Host-Pathogen Interaction (Immunology)
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Lecture - 72
Introduction to Bacterial Infection

Hi, so we have finished 10 weeks. We have studied almost all immunology. We have studied the virus infection, what are the protective immune responses against virus infection in terms of innate as well as adaptive immunity. We have also discussed several viral diseases that is influenza virus infection. We have studied two arboviral diseases that is dengue and we have also discussed Zika virus infection.

So we are going to start the week 11 and in this week we are going to study the bacterial infection. So, the overview of this week is that we will first discuss about how the bacterial infection is taking place, what kind of innate and adaptive immune responses are developed against bacterial infection and then we will take up the tuberculosis as a model disease and then we will finish this bacterial infection. So let us begin with this bacterial infection.
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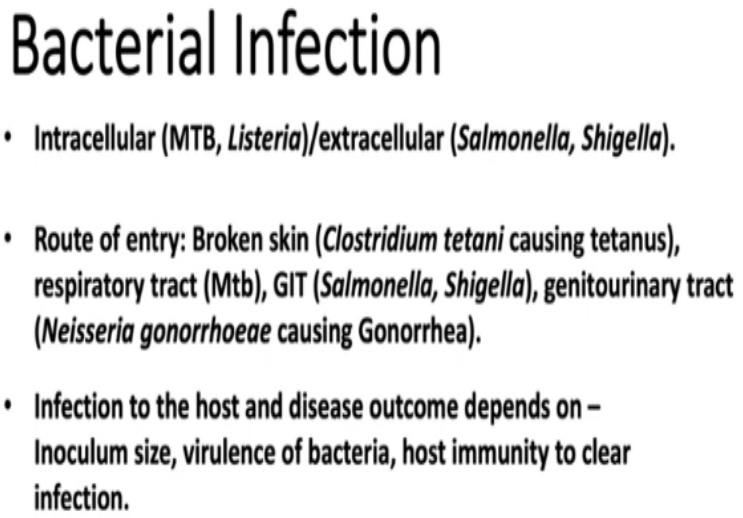

So bacterial infection is a basically or if you see the bacterial infection then it is basically two major kinds of bacterial infections are there. One infection could be the intracellular, the bacteria resides inside the target cell. Here you can see there are some examples like Mycobacterium tuberculosis, so Mycobacterium tuberculosis resides inside the cell. And

another example is a Listeria, the full name of listeria is Listeria monocytogen, so this is also intracellular pathogen.

And another infection could be extracellular, it means the infectious bacteria is outside the cell. The example is Salmonella infection. Probably you may aware that there is a disease known as typhoid which is basically caused by one of a species of Salmonella which we call it as a Salmonella typhi. There is another infection like Shigella, these are the extracellular bacterial infections. There could be multiple routes of infection as you are probably very well aware about this thing.

The infection could enter through broken skin, broken skin means if there is some wound or bruise then through that route the infection can go and one very good example of this infection where the route of infection is through skin is Clostridium tetani which cause tetanus, I think you are well aware about this because whenever you get hurt by some metal or by something then you receive one vaccine which we call it as a tetanus vaccine.

So this is in order to avoid the Clostridium tetani infection. Another route of infection is respiratory tract. So this is one of key route of infection in modern world and you know there are variety of microbial pathogen which infect the host through this route. It could be viruses, viruses you are very well aware right, you can understand there are so many viruses which can infect the host through this respiratory tract.

To name few is you have studied influenza, you know very well SARS-CoV-2 infecting through this respiratory route. So bacteria also can infect the host through this respiratory route and one of the best example is Mycobacterium tuberculosis infection. And Mycobacterium tuberculosis infection result to~~hrough the~~ tuberculosis. Basically, there are two major kind of tuberculosis. One is pulmonary tuberculosis, pulmonary means the lung tuberculosis.

Another is extrapulmonary tuberculosis and this extrapulmonary tuberculosis can happen in any part of the body. Basically, this Mycobacterium tuberculosis they infect the macrophages and you know all tissues have various kind of macrophages. So they can infect and then they can cause that particular tissue tuberculosis and all those tuberculosis we categorized as extrapulmonary tuberculosis.

There is an infection through gastrointestinal tract which is we commonly call it as GIT. Again through GIT the salmonella, shigella, Listeria all these infections can take place through contaminated food or water. Another very important route of infection is through genitourinary tract and through this tract you are probably aware that there are various sexually transmitted diseases and one of the very prominent diseases is the infection of Neisseria gonorrhea which cause gonorrhea.

This is a sexually transmitted disease. So, these are the route of infection to the host. And after infection the disease outcome it is not always that there will be a disease. It depends on various factors. So the disease outcome depends on for example inoculum size. If the host received a reasonably higher amount of inoculum if it is a respiratory route or oral route or genitourinary tract then that infection will take place.

If it is a very small amount maybe the disease will not happen because maybe your innate immunity is capable to eradicate or eliminate those infection. Another is virulence of the pathogen, the bacterial infection. If it is extremely virulent then very small doses of these bacteria are sufficient to cause or establish infection and cause disease. Another very important is a host immunity to clear the infection which is dependent on various factors.

The first very most important factor is the genetic makeup of the host. Another is the immune status of that individual at that particular time. If the individual is having some another pre-existing problem and immunity is not well, then that individual may readily infected by the infection. So here you can figure out that all these factors are interdependent, it is not only a very single entity, everything is dependent on other like host immunity depends on the genetic and status.

So for example if host immunity is very good and if inoculum size is also very big then that will cause the infection. If the inoculum size is small, then that will be cleared by the host immunity. So this is a just a brief introduction about the bacterial infection.

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Immunity against Bacterial Infection

- Innate immunity against bacterial infection by Humoral components (anti-microbial peptide such as MBL, Complement)
- Innate immunity against bacterial infection by Cellular components via innate immune sensors such as PRRs (TLRs & NLRs)
- For extracellular bacterial Infection: Ab & Th2 immunity for extracellular bacterial infection via complement activation, phagocytosis via opsonization & neutralization of bacterial toxins.

Now let us look at what kind of immune responses are elucidated against the bacterial infection and in this series first we will discuss about the innate immunity. So innate immunity against the bacterial infection is basically two major as you have learned earlier. First is the humoral component, the soluble component and you have learned there are so many antimicrobial peptides or protein. For example, you may remember that there are different kinds of defensive proteins.

There are some mannose binding lectins and above all there is a family of protein which we call it as a complement. So, these complements plays an extremely important role or in fact all these humoral components play extremely important role in defense against bacterial infection. Another is the cellular component. There are variety of cells and among all cells the most prominent and most important cell is the phagocytic cells.

You know macrophages, you know neutrophils, eosinophil also do phagocytosis to some extent. So, all these cells play a very important role in phagocytosing these microbial pathogens. Furthermore, these cells or other cells they express a very important family of molecule which we call it as a PRRs pattern recognition receptor. So various pattern recognition receptors are there and the key pattern recognition receptor which plays a very important role against bacterial infection is toll-like receptor and NOD-like receptor as we call it as a TLR and NLR.

If you remember my previous session, I have discussed about various TLR and just to sum up quickly there is a TLR 1, 2, to TLR 26. They play a very important role in sensing bacterial

component. There is a TLR4 which is playing very important role in sensing gram negative bacteria and the component which assessed by TLR4 along with another molecule right is LPS. TLR5 senses a flagellin protein from flagellated bacteria.

TLR9 if you remember they sense CpG motif DNA or CpG DNA hypomethylated. So this hypomethylated CpG DNA is also present in bacterial DNA. Besides TLR, there is NLR. So NLR if you remember one is some NLR members are present inside the cell and they sense the bacterial component and activate NF kappa B in order to induce the pro-inflammatory cytokine and there are another family of NLR.

Which makes a multiprotein complex which we call it as inflammasome and this inflammasome plays a very important role in production of IL-1 family cytokines. So you probably remember that there is NOD1, NOD2 which is intracellular sensor for bacterial component and there is a NLRP3 inflammasome. There are so many inflammasome, NLRP3 inflammasome, NLRC4 like that and most of these inflammasomes are playing very important role in sensing bacteria and inducing the pro-inflammatory cytokines.

So this is the innate component. There is adaptive component as well. So, you know the adaptive components are basically mediated by antibodies. So, antibodies are playing extremely important role in defense against bacteria and how? So, first antibody can also activate the complement and that will induce inflammation, opsonization~~xidization~~ and making a hole in the bacteria which cause the cytolysis.

Another is this is a one of important function of antibody that this will activate the classical pathway if you remember. Another is antibodies can coat these bacteria and opsonize so that it will be readily phagocytosed by the phagocytic cells. Another most important function of antibodies are, some bacteria they produce soluble proteinaceous toxin for example diphtheria. Diphtheria produces diphtheria toxin and this toxin can be neutralized by the antibody.

So these are few very important function of antibody. Another is T-cells, so mainly Th cells plays a very important role against the defense against bacteria. For example Th1 cells, they play a very important role in case of intracellular bacterial infection, for example mycobacterium tuberculosis. Th2 plays very important role in production of antibodies. So in that way the adaptive immunity work against the bacterial infection.

And for extracellular bacteria these antibodies are very important, for intracellular Th1 is very important. For extracellular Th2 immune responses are very important. So here I have discussed all these things.

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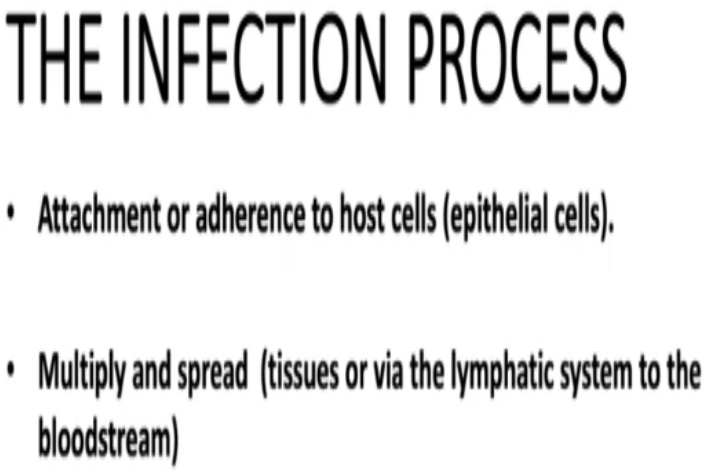

What are the steps in infection processes? This is very important, infection does not take place just in a very simple way, it is a quite complex and these bacterial pathogens are evolved in such a way that they will hook up over the host cell and then they make a micro colony and then they will expand and then there will be a bacteremia and then that will result to the disease. So the first step of infection is attachment.

Attachment to the target cell or adherence to the host cell and this attachment and adherence is mainly taking place over the epithelial cell, the lining of all body part. Another is once they will attach, they will multiply over there and spread using the host resources. So this multiplication and spread over the tissue is via lymphatic system to the bloodstream.

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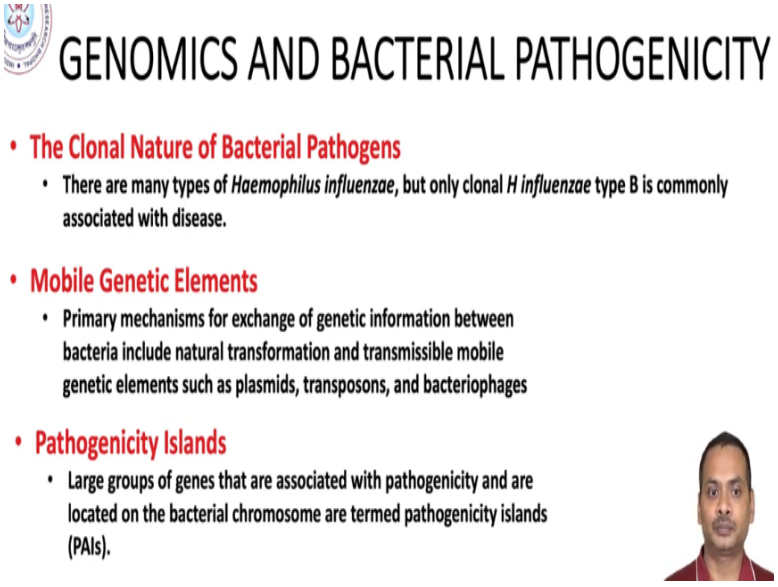

There are genomic and bacterial pathogenicity, some genomic component and here you can see that the clonal nature of bacterial pathogen. So here I would like to say that if for example there are many types of Haemophilus influenza. There are so many kinds but only some of the clone or some of the types can cause the disease. In case of Hemophilus influenza or influenzae there is a type B which is basically associated with the disease that we call it as a clonal nature of bacterial pathogen.

Not all types of Hemophilus influenzae can cause the disease, only this type B will cause the disease. There is a mobile genetic element and this mobile genetic element is basically the primary mechanism for exchange of genetic information between bacteria include natural transformation and transmissible mobile genetic element such as plasmid. So you know that these pathogenic bacteria they are having some virulence factor.

And all these virulence factors will be present on some piece of DNA and this piece of DNA could be a plasmid. This could be transposons or this can be facilitated by the bacteriophages. I will give you the example in subsequent slide. There are pathogenicity islands in this pathogen. There are large groups of gene that are associated with pathogenicity and are located on bacterial chromosome and termed as a pathogenicity island PAIs. So I will discuss each with example.

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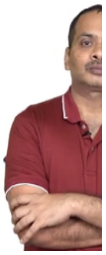
Examples of Virulence Factors Encoded by Genes on Mobile Genetic Elements

Genus and Species	Virulence Factor and Disease
Plasmid encoded	
Escherichia coli	Heat-labile and heat-stable enterotoxins that cause diarrhea
Escherichia coli	Hemolysin (cytotoxin) of invasive disease and urinary tract infections
Escherichia coli and *Shigella* species	Adherence factors and gene products involved in mucosal invasion
Bacillus anthracis	Capsule essential for virulence (on one plasmid) Edema factor, lethal factor, and protective antigen are all essential for virulence (on other plasmids)
Phage encoded	
Clostridium botulinum	Botulinum toxin that causes paralysis
Corynebacterium diphtheriae	Diphtheria toxin that inhibits human protein synthesis
Vibrio cholerae	Cholera toxin that can cause a severe watery diarrhea



So here I am going to give the example of a virulence factor encoded by genes or mobile genetic elements. Here you can see that there is a plasmid encoded by Escherichia coli and the virulence factor and disease in this Escherichia coli is heat-labile and heat-stable enterotoxin that cause diarrhea. This is a plasmid, so there is extracellular chromosome or there will be extracellular DNA and this extracellular DNA will encode these enterotoxins and which will cause the diarrhea.

For example, there is a apathogenic Escherichia coli. If you throw this plasmid in the cells then that will become a pathogenic. Another is same bacteria, there is a plasmid which can encode the hemolysin or cytotoxin of invasive diseases and urinary tract infection. Escherichia coli and Shigella, some of the species they have these plasmids encode adherence factor and gene product involved in mucosal invasion.

So this plasmid is having all component for adherence as well as invasion in the mucosal surfaces, so in that way they will make a successful infection. Another example is bacillus anthracis, please note this bacillus anthracis is a very dangerous microbial pathogen and here I am just giving you a note that this bacteria is also used as a biochemical weapon. If you are aware the world trade center accident 9, 11 probably you may look at.

At that time or after that the people received an envelope and this envelope are containing the spores of this bacillus anthracis. So this is a very dangerous bacteria. So there is a plasmid in bacillus anthracis which encode for capsule essential for virulence and there is a plasmid

which encode the edema factor, lethal factor and protective antigen which are essential for virulence. Another example is a phage encoded virulence factor which can cause the disease.

Here you can see that Clostridium botulinum which contain the botulinum toxin that cause paralysis. And here just I am going to highlight one positive point about this botulinum toxin this is used in therapy as well, this we call it as a Botox. Another is Corynebacterium diphtheriae which basically produce the diphtheria toxin that inhibits the human protein synthesis and this is also very dangerous pathogen. Another is Vibrio cholerae which encode the cholera toxin that cause severe watery diarrhea. This probably you might have some experience.

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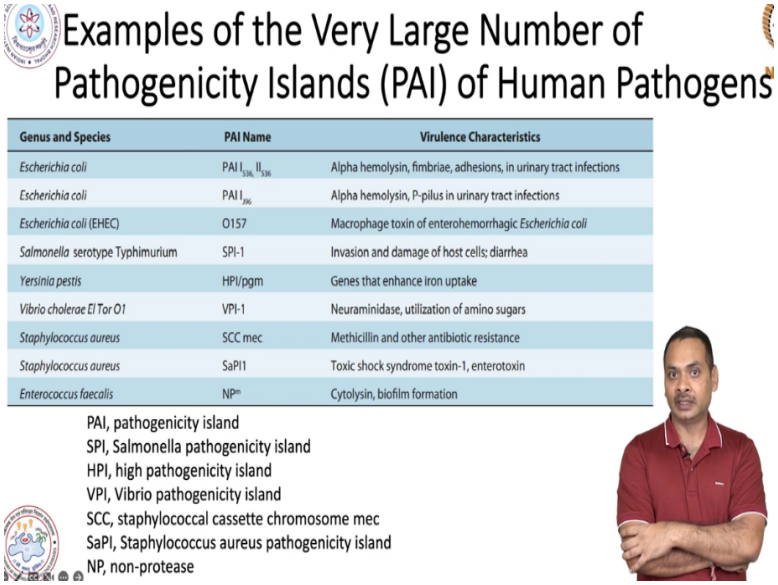

There is an example of a very large number of pathogenicity island of human pathogen. Here again there is E. coli and this pathogenicity island 1 536 and 2 536 they basically encode for alpha hemolysin, fimbriae, so fimbriae is needed for attachment, adhesion, in urinary tract. So there probably you might ~~heard~~hear that there is a UTI urinary tract infection and this urinary tract infection can be through this E. coli.

We also have another island here you can see that there is a J 96 and that also encode for alpha hemolysin, P-pilus in urinary tract infection. So here you can see there are series of this pathogenicity island and these are playing very important role in development of disease or making these bacteria as a pathogen more appropriately I can say that. So, with this I will stop this session.

And in next session we will discuss how these virulence factors are regulated because you know that these pathogens are also present in free living form. And when they reach to the human host or the host, then they trigger their pathogenicity factor, so what are those triggers we look at all those things. With this, I will stop here and thank you. We will see you in next session.