**Medicinal Chemistry**
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**RNA and Protein Synthesis**

In today's lecture we are going to look at the structure of RNA and how RNA plays a very key role in protein synthesis.

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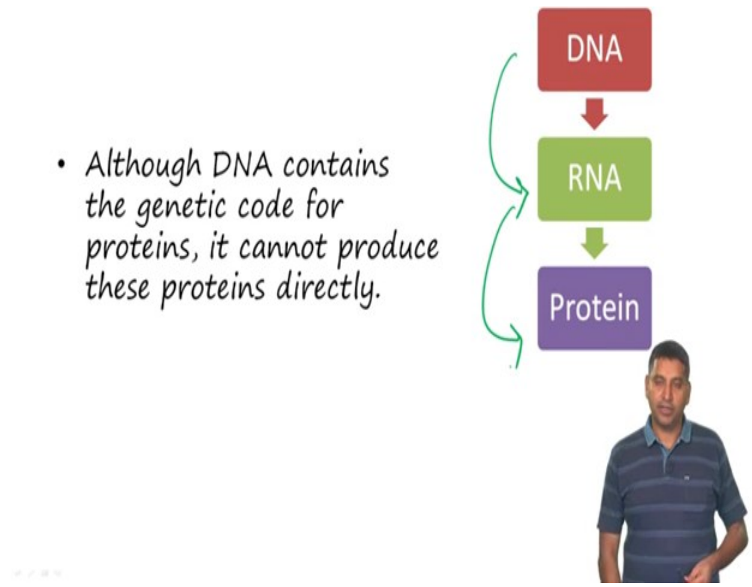


So before we get there, let us look at the central dogma of molecular biology which is basically the DNA contains the information that is present in the cell. DNA transfers the information to RNA and RNA in turn is able to use that information to synthesize protein. So although DNA contains the genetic code, it cannot produce these proteins directly.

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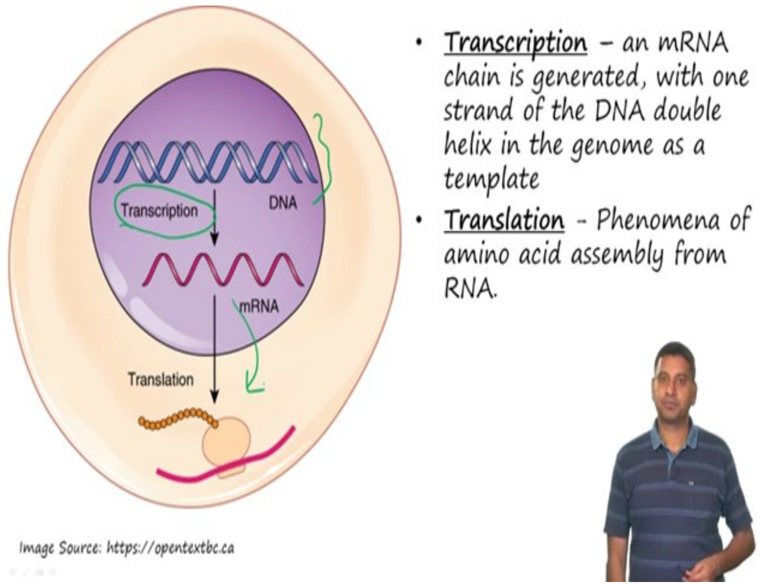


So in order to look at the big picture, let us look at a cell. Inside the nucleus, there is DNA as I mentioned earlier which contains the genetic information. And through the process of transcription which is nothing but generation of an mRNA chain, mRNA is nothing but a messenger RNA and the messenger RNA has one strand and this one strand contains the information or the code from the parent DNA. This mRNA then translocates out of the nucleus, gets into the cytoplasm and then it starts doing the process of translation which is nothing but amino acid assembly from RNA.

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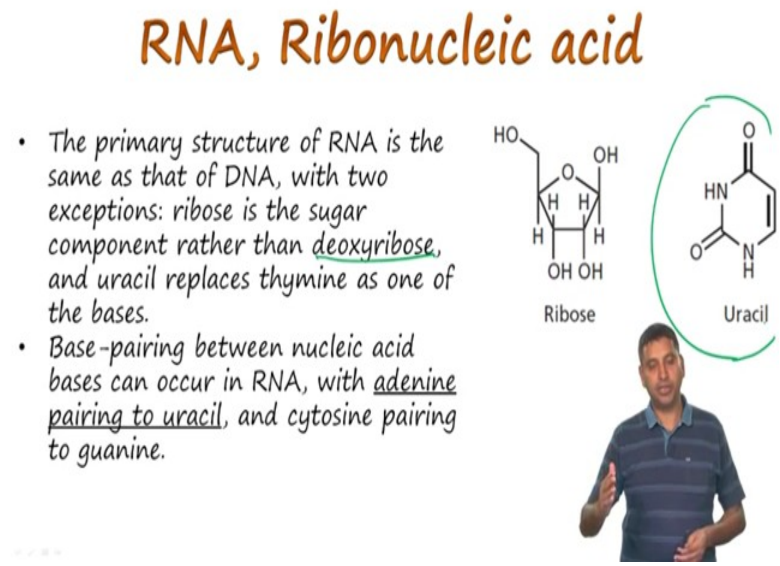


So now let us look at the structure of ribonucleic acid, also known as RNA. The primary structure of RNA is nearly identical to that of DNA except that it has a ribose sugar and it is not a deoxyribose. So deoxyribose is the main sugar in DNA whereas RNA, the main sugar is ribose. The base pairing between the nucleic acid bases can occur in RNA with adenine pairing with uracil. So that is another difference as far as RNA is concerned and as with DNA cytosine pairs to guanine.

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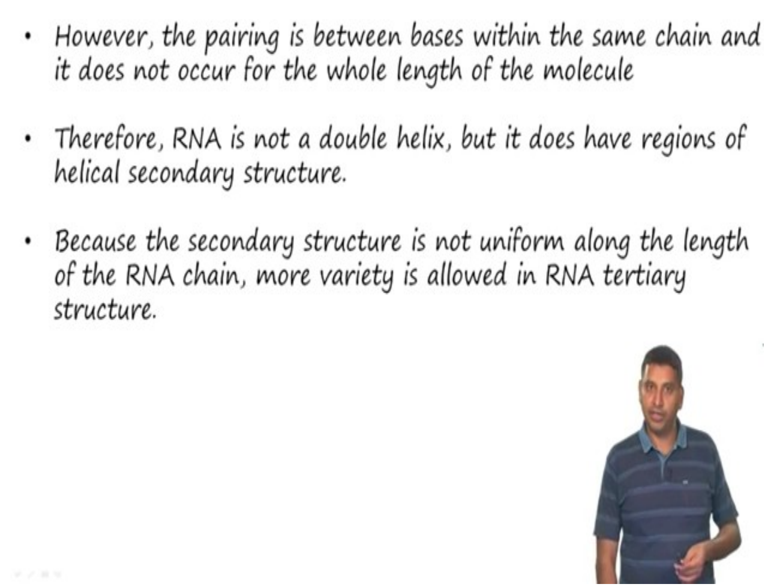


However the pairing is between bases within the same chain and it does not occur for the whole length of the molecule. Therefore, RNA is not always a double helix but it can have regions of helical secondary structure. And because the secondary structure is not uniform along the length of the RNA chain, a lot of variety is incorporated in the RNA tertiary structure. We look into some of these aspects later on in this lecture.

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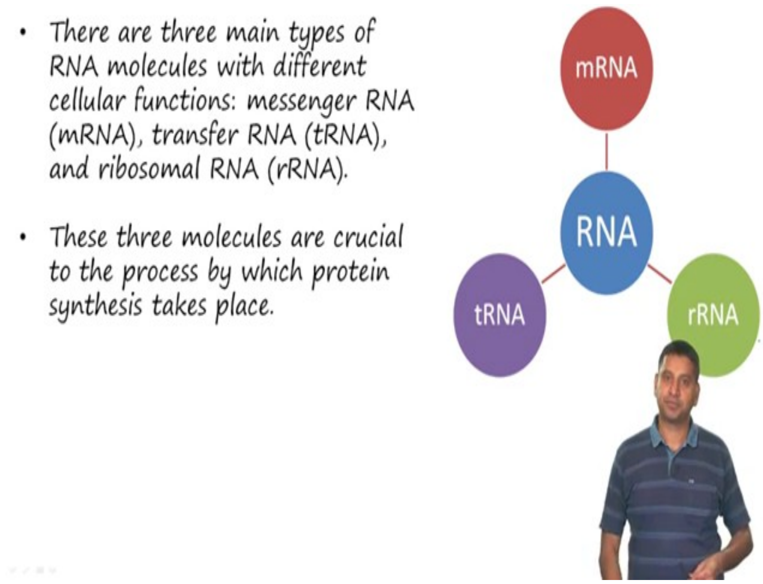


So there are three main types of RNA molecules. The first one is messenger RNA which we already referred to earlier, which is the one that takes the code from DNA. The second type of RNA is called the transfer RNA and the third one is called the ribosomal RNA. And these three molecules are crucial for the process of protein synthesis.

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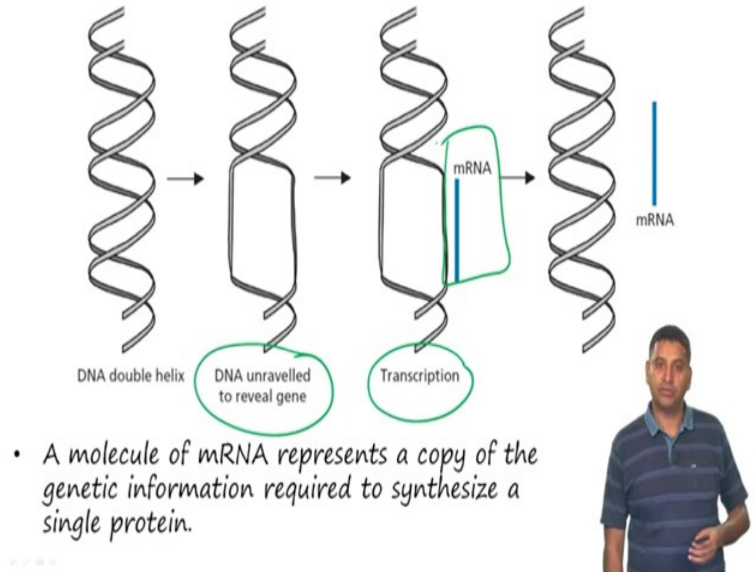


So now let us look at how the first transcription process takes place. In the previous lecture, we looked at how DNA exists as a double helix. And once the information from DNA needs to be transferred to let's say another DNA during cell division, we looked at the process of how another template is formed and DNA is synthesized and so on and so forth. Now in order for proteins to be synthesized a very similar process has to occur, that is, the information from DNA has to be transferred to what is known as messenger RNA.

So the first step in this is that DNA is unraveled and it reveals the gene. Then there is a process of transcription where a single strand mRNA is actually synthesized. And this mRNA is then, as we looked earlier is going to be released into the cytosol and it is going to help with protein synthesis.

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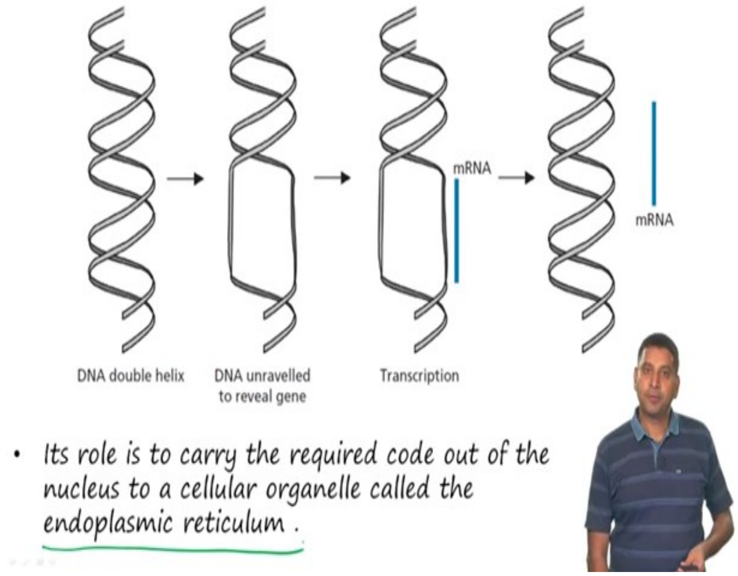


Now the role of mRNA is to carry the code out of the nucleus to a cellular organelle which is known as the endoplasmic reticulum.

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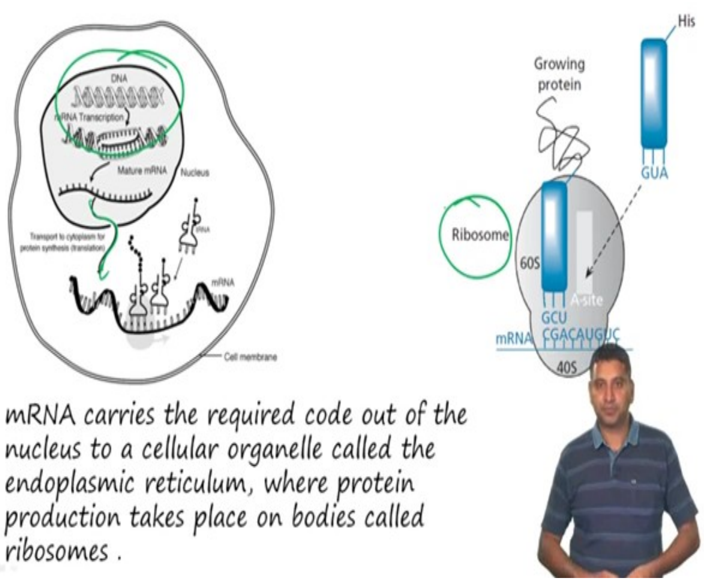


And in a nutshell, if you see how this process works, the DNA transcribes the information to mRNA and this mRNA gets out of the cytosol and it goes into the endoplasmic reticulum where along with transfer RNA and ribosomal RNA it is able to synthesize proteins. Here we can look at the picture of a ribosome. A ribosome is a very important component in protein synthesis.

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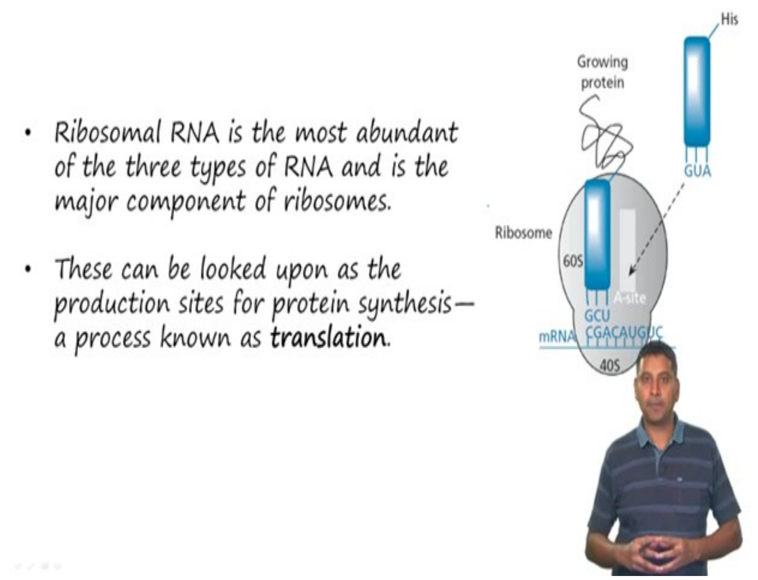


Ribosomal RNA is the most abundant of the three types of RNA and is the major component of ribosomes. This can be looked upon as production sites for protein synthesis, a process which is known as translation.

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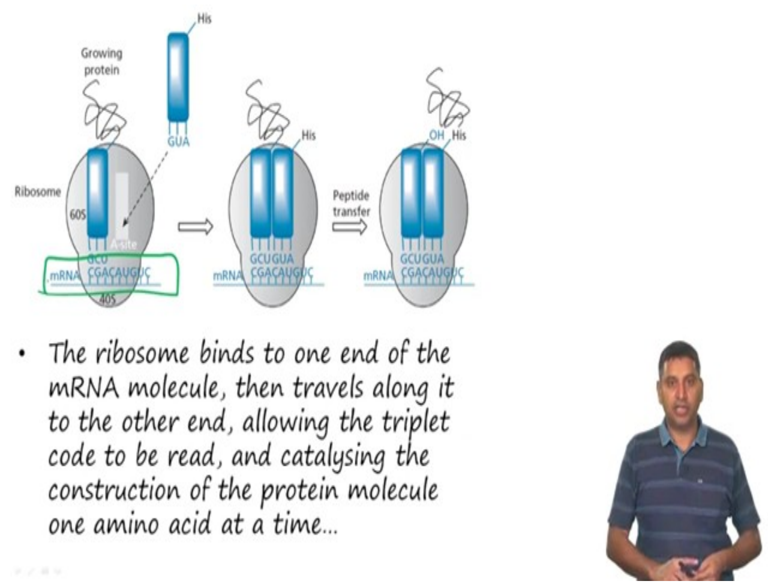


Now let us look at the, how this process of translation occurs. The ribosome binds to one end of mRNA molecule. That is, here is your mRNA molecule and ribosome binds to one end of this molecule. And then it travels along to the other end. As we looked at earlier the information from DNA is actually in the form of three units which is called as the triplet code. So each triplet code corresponds to a unique amino acid. And therefore this ribosome ends up catalyzing the construction of the protein molecule one amino acid at a time or one triplet code at a time.

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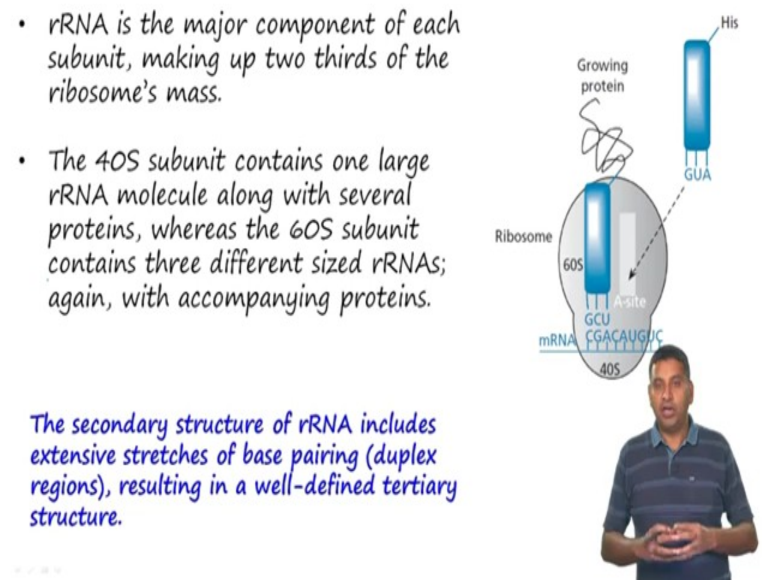


So rRNA is the major component of each subunit, making up of two thirds of the ribosome mass. And there are two subunits, one is called the 40S subunit which contains one large rRNA molecule. And the other one is the 60S subunit which contains three different sized rRNA. Of course, there are proteins which accompany this. The secondary structure of RNA includes extensive stretches of base pairing which is duplex regions, resulting in well-defined tertiary structures.

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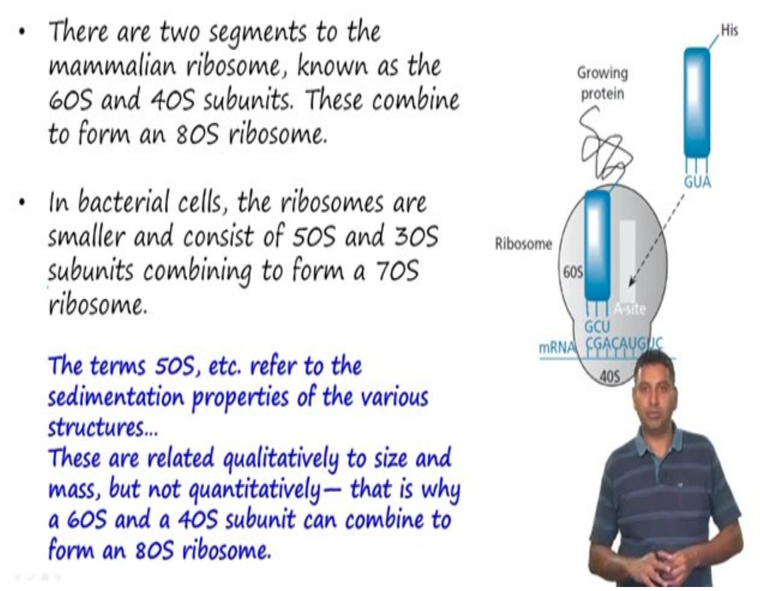

There are two segments to the mammalian ribosome, known as the 60S and the 40S subunits. These combine to form a 80S subunit. Of course the term 50S refers to the sedimentation properties of the various structures. These are related qualitatively to the size and mass but not quantitatively. That is why a 60S and a 40S subunit can combine to form an 80S subunit. In bacteria, the ribosomes are smaller and consists of 50S and 30S subunits, combining to form a 70S subunit.

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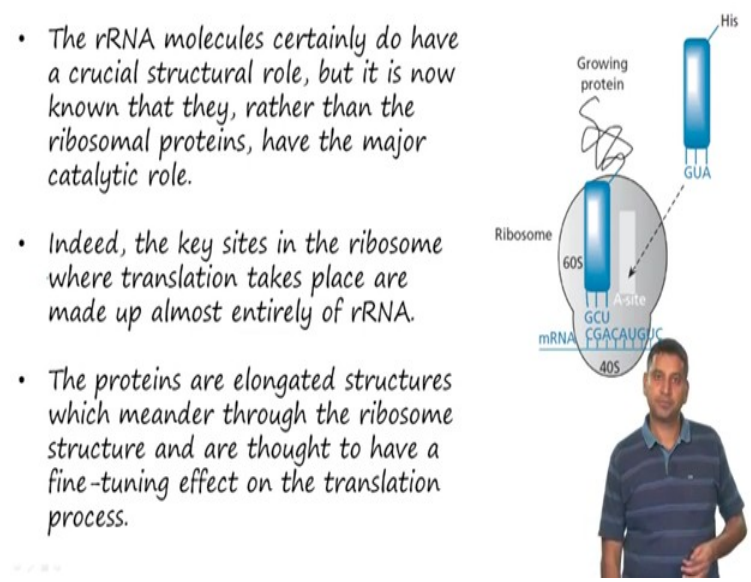


The rRNA molecules certainly have a crucial structural role, but it is now known that they, rather than the ribosomal proteins have the major catalytic role. Indeed, the key sites in the ribosome where translation takes place are made up almost entirely of rRNA. The proteins are elongated structures which meander through the ribosome structure and are thought to have a fine-tuning effect on the entire translation process.

So to understand this RNA plays, a ribosomal RNA plays the most crucial structural role as well as catalytic role in the entire translation process. While the protein helps with fine-tuning of this process.

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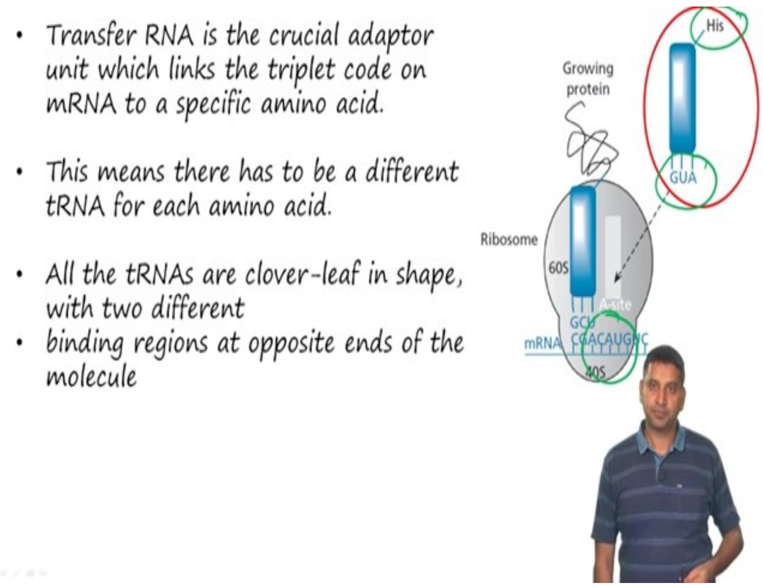


Transfer RNA which is the third kind of RNA is an important player in this. And as you can see here, this is the, the circled structure here is the transfer RNA and the transfer RNA links the triplet code on the mRNA to a specific amino acid. So this tRNA has attached to it an amino acid, in this case histidine. And it has a code which is complimentary in nature to the binding site here. Once it binds, then it charges the ribosome with the correct amino acid. So therefore there has to be a different tRNA for each amino acid. All the tRNAs are clover-leaf in shape with two different binding regions at opposite ends of the molecule.

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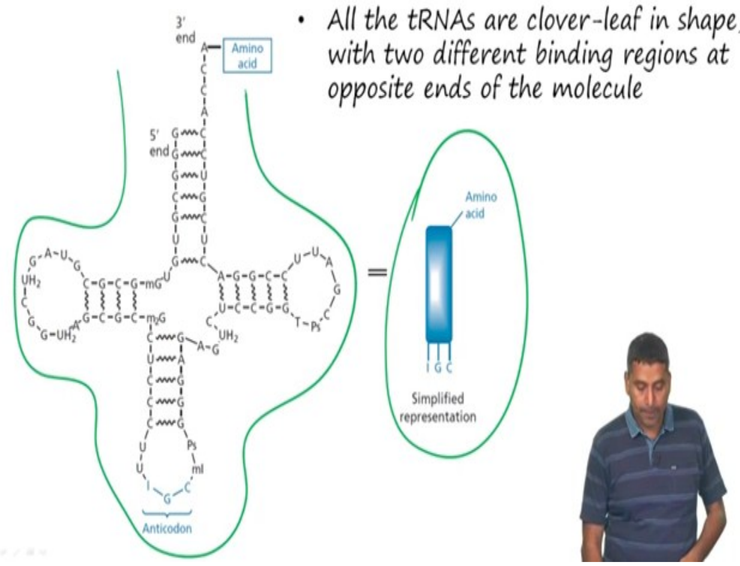


Now let us look at the structure of the tRNA. And here is the clover-leaf type molecule. And in this, there are two different binding regions at opposite ends of the molecule. So this is the simplified version that we saw in the previous slide. But the actual shape of the molecule is somewhat like this.

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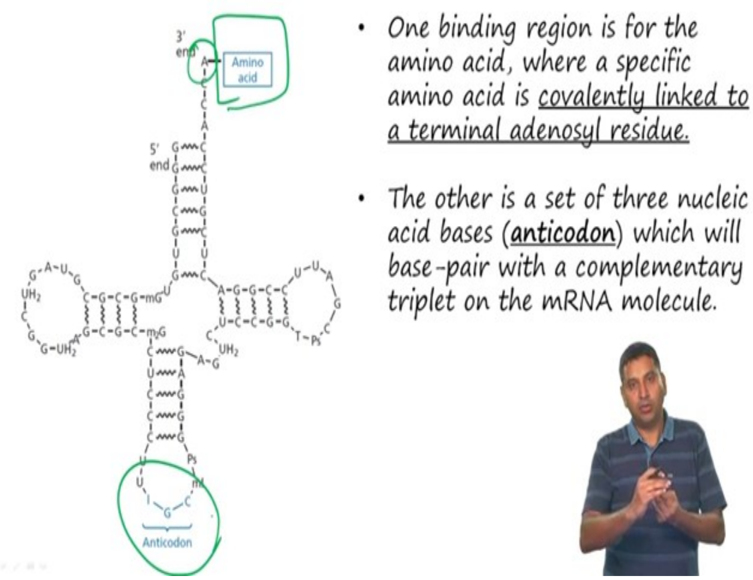


So one binding region is for the amino acid, as shown here where a specific amino acid is covalently linked to a terminal adenosyl residue just here. The other set is the, other end is the set of three nucleic acid bases which is called the anticodon. So as we learned earlier a codon is nothing but three unique bases which code for a particular amino acid. The anticodon is something that comes and can bind to this codon. So this process is called as base pairing and therefore the codon and anticodon will be complimentary in nature.

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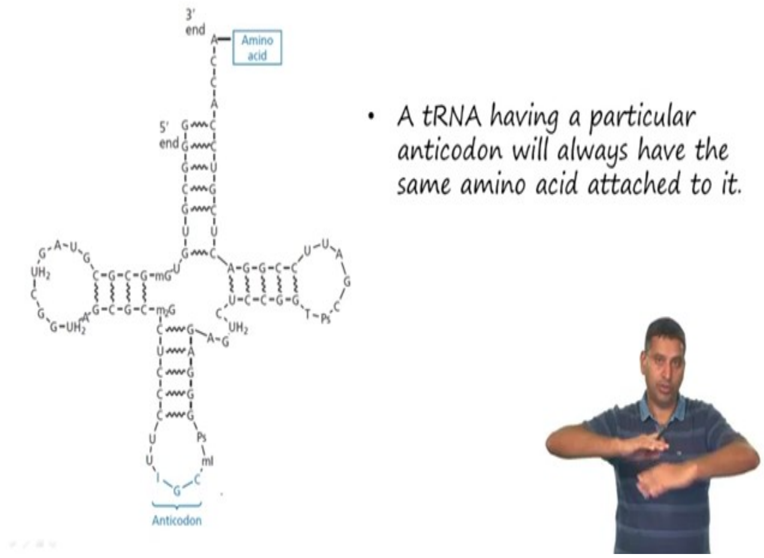


A tRNA having a particular anticodon will always have the same amino acid attached to it. So this is, this way we are assured of putting in the right amino acid when the code is read correctly. That means the information from the mRNA is being transferred with high fidelity to the synthesis of the protein because the tRNA that comes and binds to it has the right amino acid attached to it.

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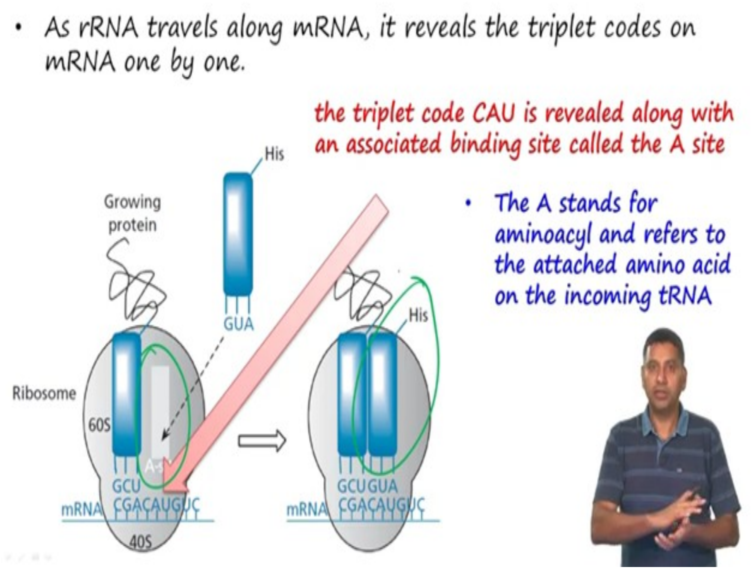


So now as the ribosomal RNA travels along the mRNA, it reveals the triplet codon on the mRNA one by one. So the ribosome has two sites. One is the P site and the other one is the A site. The A site which is here stands for the aminoacyl site. So here in this example, the triplet code CAU is revealed along with an associated binding site called the A site. Now the tRNA which has the correct complimentary anticodon will come and bind to this region and will occupy the A site. So as you see here the correct tRNA molecule will occupy the A site.

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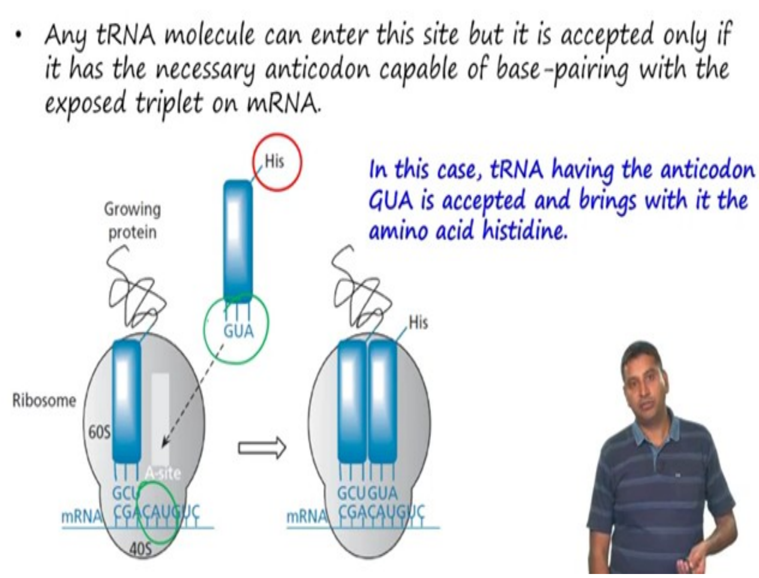


Any tRNA molecule can enter this site, there is not restriction on that. But the only one that is capable of base pairing correctly to the exposed triplet on mRNA will bind. So therefore, you could have a situation where tRNA from, which codes for glycine or for another amino acid like cysteine can come in. But since this region and this region may not match, you will have the tRNA departing.

Whereas once the tRNA molecule with the correct structure comes in, it is going to bind and the binding is so strong that it is able to occupy A site and carry forward the protein synthesis. So as I mentioned earlier, in this case the tRNA having the anticodon GUA is accepted and brings along with it the amino acid histidine.

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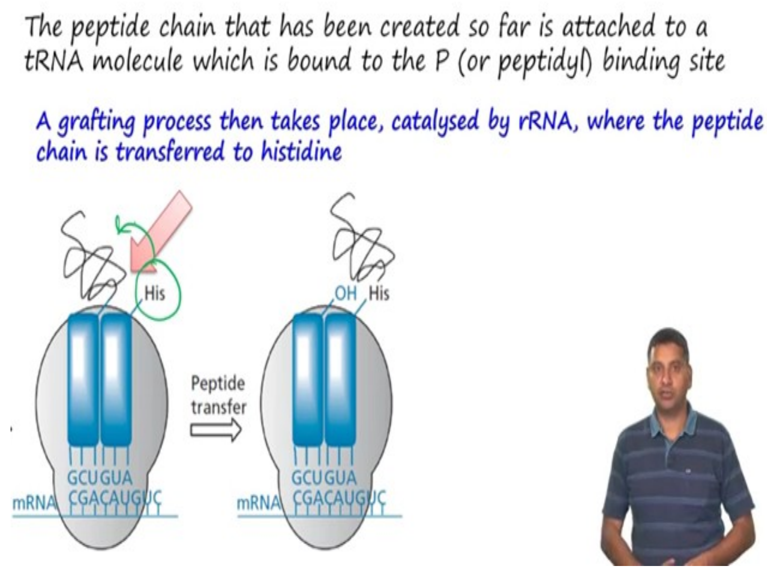


The peptide chain that has been created so far is a tRNA which is shown here, is bound to the P site which I mentioned earlier or the peptidyl binding site. Now, once these two sites are occupied, which is over here and here, there is a process of peptide transfer. So the histidine which is present over here, has to get transferred to this peptide and then the next frame can come in. So this grafting process then takes place, which is again catalyzed by rRNA where the peptide chain is transferred.

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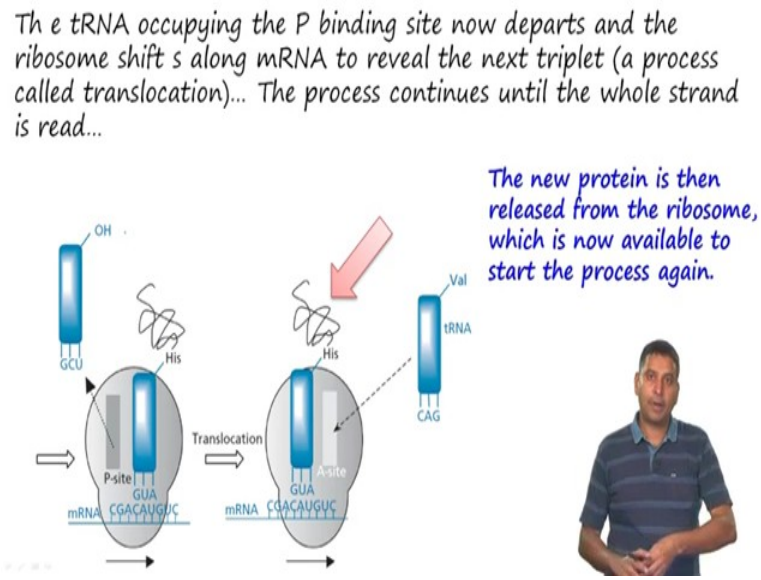


The tRNA occupying the P binding site now departs and the ribosome shifts along mRNA to reveal the next triplet codon. And this process is called translocation. And you can imagine that this process goes on and on until the entire strand of information is read. So the new protein is then released from the ribosome which is now available to start the process once again. So therefore from DNA, the information is transferred to mRNA and then mRNA migrates to the ribosome and here rRNA and tRNA in concert are able to synthesize the protein.

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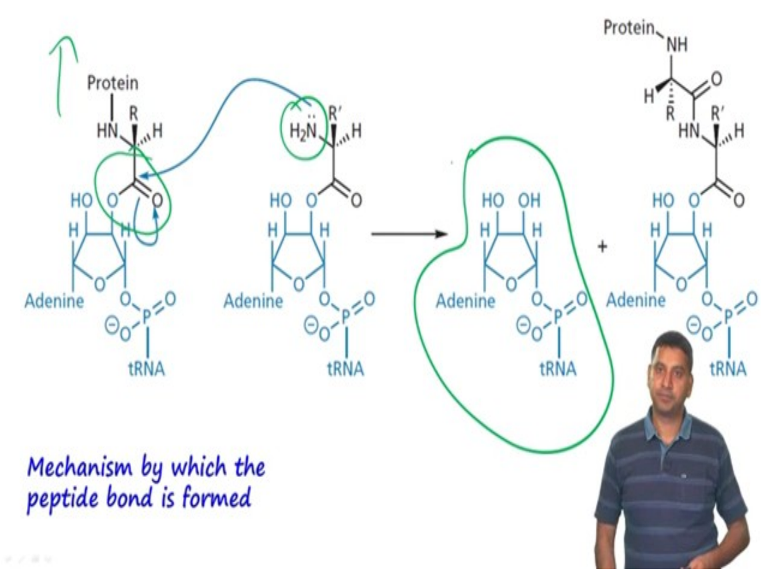


So the chemical mechanism by which this process occurs is that you have an acyl bond that is produced. Here are the amino acid, and here is the protein chain that is growing. And here is the amine of the amino acid in the A site and now this attacks and kicks out the free alcohol which is here and it produces the new peptide chain.

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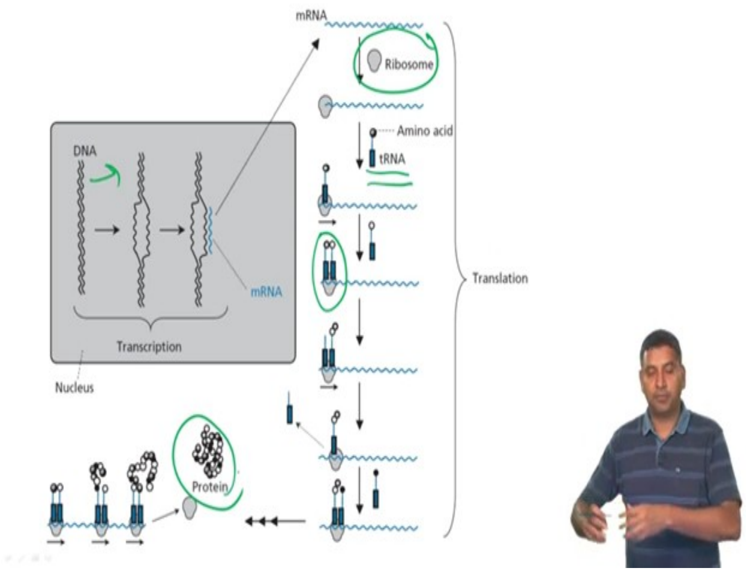


So in a nutshell, DNA it first unwinds and produces, reveals the area where the gene is and then the gene is read by mRNA. mRNA translocates; once it goes, it goes and binds to ribosome and then the tRNA is brought into picture. The tRNA is charged with the correct amino acid and once it comes, there is a P site and A site. And then here the peptide bond is formed. The tRNA in P site is kicked out and there is a shift in the frame. It reads the next triplet codon and then the correct tRNA with the right anticodon comes in and so on and so forth. And this happens until the protein is synthesized.

So the key terms here are transcription where the code from DNA is transcribed to mRNA. The second key word is translation where mRNA, the code on mRNA is now used to synthesize the right kind of protein. So together this is the process by which the information in DNA is converted to a protein.