**Cell and Molecular Biology**
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**Week 11**
**Molecular Immunology**
**Lecture - 41**
**Components of Immune System.**

Hello everyone, this is Dr. Vishal Trivedi from the Department of Biochemistry and Bioengineering at IIT Guwahati. And what we were discussing were the different aspects of cell and molecular biology in this particular course. So far, we have discussed cell biology, cell division, cell nutrition, cell uptake, and many aspects related to cell signaling. And then, subsequent to that, we have also discussed the central dogma of molecular biology. So where we have discussed replication, transcription, and translation, we have also discussed the various aspects related to the genetic material of organisms.

We have also discussed the different characters, how the characters are inherited across the different generations, and so on. So these were some of the very important aspects of, you know, cell and molecular biology. Continuing from that, we are also going to discuss today immunology, and we are going to talk about how the immune system protects and plays a crucial role in the survival of an organism. So when we talk about the immune system, it is the system that actually resists the growth of external organisms.

Remember that if the organisms are surviving, they are doing so because they are protecting themselves from any kind of threats from outside as well as from the inside. So, these external threats mostly come from other organisms, and there are internal threats that also arise because of some metabolically induced antigens or internal problems that an organism may encounter. So the main focus of the immune system is to resist the changes induced by external or internal sources. So when we talk about the immune system, the study of the immune system is conducted by a branch of science called immunology. And immunology is the study of the immune system.

And as we said, the immune system is a system that is present in all organisms. Whether it is prokaryotic in origin or eukaryotic in origin, in this particular module we are not discussing the immune system present in the bacterial system; we are only focusing on the immune system present in the eukaryotic system, especially the multicellular eukaryotic system like humans. So, immunology is the study of the immune system, the body's sophisticated defense network that protects against pathogens such as bacteria, viruses, fungi, and parasites, as well as harmful substances, right? So when you discuss the different aspects, you will understand that it is not just external organisms that are threats to the human body. It is also the internal harmful substances that are produced by

many mechanisms. And many of these substances are also being taken up or taken care of by the immune system.

So, as a subfield of biology, immunology explores how this system evolved to defend multicellular organisms against a wide array of both microscopic and macroscopic invaders. Now, let's talk about what the scope of the immune system is. So the scope of the immune system is that it is highly adaptable, correct? So, that is one of the important features of the immune system. Able to respond to threats as small as the 30-nanometer poliovirus and as large as the 100-centimeter-long parasitic worms like Dictophyllium renale, right? So you see that the immune system is very, very diversified and adaptable; it is actually going to respond to as small a thing as a tiny particle of a virus, or it could be responding to a large parasite. To handle such diversity, it uses a broad array of recognition and destruction mechanisms supported by a dynamic network of cells, molecules, organs, and pathways.

So currently, in this particular lecture, we are going to discuss only the basics of immunology. And we are also going to discuss the different components that are important for the immune system to execute its immunological responses. So in that, we need to discuss about the recognition and destruction mechanisms. We have to discuss the cells, molecules, organs, and different types of pathways. Because of this complexity, the immune system engages in a coordinated and sometimes circular process, making it one of the most integrated biological systems to study.

To play a critical role in many groundbreaking medical achievements that you know will be responsible for the eradication of smallpox through vaccination. I'm sure you have studied or heard about the many major stories about how smallpox is being eradicated by vaccinations and so on. And that's how the people understood the concept of the immune system and the defense mechanism. Then there are so many examples of organ transplants, aren't there? So then there will be treatments for autoimmune disorders, allergies, and asthma, right? So many of these terms can be very complicated for you. You may not be able to understand these, but once we discuss these terms in more detail, you will be able to understand what is meant by autoimmune diseases, allergies, and asthma.

Now the question is, why would one want to study immunology? Understanding immunology is crucial in today's world. Why? Because every day, new infectious diseases arise. You might have heard about the coronavirus or COVID-19. There are many times you might have heard about new viruses being discovered, and they are also causing different types of diseases. Then the existing diseases the organisms are actually acquiring antibiotic resistance, and you might have already experienced what the impact

of the pandemic will be.

So we have already seen the impact of the pandemic when we saw the effects of COVID-19, and there is an urgent need to explore how the immune system works and how it can be supported or modified, right? So remember that when people were severely affected by COVID-19 or the coronavirus, the immune system played a crucial role, and because we know how the immune system handles this particular virus, we advised people to take different types of medicines and various modulators. So, basically, immunology provides insight into many things. It gives insight into how the disease is spread and how it can be prevented. It gives you insight into why some immune responses fail or go overboard. For example, the development of autoimmunity and allergies.

And then it also discusses how to enhance immune responses through vaccination, as well as the different types of immunotherapy. What is the advantage of studying immunology? So, because immunology is going to give you a tool or a weapon to work against particular infectious organisms or a particular type of foreign substance, you can actually use this knowledge to develop different types of molecules. Studying immunology offers numerous practical and scientific benefits. For example, it will help you develop the vaccines, right? So there are different types of vaccines available that are actually helping us protect against different types of viruses. So basically, the vaccine development actually trains the immune system to fight against infectious organisms, right? Then number two, immunotherapies, right? So it harnesses the immune system to fight cancer and chronic diseases.

Number three: transplant success, right? Because we know how the immune system is going to respond to the different types of organs from different donors. We can actually use that information to help prevent graft rejection and to enhance compatibility between the two individuals so that the transplant can be successful. The number four is integrated into health. Right. So it reveals the connection between the immune system, the nervous system, the endocrine system, and the metabolic system, helping to maintain homeostasis for the overall well-being of a person.

If you talk about the development of immunology as a field, it started way back in four hundred thirty B.C. When people have realized that, you know, we know of the existence of the plague in the era of Athens, right? And then in the 15th century, the Chinese and Turks actually suggested that the dry crust derived from the small pustules was either inhaled into the nostril or inserted into the small cut in the skin. And that actually is going to give you protection against disease. Then, in the year 1978, the method of variolation was improved by Edward Jenner, and that's how he actually discovered a vaccine against

smallpox.

Then, in the years 1880 and 1881, Louis Pasteur developed the vaccine against cholera caused by the organisms. So you remember that cholera is caused by a bacterium called Vibrio cholerae. And Louis Pasteur actually discovered a vaccine for cholera. In 1890, the Bollinger and the chivalry gave the fourth insight into the mechanism of humanity, earning the Nobel Prize in Medicine in the year nineteen hundred and one. Then, in the year 1930, Elwin showed a fraction of serum called gamma globulin that is responsible for antibody activity and immune responses.

In the year 1940, the Merlin Chase succeeded in transferring immunity against the tuberculosis organism by transferring white blood cells between guinea pigs. In the year 1950, the scientist identified a type of cell called lymphocytes, which contributed to both the humoral and the cell-mediated responses. In the year 1956, Bruce at Mississippi State University indicated that there were two types of lymphocytes: T lymphocytes and B lymphocytes. T lymphocytes are involved in cellular immunity, whereas B lymphocytes are involved in humoral immunity, and you will understand what is meant by cellular immunity and humoral immunity in due course, and we will discuss these terms. In 1966 and 1967, scientists discovered immunoglobulin E and its role in allergic reactions and responses.

So then, in the year 1975, Kohler and Milstein developed hybridoma technology, and that's how they started developing the monoclonal antibody, which became an essential tool in diagnostics and therapeutics. In 1987, Tonegawa received the Nobel Prize for elucidating the genetic mechanism behind antibody diversity, explaining how a vast variety of antibodies can be produced from a limited number of genes. And this is a very, very important discovery that actually explains how a single gene can give rise to different types of antibodies. In the year 2005, Fraser developed the first vaccine targeting human papillomavirus or HPV. And he rolled, you know, he brought up the correlation between the HPV infection and the incidence of cervical cancer.

And that's how we still actually give a vaccine against HPV infections that protects a person from getting cervical cancer. In the year 2010, the FDA approved the first immune checkpoint inhibitors for metastatic melanoma. Since post-2010 to date, there have been many discoveries. People have developed messenger RNA vaccines. People have developed messenger RNA vaccines, as well as different types of personalized vaccines, and so on.

So, immunology is a very important field, and it is developing every day. And it is making new discoveries. First, what we are going to understand is how the immune

system functions against particular organisms and infectious diseases. What are the different components of the immune system, and then we will also discuss some aspects related to the immune system? So, what are the basics of the immune system? Vertebrates are protected by two different types of immune systems: the innate immune system and the adaptive immune system. You are going to get this from your birthright, so this is the system you will receive from birth, and adaptive immunity is the immunity you will acquire.

You know, while you are going through the process of growing from birth to adulthood. So when you go from birth to adulthood, you actually develop adaptive immunity or acquired immunity. So, these two sides collaborate to protect the body against foreign invaders. So, this is actually the innate immunity that is the starting material, isn't it? You're actually going to bond with the basal level of immunity against the different types of organisms, but that vessel level of immunity can be trained over the course of time as you grow from a small baby to an adult, and that's how you are actually going to train your system to develop adaptive immunity. So, what is innate immunity? Innate immunity includes the built-in molecular and cellular mechanisms that are encoded in the germline and are evolutionarily more primitive, aimed at preventing infection or quickly eliminating common invaders.

So innate immunity is actually an immunity that will protect you, you know, as soon as you are born, right? So, at that time, there will be an infectious organism that will start attacking you, right? So they will actually be protected from the different types of these organisms with the help of innate immunity, right? A second line of immunity, called adaptive immunity or acquired immunity, is much more attuned to the subtle molecular differences. And this part of the system relies on the B and T cells taking longer to come on board, but it requires much greater antigenic specificity. Typically, there is an adaptive immune response against a pathogen within five to six days after the barrier breach and initial exposure, followed by a gradual resolution of the infection. So basically, when our organism enters the system, it is the innate immunity that will actually protect it, and it will take that up and then start producing the immune response. And that immune response would be the adaptive immune response.

So, to understand the immune system, we first have to understand innate immunity, and then we also have to understand adaptive immunity. So, what is innate immunity? As I said, innate immunity is what you are going to be born with, right? So, for example, when you are born, you are born with two legs, two hands, and so on, right? These are the basic materials, right? But after that, you use these hands, you use these legs, and that's how some people are, you know, becoming wrestlers, some people are becoming runners, some people are becoming cricketers, so that is their adaptive immunity, right? Or those

are the adaptive features, right? So by birth, we are all born similar, right? We all have two legs, two hands, and so on, but during the course of our development, from small kids to adults, we develop some of our skills, right? And that's how it becomes a different type of person, right? So that is what the difference is between innate immunity and adaptive immunity. So the innate immune system includes anatomical barriers against infection, such as skin, both physical and chemical, and cellular responses. So the physical barriers, the body's first line of defense, are the epithelial layer of the skin and the mucosal and glandular tissue surfaces connected to the body's openings. These epithelial barriers prevent infection by blocking pathogens from entering the body.

So within the immune system, you have the physical barrier, and you are also going to have the chemical barrier. Right? The first line of defense means that you are going to have two different types of doors. You are going to have the door to protect the person from entering your home, right? So you can have the physical door. You can also have the chemical door, which means you can actually have some kind of spray or something, right? Then you have the chemical barrier. So at these surfaces, you have a specialized soluble substance that processes the antimicrobial activity, such as acids, right? For example, in our gut, there is a large quantity of acid, and that acid does not allow any organism to enter the body.

Then pathogens that breach the physical and chemical barriers due to damage or direct infection of the epithelial lining can survive in the extracellular space. Or they can infect the cells, eventually replacing and spreading to other parts of the body, right? So, what are the anatomical barriers to infection? So the most obvious component of the immune system is the external barrier to microbe invasion: the epithelial layer that insulates the body's interior from the pathogens of the exterior world. These epithelial barriers include the skin and the tissue surfaces connected to the body's openings, the mucous epithelial linings such as the respiratory, gastrointestinal, and urogenital tracts, and the ducts of the secretory glands, such as the salivary glands, lacrimal glands, and mammary glands. which produce saliva, tears, and milk, respectively. Skin and other epithelia provide a layer of plastic wrap that encases and protects the inner domain of the body from infections.

But these anatomical barriers are more than just passive wrappers. So they contribute to the physical and mechanical processes that help the body shed pathogens and also generate active chemicals and biochemical defenses by synthesizing and deploying molecules, including peptides and proteins that have antimicrobial activity. So anatomical barriers are actually going to resist the entry of that pathogen; once they enter, the active molecules will fight against these particular foreign particles. These are some of the places where you will have protection; for example, the skin will have antimicrobial

peptides and fatty acids in the sebum. Then you have the mouth and the upper alimentary canal.

Right? So you have a mouth. Right. So there you are going to have enzymes, antimicrobial peptides, and the sweeping of the surface by the direct flow of fluid toward the stomach. Right. So, within the enzyme, for example, you have lysozyme. Right. So saliva contains a large quantity of lysozyme, and lysozyme actually kills the bacteria.

Right? That is something that you are supposed to do, right? Then, within the stomach, you're going to have a low pH because the stomach has a low pH due to the enzyme called HCL. Then it also has digestive enzymes. Then you have antimicrobial peptides, and the fluid flows towards the intestine. So it actually has the running fluid, as well. So because of that, it will not allow any molecule to remain.

Then, within the small intestine, you have digestive enzymes, antimicrobial peptides, and fluid flow to the large intestine. Then we have a large intestine: the normal intestinal flora competes with the invading microbes. And then you also have the fluid or feces expelled from the rectum. Then you have the airway and the lungs, correct? So, these are the airways, right? From the nostril, the airway goes all the way to the lungs, doesn't it? So you have cilia that sweep the mucus onward. You have coughing, sneezing, and macrophages in the alveoli of the lungs.

So remember that you always have a runny nose when there is an infection. So that runny nose is because you are actually expelling mucus from your nostrils. And then the nostrils also have hairy surfaces that protect you from all the organisms coming through the dust particles. We also have the urogenital tract, which is flushed by urine aggregation from the urinary system, along with low pH antimicrobial peptides and proteins in the vaginal secretions. Then we have the salivary, lacrimal, and mammary glands.

Right. So all of these glands are actually secreting larger fluids, flushing the secretions, antimicrobial peptides, and proteins into the vaginal secretions. And then we talked about adaptive immunity. So adaptive immunity is actually going to take up the material that is present within innate immunity. Then it is actually going to train that system. So adaptive immunity is nothing but actually training your innate immune system.

And that's how it is actually going to allow them to receive training to fight against the different types of infectious organisms. So, one popular, significant, and unique attribute of the adaptive arm of the immune response is immunological memory, right? So, you actually bring the immunity, right? And you actually keep a memory of that immunity.

So, for example, if there is a memory against Mycobacterium tuberculosis, right? And even suppose I got the infection now and had the memory from 10 years back, the moment I get the infection, the system will remember how I am actually going to kill this particular organism because it has a memory, right? So it will actually start producing those different kinds of molecules that are going to take care of these organisms. So this is the ability of the immune system to respond much more swiftly and with greater efficiency during a second exposure to the same pathogen. Unlike almost all other biological systems, the vertebrate immune response has evolved not only the ability to learn to encounter foreign antigens in real time, but also the ability to store this information for the future.

And this is a very, very important feature of the adaptive immune system: it not only fights the current invader, but it also keeps a memory so that in case similar kinds of invaders come into the body, I will not have to go through all the procedures of preparation; I will actually know what I am supposed to do. During the first encounter with the foreign antigen, adaptive immunity undergoes what is termed a primary response, during which the key lymphocytes that will be used to eradicate the pathogens are clonally selected and utilized to resolve the infection. These cells incorporate messages received from the innate players into a tailored response to specific pathogens. Now, all subsequent encounters with the same pathogen are referred to as the secondary response, right? So in the primary response, the body will understand how to tackle this particular problem.

It will actually generate the memory. So which will actually, it is actually going to generate a protocol, how to encounter any such pathogen when it comes to the second time. But when it comes to the second time, it is actually going to generate the secondary response, which means it is not going to go through the entire process. Instead, it will actually going to produce that response so that this particular pathogen should be removed. So, during a second process, memory cells, which are actually going to have the task of bringing that protocol back, are basically going to produce the B and T lymphocytes that have already been trained to produce the primary response, and then they are actually going to be put into the fight so that they can produce the antimicrobial molecules, and that's how they are actually going to eradicate that particular pathogen. Those cells begin almost immediately and pick up the fight where they left off.

Continue to learn and improve their eradication strategy during each subsequent encounter with the same pathogen. Right. So this is what we said, right? So if you have the memory, you know how to kill the person. Right. For example, if two wrestlers are fighting, right? So when they encounter it for the first time, they know they will actually use different types of tactics to fight and defeat the person.

But when the same encounter happens the next time, it will not go through with all the tactics. It will know the final tactics, how it has defeated the person, and it will use those tactics, and that's how it is actually going to take care of it. So the memory lymphocytes provide the means for a subsequent response that is so rapid, antigen-specific, and effective that when the pathogen infects the body a second time, the dispatch of the offending organism occurs without any symptoms. And this is actually the purpose of getting vaccinated, right? You are basically administering a vaccination to reduce memory lymphocytes, right? So that when you are going to do a vaccination, you are mimicking the entry of that particular pathogen into the body, and so that you can actually generate the memory response, this memory response will keep the whole protocol ready. So as soon as the real pathogen enters, it is actually going to take care of that particular infection.

It is a remarkable property of memory that prevents us from catching many diseases a second time. So immunological memory harbored by residual B cells and T cells is the foundation for vaccinations, which use crippled or killed pathogens as a safe way to educate the immune system to prepare it for later attacks by life-threatening pathogens. Now, what is the difference between innate and adaptive immunity? Innate immunity, in terms of response time, takes minutes to hours. Whereas adaptive immunity develops over days, innate immunity works instantly, and that is the purpose of having innate immunity: as soon as the pathogen enters, you are supposed to have some resistance mechanism so that you can actually stop its entry for some time. And during this time period, only the person is going to evolve adaptive immunity, and that's how it is actually going to be able to defeat the immune response.

Then specificity and the specificities are limited and fixed. So it actually has a gross response rather than a specific response. Whereas in adaptive immunity, it is highly diverse and adapts to changes during the course of the immune response. In response to the repeated infections, innate immunity responded every time at the same time, right? The same way, actually. Whereas adaptive immunity becomes more rapid and effective with each subsequent exposure, Then you have a major component.

So you're going to have a barrier; for example, the skin. And then you have different types of cells, such as phagocytes and pattern recognition molecules, and so on. Whereas in adaptive immunity, there are lymphocytes like T cells and B cells. And then you also have antigen-specific receptors and antibodies. Now, within innate immunity and adaptive immunity, you probably have two different types of systems. You can actually have a system where you are using the liquid component, or you can have a system where you are going to use the cells.

So if you use the liquid component, it will be called the humoral response or humoral system. If you use the cells, then it's actually going to cause the cell-mediated response. So, let's first discuss the humoral response. The humoral immune system is also known as antibody-mediated immunity. Basically, the humoral immune response refers to all the liquid parts or liquid components that have participated in the immune response.

So, it could be an antibody, it could be complement, or it could be all the liquid components that are secreted from the cell. And it is a vital component of the adaptive immune response. It primarily defends against extracellular pathogens such as bacteria, viruses, and toxins by producing antibodies that circulate in bodily fluids. And that's why, historically, it has been considered or referred to as humor. What are the components of the immune response? So you have B lymphocytes, plasma cells, and a memory cell.

So the B cells develop in the bone marrow and express the B cell receptor on their surface for each specific antigen. Upon encountering their specific antigens, B cells become activated and differentiate into plasma cells and memory cells. Plasma cells are the effector cells that secrete large quantities of antibodies specific to the encountered antigens, whereas memory B cells are long-lived cells that remember the specific antigens, enabling a rapid and robust immune response upon re-exposure. Then we hope for the antibodies, right? So antibodies are Y-shaped proteins produced by plasma cells that specifically bind to antigens. So we will discuss the structure of antibodies in our subsequent lectures, correct? At that time, you will understand more about these antibodies.

There are five main classes. You have IgG, IgA, IgM, IgE, and IgD, each with a distinct role in the immune system, right? Then we also have the helper T cells, or the CD4 T-positive cells, that assist in B cell activation by recognizing the antigen-presenting B cells and secreting the cytokines that promote B cell proliferation and differentiation. Then we also have the complement system. So all of these are part of the humoral response. A group of proteins that are then activated by antibodies bound to antigens enhances the ability to clear the microbe and the damaged cells, promotes inflammation, and attacks the pathogens' plasma membranes.

Then we also have the cellular system. So, cell-mediated immunity is a crucial component of the adaptive immune system that defends the body against intracellular pathogens, such as viruses, certain bacteria, and cancer cells. Remember, the humoral response actually protects the body from external or extracellular pathogens such as bacteria, viruses, fungi, and so on, whereas the cell-mediated response primarily protects against intracellular pathogens such as viruses, bacteria, and cancer cells. Unlike humoral

immunity, which relies on antibodies, cell-mediated immunity involves the activation of specific cells to identify and eliminate infected or abnormal cells. Number one is the T lymphocytes, or T cells. And so T lymphocytes could be of two types: cytotoxic T cells or CD8-positive T cells.

These cells recognize and directly kill the infected or cancerous cells presenting the cell-specific antigen bound to the MHC class I molecules. Then we have the helper T cells, or the CD4-positive cells. They assist other immune cells by releasing cytokines that enhance the immune response. Then we have the macrophages. So these phagocytic cells ingest and destroy the pathogens and present the antigens to the T cells, bridging the innate and adaptive immunity.

Remember, all these cells are part of the innate immune response. But when they encounter a pathogen, they are trained to elicit an immune response, and then they also become a part of the adaptive immune response. Then we have the natural killer cells, right? So part of the immune cells, NK cells, can recognize and kill the infected or transformed cells without prior sensitization, often detecting the cells with downregulated MHC class I molecules. Then we have cytokines. These signaling molecules, such as interferon gamma and TNF-alpha, are produced by T cells and other immune cells to regulate and amplify the immune response. What is the function of the cell-mediated immune response? It targets and destroys the cells infected with viruses or certain bacteria that reside within the host cells.

For example, the TB bacterium, or Mycobacterium tuberculosis. So, Mycobacterium tuberculosis is an intracellular pathogen. So, it is an intracellular pathogen. So what the body decides is actually going to destroy the whole cells. Then it identifies and eliminates the cancer cells presenting the abnormal antigens, and it recognizes and attacks the transplanted tissue or organ perceived as foreign. Cell-mediated immune responses work against large objects or intracellular pathogens.

Then we have different types of immune responses. We have immune responses when pathogens infect us, so pathogens are microbes that cause diseases, including viruses, bacteria, fungi, and parasites. Pathogenesis refers to the process through which these organisms invade the body and cause illness; the immune system identifies the pathogen by detecting the unique molecular patterns that are not found in human cells, correct? So you are actually going to have a unique pattern that is present on the outer surface of these pathogens, right? And that pattern is not present in the human system, correct? So what will be the first line of defense? There will be physical and chemical barriers, such as skin and the mucous membranes, which actually work as physical barriers and block injury. Then we also have the acidic environments in the stomach, vagina, and sweat,

which prevent microbial growth. And when these barriers are compromised, such as when you have a cut, there will be a burn and an insect bite. So when the insect bites, it actually injects the particular pathogen directly into your skin, right? So it doesn't get blocked by all these kinds of barriers.

The risk of infection increases significantly. Then we have the role of the microenvironment. So the body's location and context influence immune responses. Some regions, for example, the central nervous system, are protected from complete immunity to prevent damage. Then we have tolerance.

Tolerance occurs in the digestive tract for harmless and beneficial microbes. And the same microbe may trigger a strong immune response if it enters the bloodstream. So basically, there are places that are being tolerated which are not immunologically that active. For example, you have a digestive tract, you have the fallopian tubes, and you have, you know, that tract of vagina and all that. That place is not very immunologically active, you know. So, because of that, it actually allows the proliferation of harmless and beneficial microbes so that you can have the gut microflora and all those kinds of things, as all these microbes are actually going to help you in terms of producing the different types of vitamins.

It also helps you digest food material and so on. So recognizing triggers the immune response. The immune system is activated only after the pathogen breaches the physical and chemical barriers. So the host cell uses the recognized molecules to detect whole pathogens, pathogenic fragments, or pathogen-secreted products. So these are the three categories that the immune system is actually going to recognize as non-cells.

Right. Either it is going to recognize the whole pathogen, like the entire bacterial cell, or it is not. It could actually be able to, you know, recognize the pathogen fragment like the broken bacteria, or it could also be able to, you know, identify it from the secreted protein product. Then binding these molecules starts a signaling cascade leading to the destruction of the invader. Then we have intracellular pathogens, such as viruses, specific bacteria, or cancer cells.

So viruses live and replicate inside host cells, hiding from many immune defenses. So cytotoxic T lymphocytes detect changes in the infected cells and kill them. And the intracellular receptors alert the immune cells to the presence of viruses in the cytoplasm. For example, HIV targets helper T cells, weakening the immune system and leading to immunodeficiency. Then we have extracellular pathogens, such as bacteria, fungi, and some parasites. So, from outside the cell, these are targeted by the B cell and the antibodies, and the antibody binds to the pathogens, marking them for destruction or

neutralizing them directly.

Antibodies can reach places where immune cells may not be able to go. Now let's talk about some of the immune responses. So, the first immune response is phagocytosis, right? So phagocytosis is basically a process that is called "eating," right? So, eating by the cells, is that right? So despite the strong defense of our protective epithelial cells, some pathogens have evolved strategies to penetrate these defenses, and epithelia may be disrupted by wounds, abrasions, or insect bites, which may transmit the pathogens. Once the pathogen penetrates the epithelial barrier into the tissue space of the body, an array of cellular membrane receptors and a soluble protein that recognizes the microbial component play an essential role in detecting the pathogen and triggering an effective defense against it. Phagocytic cells make up the next line of defense against pathogens and penetrate the epithelial cell barriers. So, we have the macrophages, neutrophils, and dendritic cells in tissues, and the monocytes in the blood are the main cell types that carry out phagocytosis.

That is the cellular uptake of particulate materials such as bacteria, a key mechanism for eliminating pathogens. So, phagocytosis means cellular uptake or the eating of particular material, right? How does it happen? So, what is the mechanism of phagocytosis? So, through the cell surface receptor, the cell recognizes microbes such as bacteria, extends its plasma membrane to engulf them, and internalizes them in a phagosome, right? So this is exactly what happens. The bacteria become attached to the membrane, and when they actually touch the membrane, it induces a series of signaling cascades. And because of that, the pseudopodia come out of this particular cell. And slowly, these pseudopodia are actually going to fuse, and as a result, the bacteria will be encircled in a membrane vesicle.

This membrane vesicle is called the phagosome. Phagosomes fuse with the lysosomes, right? So lysosomes then fuse with the phagosomes, delivering the agents that kill and degrade the microbes. Remember that the lysosomes contain the hydrolytic enzymes. They are actually going to have a low pH, and they are going to destroy all the material, right? Neutrophils are the second major type of phagocytes that are usually recruited to the site of infection, where the bacteria are killed and digested by lysosomal enzymes, and the digested products are released from the cell. Some of these digested products, such as the small peptides, are also going to be expressed along with the MSC molecule, and that's how they will actually signal the neighboring cells, such as the T cells and B cells, to elicit a more pronounced immune response. So basically, phagocytosis is meant to eliminate pathogens and also to alert the immune system in the body that there is a pathogen of this particular type of peptide or this particular type of antigen, with antigenic characteristics, and induce an immune response against this particular type of

antigen.

So, the second part is antigen presentation. And for antigen presentations, we have to understand the major histocompatibility complex, or the MHC. So the MSC complex is a collection of genes arranged within a long continuous stretch of DNA on chromosome 6 in humans and chromosome 17 in mice. The MST in humans is called HLA or the human leukocyte antigen. There are three different types of MST molecules.

You have class one MST molecules, a class two MST molecule, and class three MST molecules. So in a class of MST molecules, which encode the glycoprotein expressed on the surface of nearly all nucleated cells, there is the presentation of peptide antigens to the T lymphocytes. Then you have class II MSC molecules that encode the glycoprotein primarily expressed on the antigen-presenting cells known as macrophages, dendritic cells, and B cells, along with the presentation of peptide antigens to T helper cells. Then we have three class MSC molecules that are encoded with other types of products, like secreted proteins that have immune functions, including components of the complement system and molecules involved in inflammation.

Then we have different types of antigens. You have endogenous antigens; you have exogenous antigens. So endogenous antigens, which are the antigens processed within the cytoplasm, could be virus-based or from bacteria-infected cells. So these are displayed on the surface of the class 1 OST molecules, and the pathway for processing is being called the cytophilic pathway. Whereas the exogenous antigens are processed by endocytosis, they could be any foreign substances. Two molecules are displayed on the surface of the class.

The pathway for the processing and presentation of exogenous antigens is called the endocytic pathway. Now, let's first talk about the endogenous processing pathway. So large endogenous antigens, either viral or bacterial-infected proteins, are digested into small fragments by the ubiquitin-mediated proteasome. and the abnormal protein that is digested into small peptide fragments of eight to ten amino acids Then the digested peptide fragment transported from the cytosol to the RER, mediated by a dimeric protein on the surface, is called the tap, and the alpha chain and beta chain are synthesized into the polysomes of the RER. A type of molecular chaperone called calnexin, present in the RER, is involved in the folding of the alpha chain and the release of beta-2 microglobulins. And another molecule, which is called tapasin, is associated with the folded class 1 molecule, binds with the peptide, and is expressed on the surface of antigen-presenting cells.

Then we also have the exogenous processing. So antigen-presenting cells can internalize

antigens by phagocytosis, endocytosis, or both. And then the macrophage internalizes the antigen by both processes. When the antigen is internalized, it is degraded into peptides within the compartments of the endocytic processing pathway. Internalized antigen takes one to three hours to transfer through the endocytic pathway and appears at the cell surface in the form of peptide class II MST molecules. The endocytic pathway appears to involve three consecutive acidic compartments: early endosomes, late endosomes, and lysosomes.

Interline antigens move from early to late endosomes and finally to lysosomes, encountering hydrolytic enzymes and a lower pH in each compartment. Within the compartment of each endocytic pathway, the antigen is degraded into oligopeptides of 13 to 18 residues, which then bind to the class II molecules. When the class II molecules are synthesized within the RER, three parts of the class II molecule associate with a pre-assembled trimer of a protein called DM74. This trimeric protein interacts with the peptide-binding cleft of the class II molecule, preventing any endogenously derived peptides from binding to the cleft while the class II molecule is within the RER.

The invariant chain also appears to be involved in the folding of the class II MHC chain. They exit the RER and subsequently route the class II molecule into the endocytic processing pathway. The invariant chain is digested, leaving the peptides called CLIP or the class II-associated invariant chain. A non-classical class II molecule called HLA-DM is required to catalyze the exchange of CLIP for antigenic peptides. And then HLA-DUO also called to dissociate HLA-DM and finally dissociated from the antigenic peptide.

And the class II MSC with the peptide activity activates T-helper cells. So this is exactly what it shows in the exogenous processing pathway, where the first antigen is actually going to bind to the receptor that is present on the cell surface. Then it is actually going to be internalized into the vesicle. Then these vesicles will pass through different steps, where they will first be in the early endosomes. Then they will be in the late, you know, lysosomes.

And then it is actually going to be where all the antigens are digested. Right. And then it is going to be bound to the MSC Class II molecules. And then ultimately, the MSC class II molecule containing peptide is going to be expressed along with the MSC class II on the cell surface of the antigen-presenting cell. So these are the major, you know, steps that are happening in the endogenous antigen versus the exogenous antigen. Then we also have another aspect called graft rejections and MSDs because MSDs are, as we said, two important different types of MSDs: MSD class 1 and class 2.

Class 1 is present on all cells, whereas class 2 is only present on the antigen-presenting

cells. So class 1 is actually a representation of, or specific to, a particular organism, and the class one molecules should actually match with another person who has the class one molecule. And that's why that is the main basis for the graft rejections, the main basis for the transplant, right? If that does not match, then it is actually going to cause graft rejection. So, what are the different types of transplants? So the degree and type of immune response to a transplant vary depending on the type and source of the grafted tissue.

The following terms denote the different types of transplants. You have the autograft, the isograft, and the allograft. So an autograft is the self-tissue transferred from one side of the body to another in the same individual. So autograft means you are taking out skin from the thigh and putting the skin onto the face. So this is actually the same tissue, but the location has been different. Examples include transferring healthy skin to a burned area in a burn patient and usually healthy vessels to replace a blocked coronary artery.

Then we have the isograft. The isograft is transferred between genetically identical individuals. This occurs in an inbred strain of mice or in identical human twins when the donors and recipients are synergistic. Then we have the allograft. Allograft is tissue transferred between genetically different members of the same species. For example, one person is taking an organ from another person or from a family member.

So, in mice, this means transferring tissue from one strain to another. And in humans, this occurs in the transplant in which the donor and recipient are not genetically identical. Then we also have a xenograft. So xenograft means that it should be derived from different species. For example, you're taking a graft of the heart from a pig, aren't you? So you're going to have a pig heart implanted in a human. So, because of a significant shortage of donated organs, raising animals for the specific purpose of serving as donor organs for humans is under serious consideration.

So autografts and isografts are usually accepted owing to the genetic identity between the donor and recipient, while an allograft is genetically dissimilar to the host and therefore expresses unique antigens. It is often recognized as foreign by the immune system and is therefore injected. Obviously, xenografts exhibit greater genetic and antigenic specificity, enabling a vigorous graft rejection, right? Because xenograft means you are taking the tissue, even though you have changed the species as well, right? So, in that case, the immune response will be more robust compared to the allograft. Now, what will be the role of the MSTs? So, the most intense graft rejection occurs due to differences between the donor and recipient in terms of the ABO blood group and the MST antigens.

So, the blood group antigens are expressed on the RBCs. You know that you have A antigens, you have B antigens, and then you have O. So, A and B antigen combinations give rise to the four blood groups, right? You have A blood group, B blood group, AB blood group, and if neither A nor B is present, then it becomes the O blood group, right? So, epithelial cells and endothelial cells require that the donor and recipient be screened first for ABO blood group compatibility. Which means if you want to check whether the two people can receive, you know, the organ from the other person or not? The first thing is that their blood groups should be identical, right? And then, if the recipient carries antibodies to any of the antigens, the transplanted tissue will induce the rapid antibody-mediated lysis of the incompatible donor cells, right? So for this reason, most transplants are conducted between individuals with a matching abioglutamate. Next, the MSC is compatible. The MSC contains potential donors and recipients, which means you are going to check whether the MSC1 present on the donor and the MSC1 present on the recipient are the same or different.

If they are different, then it is actually going to recognize that as a foreign antigen, and it is actually going to elicit the immune response. So, if these two are the same or similar, then there is a possibility that you can take the organ from one person and put it into another person. The first choice is usually a sibling with at least a partial match, followed by other family members and even friends. Given our current success with immunosuppression and the immune system in the recipient prior to transplantation, the importance of careful cross-matching was shown in a seminal 1969 study where 80% of the kidney transplant patients with a positive cross-match experienced almost immediate graft rejection, while only 5% of patients with a negative cross-match had this outcome.

The MSC makeup of the donor and host is not the sole factor determining tissue acceptance. Even when the MSC antigens are identical, the transplanted tissue can be rejected because of differences at various other loci; for example, the minor histocompatibility locus. The major histocompatibility antigens are recognized directly by the T helper cells and the T cytotoxic cells, a phenomenon that is referred to as LO reactivity. In contrast, the minor histocompatibility antigens are recognized only when the peptide fragments are presented in the context of the self-MHC molecules. So rejections based only on the minus derivative difference are usually less vigorous and can still lead to graft rejection.

Therefore, even in the class of HLA-identical matches, some degree of immune suppression is usually still required. Now, the second response is called inflammation, correct? You might have experienced inflammation, haven't you? For example, when there is a bite from a honeybee. So that portion becomes red and solid, correct? That is because there will be an inflammatory reaction. So when the outer barrier of innate

immunity, for example, the skin and the epithelial layer, is damaged, the resulting innate immune response to infection or tissue injury can produce a complex cascade of events called inflammatory response. Inflammation may be acute, which means short-term, or it can be chronic, for example, long-term.

Contributes to conditions such as arthritis, inflammatory bowel disease, cardiovascular diseases, and type 2 diabetes. The hallmark of a localized inflammatory response was first described by Roman physicians in the first century AD as robust, with low redness and swelling, along with heat and pain. An additional mark of inflammation added in the second century by the physician is the loss of function, which is, today, known to reflect an increase in vascular diameter, specifically vasodilation, resulting in a rise in blood volume in the area. Higher blood volume heats the tissue and causes it to redden, doesn't it? Vascular permeability also increases, leading to the leakage of fluid from the blood vessels and resulting in an accumulation of fluid, which is called edema. So it becomes swollen, doesn't it? You might have seen that it becomes swollen and then the different types of skin become slightly loose.

Right? Within an hour, the leukocytes also enter the site through the local blood vessel. These hallmark features of the inflammatory response reflect the activation of the resident tissue cells, for example, macrophages, mast cells, and dendritic cells, to release chemokines, cytokines, and other soluble mediators into the vicinity of the infection or the wound. Recruited leukocytes are activated to phagocytose bacteria and debris, amplifying the response by producing additional mediators. Resolution of this acute inflammatory response includes the clearance of invading pathogens, dead cells, and damaged tissues; the activation of the systemic acute phase response; and additional physiological responses, including the initiation of wound healing. And the induction of the adaptive immune response. However, if the infection or tissue damage is not resolved, it can lead to a chronic inflammatory state that can cause more local tissue damage and potentially have systemic consequences for the infected individual.

So this is exactly what is separate, right? Suppose you got pricked by, uh, you know, the thorn actually. So if you get pricked by a thorn, it is actually going to get inserted, right? And that is actually good enough to inject some of the bacteria, right? So, in response to bacteria, right? The first thing that will happen is there will be tissue damage, and bacteria will cause the resident cells to release the chemotactic factor. That will also cause the local increase in blood vessels and capillary permeability. So it will actually go; what will happen is this area is going to swell, right? It's going to swell because there will be vasodilation, and because of the vasodilation, there will be a greater supply of blood, and that's how it becomes red in color.

Right. And then the second thing is that it is actually going to, you know, invite all sorts of, you know, phagocytic cells. It is going to bring neutrophils. It is going to bring all those cells, right? So that there should be a robust immune response could be generated. Right. And that's how it is actually going to help in terms of developing the immune system to protect itself against the different types of infectious organisms, because anything that actually breaks the physical barrier will be alarming for the body. And that's how the body has created a system that actually initiates the cascade of inflammatory reactions, where different types of phagocytic cells are going to arrive at the site.

It will actually create a protective layer against that particular infectious organism. And it is also going to increase the blood vessels and the blood volume so that more and more immune cells can actually arrive at the site of the infection. And that's how it is actually going to cause inflammation. Bacteria enter through a wound, right? Initially, the innate immune response includes phagocytosis by the activation of resident cells such as macrophages and dendritic cells. Recognizing the bacteria by the soluble and cellular pattern recognition molecules initiates an inflammatory response that recruits antimicrobial substances and phagocytes to the site of infection. So far, what we have discussed in this particular lecture is the importance of the study of the immune system and the development of a branch of science called immunology.

We have also studied and understood why there is a need to study the immune system and how it actually helps in developing different types of vaccines. It also helps with what we have discussed about the different components of the immune system. So we discuss the innate immunity response.

We discuss the adaptive immune response. And in terms of the executory molecules, we have also discussed the humoral response or humoral immunity. We have also discussed cell-mediated immunity. So within humoral immunity, we discuss the antibodies and other kinds of molecules that participate in immune reactions. And within the cell-mediated immunity, we have discussed the B cells, T cells, and macrophages, as well as all those kinds of cells that are involved in responding to the different types of foreign antigens and how they are actually eliciting the immune responses.

As far as the immune response is concerned, we have also discussed phagocytosis. We have also discussed the inflammation. And very briefly, we have also discussed the MSP molecules. We have also discussed its relevance in terms of determining the tissue compatibility between the donor and the acceptors. So, with this brief discussion about the basics of the immune system, I would like to conclude my lecture for today. In our subsequent lecture, we are going to discuss some more aspects of molecular immunology. Thank you.