Introduction to Complex Biological Systems
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Lecture 43
Understanding viruses - the smallest enemy

Hello everyone, currently we are discussing Module 9 and in this lecture I will be discussing viruses. They are also known as the smallest enemy. So, in this lecture I will be covering a general introduction about viruses followed by their unique multiplication strategies and then also I will introduce about equilibrium and non-equilibrium viruses and at the end, the link between viral infection and cancer. Because all of us, we are aware of viral infection and it causes different types of diseases like flu, fever, something like that. But also viral infection can cause cancer. So, let us start from the introductory part.

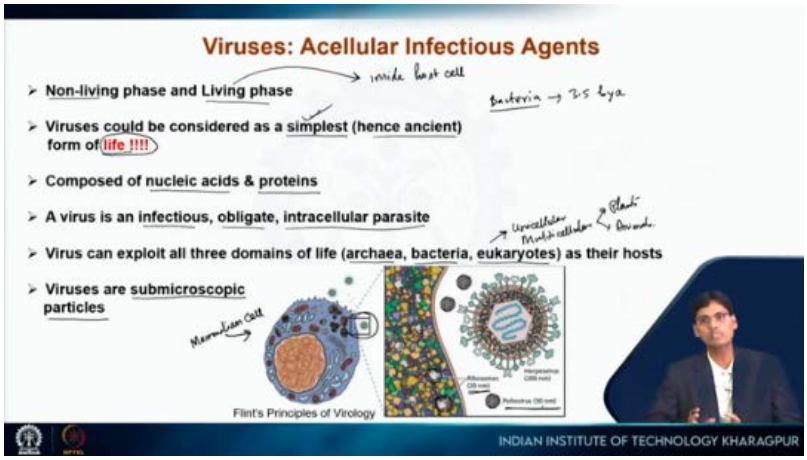
So, virus is a cellular infectious agent and they have two phase one is non-living and the other one is living phase because viruses are not cells; they are not truly an organism. Sometimes when we speak or talk, we mention them that way, but strictly speaking, viruses are acellular. They only stay or, I would say, they show some of their living properties when they are present inside the cell. So, as a result of that living phase only you will be seeing inside host cell otherwise outside host cell is just a non-living object. Then another important feature is virus could be considered as a simplest and hence ancient form of life. So, here this life term is a problematic because I just mentioned that whether it is living or not living that is the problem. Inside the host cell it is showing some state and on the basis of that we can say it is living for example, it can multiply itself but totally it is not living system in that way and also it is simplest because it has not that much of complexity; only it has some nucleic acid and protein, that is all and that this point hence ancient ancient I am mentioning here because it is simplest, but still scientists believe that viruses are not as ancient as bacteria. Because I already mentioned virus need host in order to survive in order to multiply so that host should be evolved even before the virus. So, that is why generally scientists considered that bacteria.

So they evolved around 3.5 billion years ago, and in comparison to that, viruses came a little later, around 2 to 2.5 billion years ago, because they need a host to multiply, so they evolved a little later, but still they are the simplest. This is just composed of nucleic acids and proteins that I have already mentioned and a virus is an infectious obligate and intracellular parasite so it needs to infect some host. It can be a plant or an animal, but it doesn't matter; what matters is that it is an infectious particle and an obligate intracellular parasite. Without entering the host, it cannot multiply.

Another important property is that viruses can exploit all three domains of life. So, these are the three domains of life: archaea, bacteria and eukaryotes. In eukaryotes, you can say unicellular eukaryotes and then multicellular, and here you can put plants, animals including humans everything so virus can exploit all of them virus can infect all of them so although report about viruses they are attacking archaea is much less but virus. They depend on eukaryotic hosts or infect eukaryotic hosts, particularly humans. There are huge numbers of examples, and the last thing is viruses: they are sub-microscopic particles.

So, they are very small, as I mentioned at the beginning, they are the smallest enemy. So, you need to have an electron microscope to see through it. So, that you can really visualize how viruses look like. So, here just for comparison I am just showing. So, this is some mammalian cell.

So, this is a mammalian cell. Now here only this portion we are showing in a much larger view, as you can see these are the ribosome present in this cell, and the diameter is roughly 20 nanometer, and as you can see the smallest virus or the viruses which are on the smaller side are approximately 30 nanometer, for example poliovirus. So, as a result, a virus particle is almost the same dimension as a ribosome, and you can understand that inside one eukaryotic cell, such as a mammalian cell, there are thousands of ribosomes present, and not just ribosomes; there are also many other cellular organelles and various structures. So, that is why what I am trying to explain to you is that viruses are very small, but still, see how dangerous they are, creating a lot of problems for human societies. Now I would like to focus on some general structural features of viruses.



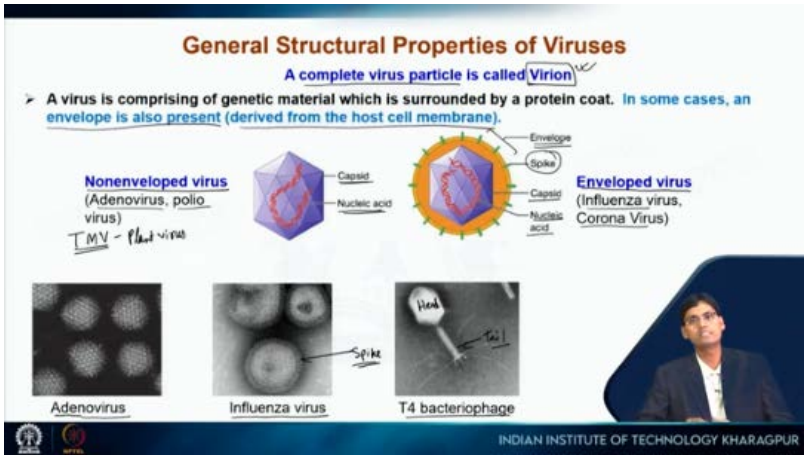
A complete virus particle is also called virion. So, this is called virion. So, you will come across this term also sometime in a textbook or any place, that is why particularly I am mentioning virion, although I am mostly referring to a virus. So now the virus is composed of genetic material, which is surrounded by a protein core. It's a very simple structure and in some cases, an envelope is also present, but it's rare. And this envelope is derived from the host cell membrane, so when the virus is there multiplying inside the host and when they are coming out from the host, during that time they acquire this envelope, so that is why i'm explaining that this is derived from the host cell membrane, and now if you see how the virus looks like. Although they are very small, they still look like this is the thing in a living system, you will get a lot of diversity. Although I am saying that a virus is not truly a cell or a living system, you cannot say that but inside the host cell it is showing its living properties and you will see they are so small but they have so diverse features also in terms of their shape, size, and everything. So here, as I already mentioned, that non-enveloped virus means they do not have this envelope outside; for example, adenovirus and poliovirus are non-enveloped viruses. So, then what is this?

So, outside this is the protein coat; this is called capsid. The protein coat of virus is called capsid and inside the protein coat, you have nucleic acid here; this is the simplest structure, and sometimes they might have an envelope, as I already mentioned, for example, in influenza virus or coronavirus they have an envelope outside, so as a result of that, you have the capsid, you have nucleic acid, and in addition to that, they have an envelope and sometimes they have some protein which are known to be present on the surface; this is called spike protein, like coronavirus, influenza virus, all of them have spike proteins. Now,

whatever this simplest structure I mentioned, this protein code can be made up of just one protein or it could be many proteins also. So, that is why the variation is coming.

For example, if I say TMV, then this is tobacco mosaic virus (TMV). This is a plant virus. So, in this virus, if you look at the center, it has one nucleic acid, and it is surrounded by protein, which is the capsid, but the same one protein is present in many, many numbers, and it forms some helix structure, a helical structure of this protein, and they are covering this nucleic acid at the center. So, some other viruses might have multiple proteins also, and they form this capsid. Now, here are some electron micrograph images. For example, this is adenovirus, and here is influenza virus. As I already mentioned, they have some spike-like structure. So, that is why you can see here.

So, this is a spike and now, this is a bacteriophage, for example, T4. As you can see, their structure is completely different. They look completely different: they have a head and a tail, which looks different compared to other viruses. But their basic features are that they are made of only nucleic acid and protein, and some viruses have an envelope. And now, some unique features of viruses: viruses possess DNA or RNA as their genetic material. This is a unique feature because all other living systems, like plants, animals, bacteria, and fungi, have DNA as their genetic material, but here I am mentioning that DNA and RNA both can be the genetic material of a virus, for example, influenza virus has RNA as its genetic material. Now, the interesting discussion should be here: if some viruses contain RNA as their genetic material.

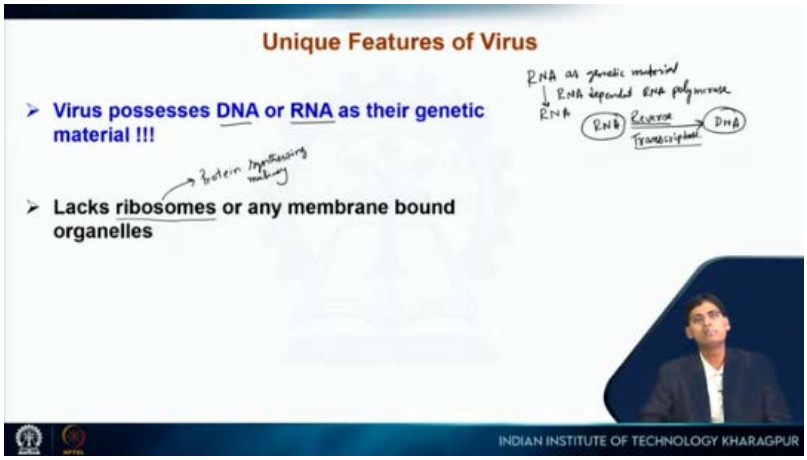


Then, when this virus multiplies inside the cell, it somehow needs to make more RNA in order to multiply. So, as a result of that, you need some enzyme which can make RNA from RNA. So, that is why they need some enzymes. It is called RNA-dependent RNA polymerase. So, you know that in our system, during transcription, I mentioned that we have RNA polymerase, which uses DNA as a template to synthesize RNA, but this is RNA-dependent RNA polymerase.

So, it can synthesize RNA out of RNA which is only present in viruses. So I would say the information to code this enzyme should be there in the viral genome itself, and when it enters inside the host cell, it will make this enzyme. Similarly, some viruses can convert their RNA into DNA. If their genetic material is RNA, they can convert this RNA into DNA, and this is done by some enzyme called reverse transcriptase because as you can see, this is just the opposite of transcription; that is why reverse transcriptase is another enzyme which is only encoded by viruses, for example, HIV, so they have this reverse transcriptase-encoding gene. Now, it is very interesting that these enzymes, particularly this reverse transcriptase, as it is very useful for genetic engineering also. During the genetic engineering lecture, I will discuss how for a routine genetic engineering approach, we use this enzyme in order to make DNA out of mRNA. So, we say that cDNA synthesis by reverse transcriptase enzyme. So those are very essential to carry out genetic engineering techniques.

Now, I am coming back to the virus again. They lack ribosomes or any membrane bound organelles. They are very small; I just mentioned that their size is comparable to ribosomes. They do not have any other organelles and even they do not have ribosomes, i am mentioning because if they do not have ribosomes, that means they cannot synthesize protein.

So, ribosome is protein synthesizing machinery. So, as a result of that If they do not have ribosomes, they cannot make their own protein, so they need to rely on host cells, and then the virus hijacks host cell machinery for their own good, as I just mentioned, to make more and more virus particles. I will discuss how it is happening. Here viral multiplication refers to how viruses actually multiply inside the host cell. So, here in particular I will give an example; I will discuss this with a mammalian cell or animal cell as an example.

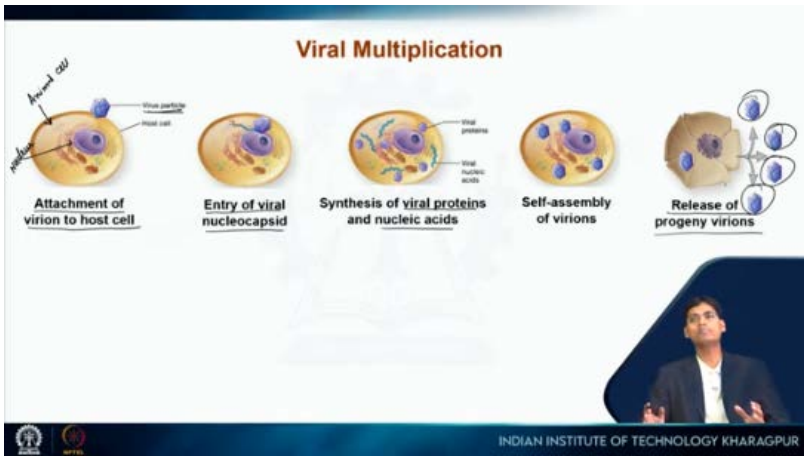


So, as you can see, this is some eukaryotic cell, I can say some animal cell, as you can see the nucleus is present here, this is. nucleus, now what happened to the virus particle? So it is first attached to the surface of the host cell. This is the first step, the attachment of virion to host cell or attachment of the virus to the host cell. Now in the next step what will happen? The virus particle will be inside the host cell. So, this is an entry of viral nucleocapsid.

So, the process is different for different viruses; sometimes endocytosis may happen, and that is why this virus particle goes inside the host cell. Sometimes if you see a bacteriophage. So, in the case of a bacteriophage, the protein coat does not go inside the host cell. So, host cell means here in this case some bacteria because bacteriophage they attack bacteria. So, what do they do? So, they just inject their genetic material inside the bacteria, and from that genetic material, new virus particles will be generated.

So, the mechanism differs, but the major step here is the entry of viral nucleocapsid inside the ah cell and the next step, the synthesis of viral proteins and nucleotides, see both are important. I just mentioned that in the case of bacteriophage, the protein is not entering inside the host cell; that is true. So, that is also what I explained in the first module when I was explaining about the Hershey and Chase experiment. But the thing is, whatever the nucleic acid went inside, it has the information to make both protein and nucleic acid, so as a result of that, synthesis of viral protein and nucleic acid should be the next step and then self-assembly of virions. So then, proteins and nucleic acid should all be assembled together to generate new viral particles, and the final step here is the release of progeny

virions, which means progeny viruses. So, as you can see, they are coming out from the cell; these are all new virus particles coming out from the host cell. So this is a very brief introduction about viral multiplication different stages, but now if I discuss this in a little bit more complex way, then it is something like this, so I will not go into much more details, but a little bit more I will add here in this slide, so as you can see this is one virus. This virus has the protein layer outside, which is called the capsid, and also it has the genome inside. As I mentioned here, the viral genome is present inside the capsid, and now if you see, this virus will first attach to the receptor present on the mammalian cell surface, for example, there are many receptors present; virus-specific receptors are present in host cells, so, for example, many of us know about the HIV virus, human immunodeficiency virus. So, it recognizes some receptor which is present on some T cell. So, which receptor it recognizes CD4 receptor. So, CD4 receptor present in T cell. So, that is why the HIV virus attacks CD4 T cells.



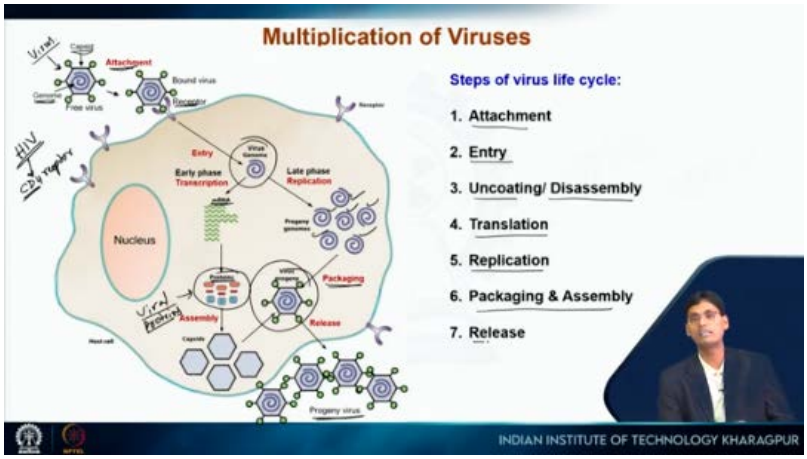
Similarly, I would say HSV virus herpes simplex virus uses different cell adhesion molecules present in our cell surface as their anti-receptor. So, somehow they are hijacking our own system, our own surface protein they are utilizing, and that way they are getting attached, as you can see this is the attachment, and then whenever the virus genome is present inside the cell. Then, the viral genome will do many things, and this is a very complex process that depends on what kind of viruses we are talking about. So, for RNA virus, for DNA virus and then negative strand, positive strand, there are so many complexities there, but in brief, what I want to mention here is that on one hand, from the viral genom. mRNA will be produced in order to make protein because all the raw

materials, the machine, everything present inside the host cell, including ribosome, tRNA, everything present inside the host cell, and that way it will utilize host machinery and it will make viral protein.

So, for example, all these are viral proteins. Maybe they will form the capsid viral protein and at the same time they need to replicate their genome. So, as you can see, this is a replication of their genome. So, whenever the viral proteins are ready as well as the viral genomes are already replicated, then they will assemble; this is a very complex step, even scientists are not aware of everything about the packaging part; this self-assembly process is very interesting for viruses. So, whatever protein and this genomic material they will pack together, and this is a very nice self assembly procedure, and finally, you will be seeing that the complete variant here, complete virus particles, and they are coming out as progeny virus from the host cell.

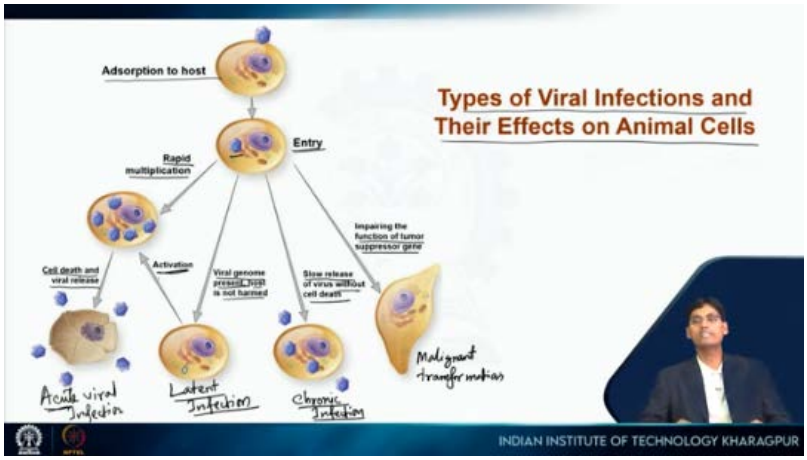
So, this is the overall procedure of how a virus multiplies inside the host cell, and as you can see, I just listed the steps like the first step is attachment, then entry, followed by uncoating or disassembly. So, the viral genome is available and followed by translation of protein. Then replication of the viral genome and then packaging and assembly followed by release of viral particles. Now here whatever I mentioned now this is I would say most of the viruses they infect in this way they multiply in that way for example flu virus like influenza virus something like that but I would say there are Several different types of viruses and their strategy is a little bit different, for example, here I am trying to explain the types of viral infection and their effect on animal cell, you can consider in context to human cell same thing, so here whatever I mentioned, I just mentioned that viral will enter, it will multiply, and then it will rise the host cell and progeny virus will come out. But here is a little bit different way I would like to present this: when the virus attaches to the host cell surface, this is also called adsorption to host, followed by entry and, then there could be different possibilities from what I mentioned; I mentioned this part that rapid multiplication inside the host cell. So, as a result of that, you will say that cell death and the viral particle will be released, as I discussed in the previous slide, and this is an example of acute viral infection. But another case can be something like this: the virus enters inside the host just like this, but the viral genome is now present inside the host cell, but the host

is not harmed, the host cell is not dying, and the virus is not multiplying in that way; it is only residing there. Sometimes some viruses even integrate their genetic material to the host cell DNA.



So that way they are maintaining their DNA inside the host cell. But they are not immediately destroying or lysing the host cell. So this is, I would say here, a latent infection. Some other factors might activate them, and then again from this latent infection it can go to this rapid multiplication stage so that again it can go in that direction, and in another case what can happen is that the virus enters inside the host cell but the virus is multiplying very slowly, their process is slow, and the virus is getting released without cell death so as a result of that this leads to chronic viral infection. Last one here is although not very common some viruses make some protein. So, those are particularly oncoviruses; they are causing some kind of cancer. So, those proteins impair the function of the tumour suppressor gene. So, as a result of that, those host cells are going into, I would say, a cancerous transformation.

So, I would say this is a malignant transformation. So, these are the different options; it can happen because of viral infection. Now, viral growth versus bacterial growth. So, whatever I mentioned about the process of multiplication, but here I would like to focus a little bit on a different approach. So, if you see here, in the x-axis, this is time, and in the y-axis, this is cell number, and whatever curve you can see now, this is for the bacterial growth curve.



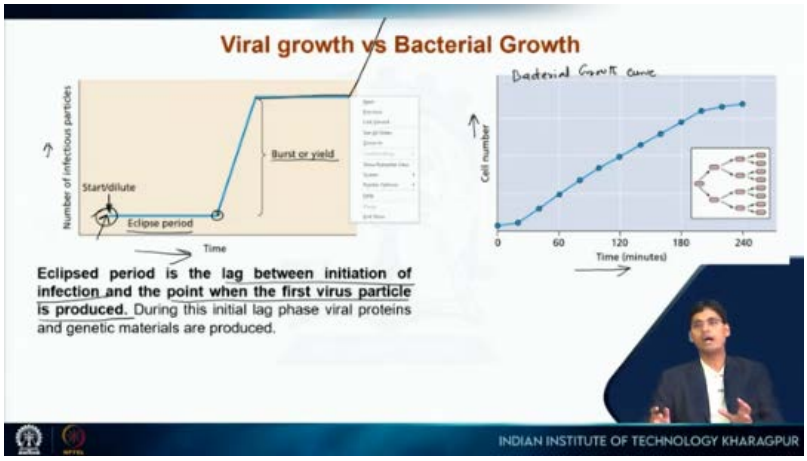
So, this is a bacterial growth curve. For example, E. coli, under optimum conditions, this E. coli can multiply every 20 minutes. So, as a result of that, E. coli grows in a kind of binary fashion from 2 to 4, 4 to 8, and that way it will grow, and you will get some kind of this curve: initial is lag phase, then it is going like this, but in the case of viral growth, it is completely different. As you can see, again, in the x-axis, this is time, and in the y-axis, the number of infectious viral particles. So now, if this is the starting point here, the infection starts, the infection means the host cell is infected by some virus.

Now, at the very beginning, for some time, I would say this is called the eclipse period. What is the eclipse period? It is the lag between the initiation of infection and the production of the first virus particle. So, from the burst phase up to that time. Nothing—no viruses you can detect inside the cell or outside the cell. This is very interesting because the way I just explained how viruses multiply. So, a virus is not like from 1 virus to 2, 2 to 4 not like that, not like bacteria.

So, the virus enters inside the cell, and they are somehow using our own machine, the host cell machinery, to make all these raw materials like capsid protein and genome, everything and after some time, when those things will be ready, they will assemble and come out from the host cell, which is called burst or yield. So after some time, we will see the number of viral particles increase like something like this; there is a lot of increase there. They are coming out from the cell and they will infect the nearby host cell. So, this is the viral multiplication strategy.

So, as a result of that, this eclipse period, how long it should be, depends on the virus. Also, some viruses might have different eclipse phases, and after this period, again, I would say this is again the eclipse phase, as you can see here. But after some time, again, it can go burst or yield. Just whatever you have seen before here, I just explained. But at some point, our immune system will take over. So it will most likely clear the infection.

So as a result of that, no more viral growth should be there. So this is a major understanding between the growth pattern of virus and bacteria. So now I will explain about equilibrium and non-equilibrium viruses. Equilibrium viruses have been associated with the host system for a very long period of time, so that means they are usually non-lethal. That means they can cause some disease, but that should be a mild disease. So that host will not die. The host cell will not be completely destroyed or I would say the host organism will not die.



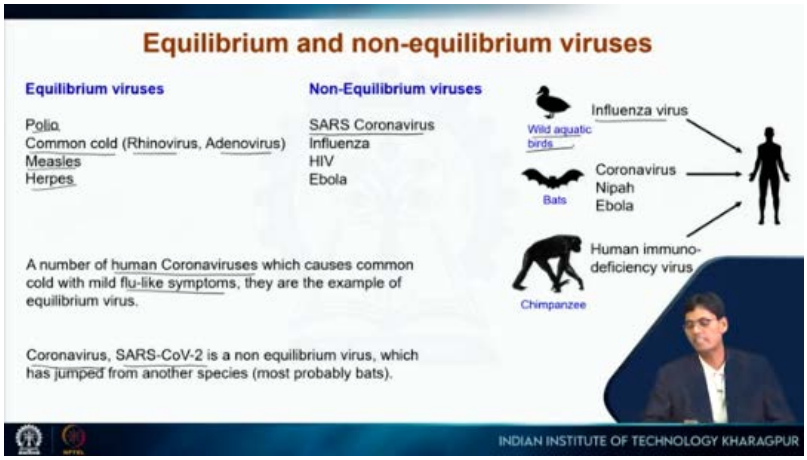
So that will ensure their existence. The host will help them to spread. So that is the strategy of the equilibrium virus. So, as a result of that they are non lethal, but they spread very well. Some examples of equilibrium viruses I would say are the common cold virus; many of us every year we are getting a common cold, most likely sometimes rhinovirus. These kinds of viruses cause the common cold.

So, they are examples of equilibrium viruses. On the other hand, non-equilibrium viruses have jumped from another species. That means they are not in equilibrium with the host. They are often lethal, so they cause different types of deadly diseases even in humans, and they spread poorly or they spread well, so both can happen. I would say examples of non-

equilibrium viruses are mostly various deadly viruses; they are like non-equilibrium viruses. In the next slide, I will explain with more examples.

So, as I already mentioned, equilibrium viruses like common cold, rhinovirus, adenovirus, then measles, herpes, and polio. All of them are equilibrium viruses; they cause disease to humans, that is true. But in most cases humans will suffer a little bit but not that much; lethal non-equilibrium viruses like SARS coronavirus (Severe Acute Respiratory Syndrome coronavirus) can be more severe. Influenza virus, HIV human immunodeficiency virus, and Ebola virus are all non-equilibrium viruses; there are so many examples, but I am just restricting here. Now If you see a number of human coronaviruses which cause common cold with mild flu-like symptoms, they are also examples of equilibrium virus. I mentioned here that SARS coronavirus is non-equilibrium, that is true, so coronavirus is not a specific name of a virus, it is a category of virus. On their surface, they have small spike-like structures, so those are called coronavirus.

So, now coronavirus, particularly a few years back, whatever the pandemic happened to us like that, it was, you know, because of SARS-CoV-2. This is again, if I write, this is a severe acute respiratory syndrome then. Coronavirus SARS-CoV-2 is a non-equilibrium virus which has jumped from another species. Most probably, it has jumped from bats, but, anyway, as I already mentioned, most of the non-equilibrium viruses recently jumped from some other species. That's why I'm just giving some examples, like the influenza virus. Their natural host is wild aquatic birds. They are also infecting humans now. Similarly, bats are the reservoir of coronavirus, Nipah, and Ebola virus; similarly, HIV came from chimpanzees to humans. This is the last point I want to discuss because, as I mentioned at the beginning, all of us are very much aware of viruses, particularly those viruses that are the cause of infectious diseases, but here, I would like to link viral infection with cancer. So, some viruses which cause cancer are called oncoviruses.



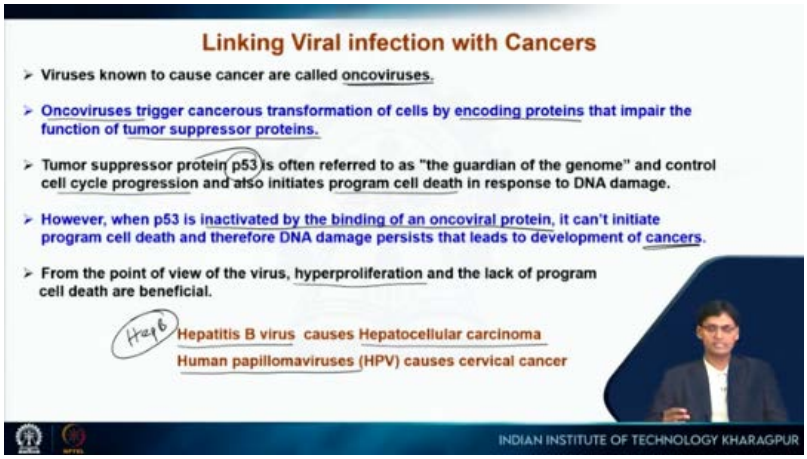
The study of cancer is called oncology. So, from that point, we say that viruses which cause cancer are called oncoviruses. Now, what happens? What is the mechanism here? Oncoviruses trigger cancerous transformation of cells. How? The viral genome encodes some proteins. The virus itself encodes some proteins, and those proteins. Impair the function of tumor suppressor proteins. So, as you know, in our bodies, for example, we have many tumor suppressor genes that encode or make tumor suppressor proteins.

So, they control our cell cycle, and whenever some mutation or DNA damage happens it cannot be repaired by the normal machinery. Then, these tumor suppressor proteins actually detect this fault, and then those cells should undergo programmed cell death. But here, what I am trying to explain is that these proteins coming from some oncoviruses impair the function of tumor suppressor proteins. So, as a result, the outcome will be bad. Let us see one very good example of a tumor suppressor protein that is p53. It is often referred to as the guardian of the genome. It controls cell cycle progression and initiates programmed cell death, as I just mentioned, in response to DNA damage.

So, as a result, when p53 is inactivated by the binding of oncoviral protein. Then p53 or this tumor suppressor protein cannot initiate programmed cell death, and therefore DNA damage persists inside the cell, and finally it will lead to cancer, so this is how viral infection also causes cancer, and I would like to give a few examples also. But if you see from the viral perspective, from the point of view of the virus, this hyperproliferation of host cell and the lack of programmed cell death are beneficial. Because cells are not dying, so as a result, if the cells are surviving and proliferating, like in the case of cancer, then

viruses can also multiply there. So that's why I am saying that from a viral perspective, this is advantageous for them. Here, there are many examples; I am just now giving some examples which many of us are aware of. So, for example, the hepatitis B virus causes hepatocellular carcinoma.

So, some kind of liver cancer and particularly Hep B. This is called Hep B vaccine, so this is already in our national immunization program. As a result of that, even in India whenever kids are born, they are administered this Hep B vaccine. So this vaccine is mandatory so that it protects us from this kind of cancer transformation and another virus is called Human papillomaviruses. So, HPV causes cervical cancer. So, these are just a few examples of virus mediated cancer transformation, but there are more and this is all about viruses.



Thank you very much. So, you can follow any of the textbooks like Prescott's Microbiology or Molecular Cell Biology by Lodish.