RNA Biology
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Lecture - 04
Introduction to RNA Biology and RNA World-Shift to DNA

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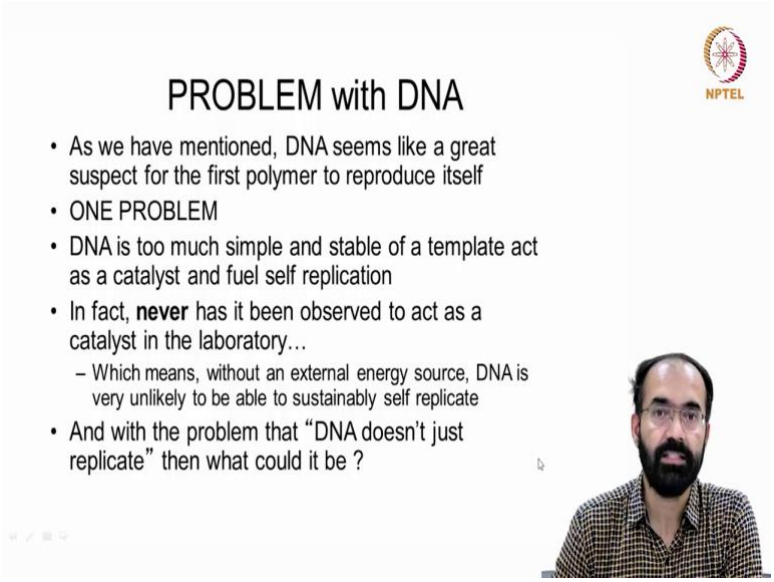

Welcome back for another session of RNA Biology and this is the last slide where we left in the previous class and we were discussing about the problems with the DNA. Why DNA is not a likely candidate for the storing of the genetic information etcetera. So, so we have seen that why DNA can be a very good prospects; however, it comes with certain limitation and one of the major limitation of the DNA that it is less reactive, it is very stable and less reactive.

So, we should understand in order to perform some task the molecule need to undergo some activity which in turn is an antagonized by the stable structure. So, you do not want an unstable structure; however, the extreme stability of the DNA renders it reasonably inactive when a catalysis is concerned.

So, that is what we discussed in the previous class and there are no reports or no experimental evidence was demonstrated to show that the DNA can act as a catalyst even in a laboratory condition. So, now let us see what are the circumstance in which

RNA got converted into DNA as a storing of genetic or storage house of genetic information.

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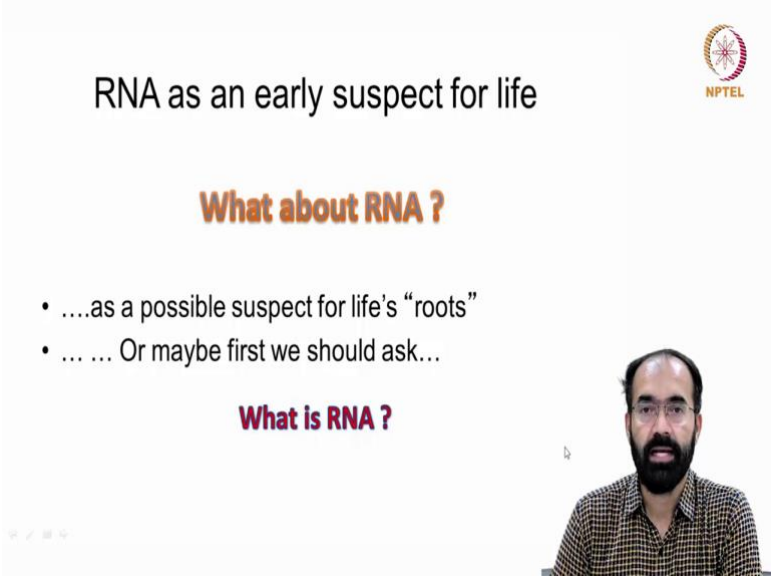

So, now, based on the exclusion of DNA as a possible early molecule to start the life on earth, we should shift back into the RNA as an early suspect for life. And let us see what are the plus point or the benefits RNA has and it is a very possible molecule to have started the initial reactions on the prebiotic world. And we should try to understand little bit more in depth that what is actually RNA means.

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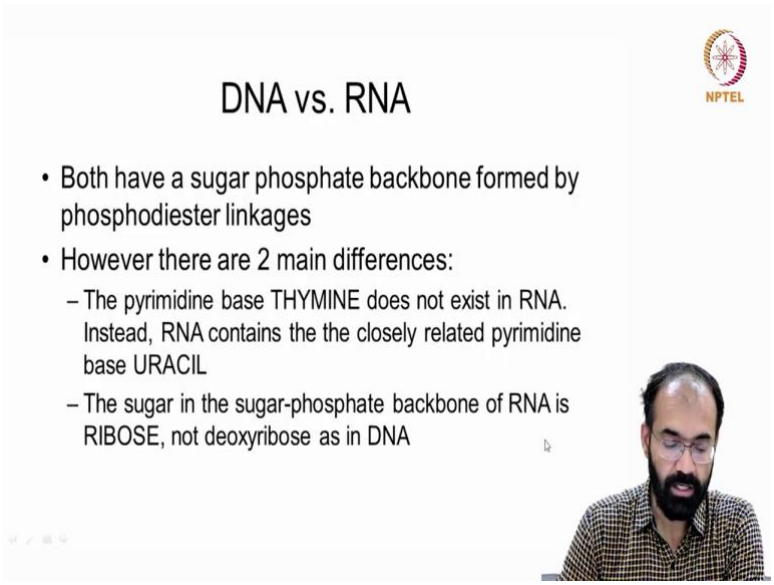

To do know, to know that more to do further analysis on this we must compare DNA and RNA and both of them have got a sugar phosphate backbone that is formed by the phosphodiester linkage. Because these nucleotides are held together by the phosphodiester backbone and there are two main differences are there and what are those differences?

One is the pyrimidine thymine is preferred in the DNA it do not exist in the RNA instead the RNA contains a closely related pyrimidine or uracil and the sugar that is present in the RNA is normal sugar; that means, the two prime carbon has got a hydroxyl group. Whereas, in the DNA it is called deoxy ribose; that means, the oxygen is missing from the two prime carbon. So, these are all the two main difference between the DNA and the RNA.

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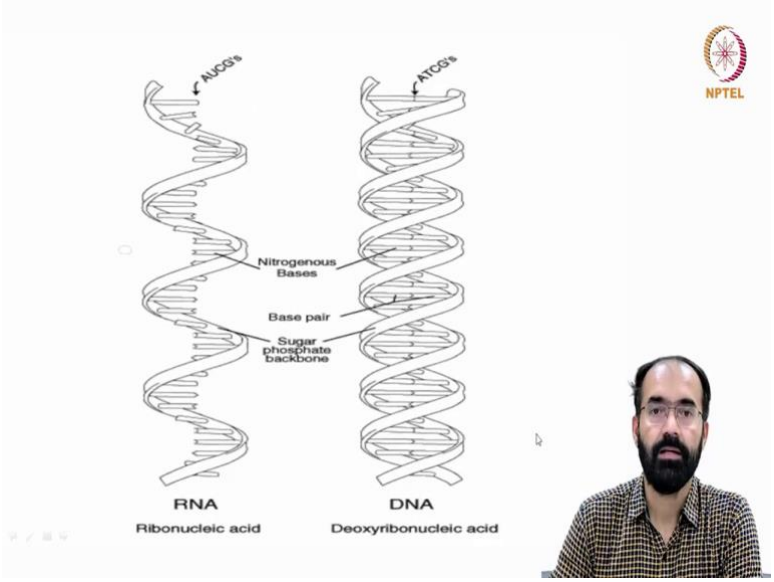

So, this is a cartoon of the RNA and the DNA. In the left hand side you have got the RNA molecule on the right hand side you have got the DNA molecule they look more or less the same except for the variation in the thymine versus uracil. And the backbone has or the ribose sugar has got deoxy ribose in the DNA and ribose confirmation in the RNA. Other than that they look more or less the same and the DNA has got two stranded which also adds to the stability of the RNA DNA molecule.

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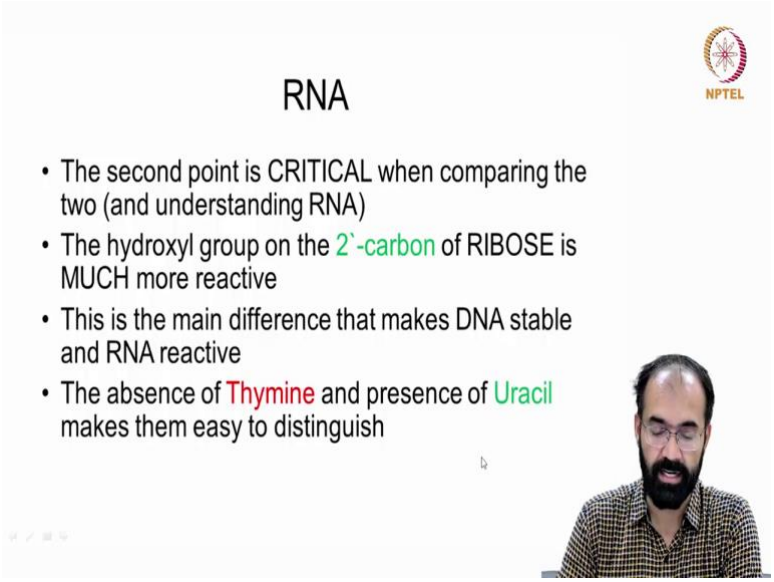

And another important critical points when comparing the two in while understanding the DNA is the two prime carbon which we have been discussing about the in the ribose sugar is much more reactive. That means, the 2 prime carbon in the DNA has got deoxy; that means, the OH is now changed into just H; that means, oxygen is missing which makes it less reactive whereas, in the RNA the hydroxyl group of the two prime carbon is highly highly reactive.

And this is the main difference which that makes the DNA stable; that means, the absence of this oxygen makes the DNA more stable. If it is less reactive then it allows the molecule to be more stable that this DNA is more stable the credit goes to the deoxy 2 prime carbon in the RIBOSE sugar the opposite is seen in the RNA the presence of hydroxyl group in the two prime carbon makes the RNA more reactive.

And the absence of thymine and the presence of uracil makes them easy to distinguish when various enzymes like various RNA and DNA modifying enzymes make use of this uracil versus thymine to recognize whether a given nucleic acid is RNA or DNA.

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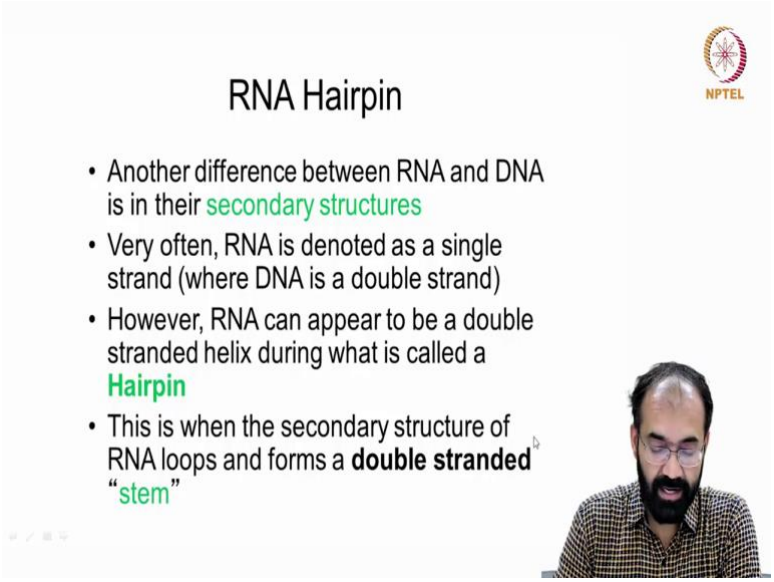

And now the most important part is the RNA hairpin we will see them more in detail what does it mean. A different major difference between RNA and DNA is the ability to form secondary structure. DNA is a very stable molecule, but it is a secondary structure is limited to the double helical confirmation both strands are in anti-parallel confirmation whereas, RNA has got innumerable confirmation possibilities and we generally call them as secondary structure. Very often the RNA is denoted as a single strand for convenience.

Ideally it is a single strand, but does it stay like a single strand? The answer is no. It can allow a lot of variations and also it can undergo pairing similar to that what you see in the DNA; that means, some places it can be even form helical confirmation and it can form secondary, tertiary and even quaternary confirmation which makes it a three proper three dimensional structure which is a necessity for carrying out biological reactions.

When RNA can appear to be a double stranded even while staying as a single stranded molecule and we usually call this double stranded structure as a hairpin structure and this is happening when the secondary structure of the RNA loops forms a double stranded stem. We can see in a pictorial manner in the next slide.

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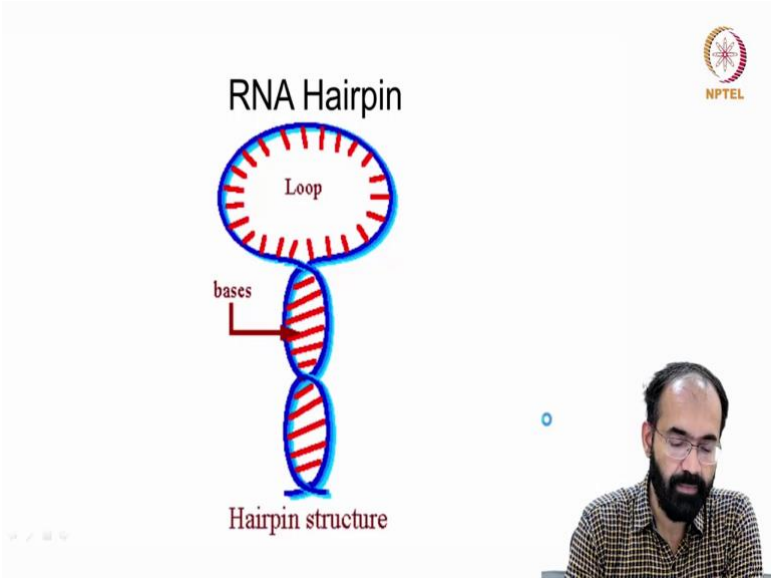

What you see here is a loop ridge; that means, it do not form any pairing it do not find any complimentary. Whereas, in the bottom as you come down you see some pairing; that means, Watson crick base pairing like we told you in the yesterday's class A pairs with T in the DNA or a pairs with U in the RNA and G pairs with C.

So, A is adenosine, U is uracil, G is guanosine and C is cytosine and in the bottom what you are seeing the so, called stem structure is similar to that of the double helical structure such a molecule we call it as hairpin structure or its also called as RNA hair pin. And the RNA hair pin stabilizes the molecule and also allows the molecule to undergo different confirmation.

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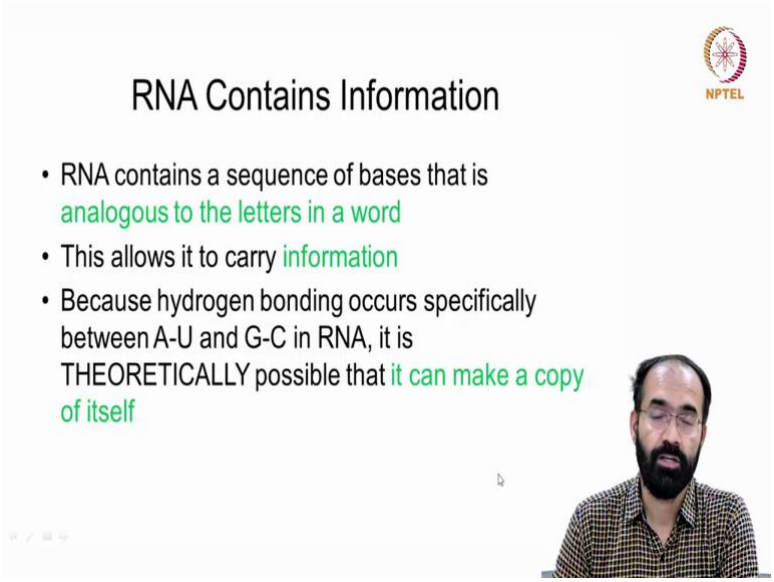

And RNA can also contain information we will see what kind of information they are. RNA contains sequence of bases that is analogous to letters in a word we know if someone writes a English letter r we call it as r symbol r letter r, but also there is a word a r e are that is also pronounced as are, but both have got a different meaning.

Same way a letter number of letters present in one word decides how that letter how that word is pronounced and also what is the qualitative meaning that word is imparting. So, like that the sequence present in the RNA can contain information that can specifically mean something it means, something and we will see them what does that mean in.

And this also allow to carry the information because the hydrogen bonding that occurs specifically between A-U and G-C. A-U is double bond G-C is triple bond and it is always theoretically possible that it can make a copy of itself because you think about A can pair with U, G can pair with C. So, a stretch that has got A C C U G C C something like that can make a complimentary copy.

That means, it can attract another nucleotide and pair it can make a copy of itself that will be a mirror image like if you seeing yourself in the mirror is not what you actually look like. So, actually you see is a mirror image and if you reverse it with another mirror that is your actual image.

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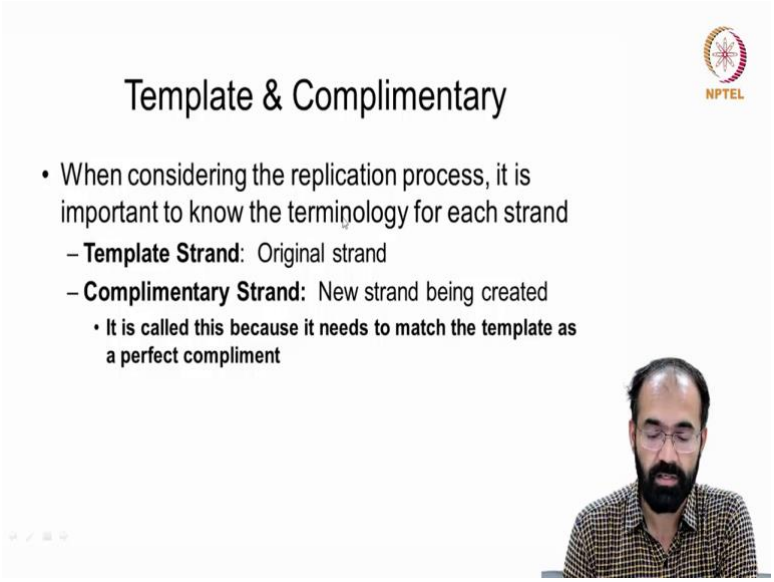

So, let us think about the template and the complementarity and they always will be complementary to each other. When a strand is there when RNA strand is there it will always attract a complementary strand which is the basis of formation of a stem structure and when there is no complementarity is there it will remain like a loop structure.

When considering the replication process whenever an RNA or DNA whatever it is making a copy of itself it is important to know that these kind of terminology means that there is always a pairing a region that can pair or a sequence; that is, newly made while pairing on to a template like template basically means a mold you may have seen how people make different structures like if you have a molten plastic you can pour out to a mold and after once the plastic solidifies it becomes shape of that particular mold.

So, same concept applies in while making a new copy you need to have a template and the newly formed molecule will be complementary to that. We call the master copy as a template strand that is the original strand and the newly formed the new strand is called a complementary strand. So, the new strand being created is very much similar to that of the template strand, but it is not identical.

Now, you make another strand from this complementary strand that will look exactly like the template strand. So, what you should understand? A complementary strand is a mirror image of the template strand and you make another complementary strand from

this complementary strand it will be the template strand. So, it is called so, because it needs to match the template as a perfect complement, complementing to each other.

It is like you can if you look your left hand and the right hand left palm and right palm you can join them together they look like a mirror image of each other, but your right hand and another person's right hand they look same, but they are not mirror images. So, that is the similarity you should know between the template and the complementary strand.

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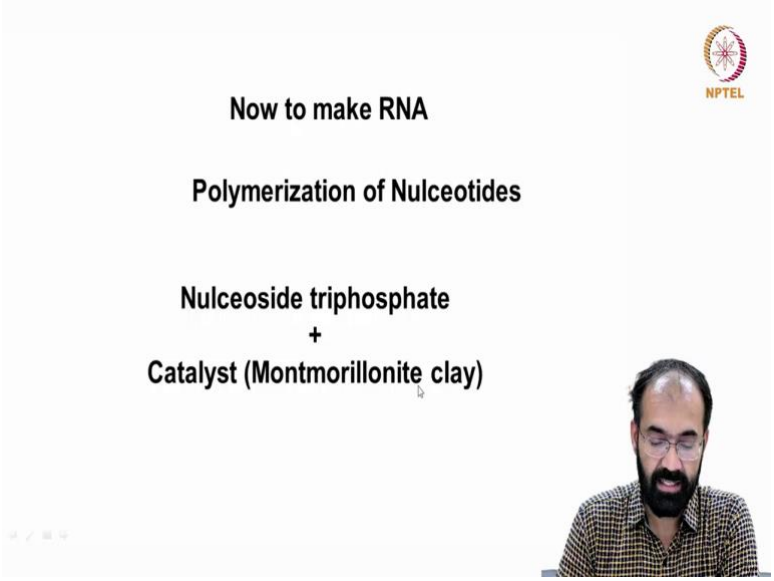

So, now let us think how we proceed with formation of RNA in the prebiotic world? and we know that it has to happen through the polymerization of the nucleotides. So, nucleoside, triphosphate plus a catalyst we saw the borate can provide selectivity one such abundant mineral that is known to contribute for this catalysis is called montmorillonite clay, which is mineral rich and that allows that can act like the substratum act like a venue for this polymerization to happen.

So, the initial polymerization could have been carried out by montmorillonite clay that was abundant in the prebiotic world.

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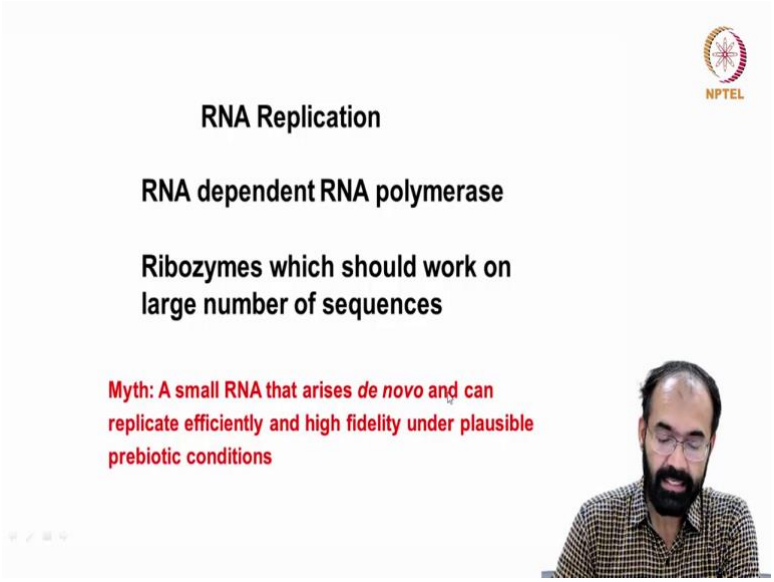

So, if you look into the RNA replication part RNA dependent RNA polymerase is there in this modern world like if you think about any influenza virus or COVID virus or any RNA virus you can think of they always depend on a enzyme protein enzyme. Remember that is called RNA dependent RNA polymerase we do not produce an RNA dependent RNA polymerase in our body humans do not produce.

It is a feature of viruses normally because they carry that information in their genome and they make use of the machinery from the host and produce this protein and make a copy of them self when you get a viral infection. Say COVID infection or influenza infection like influenza means common cold you get you know sore throat etcetera.

So, another example you can see that is known to help in the replication of the RNA that is formed in the prebiotic world is the ribozymes which should work on a large number of sequences remember in prebiotic world we are not talking or considering about enzymes made of amino acid or protein enzymes are missing them we do not have a protein enzymes.

So, the ribozymes have to take the job of making a copy of itself. So, coming back to the myth a small RNA that arises de novo and can replicate efficiently and in high fidelity under possible prebiotic condition. Why it is referred to as myth? Because nobody was there to witness it and this is too good to be true, but if this truth has not happened there is no way you could have had any life form existed.

Because it all originated from the RNA without which it is out of question the spontaneous formation of life is out of question.

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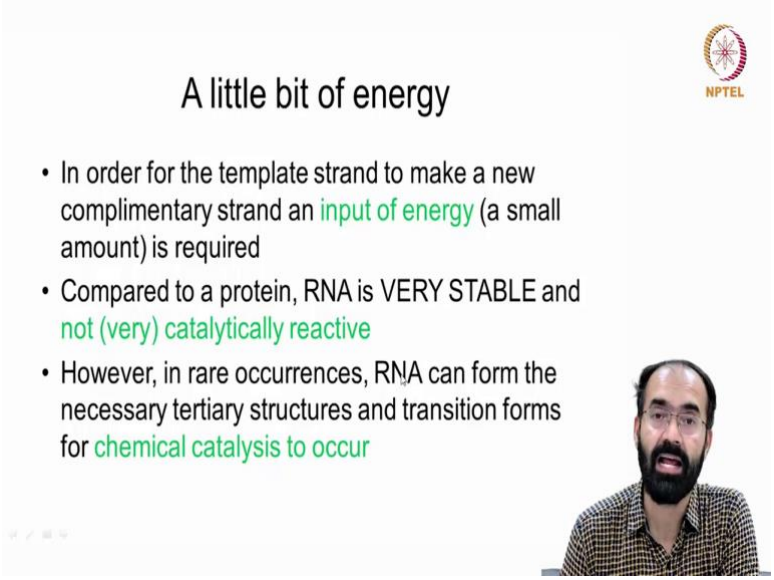

Now, let us think about a little bit of energy addition of energy how does that contribute? Because many biological reaction no matter whether you talk about ribozyme or whether you talk about formation of RNA itself independent of ribozyme everything require energy.

In order for the template strand to make a new complementary strand an input of energy is must and it can come from various sources it can even come from the UV radiation and compared to a protein RNA is very stable and is not very catalytically reactive compared to DNA RNA is very catalytically reactive and biologically active, but compared to a protein it is less active.

But the life forms have to depend on this less active RNA in the prebiotic world, but the times available was so, high that this RNA the so, called ribozymes even with its low activity it was able to perform the task of making a copy of itself. Remember the early ribozymes or the early RNA molecule that had a catalytic role was always bothered about making a copy of itself because its goal is to survive.

However, in a very rare occurrences RNA can also form necessary tertiary structures and transition forms that can make use of chemical energy that is chemical catalysis can

occur and there are evidence even in modern world to show the ribozymes can perform the chemical catalysis of various nucleic acids.

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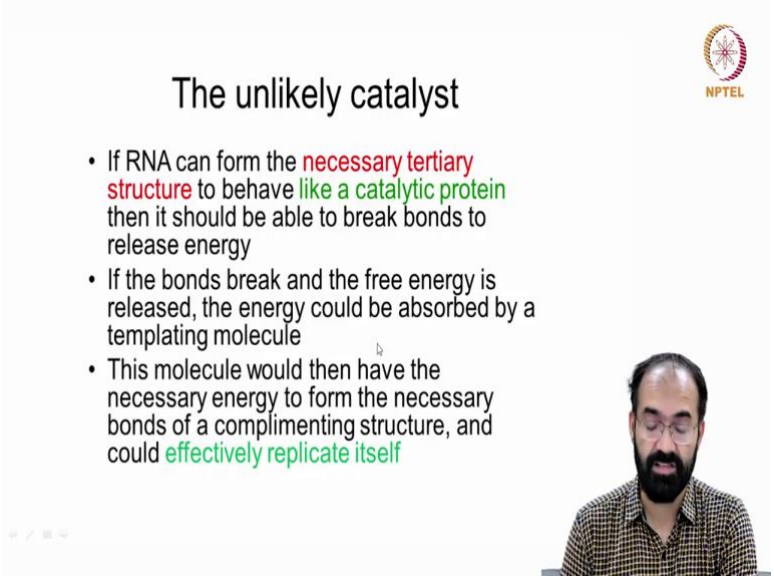

So, let us see how good or how bad an RNA can be as a catalyst. If RNA can form necessary tertiary structure necessary is a loaded word which means that it should form the structure which actually is going to be useful and there is no director sitting or there is no guide sitting to tell that this is how you should be folding so, that you can perform this task. So, we should understand the folding is happening random and the functioning the output also is random.

Now, the question is, are this random folding and the random function are going to be beneficial for the survival of this molecules? So, they have to have a necessary tertiary structure to behave like a modern day catalytic protein and then it should be able to break the bonds to release energy. Because to perform a task you need energy either it should be a physical energy or it should be a chemical energy.

If the bonds break then the free energy is released and the energy could be absorbed by a templating molecule because then a phosphodiester bond can be easily formed and a copy of itself can be made. So, this molecule when would have the necessary energy to form the necessary bonds and of a complementing structure, and this could effectively end up in replicating itself.

So, what are the points we covered so, far? We should have a clear template and that template should have necessary secondary structure which is powerful enough to capitalize the chemical energy from whatsoever possible surrounding and it should be able to catalyze the polymerization of nucleotides which is complementary to the template. So, that you end up getting a new RNA molecule which is complementary to the template then it is a successful ribozyme.

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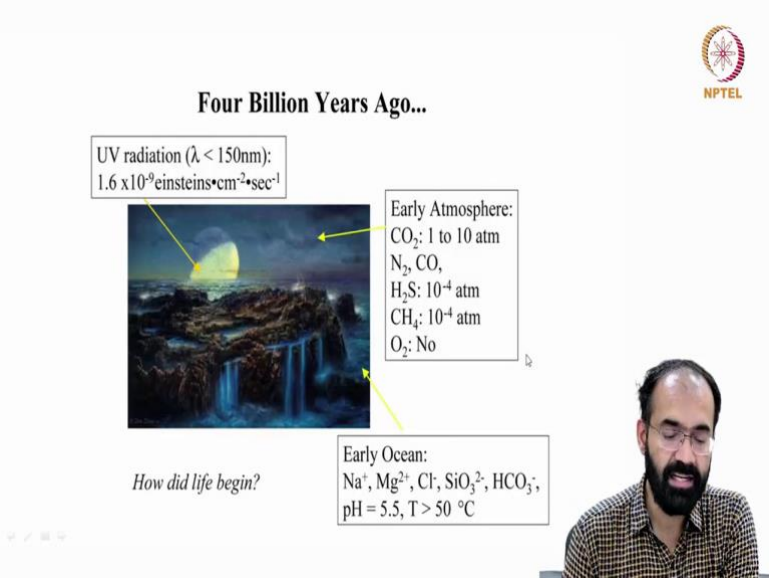

Now, four billion years ago what are we seeing we had abundant UV radiation remember we do not have too much of oxygen and hence not too much of ozone and hence there is no protection from UV radiation and the atmosphere was quite porous for the UV radiation.

And plenty of UV radiation was abundantly available during then which acted like a physical source of energy in early atmosphere plenty of carbon dioxide. Plenty of nitrogen carbon monoxide hydrogen, sulphide methane gas and oxygen was nil because oxygen was produced much later in the excuse me.

Now, let us think about in early ocean what are the points that contributed to the production of ions. Various ions that were present in the ocean water also could have contributed to maintaining the proper pH for a biological reaction and the hydrothermal vents also allow the temperatures to be kept quite high.

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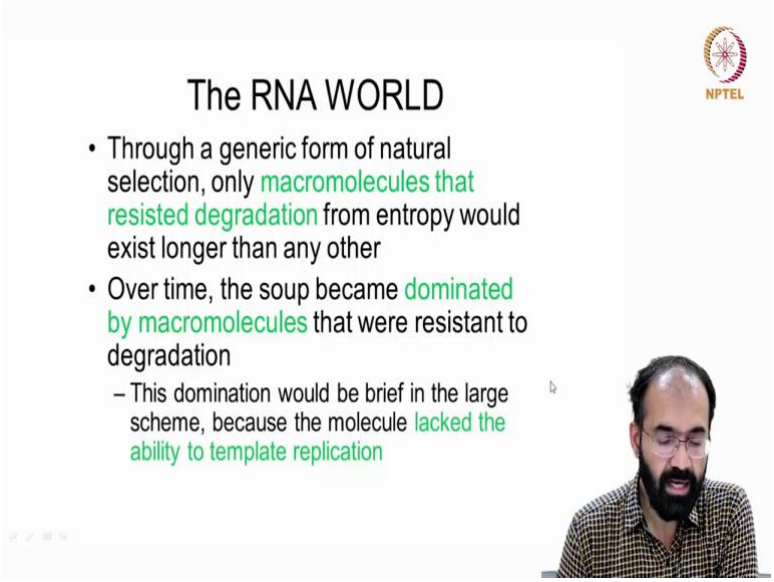

Now, coming back to the RNA world although we can say in a generic form of natural selection only certain types of macromolecules that resisted degradation. There is a saying right like in the in a war field if you kill or you be killed; that means, the molecules also have like you can see in if you go to any national park or you know wildlife sanctuary there is no rules and regulations etcetera. So, if a lion or a leopard is hungry, it will just go and chase a buffalo or an animal and it will eat.

And if buffalo want to live it should flee or give a fight it may or may not win. So, it is free for all lion is hungry it will attack, leopard is hungry it will attack and it will eat same logic applies at the molecular level also. So, those macro molecule resisted degradation it is available for doing something or just be there, it can do something at a later time point. So, it has to protect itself from the entropy that could exist longer than any other.

So, you think about it if 10 molecules are born one molecules can live only 10 minutes then it disappear whereas, the other molecule can live for ten hours it will stay for long another molecule can live for 10 years; that means, it will be much much represented. So, this is nothing but stability of a molecule allow or give the opportunity for this molecule to perform some possible task in the future time.

Over the time the soup became dominated by those macro molecule that were resistant to the degradation. This domination would be brief in large time scheme because this

molecule lack the ability to template replication. Remember if a molecule cannot do any next step then it will be dominated and it will be stuck there you may have heard about Liebig's law of minimum in some of your biochemistry class.

Which basically means say for a reaction to happen if 10 molecules are needed 9 of them are super abundant, but 10th one is least abundant then the rate of reaction is depended by the least available molecule so, that decides whether or not the reaction has to happen. In same way here the ability of a dominant macro molecule to proceed further decides whether or not that molecule is present in this current environment.

If it is present that simply indicates it is stable of course, it is available, but it do not have a downstream track.

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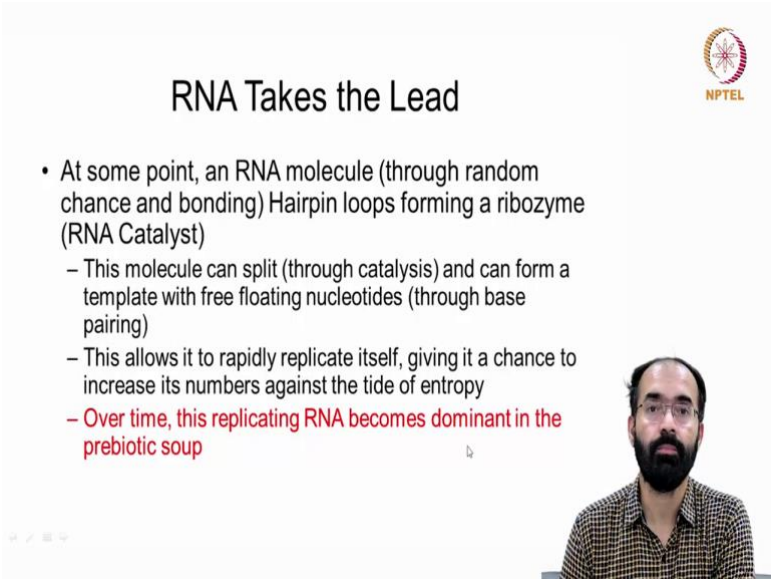

And now let us see how RNA acts as a dominant molecule. At some time point RNA molecule through random chance on and bonding the hairpin loops forming ribozymes can eventually perform a catalystic role and we call it as RNA catalyst and this is a random event.

Now, you imagine if a given RNA molecule by virtue of its sequence which in turn allows a proper secondary structure to form. It now can easily make a copy of itself then what will happen all these macro molecules that are present can technically get converted into those RNA here macro molecule we are referring to the intermediates of RNA. So,

this molecule can then split through catalysis and then form a template with free floating nucleotides.

So, then if there are 10 molecule that have say an RNA molecule that has got 10 bases, another RNA molecule that have got 50 bases, another RNA molecule that has got 200 bases none of them are able to make a copy of itself. Now comes a new RNA molecule that is having 200 or 500 base which can make a copy of itself then what it will do?

It can catch hold of this non replicating RNA molecule and cleave its bond and use that energy and try to make a copy of this newly formed molecule. As a result of which you can end up having a dominant soup of molecules that have this ribozyme or this RNA that has got a catalytic role. So, this dominance is allowing the propagation of this group of RNA molecules.

So, this allows it to rapidly replicate itself giving it a chance to increase its number against the tide of entropy. Remember entropy is always there the molecule is always challenged. So, it should be able to resist itself from the degradation over time this replicating RNA became dominant in the prebiotic soup. So, I will end the class with this and we will resume in the next class.