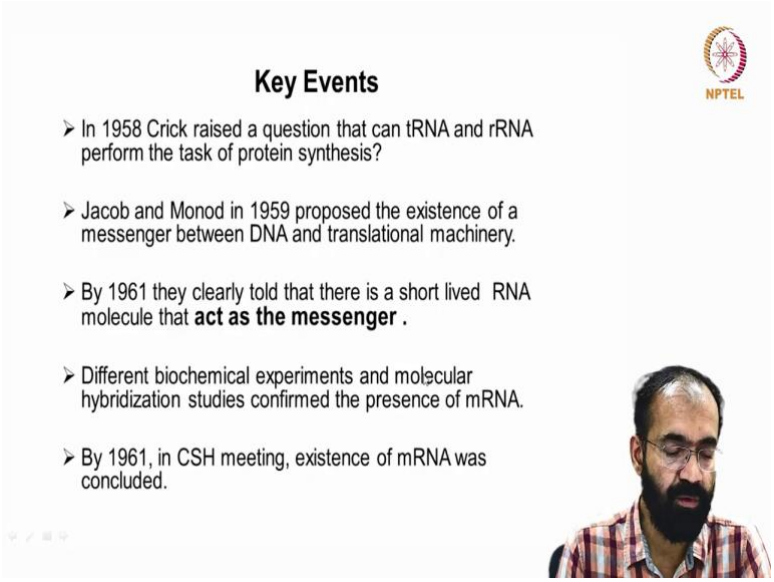

In 1958, Crick Francis Crick raised a question that can tRNA or transfer RNA and rRNA or ribosomal RNA can perform the task of protein synthesis he asked this question. Because evidences were supportive of these facts and later Jacob and Monod in 1959 proposed the existence of a messenger between DNA and translational machinery. What it says the DNA need to get converted into protein not directly there has to be an intermediate.

So, we do not know who is that intermediate now we know it is nothing but messenger RNA but there could have been a messenger in between. By 1961 they clearly told that there is a short-lived RNA molecule that is acting as a messenger. Different biochemical experiments and molecular hybridization studies confirmed the presence of mRNA. By 1961, in a cold spring harbor meeting the existence of mRNA was accepted or concluded.

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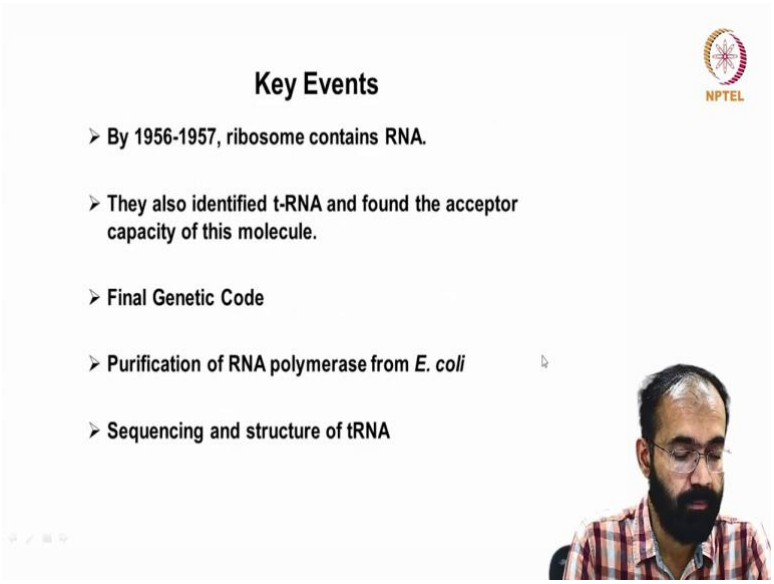

And in 1956-57 ribosomes are known to contain RNA molecule. And they also identified transfer RNA and found an acceptor capacity of this molecule for amino acids and much later the genetic code was discovered and one of the Indian scientist is very instrumental and he received the Nobel Prize for the discovery of genetic code his name is Har Gobind Khorana and purification of RNA polymerase from E. coli happened later on and the sequencing and structure of transfer RNA also happened in subsequent years.

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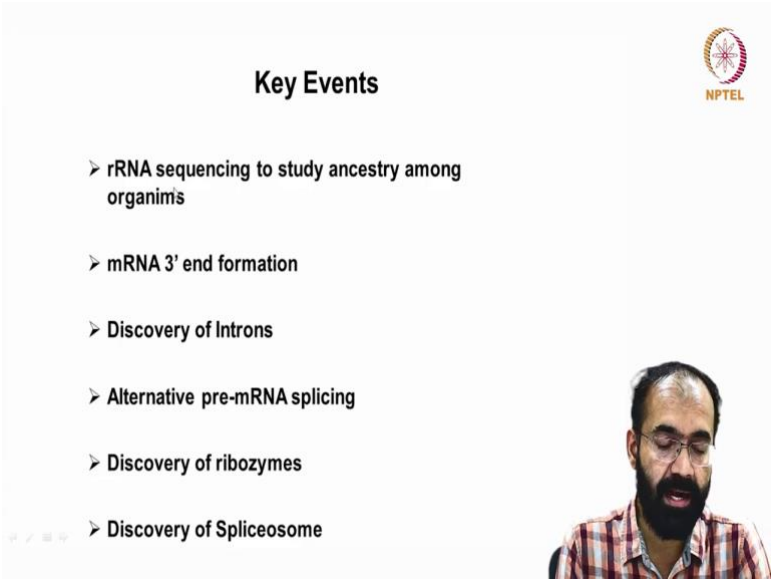

And ribosomal RNA sequencing to study the ancestry among the organism even today we use ribosomal RNA sequencing and we refer to as ribo typing for identifying the identity of various lineage of organisms. And mRNAs 3' prime end formation, 3' prime end formation you will study more in detail that was discovered in the various years to come subsequent to the earlier discoveries and the discovery of introns happened, alternative pre-mRNA splicing happened, discovery of ribozymes happened and discovery of spliceosome happened.

Spliceosome is basically a machinery that allows the maturation of the mRNA we will see about those more in detail in the coming classes.

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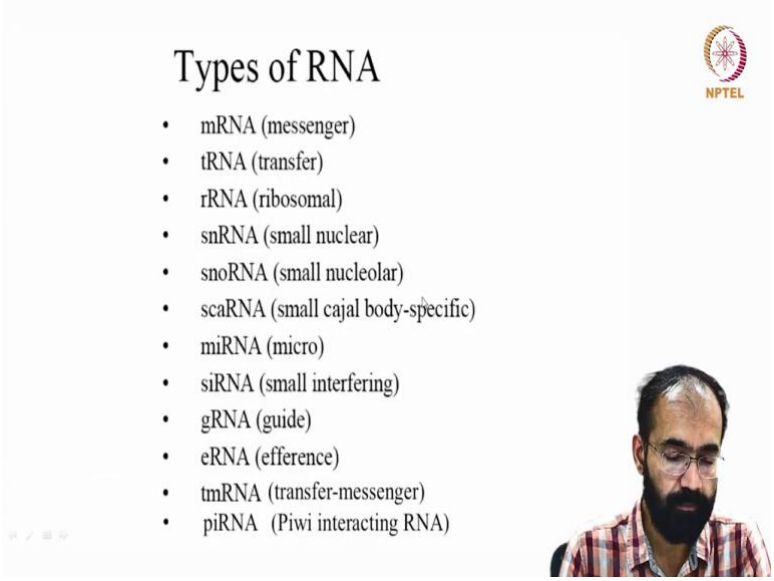

Let us quickly look into different types of RNAs. This list may sound little longer, but we will quickly go through their names. mRNA stands for messenger RNA, tRNA stands for transfer RNA, rRNA stands for ribosomal RNA. SnRNA for small nuclear RNA, snoRNA small nucleolar RNA, scaRNA small cajal body-specific RNA, miRNA stands for micro-RNA, siRNA stands for small interfering RNA, gRNA stands for guide RNA, eRNA stands for efference RNA, tmRNA stands for transfer messenger RNA.

It is a hybrid RNA you see about those also in detail, piRNA Piwi interacting RNA and the list continues few more are there, but important ones are listed here.

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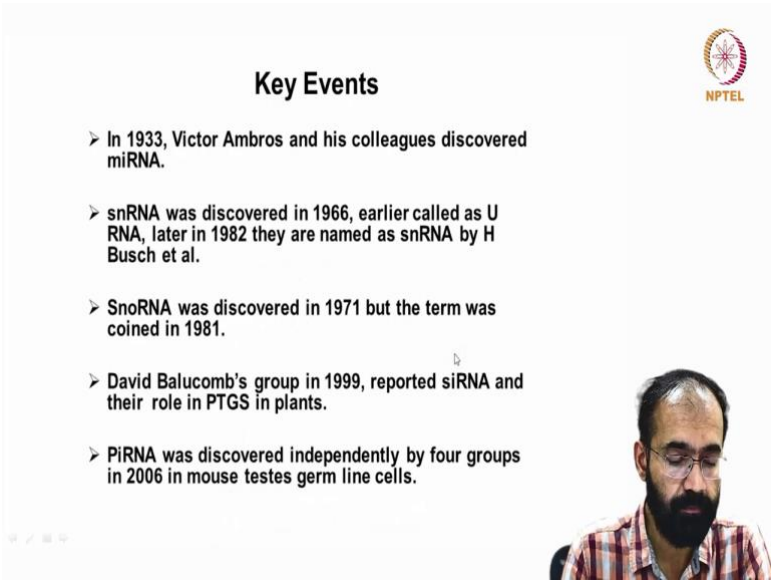

And coming back to some more key events in 1933, Victor Ambros and his colleagues discovered miRNA, but they did not know its importance much later in the lines of other evidences they discovered why miRNA or micro-RNA are important. snRNA was discovered in 1966 earlier it used to be called as URNA, later in 1982 it was named as snRNA by Busch et al.

So, snoRNA or small nucleolar RNA was discovered in 1971, but the term was coined in 1981 only and David Balucomb group in 1999 reported siRNA and their role in post transcriptional gene silencing in plants; that means, genes can be silenced even after the transcription of an RNA normally when you say gene expression production of an m RNA from the gene and then it undergoes translation.

But post transcriptional gene silencing means a gene is transcribed from the DNA but it is not allowed to express into protein. So, that is PTGS. So, piRNA was discovered independently by four groups research groups in 2006 in mouse testes germ cell lines.

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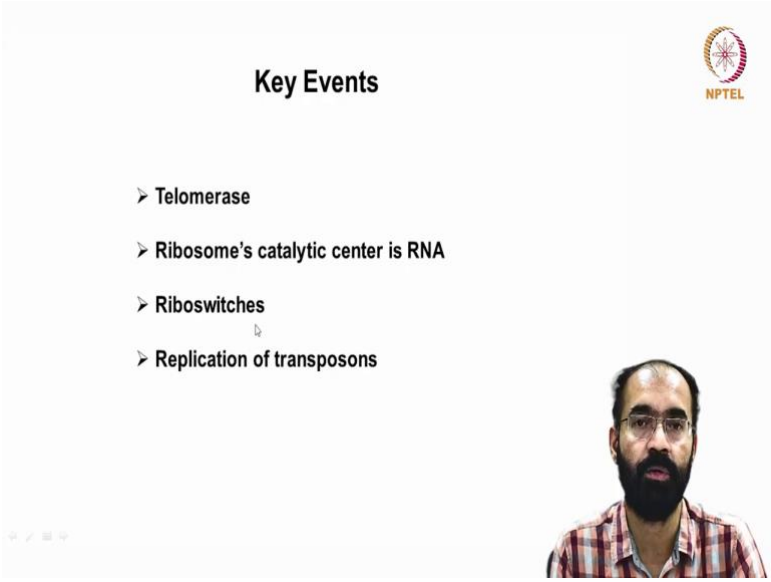

So, some more key events in the RNA biology are the discovery of telomerase and ribosomes catalytic center is known to be RNA molecule and also riboswitches and the replication of transposons. Telomerase is a structure that stabilize the ends of chromosomes and every organisms have got this structure called telomeres.

And telomerase is constantly repaired in germ cells and also in some case of cancerous cells otherwise the telomere length gets shortened and shortened and shortened due to the end replication problem. But telomerase is able to rejuvenate the telomere length when the germ cells are found. So, that when an organism is bound it is not having a standard telomere, but in your somatic cells say your cells in your hand finger some any other part of your body except the germ cells where the gametes are produced.

They nowhere there is expression of telomerase. So, you will have short end and short end telomere length. Once the telomere length falls below certain length then the cell has to undergo cell depth that we call cellular senescence and that is why you end up getting wrinkles in your skin.

Because you are constantly frowning a particular part of your skin say people call it laughing lines or on your forehead you have lines because you are shrinking the skin and the cells are dying there and they are being replaced also; however, the rate of death is much much higher that their replacement is slower because of which the amount of cells required in that particular spot is not present.

Say to fill that gap you need 100 cells, but body is able to produce only 60 cells and why only 60 cell? Because their rate of death is very high because constantly that area skin is holding and the cell is getting older because the telomere length is getting shorter and shorter hence, they are not able to perform the task effectively that is why old people will have lots of wrinkles on your their body because of cell death that is occurring.

So, telomerase is very important in rejuvenating. In cancer that will do some effective ingenious or very skillful way it will revive the telomerase enzyme so, that cancer cell will not die in the because of short telomere. So, it will resist the degradation of the telomere length.

And ribosome's catalytic role is mainly played by RNA part not the protein part all though ribosomes contain both RNA and protein then comes the riboswitches. Riboswitches are somewhat like that electric switch like all of you know how to put on a light or how to put on a you know TV etcetera. So, without a switch you cannot turn on or turn off a any electrical instrument.

So, riboswitches are also something like that. So, they are sequences that is present in an mRNA which will be recognized by the products formed from that mRNA. So, if the product is present, it will not allow this mRNA to make more products say given cell need 100 products and mRNA is there and 100 protein molecules are formed from that mRNA, but when hundred is there, you do not want a 101 or 102 or 103 proteins.

So, these molecules will go and bind to the specific sequence on this mRNA and it will not allow this mRNA to translate, but when the level of this protein go below 100 then there is no one to go and bind and this mRNA will start translating again. So, it acts like a control switch we will see more in detail about riboswitches. I am just quickly saying. So, that when we study about riboswitches it will be stay in your mind and then replication of transposons.

Transposons are also called jumping genes. That they can move from one place to another we call them as the jumping genes and the replication of transposons also was a key event and which also fetched Nobel Prize.

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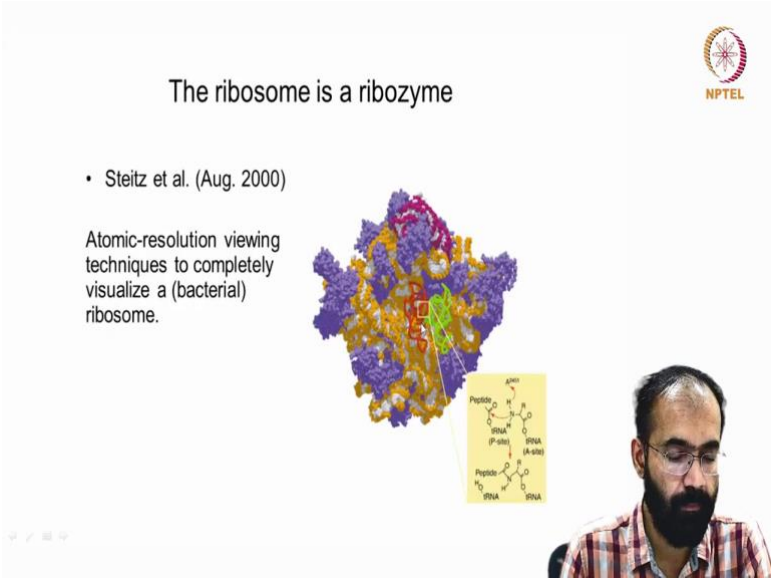

So, if you look into the structure of the ribosome, ribosome we know it is a ribozyme and structure was revealed in 2000 at atomic resolution level a bacterial ribosomes structure if you look closely, it has got two important site that is an acceptor site and a peptide bond forming site. So, we acceptor site we call it as A site and the peptide bond forming region is called as P site.

So, acceptor site is a place where a tRNA will come with an amino acid and it will enter into the ribosome and the P-site will allow the peptide bond to form by adding a amino acid which is a pre existing amino acid that came from an earlier tRNA carrying a amino acid.

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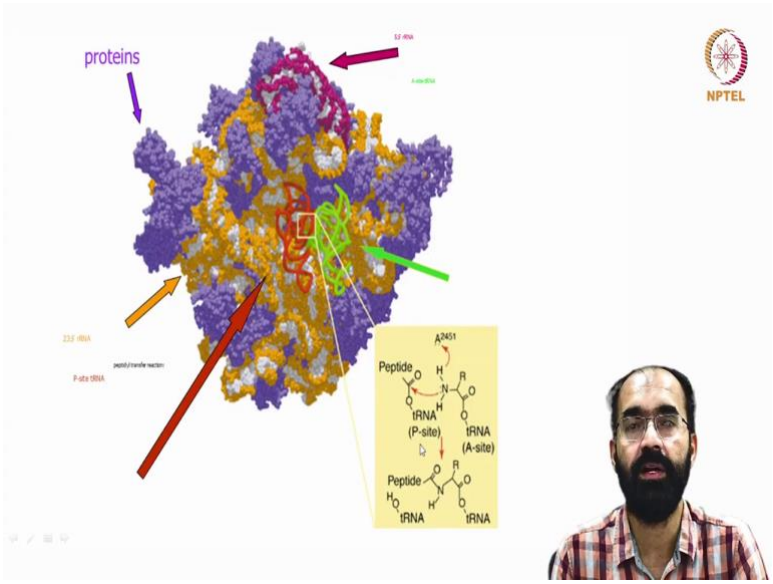

So, we will study more in detail when we study about the protein synthesis. So, this is an enlarged structure what is important to understand is that the congregation of various RNA molecule and the protein molecule stabilize the ribosome structure; however, the A- site of the ribosome allow the entry of the tRNA containing amino acid, but the P-site allows the peptide bond to form, but this bonds formation is done by the RNA part not the protein part of the ribosome.

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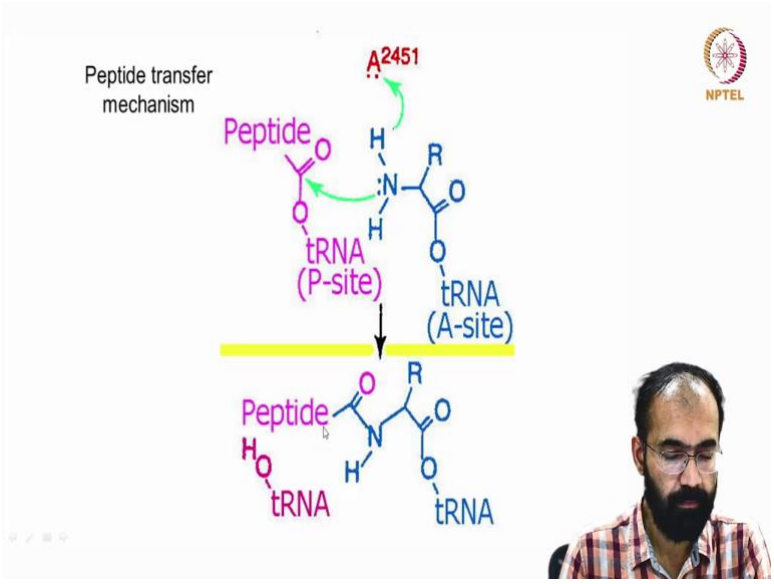

And this you can see here this is a A-site and you have tRNA with an amino acid and then this is the P-site where you have the already growing peptide attached on to a tRNA and this peptide now will be released onto the incoming tRNA and now the incoming t RNA will occupy the P- site. So, the left out tRNA will be expelled from the complex and the newly growing peptide will come out of a lumen and that is what you can see in this picture.

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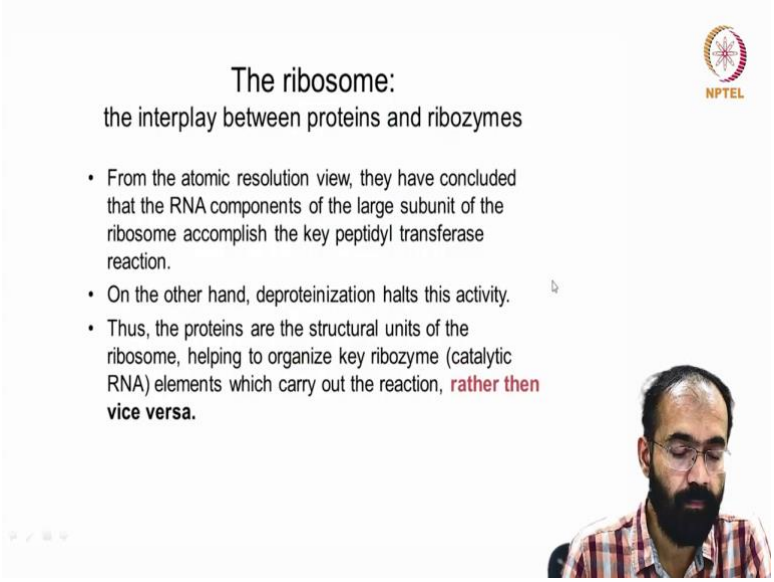

So, if you look further into the ribosome the interplay between protein and the ribozymes are very important from the atomic resolution view, they have concluded that the RNA components of a large sub unit of ribosome accomplish the key peptidyl transferase action. On the other hand, deproteinization can halt the activity because the protein is very important for the stabilization of the ribosome structure.

Thus, the proteins are the structural units of the ribosome helping to organize the key ribozymes means RNA molecules catalytic RNAs elements which carry out the reaction rather than vice versa.

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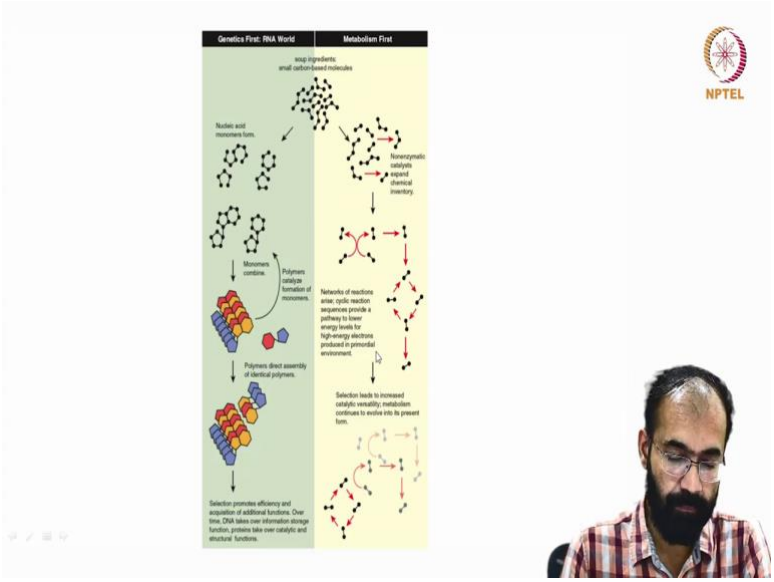

So, if you look into the prebiotic world, we know there are two kinds of argument metabolism first or the genes first or genetics first. Actually, both were first both were present simultaneously, but only the genes first was able to acquire qualities and characters unlike the metabolism first. Metabolism first hand got lipids carbohydrates amino acids etcetera.

But they were not able to carry out a function, it is always the nucleic acid that was able to carry out the function which later on congregated to form the LUCA Last Unique Common Ancestor which is a cell like structure.

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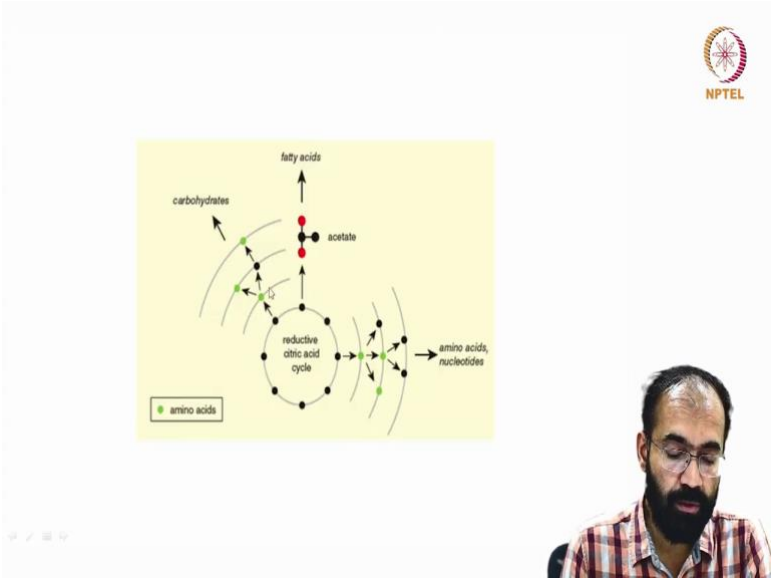

And also, we should understand the various biochemical molecules can contribute to the production of energy or ATP. We know what is the two fundamental principle of life one is ability to utilize energy another is ability to make a copy of itself. So, energy is an important molecule. So, citric acid cycle is very very important and various carbohydrates, fatty acid intermediates and amino acids were able to contribute to the production of energy.

When the genetic information was holding the key information whereas, all the other three molecules were able to help in the production of energy. So, these two acted together to sustain the life form. So, here ends the RNA world part and we will continue with a new topic in the next class.

Thank you.