Introduction to Cell Biology
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Central Dogma: The DNA structure Part 2

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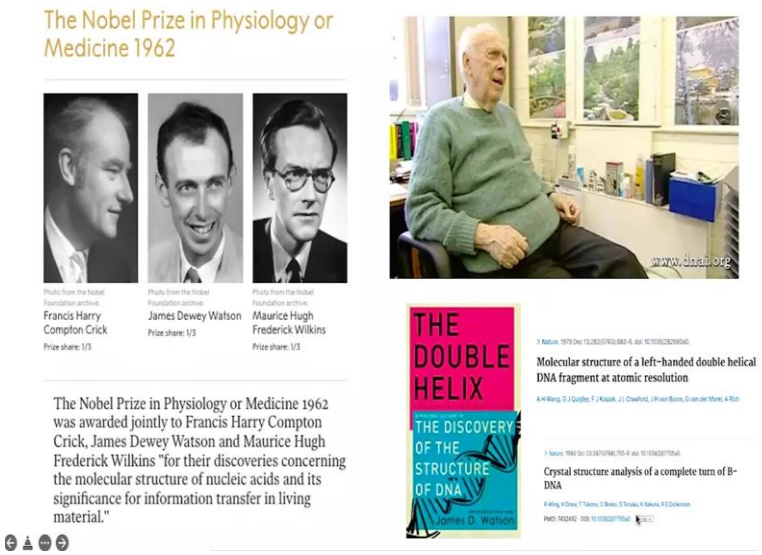

In 1962, almost nine years after the model was published, and fiber diffraction images were published, Crick, Watson and Maurice Wilkins got a Nobel Prize for Physiology and Medicine in 1962. Now, let us just hear Watson, he is fairly senior at the point this particular interview was taken. Let us just hear his voice, because he is one of the very, very major figures of biology in the last century.

James Watson: I guess my chief advantage came from my coming from the field of genetics, where the big question is, what is the gene and I tend to box myself in and that was the only problem we were solving. Whereas Rosalind was trained as a physical chemist, Maurice is a physicist. They did not see themselves as having only one objective. So, my advantage one was, it was the only thing I wanted to do.

And second, the other advantage was I had a collaborator who was Francis, so one cannot underestimate the importance. If I come to Cambridge and Francis was not there, I would not have found the structure of DNA. I would not have, had someone to talk about the meaning of the X-ray diffraction Preutz and group were more interested in proteins. So, Francis, saw DNA is tremendously I should say, Francis thought that DNA is potentially the most exciting molecule around.

Professor: So, that was James Watson, sitting here in Cold Spring, Cold Spring Harbor Laboratory. He joined Cold Spring Harbor Laboratory and was its director for a very long time. And he settled over there, major role in setting up leadership in that particular institute. Francis Crick went to Salk Institute in San Diego, and then he set up again, a very, very nice set of units. The actual structure of DNA came fairly late.

There is a paper in 1979, about the Z form of DNA, which I will talk about. And another paper in 1980, from Dickerson's lab, where the first turn of B-DNA was solved. Now, these structures came almost 20 years after protein structures came. And part of the reason was that DNA is a very flexible and a very floppy molecule.

And it is this floppiness of DNA, which makes it extremely difficult to crystallize which is why fiber diffraction was the means to get gather data on DNA in the.

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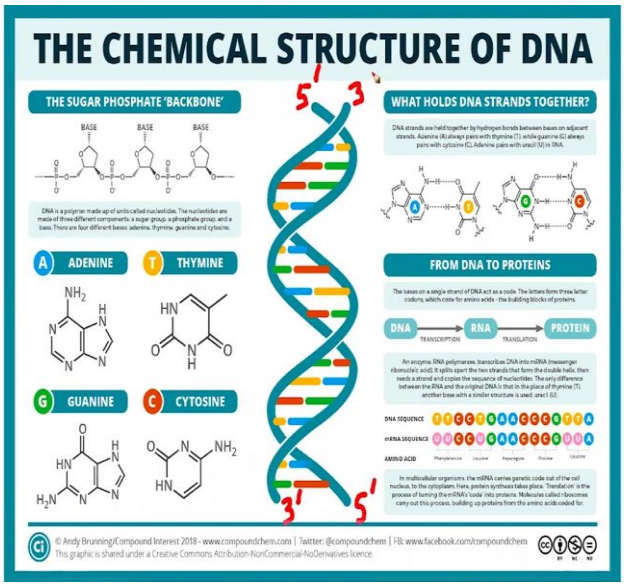

So, let us now go into the chemical structure of DNA. Here is the DNA double helix in front of you. And in blue, orange, green and red are the bases which are inside the double helix with the phosphate backbone outside the double helix. This is the way the backbone looks phosphate sugar, phosphate sugar, phosphate sugar, with the bases sticking out.

And these bases sticking out form hydrogen bonds with an opposite base to make the DNA double helix. And effectively what is holding these two strands together are hydrogen bonds. You can see these hydrogen bonds as dotted lines between adenine and thymine, which is a double bond and between guanine and cytosine, which is pretty much a triple bond.

So, the double helical structure of DNA consists of two anti-parallel sheets. And these two anti-parallel sheets are anti parallel because one is running to a 5 prime to 3 prime orientation and other is running in completely the opposite terminal direction.

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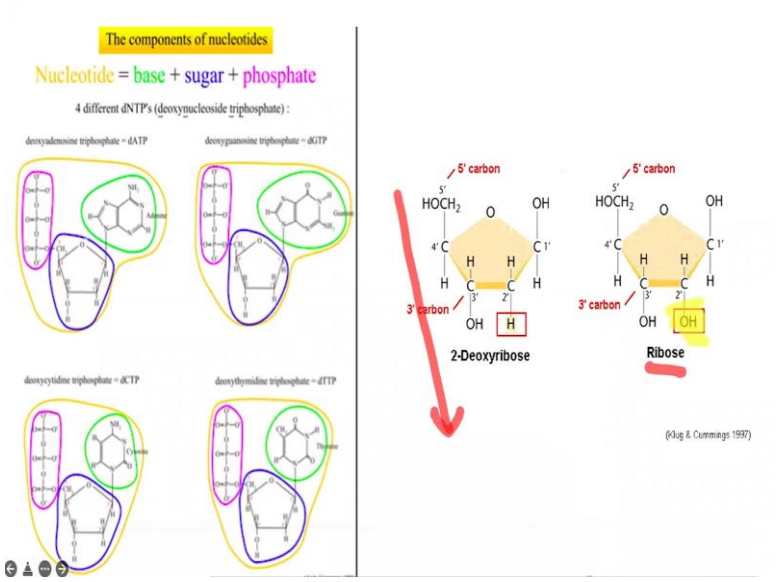

Because some of you asked, here is a little bit more detail. These are the four different nucleotides with the base, the sugar and the phosphate. Basically, circled over here, this is deoxyadenosine triphosphate, which is used to which is polymerized along with the other nucleotides to make up DNA. This is dGTP I am using the small form, dCTP and dTTP. This is the sugar itself.

And one of you asked me a question about labeling. So, this is the labeling of the carbon atoms in the sugar, carbon 1, carbon 2, carbon 3, carbon 4 and carbon 5. And the polymerization of the nucleotides is happening from 5 prime to 3 prime direction, which is basically this direction, which is why we say 5 prime to 3 prime, and deoxyribose ribose is the sugar used for DNA.

But for RNA, the sugar, which is used by the molecule is different, it is basically ribose. And you can see that difference primarily is at this point where the oxygen group is missing in the case of the sugar in DNA, but not in the sugar in RNA.

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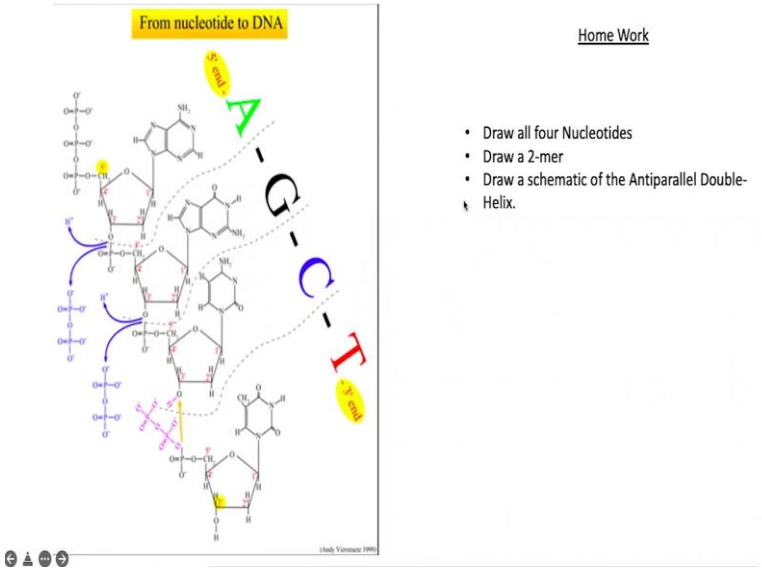

Here is how the nucleotides are coming together. And this is done by basically by DNA polymerase, it is taking a nucleotide at a time and putting them in a very specific sequence one after the other. And this is usually done when it is copying of the other strand something I will show you.

And you can see the release of a proton and the release of a di-phosphate group each time this is happening. I strongly urge all of you to do this homework, I would ask you to draw all four nucleotides, draw a 2-mer that is put two nucleotides together and see how you lose two phosphates and a proton. And also draws schematic of anti-parallel double helix.

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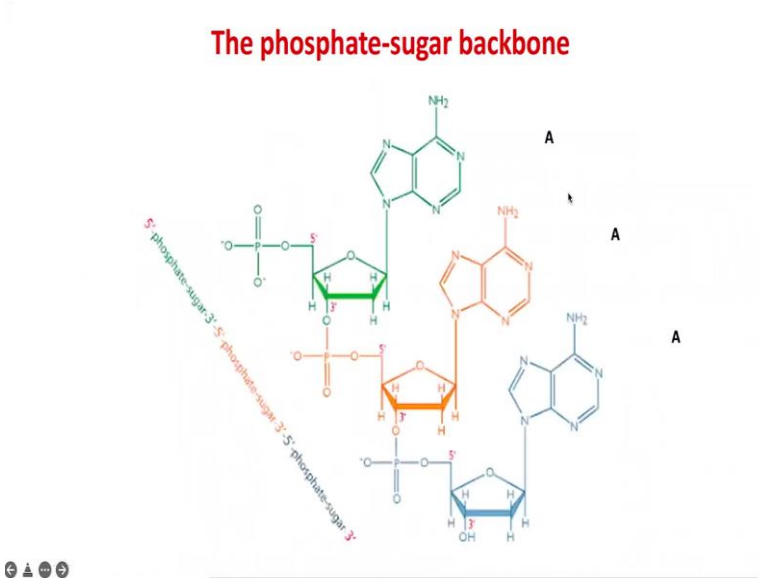

Here is again a picture showing you the phosphate sugar, phosphate sugar, phosphate sugar, phosphate sugar backbone, and the nucleotides in this case adenine sticking out from the sugars, which makes up one strand of the DNA double helix.

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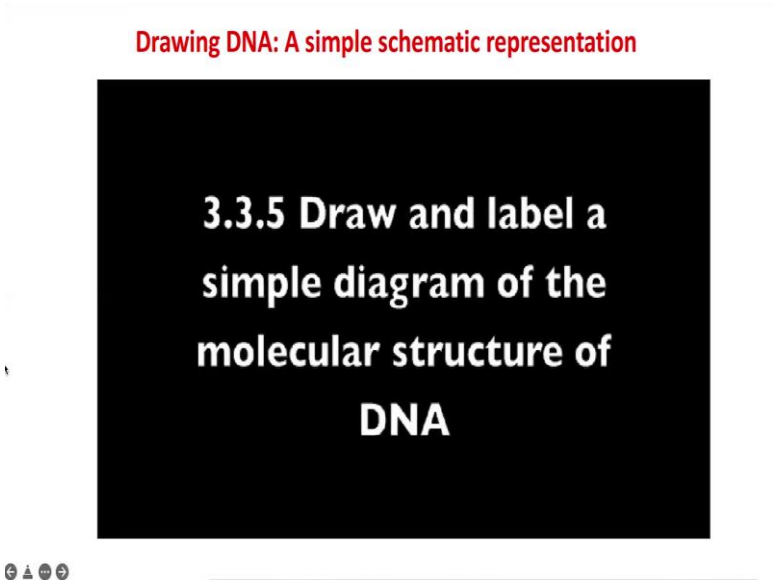

This is something you can practice it is useful for you to do so.

Unknown speaker: So, here I am going to demonstrate drawing the simple structure of DNA. And now you do not need to be an artist to do this. So, what one only cares about is that you get the relative positions of the phosphate group that deoxyribose sugar by most known as the sugar phosphate backbone and the nitrogenous bases relatively they need to be in the correct positions.

Now as I draw the second strand here, please note that it is anti-parallel, my deoxyribose pentose sugar is effectively like pointing down. This is somewhat difficult to draw on a computer screen for you, what you might want to do is actually turn the page upside down so you are drawing the same shape, it is just in the opposite direction.

Now once you have drawn it, you want to make sure that you label everything so that is the hydrogen bonds, the covalent bonds, the nitrogenous bases, deoxyribose, the phosphate group and go ahead and draw a line around a nucleotide as well.

Professor: So, this gives you an idea of the biochemistry as well as the structure of DNA. And this is something you should sit down and draw.

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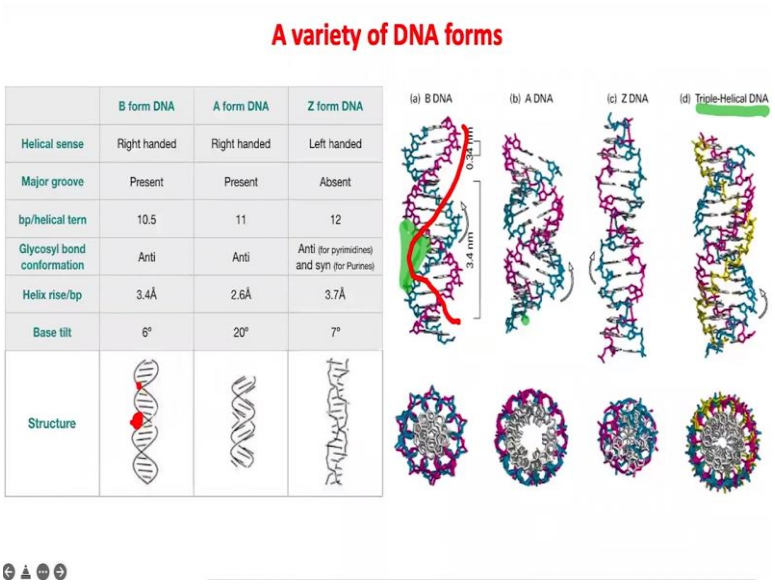

So, let me move on now from the last five minutes to the last topic, which is basically the variety of DNA forms. Now, so Rosalind Franklin could move between these two forms, which gave different patterns on fiber diffraction images, by just changing the humidity of the chamber in which the DNA was there.

So, in other ways, it so to emphasize, if this particular strand of DNA which you are seeing here is B form of DNA, had a sequence and I am just going to write down a random sequence this does not have any meaning, A, T, G, C, C, C, C, A, A, if this was the sequence, the same sequence could make B form of DNA or A form of DNA depending on the humidity of the chamber and the salt concentration, which was there in the solution in which the fiber was sitting.

Now, the three major forms of DNA there are many many forms of DNA which have been discovered over the years, but the classical forms are B form DNA, A form DNA and Z form DNA. B and A form basically are right handed whereas the Z form is kind of left handed and the handedness can be seen, if you look down the axis and follow 5 prime to 3 prime whether it is turning its right handed.

It is going in a clockwise fashion or in an anti-clockwise fashion, there is something called as a major groove and this is an architectural feature which is over here and there is something called as a minor groove which is basically somewhere over here. The base pairs per helical turn, so, this is a helical, turn are slightly different as you can see, the A form of DNA is basically a little bit more compact.

So, this is one term. And again, this is one term. So, you can see that the base pairs per seemed to change. And there are other small differences which finally lead to kind of different, let's use the term confirmations of DNA, which you see and there are biological implications of these different forms of DNA which I will really not be talking about it at this point.

Student: Sir, please re-explain the groove part what is exactly the groove?

Professor: Groove is that it is basically a large let us call this a hole over here or it is a sort of a docking site. So, this would be the major groove of DNA, this one, architecturally. And in fact, if you see over here, we know that there is a triple helical form of DNA which also exists and if you look carefully at the triple helical form, specifically if you look at the way the yellow is the third helix is coming, you will realize that it actually sits in this major group like this.

So, the major grove is an architectural feature and it is actually used by proteins which are docking to DNA, the B form of DNA has a very large major groove, so over here this is the major groove and this is the minor groove.

Student: And sir, what is exactly meant by anti and syn glycosidic bond contribution.

Professor: So, this is basically basic chemistry can you just do a search Google as to what anti and syn means?

Student: I understand the meaning but here what does it mean?

Professor: There is no difference in the meaning. Remember, DNA is nothing but a chemical entity. So, the same definition for anti and syn which is there in chemistry is the definition over here.

Student: Sir, there are 10 base pairs per helical tern in B form, there are written 10.5. Okay,

Professor: So, I have got this from a textbook, and I guess they are small variations between textbooks. Remember, DNA is a floppy flexible entity, which is a dynamic entity, it is constantly jumping around. So, measurements of different people may change slightly.

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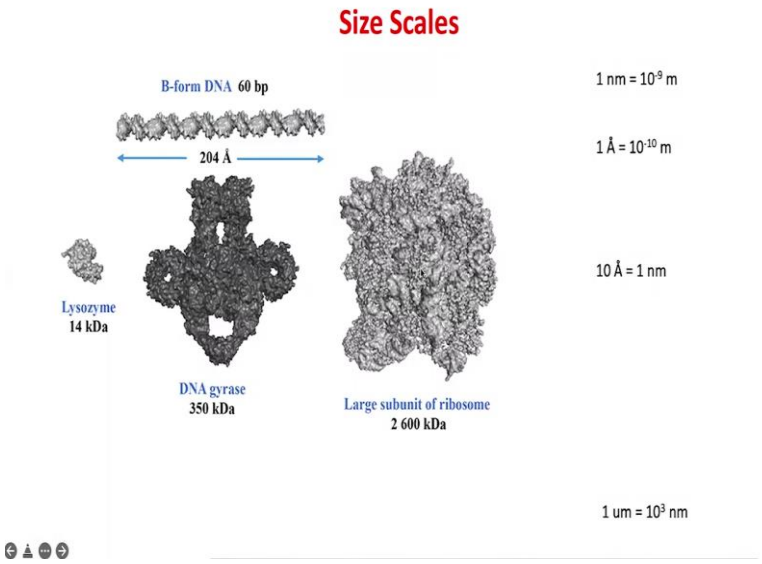

Let me end by talking about size scales, I just want you to appreciate the volumes of these molecular entities. On the right hand side, I have explained very basic things which you already know that a nanometer is 10 raised to 9 meter. And a micrometer is basically 10 raised to 3 nanometers. The term the unit angstrom is used in crystallography quite a lot. 10 angstrom is basically 1 nanometer. Now, this is the B form of DNA 60 base pairs, you know what a base pair is now. And it will basically be about 204 angstroms in length.

These are three proteins, a small protein lysozyme, middling protein DNA gyrase, you can see all these holes in DNA gyrase, where DNA will actually slide through these holes. And there is a large protein over here, which is one of the largest known in the cell, which is the ribosome. So, you can appreciate volume scales and size scales by looking at DNA with respect to Gyrase lysozyme and ribosome.

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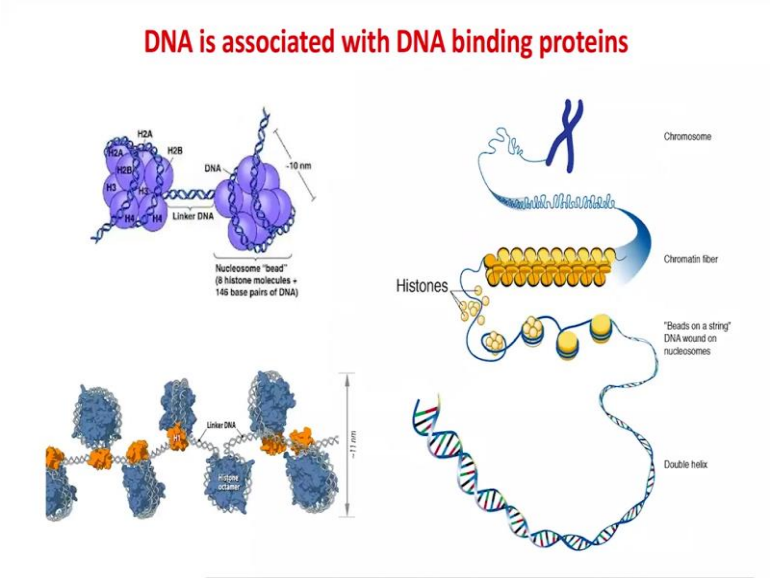

Now, DNA is not naked in the cell, especially in the eukaryotic cell, it is wound around a set of proteins called nucleosomes. And on the left hand side, you see a picture of these nucleosomes and two and a half turns, which is what DNA wraps around octamer of the nucleosomes. These octamers can slide along the DNA, which is also a very interesting feature of DNA.

And at the bottom is a more realistic representation, rather than just a ball and stick representation of the histone octamer and the linker DNA between them. The histone h1 acts as a sort of a clip, clip making sure that the octamer does not fall apart. And this naked DNA is then folded around the nucleosome, nucleosomes themselves fold into higher order chromatin structures. And these chromatin fibers keep on folding into higher and higher order structures finally making up a chromosome. So, I will stop over here.