Introduction to Complex Biological Systems
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Lecture 44
Pathogenicity and infection

Hello everyone. Today I will be discussing pathogenicity and infection. This is module 9 and during the last two lectures, I mostly discussed viruses as well as bacteria. Today I will be mostly focusing on understanding microbial pathogenicity and infection, followed by virulence factors of both bacteria as well as viruses, and finally exposure and transmission of pathogens.

So, here if you see the understanding microbial pathogenicity and infection. So, there are different types of microbes. It includes bacteria, viruses, different types of fungi, and even some unicellular organisms, some eukaryotes; they are also pathogens, as well as some multicellular organisms, which can also be pathogens. Now, what is a pathogen and what is a host that I will clarify. So, the relationship between two organisms can be very complex.

So, a larger organism in this context that supports the survival and growth, particularly survival and growth of a smaller organism is called the host and any organism that causes disease is known as pathogen. Here I will be mostly focusing on two different types of pathogen one is bacteria and the other one is viruses and their ability to cause disease is

called pathogenicity So, I just discuss host-pathogen and pathogenicity, and together we say that host-pathogen interaction involves pathogens coming into the host organism, and then some kind of complex relation; there are many things that actually determine whether an infection or a disease will happen or not. So here if you see the chain of infection, this is a very interesting figure. So if I just go through this first, the infectious disease process requires a specific agent of substantial virulence to be exposed to a susceptible host in an appropriate dose. So, as a result of that if you see the chain of infection.

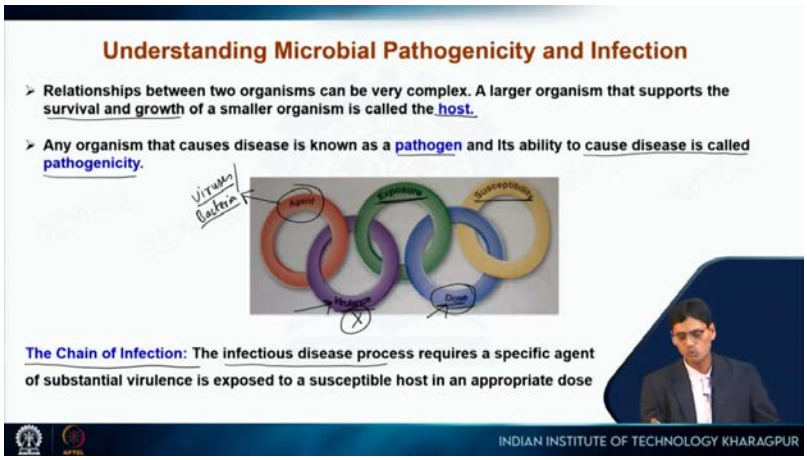
So, the first one is the agent. What kind of agent is this? This is some kind of microbial agent, some pathogen, for example, some viruses or bacteria. So, this is the agent, and then if those bacteria or those viruses have some kind of virulence factor or some kind of virulence that means they have the ability to cause the disease. That is called virulence. So, this is the virulence factor of a virus, bacteria, or any other pathogen. Then, some pathogens need to be exposed to a host organism, which is why this is exposure followed by another very important thing is dose, because although some pathogens are actually virulent.

That is why they are causing disease, and we are mentioning them as pathogens. But the question here is if the dose is very small and the number of pathogens infecting a host is very small then again, it will be a problem. So, there should be a sufficient amount of dose so that they can create a problem in the host. So, as a result, the dose is very important and finally, the susceptibility of the host. Some hosts can be very resistant against a particular pathogen, so even if that pathogen has all these properties, the host can still defend against it.

At the same time, if the host is susceptible, then the pathogen will establish the disease or the infectious disease inside the host. So, that is why I am explaining this chain of infection. Here, if one of these steps is broken, if you just stop one of these steps, then the infection will not progress. For example, if some microbes do not have this virulence, then it is not a pathogen; it cannot cause the disease, or if the dose is not sufficient, again, it will not cause the disease.

So, that is why this is very important and interesting to understand. Now, the virulence of bacteria, particularly I will discuss here, and then after some time, I will also be discussing

the virulence of viruses as well. Now, many bacterial virulence factors that facilitate survival are encoded in unique sequences of DNA that are readily swept between bacteria through horizontal gene transfer. This is very important and this is happening in bacteria particularly I would say in microbes. So, in our body this is not happening, that horizontal gene transfer I will be discussing.



But here if you see E. coli cell, here, you have just one E. coli chromosome. On the other hand, this bacteria Shigella flexneri. So, here if you see, it has one plasmid and the virulence plasmid containing virulence gene. So, it will coat something and that is why it will show its virulence. So, it is pathogenic, it will cause the disease to a host.

Here, Salmonella enterica is another pathogen, and the pathogenicity islands are very important terms in the context of the virulence of microbes. So, in the chromosome itself some regions are present that are called pathogenicity island. So, that encodes multiple factors, maybe it can be proteins. So, multiple factors which actually provide some virulence factors to that particular microbes. So, this is called pathogenicity island.

But, the major question here is that some bacteria might not be virulent; they do not have the power to infect and cause the disease, but the thing is they can acquire that power from horizontal gene transfer that means another bacterium. They have some virulent genes, and they can acquire virulence genes from those bacteria also, but there could be different procedures I will be discussing very briefly, but this is very important in overall understanding this concept. So, the first one I would say is transformation. So, this is one strategy of horizontal gene transfer.

So, transformation particularly I discussed in module 1 during the Griffith experiment. So, transformation means bacteria are taking up free DNA present nearby. So, I would say this is one bacteria and it has its own chromosome Now for example, in the nearby you have some DNA available, it can be plasmid also it can be other DNA. So, better if I say this is plasmid.

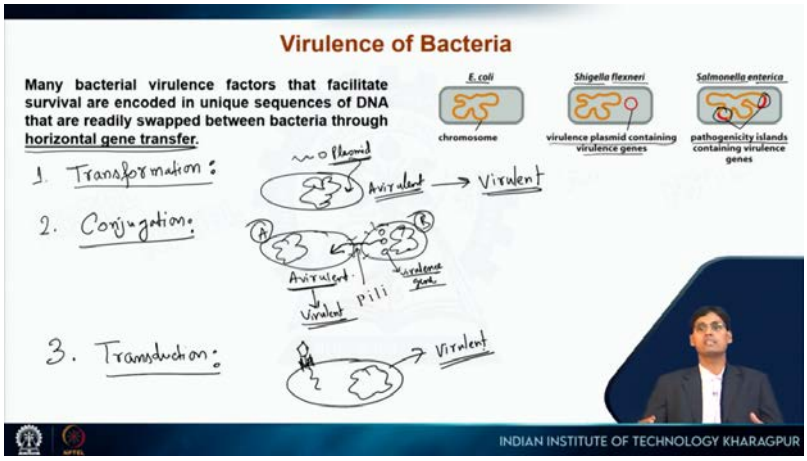
So, as I already explained, plasmids also contain virulent genes. So, although initially this bacterium is avirulent that means it cannot cause the disease, for example, during Griffith's experiment, I mentioned that the rough surface bacteria, that is, streptococcus pneumoniae, cannot cause the disease. But whenever it took some DNA, then it became smooth surface bacteria, and it caused the disease and it killed the mouse. So, similarly, if they take this free DNA, then this avirulent bacteria now can be virulent, that means it can cause the disease again, it can be lethal.

So, this is called transformation of taking free DNA, and this is happening in nature. So this way bacteria can acquire these virulent factors from other bacteria, from the surrounding. Now, the number 2 is conjugation. So, conjugation is a process where bacteria take DNA directly from another bacterium, not from free DNA in the surrounding. So, here is what will happen. If this is one bacteria so it has its own chromosome, but again, this is avirulent. So, I am just naming this bacterium as bacteria A, and now in the surrounding area, you have another bacterium, which is bacteria B, but it has some kind of virulence gene. So, it encodes some virulence genes. Now, as I discussed before, some of these bacteria have fimbriae and pili; particularly, they do conjugation by some kind of pili. So, through this pilus-like structure, they directly communicate between two bacteria.

So, this DNA can come into this bacteria, and now this avirulent bacteria will become virulent. So, this is another way of horizontal gene transfer, and the number 3 is transduction. Transduction is a process where bacteria acquire DNA through some viruses. So, in this case, what will happen? Say, for example, this is one bacteria. Now, this bacterium can be attacked by some virus, particularly, these viruses are called bacteriophages.

So they will inject DNA into this bacterium and this first virus, they are actually attacking many bacteria at different time points and they acquire some virulence encoding gene. So therefore, they can also transmit, they can also send this virulence encoding gene to this bacterium and now this bacterium becomes virulent. Although before this process, it was avirulent.

So this is called transduction when a virus is injecting DNA into some bacteria. So because of this horizontal gene transfer, bacteria, particularly, are very powerful sometimes, and this is one of the reasons why they acquire antibiotic resistance. So, some bacteria are still susceptible to some antibiotics, but over time they will acquire some new resistance genes and they can defeat that particular antibiotic. Now I will particularly discuss some virulence factors. So, as you can see here, this is a host cell, and you can see some bacteria here; I am just showing them in purple color. Just imagine that these are maybe gram-positive bacteria, that is why.



So, now this bacterium has different types of adhesion factors which are also called adhesions. So there are many adhesion molecules that can be present on top of bacteria. So, particularly Fimbriae, for example, helps in adhesion, and also some bacteria, as you can see here, have a slimy layer outside called the capsule layer, which again helps in attachment with the host.

And not only attachment, sometimes this capsule, this slimy layer, can also act as a virulence factor. Again, I am going into Griffith's experiment, as you already know that the surface, whatever the slimy layer that is present, the polysaccharide layer present outside

that streptococcus. Pneumoniae that prevents even the host immune system. So, host immune cells cannot quickly phagocytose those cells. So, as a result of that, this layer, the capsule layer, is also very important as a virulence factor besides its attachment.

Now, more specifically, if I say, here I'm providing one example of Listeria monocytogenes. This is one intracellular bacteria, so this bacterium enters inside the host cell and it causes listeriosis. This is some kind of foodborne pathogen, and it enters inside the host cell and then it causes problems to the host. So, what happens? This bacteria, Listeria. So, this is Listeria monocytogenes. So, they have some protein, this is adhesin. The name of this protein is internalin A. Adhesin is a group name, like some of the adhesion molecules present on the surface of bacteria. We are saying those are adhesins, but internalin A is the specific protein present on. Listeria surface, and now this internalin A interacts with E-cadherin; I discussed in some different lectures that E-cadherin is a very prominent cell adhesion molecule present on epithelial cells. In our body, in our epithelial cells, a lot of E-cadherin is present.

So, as you can see, internalin directly binds to E-cadherin and that drives endocytosis. I am not going into the details of the signaling procedure, which is not that much important here, but the thing is. What I'm trying to say is, this specific interaction between internalin A and E-cadherin drives endocytosis so that the bacteria can come inside the host cell and as I already mentioned, this bacterium is an intracellular bacterium. So, as a result of that, now the bacteria can multiply and it can cause problems.

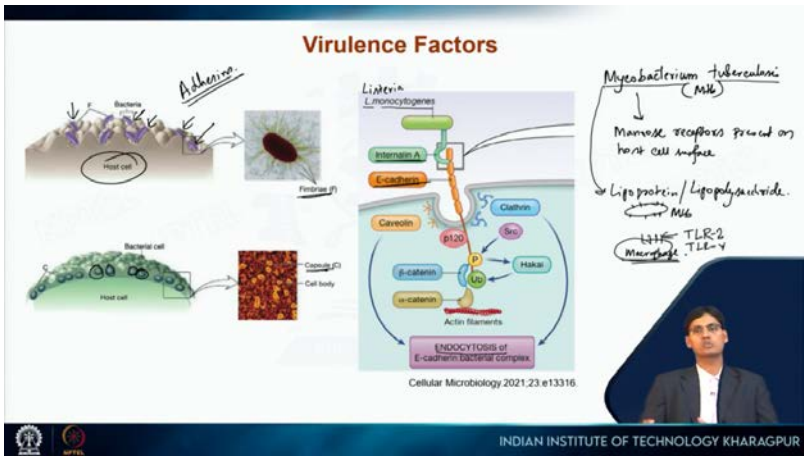
Similarly, not just Listeria, there are many bacteria. I am just giving one example and another example I should give. So, here all of you are aware that it is Mycobacterium tuberculosis. So this is commonly known as Mtb mycobacterium tuberculosis, so all of you know that it causes TB or tuberculosis disease, so now it is also an intracellular pathogen, so now what happened is it binds to receptor mannose. The receptors present on the host cell surface.

So, the mannose receptor means that some mannose-like structure, some mannose-like chemical moiety is also present on the surface of this Mtb. Therefore, it binds to the mannose receptor present on the host cell, for example, a human host cell, and therefore, it

leads to the internalization of this bacteria. So, now another virulence factor I would say is present or they utilize is some lipoprotein, particularly lipoprotein and lipopolysaccharide. So, this micro bacterium has lipoprotein and some lipopolysaccharide as its virulent factors. So now, this is present on Mtb.

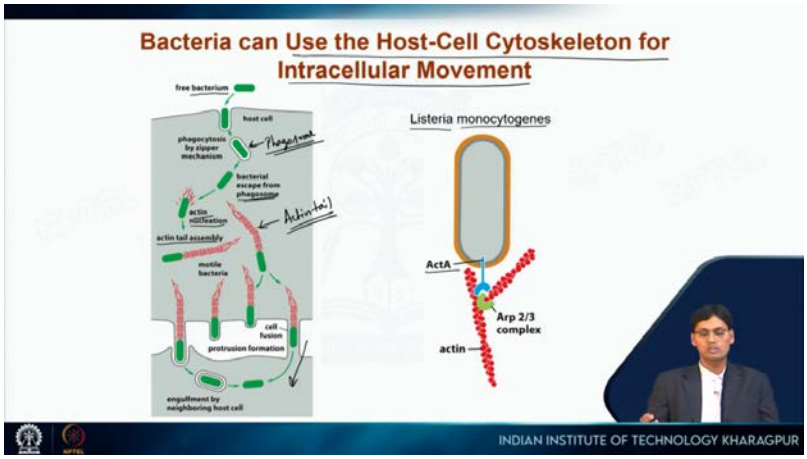
So this is present on the surface, for example. Now, in hosts, particularly some immune cells, for example, macrophages. So macrophage we have, again this is some immune cell and on the surface of this macrophage it has TLR toll like receptor TLR-2, TLR-4. So, this lipoprotein and lipopolysaccharide bind to this TLR and drive the internalization of this bacteria.

So, as a result of that, they establish infection. Now, not only are they going inside the host cell, but after that, they can use the host cell cytoskeleton for intercellular movement. So, this is an interesting aspect, as you can see with this bacterium. So, it is coming into the host cell, and then this bacteria escapes from the phagosome; this is a phagosome. When they are entering inside the host cell then this bacteria escapes from the phagosome, and they are using host cytoskeletal material, for example, actin. They are actually nucleating actin and making some kind of actin tail. So, this is an actin tail, and they are using this actin tail to move inside the host cell. Not only that, sometimes they leave the host cell and then infect some surrounding cells, as you can see in this figure. So, as a result of that, you can understand how they are exploiting our own system.



So, they are actually using host actin for their own good. So some kind of little bit of mechanism, for example, if you consider this is Listeria monocytogenes, then this bacteria,

on the surface, has this protein ActA. It binds to some protein and therefore links to actin, establishing this actin tail, and therefore it can move inside the host cell. So now, besides this intercellularization, they are moving inside the cell and infecting the surrounding cells. Besides that, another important strategy of bacteria is producing toxins.

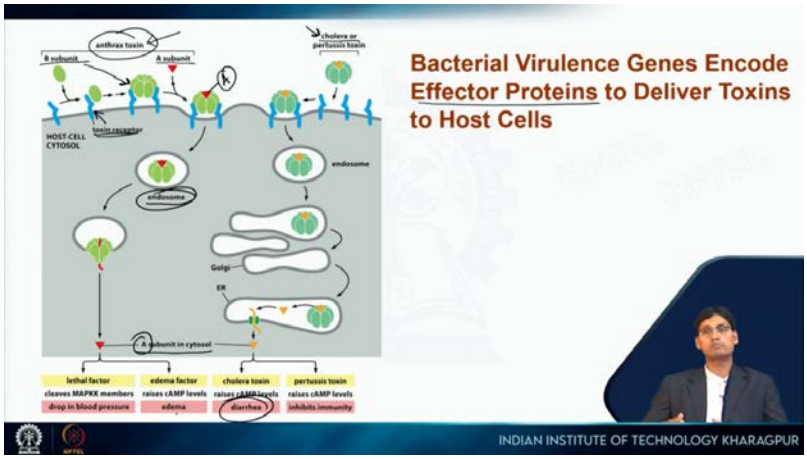


Different types of toxins they can produce, and they can cause problems for the host. So, as you can see here, bacterial virulence genes sometimes encode effector proteins to deliver toxins to host cells. This is true for many bacteria. Here, we are giving some examples with anthracitoxin as well as cholera toxin. So, here the idea is that there are many mechanisms mentioned in this figure, but I would mostly focus on the basic concept here in this toxin, particularly if we consider anthrax toxin.

It has two subunits, A subunit and B subunit. So, the B subunit here is the effector protein. So, the B subunit binds to the toxin receptor that you can see here. This is the toxin receptor present on the host cell surface and now, this B subunit forms some kind of multimeric structure.

So, this is the multimeric structure of the B subunit. So, therefore, now it will bind to the A subunit, and the A subunit is actually the real toxin, but B is some kind of carrier. So, it is helping to take the toxin A inside the cell. So, as you can see, here, this is coming into the cell, the host cell, and it is from the endosome, and finally, this A subunit will be released into the cytosol, and this is the toxin, this is the lethal factor, and it will cause the problem.

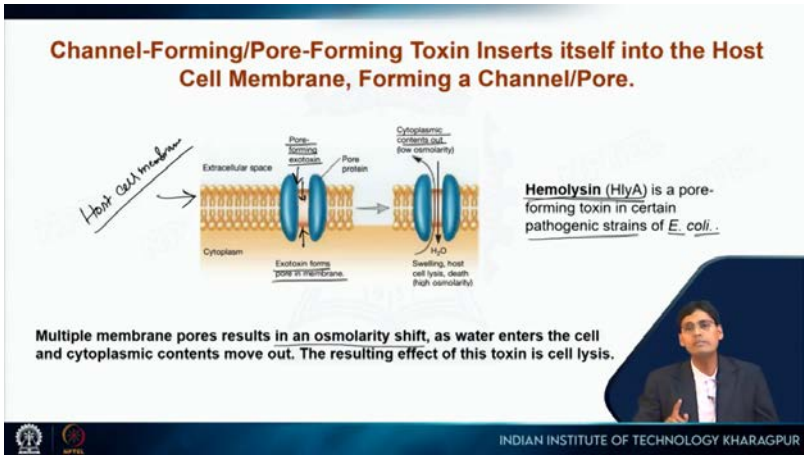
Depending on what the toxin is and which bacteria it came from, different types of diseases might be established inside the host. For example, as you can see in the case of cholera toxin, particularly if you focus on cholera toxin, it can cause diarrhea. But overall, if you see the entry mechanism in this case, the bacteria itself does not enter inside the host. This is the major point I am trying to cover. So in this case, as I previously mentioned, Mycobacterium tuberculosis and Listeria enter inside the host cell. But in this case, bacteria produce some toxin and have a complicated mechanism so that the toxin can enter inside the host cell, and therefore they can create problems and disease symptoms. If you see here, another interesting type of toxin is channel-forming or pore-forming toxin.



It inserts itself into the host cell membrane and therefore forms a channel or pore. So as a result, as you can see, this is the host cell membrane. It is a lipid bilayer and a kind of continuous layer; some integral proteins are there, which are important for physiology. But now what happens is some bacteria can make this pore-forming toxin, and it will be inserted into the membrane itself.

So, therefore, it will make some kind of gap here. So, this is some kind of gap, this is called exotoxin forming a pore in the membrane. Therefore, what will happen is the cytoplasmic content can come out, and then some other things like nutrients or molecules can go in and out. As a result, it will cause an osmolarity shift, so as water enters the host cell and the cytoplasmic content moves out, the cell will be lysed. So, this is also very common. For example, hemolysin A is a kind of pore-forming toxin present in some pathogenic strains of E. coli.

So, I will be mentioning another interesting type of toxin then I will move into viruses. So here, this is again another very different category of toxin. So this is called superantigen. So T cell activation by super antigen stimulates massive amounts of cytokine production that result in shock and death of the host.

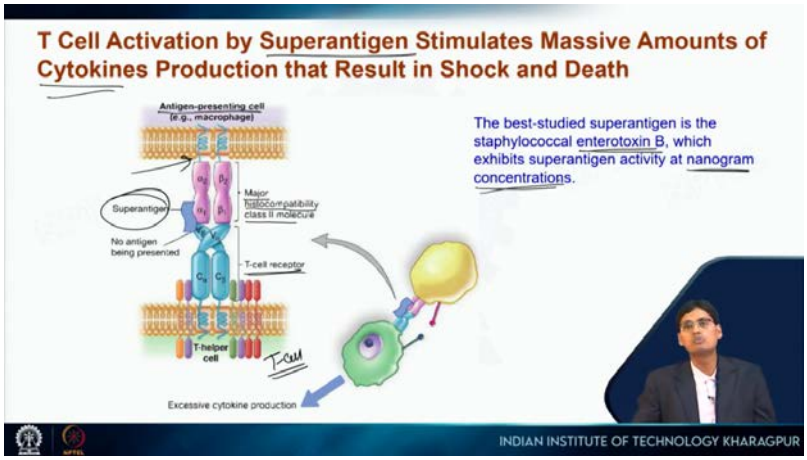


So, this T cell activation part I will discuss in much more detail in the next module when I will be discussing our immune system, but very briefly if I want to say here. So, what is happening? This antigen presentation happens particularly for adaptive immune response that the host cell. So, some cell particularly antigen presenting cell they have here; this is called MHC or major histocompatibility complex.

As I already mentioned I will be discussing in more details in the next module. Now, this MHC presents some kind of peptide antigen to the T cell receptor. This is a T cell receptor present on the T cell surface and therefore, adaptive immune response initiates. Now the problem is some kind of superantigen; it is completely behaving in a different way. Somehow, this super antigen stimulates this interaction. They are not the proper antigen, but they are superantigen; they somehow activate this T cell in a massive manner and as a result of that a lot of cytokines will be produced and it will cause the problem.

One of the best-studied superantigens is staphylococcus, enterotoxin B. This is a superantigen which exhibits superantigen activity at nanogram concentrations. So, as you can see, it is very toxic at nanogram concentrations. So you can understand bacteria have different types of multiple arrays of techniques and different procedures in order to establish infection inside the host cell. Now, virulence of viruses. So, viruses, I would say

are more simple compared to bacteria because they do not have so many things, as I already discussed in the last module, in the last lecture.

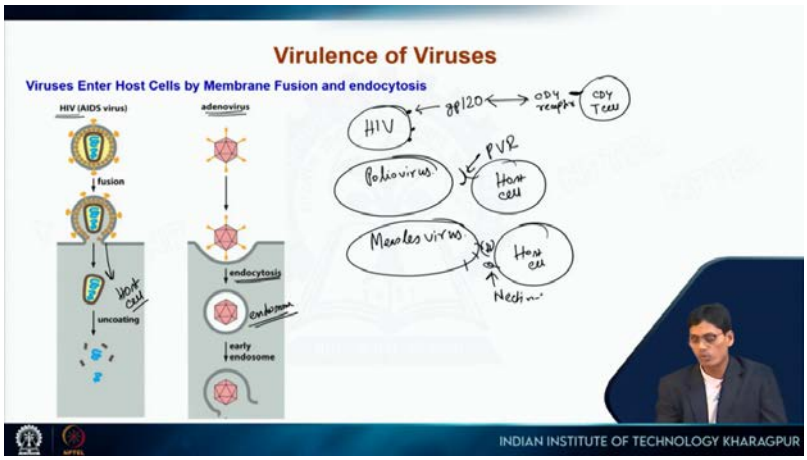


So, mostly, they are utilizing different types of host machinery for their own good. So, as you can see, HIV virus and adenovirus, I am just giving two examples here. The HIV virus gets fused with the host cell membrane, so this is membrane fusion, and therefore, they come inside the host cell. So, this is the host cell, and this is the HIV virus. On the other hand, adenovirus becomes endocytosed inside the, so this is then endosome inside the host cell. And finally, they will come out from the endosome, and their genomic content, particularly nucleic acid, will come out, and then it will establish, multiply, and all those things will happen.

So, now, this membrane fusion or endocytosis can properly happen if some special factors are also present on the surface of viruses. So, I will give you a few examples. For example, this HIV, human immunodeficiency virus. On the surface of this virus, it has some glycoprotein. This is called gp, glycoprotein 120, gp120. This is HIV virus, and now I mentioned before that GP 120 interacts with the CD4 receptor present on CD4 T cell. So, for example, this is our CD4 receptor.

So, as a result of that, that helps to go inside the host cell, and similarly, many other viruses also utilize different types of virulent factors. For example, if I say ah poliovirus So, this poliovirus they also use some host receptor. So, they use a poliovirus receptor present on the surface of the host cell.

So, if I say this is a host cell. so they utilize a receptor called PVR poliovirus receptor. Now another common virus is measles. On their surface they have some protein called hemagglutinin. So, this hemagglutinin will bind to the host cell. This host cell surface they express some protein, this is called nectin 4, this is another cell adhesion molecule present in many host cell surfaces and that drives the entry of this measles virus inside the host cell, so I just give a few examples, so this way many viruses enter inside the host cell and then they multiply.

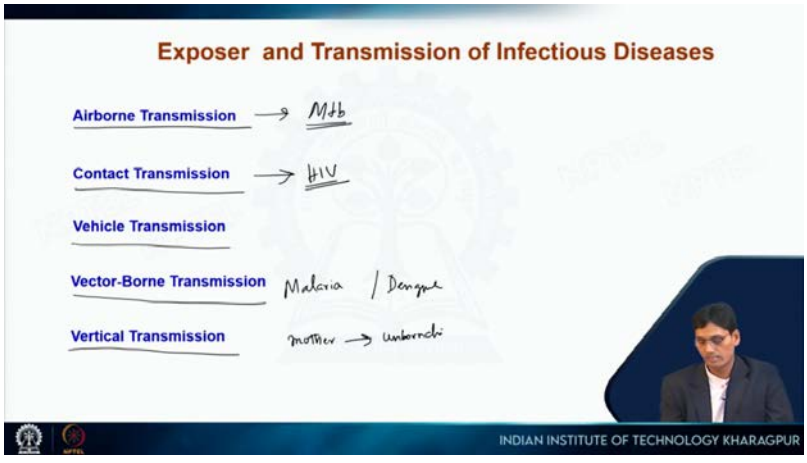


Now as I already mentioned, just having virulence factors is not enough. So there should be exposure with the host so that they can transmit and they can cause the disease. They can establish themselves. So here we have to understand that in order to survive, those microbes are utilizing the host, particularly viruses, so as a result of that, they need to go inside the host cell, and they can survive there. Also, if you think that they can cause very severe disease, for example, that host is very sick, that is sometimes not good for the microbes Because if the host dies, then they will not survive for long; they need to find another host soon. So, as a result, there are so many complex relations between the host and pathogen, and some pathogens which cause mild disease establish themselves better, so they can multiply and infect more hosts quickly.

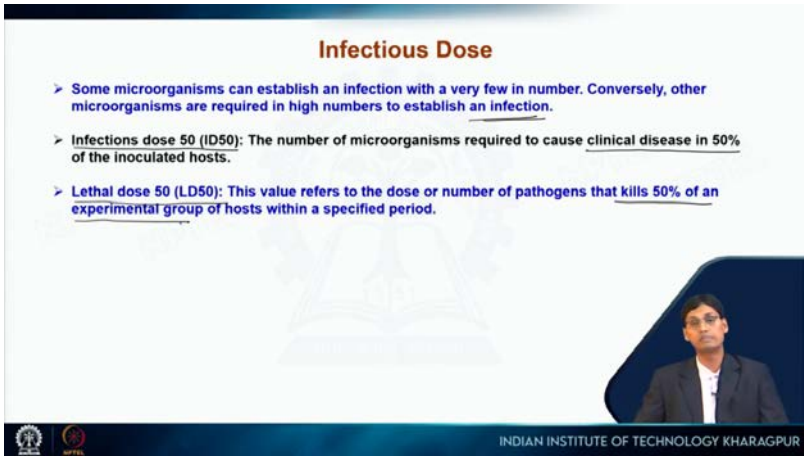
So, there are different types of routes that some pathogens can take to establish the disease, for example, airborne transmission. So, I would say some pathogen for example, already I mentioned Mtb Mycobacterium tuberculosis. So it can be airborne; so from some Mtb patients when they are sneezing or coughing during that time, it can be airborne. So that it

can travel through the air and some small droplets and infect surrounding people very close by. This is called airborne transmission and then contact transmission it is direct contact. For example, HIV is transmitted through direct contact, such as human immunodeficiency virus infection due to sexual contact, for example, HIV can occur.

Similarly, syphilis also happens because of contact transmission. There are many diseases like that. Now the vehicle transmission, this is some pathogen, some microbes; they are present on some kind of object, for example, and that is being used by many people, and that way some diseases can be carried over. For example, in a gym, like a lot of people, they are going there and they are utilizing the same equipment present in the gym, and from there also sometimes some pathogens may enter and infect, so this is called vehicle transmission. They are using some kind of vehicle; it can be some inanimate object, that's all. Now, vector-borne transmission, so they utilize some vectors. This is the best example I would say malaria and dengue, for example, malaria is carried by some mosquitoes. Similarly, dengue, although it is a viral fever, is carried over by some mosquitoes. So, this is vector-borne transmission. So the disease is malaria and is transmitted; I would say the vector here is mosquito. Similarly, dengue is again another viral disease, but mosquitoes also act as vector in this case and vertical transmission is a unique thing, not very common here. Vertical transmission means, for example, an unborn child before birth can acquire an infection from the mother itself. Although, as I am saying, this is very uncommon, it can happen. This is vertical transmission; this is mother to unborn child. Now, this is the last slide of this presentation, the infectious dose.



Some microorganisms can establish an infection with very few in number. On the other hand, some microorganisms are required in very high numbers to establish infection; both are possible. So there are some infectious doses called ID50, which means the number of microorganisms required to cause clinical disease in 50 percent of the inoculated host. It's kind of an experimental setup. Similarly, the lethal dose 50 means a similar concept, but here it's lethal dose, and previously I just mentioned the infectious dose. So, in this case, this value refers to the dose or number of pathogens that kills 50 percent of an experimental group. So, here, it kills 50 percent of an experimental group of hosts within a specified period, so this is called LD50. Now, host susceptibility, this was the last circle of that infection chain I mentioned at the beginning. But host susceptibility will be better for discussion during the immunology lecture, where you will get a better feeling about this host susceptibility.



So here I would stop, and you can follow Prescott's Microbiology as well as Molecular Biology of the Cell by Alberts et al. Thank you very much.

REFERENCES

1. Prescott's Microbiology (9th Edition)
2. Molecular Biology of the Cell by Alberts et al., Sixth Edition