

Introduction to Complex Biological Systems
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Lecture 47

Innate immunity: the first lines of defense

Hello everyone. During the last lecture, I discussed our immune system, mostly the introductory part. During today's lecture, I will focus on our innate immunity, which is also known as the first line of defense. So, in this lecture, I will mostly explain the basic concept of innate versus adaptive immune systems, followed by the mechanism of innate immune response and how over time, the innate response transitions to the adaptive immune response, which I will also explain. To start here, I would like to mention first that in response to pathogens, our immune system uses two interconnected systems. The first one is innate immunity, and the other one is adaptive immunity. So, from the name itself, it suggests that innate means it's inborn.

CONCEPTS COVERED

1. Understanding the Basic Concept of Innate and Adaptive Immunity
2. The Mechanism of Innate Immune Response
3. Transition from Innate to Adaptive Immune Response

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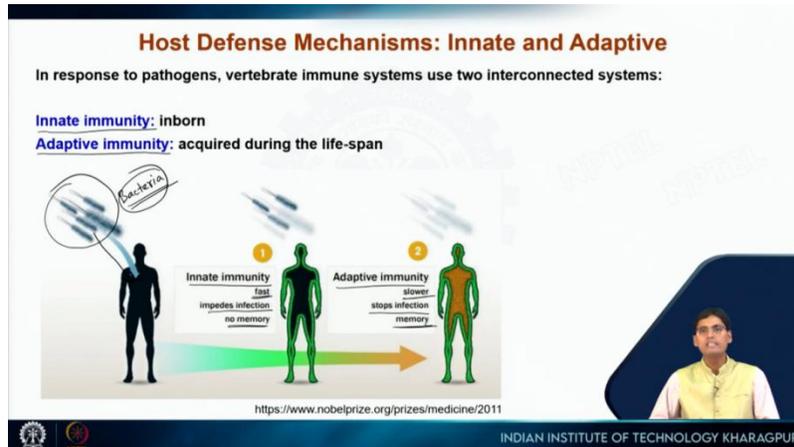
Whatever response we use in the case of innate immunity, those are present from our birth, inborn and adaptive immunity is acquired during our lifespan. Over time, our immune system learns about different types of enemy pathogens, microbes, and as a result, it develops in such a way that it can defend better. So, I will explain all those things at the right time. But now, just an overall idea about innate and adaptive immune responses. So, here, if you imagine that these are some bacteria but these are some pathogenic bacteria, not the common cells present in our body.

Now when this bacterium invades some human individual when we are getting infected by some bacteria, what will happen? So, as I already mentioned, both the innate and adaptive arms of the immune system will act on it, but at the beginning we will be seeing that innate immunity is responsible to protect us. Because the innate response is very fast and it initially tries to halt the infection. So somehow it is trying to prevent the infection so that bacteria, whatever enters our body, cannot multiply so quickly. Then if you see the next point there is no memory. So what I am trying to say by "no memory", is that again, after six months, after one year, if I am getting infected by the same bacteria, my innate immune system will work in the same way. So they will think that again it is coming for the first time.

So this is how our innate immune system works. On the other hand, if you concentrate on our adaptive immunity, you will see that the response is slower. It will take some time, at least four to five days, sometimes even more, in order to initiate the adaptive immune response. So that's why I said at the beginning that the first few days our innate immune system is taking care of disinfection. So that it cannot spread so quickly and then the adaptive immune system is also coming into place. So its response is slower and it will be able to stop the infection. It will properly control the infection and at the end there will be some kind of memory. This is immunological memory. Some immune cells will have this memory so that again, maybe six months, one year or two years later if we are getting infected by the same bacteria. then our adaptive immune cells, those memory cells, can quickly understand what happened before and accordingly they will make weapons to defend themselves, that means to defend the host.

As a result of that, next time with the same bacterial infection, most of the time I would say we will not even understand that something happened to our body. The disease will not be there itself because our adaptive immune system is already properly able to tackle this problem in a much more efficient way because of this memory. Because of this huge understanding about innate and adaptive immune response, the 2011 nobel prize was awarded to these two groups of scientists who contributed a lot in this field. Now, here I would like to explain the innate and adaptive immune response in context to a typical

acute infection. Whatever I mention in the last slide I will tell you almost same thing in much more detail.



So, as you can see here on the y-axis, we are showing the level of microorganisms. So for the time being, you can imagine this is the level of bacteria, some pathogenic bacteria, and on the x-axis, the duration of infection. So, this is the starting point, 0 days, and I would say at the end it is 15 days something like that; not a hard and fast rule but it should be somewhere around 0 to 15 days. Now, at the beginning, at day 0, that time point marks the entry of microorganisms, meaning an infection occurred.

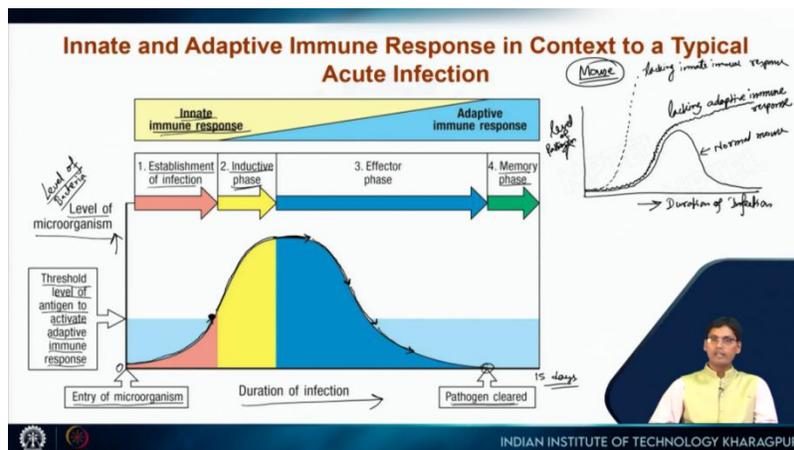
So, some microbes, some bacteria enter our body. Now, what will happen? The bacteria will multiply; they will grow through binary fission. So, from one bacterium to two, to four, to eight, and that way they will grow in our body. As a result, we will see that the number of bacteria is increasing. So, this bacterial number is increasing. In this curve, as you can see, it is going this way.

At this moment, from the bacterial point of view, you can see they are trying to establish the infection. So, this is the establishment of infection. But at this time point, from the very beginning, our innate immune system is trying to prevent infection, trying to kill bacteria by different methods, which I will discuss soon. So from the beginning, the contribution of the innate immune response is already there. Over time, the innate response will gradually decrease, and the adaptive immune system will take over to completely clear the infection. Let us see what happens.

So, at this point here, as you can see, bacteria have already increased the number to some extent, and this is what we are saying is the threshold level of antigen to activate adaptive immune response. So the threshold level of antigen means here I would say it can be some protein, some peptide coming from that particular pathogen or particular bacteria here. So, that antigen is required in order to stimulate our adaptive immune system. So, that is why we are mentioning that threshold level of antigen to activate adaptive immune response. Then this phase when our adaptive immune system is getting activated is called the inductive phase.

So, induction of the adaptive immune system is happening. Still, if you see that the innate immune system, innate immune response is still there, they are still trying to protect us because if that is not protecting, then bacteria or pathogens can multiply very fast and we will be too sick. So it is trying to protect so that our adaptive immune system can take over this challenge, and together innate and adaptive can clear the infection and you will be seeing no more growth of pathogens or bacteria. So, that means somehow innate and adaptive together they are tackling in a better way so that they cannot multiply anymore. Now this is the effector phase here you can see the adaptive immune system is already came into place and it is properly clearing the infection, and the level of microorganism is gradually going down, and at this point, as you can see, the pathogen has been cleared, no more infection, the disease is gone. After that, I would say this is the memory phase, which means some memory cells, some immune cells with immunological memory, will remain in our system so that if we get infected with the same pathogen again in the future, it can be properly tackled by these memory cells. So, this is how the innate and adaptive immune system work together in context to an infection. So, now if I discuss in this way because here I mention both innate and adaptive immune systems. So, what do you think that if, experimentally, we can develop some mouse model? So, some mouse models. Some mice don't have an innate immune system; the innate arm is missing, and another group of mice don't have the adaptive immune system, they lack an adaptive immune system. So, what do you think: which one will survive better, the mice that lack an innate immune system or the mice that lack an adaptive immune system? So, the answer is something like this.

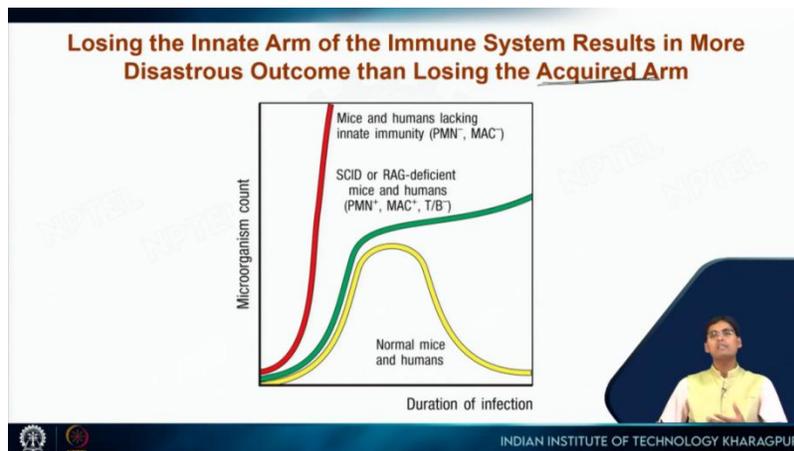
See, this is our duration of infection, and this is the level of pathogen, the level of bacteria or pathogen, whatever you say. Now, in a normal condition, in a normal mouse, you have already seen this is a curve, the number of pathogens. Now, when we do not have some mice experimentally, if they do not have the innate immune system, that will be a bigger problem because, at the beginning, no one is there to check the multiplication of bacteria or pathogens. So, as a result of that, without an innate immune system, it will go like this. So, the mouse will die very quickly because the adaptive immune system is not yet activated before the number of pathogens is too high.



So, this is lacking an innate immune response. lacking immune response. But in the case of mice which lack an adaptive immune response, you can understand that the first part will be similar. So I would say if this is a mouse that lacks an adaptive immune response, see, this is going in a similar way because, up to this, there is no such role of the adaptive immune system; then the number of bacteria will not decrease. So, it is going like this now. So, this is a mouse lacking adaptive immune response and this is a normal mouse.

So, now I hope you understand the contribution of innate and adaptive immune response. This is already present in the next slide, but I just wanted to discuss in this way so that you can think also. So, I would say that losing the innate arm of the immune system results in a more disastrous outcome than losing the acquired arm. Acquired arm means the adaptive immune system and innate arm means the innate immune system here. So, experimentally we can generate some mice that almost do not have either an innate or adaptive immune system, and that way an experiment can be done. Now I will summarize

the innate and adaptive immune system and then I will be discussing the mechanism of the innate immune response. So, as I already mentioned, in the case of the innate immune system, the response time is very fast, minutes to hours, but in the adaptive immune system, it will take some time; it will take some information. While the innate immune response is going on, that's why it will take some time. After a few days, the adaptive immune system will start functioning against a particular pathogen, and the specificity in case of the innate immune system is limited. But the adaptive immune system is highly diverse. It adapts to improve during the course of infection or the course of immune response, and as I told today that our immune system, our body, if it sees some new pathogen, it will develop some weapon against that pathogen.



So, the pathogen will be cleared. But again I would say five years later, whenever some new pathogen comes, again, our adaptive immune system will learn how to defend against that and, accordingly, it will produce substances so that it can clear the infection. So, it is highly diverse, it can adapt properly. Now response to repeat infection already I mentioned, same each time, but more rapid and effective with each subsequent exposure; major components of the innate immune system are anatomic barriers, for example, skin, phagocytes, those cells which directly engulf microbes, and some pattern recognition molecules can understand that microbes or some pathogens are in the surrounding, and they can act on it. So, on pathogens, they have some other molecules that are called PAMPs, which is a kind of group name, not a specific name, pathogen-associated molecular pattern (PAMP), and that can be recognized by pattern recognition molecules or pattern recognition receptors present on our immune cells. In the case of the adaptive

immune system, mostly T and B lymphocytes can be seen. Commonly, we say that T cells and B cells are the major components of our adaptive immune system. Now, what is the mechanism of the innate immune system? How does the innate immune response actually appear?

Innate vs Adaptive Immunity

In response to pathogens, vertebrate immune systems use two interconnected systems:

- > Innate immunity
- > Adaptive immunity

TABLE 1-4 Comparison of innate and adaptive immunity

	Innate	Adaptive
Response time	Minutes to hours	Days
Specificity	Limited and fixed	Highly diverse; adapts to improve during the course of immune response
Response to repeat infection	Same each time	More rapid and effective with each subsequent exposure
Major components	Barriers (e.g., skin); phagocytes; pattern recognition molecules	T and B lymphocytes; antigen-specific receptors; antibodies

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So I would first focus on mechanical, chemical, and biological factors. So, mechanical factors, for example, some anatomic barriers, the first thing coming into place is skin. So, throughout our body, almost all places are covered by skin; it is an epidermal layer. So, it directly prevents pathogens from entering inside our body. So, that is some anatomical barrier, some kind of mechanical factor.

Number two, the mucus It is also present in many places, particularly in our digestive tract. In the inner lining, a lot of mucus is present, and it also prevents microbes from directly invading our epithelial cells, which are present in the inner lining of our digestive tract and also, in the airways, in the respiratory tract a lot of mucus is present, and it prevents bacteria from directly invading those epithelial tissues or cells. Number three is the flushing action of saliva and tears. So tears, coming from the eyes, and saliva, from the salivary glands, because of their continuous secretion, have a flushing action. They can flush away small particles, foreign particles, and sometimes microbes as well. So, that way, these are the mechanical factors or anatomic barriers that are constantly protecting us from infection. Now, if I move into chemical factors, there are a huge number of chemical factors that are part of our innate immune system.

I will give you a few examples, many antimicrobial peptides present in sweat. So, when we are sweating, a lot of antimicrobial peptides also come out, and that helps us. They also protect us from infection and apart from that, as you all know, a lot of HCl, hydrochloric acid, is constantly secreted in our stomach.

So, HCl is present in the stomach. That also prevents pathogens because the pH is too low, almost around 1 to 1.5, and as a result, most pathogens, almost all microbes, will die there. Some bacteria, like *Helicobacter pylori*, can survive at very acidic pH. Then, the number three. Another important chemical factor is lysozyme, an enzyme that acts against the peptidoglycan layer of bacteria.

So, you can consider that lysozyme can destroy bacteria. Lysozyme is present in huge amounts in saliva and also in tears. So, these are some examples of chemical factors that also protect us. Then, coming to biological factors, as you know that there are a lot of microbes. Those are not pathogenic; good microbes called commensal are present.

I would say around 1000 different species of bacteria are present in our oral cavity and digestive tract. So that means a lot of different types of bacteria are present in our digestive tract, and they are not creating problems for us. Rather, if some pathogenic bacteria or pathogenic microbes try to colonize in our body, they need to compete with these good bacteria which are already present. So these bacteria are also protecting us. They are actually helping us from infections. So, the pathogenic bacteria need to compete for nutrients, for colonization, and for all those things.

So, this is also very helpful, and that is why in the previous module I particularly mentioned that we should not take antibiotics randomly without requirement. We should not take antibiotics because that will kill these good bacteria and that will create more problems for us. These are some of the mechanical, chemical, and biological factors involved in our innate immune response. Now, I would like to focus on the cells of the innate immune system. This figure, which I explained during the last lecture, shows how different types of blood cells originate from bone marrow. But now I will focus on only four to five different types of cells present here. One is neutrophils, the second is dendritic cells, the third is macrophages, and the fourth is NK cells. So, these four cells

are the major innate immune cells present in our body. So, from the beginning, they try to protect us by preventing pathogens. Let's see how. Neutrophils are very good at phagocytosis. So, phagocytosis means that they are trying to engulf, they are engulfing, and they are eating those pathogen microbes. So, as a result of that, they are reducing that number. Then the next one is macrophage.

Innate Immune System
(Mechanical, Chemical and Biological Factors)

Mechanical Factors/Anatomic Barriers	Chemical Factors	Biological Factors
1. <u>Skin</u> 2. <u>Mucous</u> 3. <u>Flushing action of saliva and tears.</u>	1. antimicrobial peptide present in sweat. 2. HCl present in stomach 3. Lysozyme is present in saliva or tears.	~ 1000 diff. species of bacteria present in our orality/gastrointestinal tract.

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They have two major functions, one is phagocytosis and antigen presentation. So, I will discuss in detail what antigen presentation. This antigen presentation is the beginning of the adaptive immune system. So, because of the antigen presentation, the adaptive immune system will start acting and then the next one is the dendritic cell. So their function is both phagocytosis and antigen presentation and the fourth one is natural killer cells, this is as their name suggests that naturally they have some killing activity, natural killer cells. So, they are very good at killing some defective cells, particularly I would like to mention that they kill virus-infected cells. They are very good at it. So, now all those cells together actually take part and they play an important role in innate immune response, and in addition to that, they initiate the adaptive immune response also.

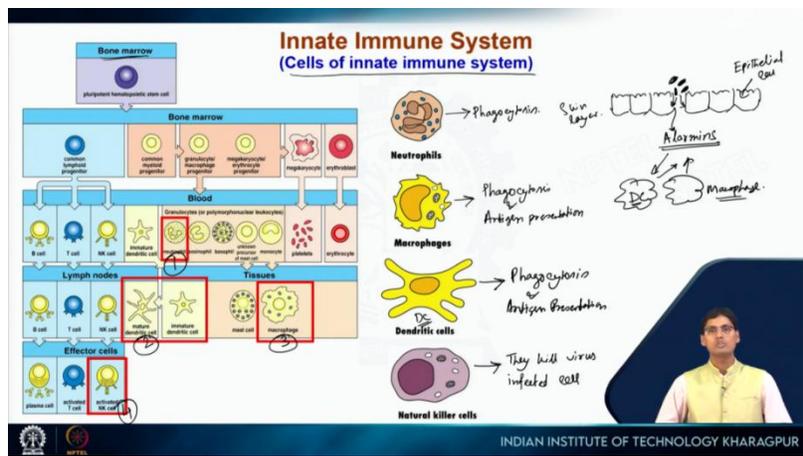
I would also like to mention how macrophages and dendritic cells understand that some problem is happening, and they will take care of it. I am just giving you one example. See, for example, if this is an epithelial layer; some epithelial cells, I am mentioning. So, for example, this is the skin layer. So, this is an epithelial cell.

Now, if some bacteria breach the skin due to some damage or a small cut, they can enter and create problems for the surrounding cells. So, from the damaged cells, some kind of

signature molecules emerge. So, those can be different types of molecules, but those molecules together are coming from our own cells, particularly damaged cells. Those are called alarmins.

So, as the name suggests, they are sending an alarm that some problem is there, some damage has happened. These alarmins will alert dendritic cells. So, this is a DC or dendritic cell as well as macrophages.

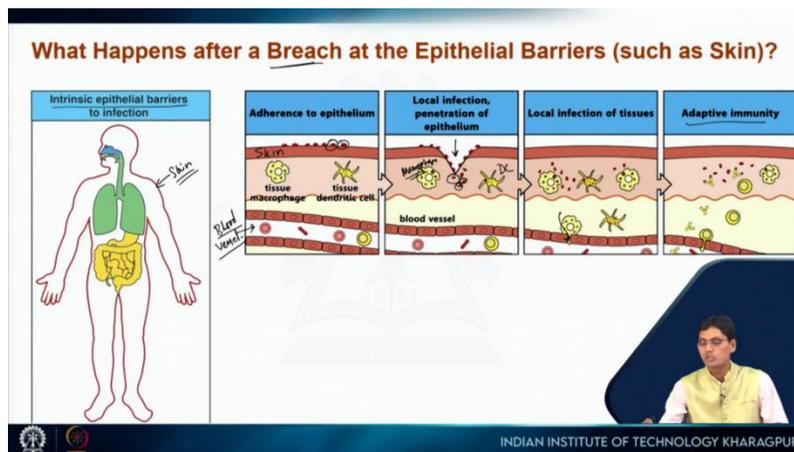
So, they will alert dendritic cells and macrophages so that they will take care of this problem. So very quickly they will try to phagocytose those bacteria. This is just one example I am giving. Now let us see in more detail. I will be discussing what happens after a breach at the epithelial barriers, such as the skin. As you can see, this is the intrinsic epithelial barrier.



So, it prevents infection. So, this is skin, present everywhere, and it helps a lot. Now, as you can see, this is the skin, and just below the skin is the subcutaneous layer, and here is our blood vessel. Now, some bacteria, as you can see here, adhere to the epithelium, meaning they adhere to the skin. Now, a local infection might happen because of a breach at the epithelial barrier.

So, this is a local infection, as you can see those bacteria are now entering inside the tissue. So, these are the bacteria entering inside the tissue and as I just mentioned, alarmin and all those things. I am not going into those details. But what is happening here? This is DC, and this is macrophage. So those are tissue resident macrophage or tissue resident

dendritic cells. Most of those cells are generally present inside blood and in some lymph nodes or in some other, specific portion of our body, but they are also present in tissue; those are called tissue resident macrophage and tissue resident dendritic cell. They quickly assess this problem, and they will defend. They will try to kill those, and not only that, they will send the signal. You can see this dendritic cell again is recruiting more dendritic cells and macrophages inside the local infection so that the challenge can be taken over in a better way, so all these things will create some symptoms, symptoms of local infection, and because of this interaction between the pathogen, these dendritic cells and macrophages, they will also activate our adaptive immunity. So, that I will discuss in the next lecture. But now, what are the symptoms of this local infection and this epithelial bridge? So, that I will summarize in this slide.

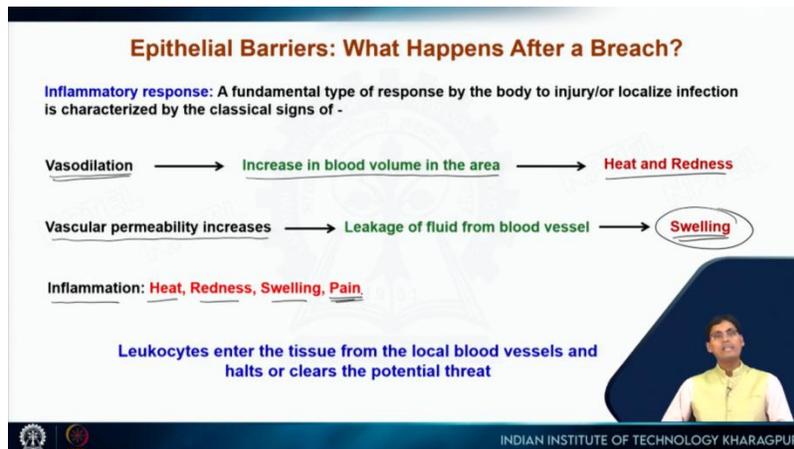


A fundamental type of response by the body to injury or local infection is characterized by some classical signs. As you can see if an infection or a small cut happens on our skin, you will notice that in that portion it becomes a little bit red or a little bit warm; it's a little bit hot, and there is some redness. Some of these symptoms appear very soon. Why? Because during that time, vasodilation happens. What is the meaning of vasodilation? So, see, I was showing that blood vessel.

So, in that blood vessel, in that layer, we have the endothelial cells. Now, that layer is getting dilated so that more immune cells can come into the place, the local site of infection. So, as a result of that, see, if vasodilation happens, the increase in blood volume in that area is why that portion is a little bit warm, some heat is generated, and

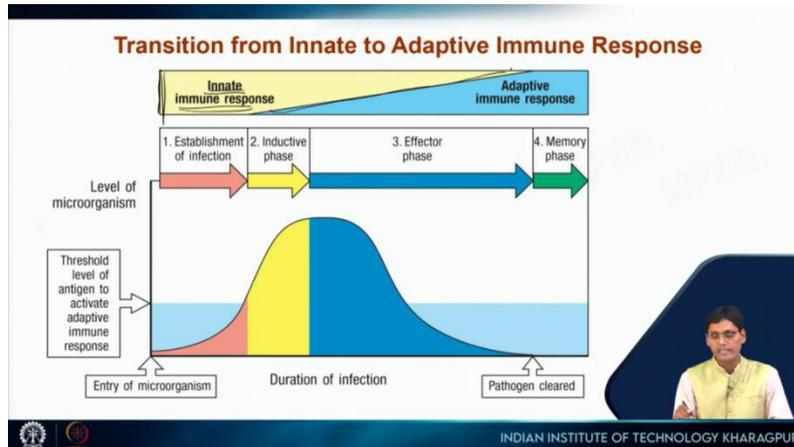
some redness also happens in that area. This is the starting point of this response. Then, because of the vasodilation Vascular permeability also increases, so vascular permeability means some fluid will be leaking from the blood vessel. So, as a result of that, some fluid will be there, and some additional cells, neutrophils and some other innate immune cells, will be coming into place. So, because of that, that portion will be swollen. This is swelling.

So, as you notice, because of the small infection or small cut, we see some heat, some redness, also some swelling, and sometimes a little bit of pus formation also. So, this is all because of this reaction, that immune reaction, and finally, inflammation. As I already mentioned, heat, redness, swelling, and some pain you will also feel. So, these are the classical symptoms of this response, which is happening because of the infection, followed by our immune response as well. Finally, leukocytes enter the tissue from the local blood vessel and halt or clear the potential threat. But at that time, they cannot always clear the potential threat; by then, they are trying to induce our adaptive immune response. So, here we will be discussing the transition part: how the adaptive immune system is activated, the transition from innate to adaptive immune response.



This curve, this chart, I already explained. I am not going into the details, but as you can see here. At the very beginning, the whole contribution is coming from the innate immune response. Then slowly, as you can see, the innate response is coming down. It is not that much required for that particular pathogen. On the other hand, you can see the

adaptive immune system response taking over this infection so that it can clear the infection.

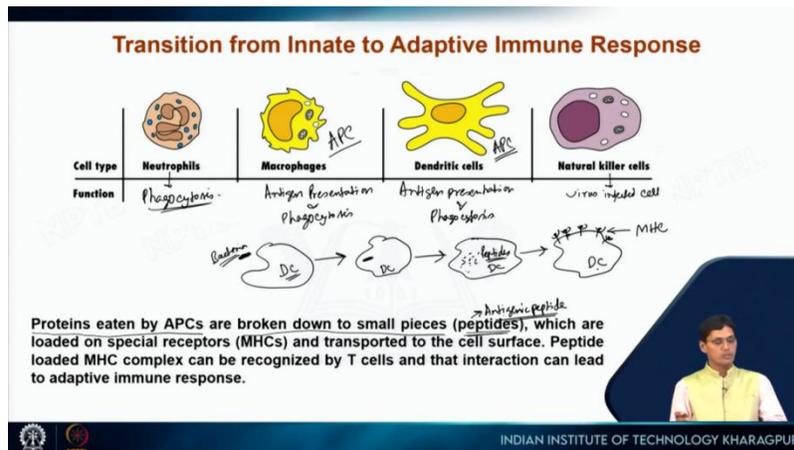


Let us see how it happens. That is the last point of this lecture. So, that is the transition from innate to adaptive immune response. As I already mentioned, neutrophils and their role is phagocytosis. So, I just mentioned that because of the local infection, sometimes some pus formation happens. So, in that pus formation, a lot of neutrophils are also present because they were actually the ones initially fighting with the pathogen. They are also there, and natural killer cells, as I already mentioned, destroy defective cells, particularly virus-infected cells and macrophage dendritic cells, they do phagocytosis. In addition to that major thing here is antigen presentation, antigen presentation and phagocytosis. This is very important. They phagocytose pathogen microbes and process that information about what is present inside the microbes, then display some antigenic signature on their surface To activate our adaptive immune system, so here if you see I mentioned here proteins eaten by APC. APC means antigen presenting cell, so I can say macrophage is one APC, dendritic cells are also APC antigen presenting cells. So proteins eaten by APC. How are they eating the protein? Basically they are engulfing or they are phagocytosing those microbes and they are breaking down those microbes into small pieces. In microbes, you have different types of biological macromolecules, proteins are also there. So from this protein, they will make small peptides. So these proteins are broken down to small pieces, which are called peptides and you can say these are antigenic peptides or just antigen. You can say which are loaded on special receptors which are called MHC major histocompatibility complexes present on the surface of

macrophage and dendritic cells. So, the basic idea if I show you this is some kind of bacteria, pathogen. Then this is one dendritic cell DC. What will happen?

So, DC will engulf this bacterium. So, this is DC. I am not showing the nucleus of DC or all those things; it is not important here. Then inside the DC this bacterium will be broken down into small pieces and they will make some peptides also. Those are called protein antigen particularly. Now DC on their surface have some specific type of receptor which is very important, called MHC major histocompatibility complex.

They are presenting this antigen. So, where are these antigens coming from then? These antigens are coming from the bacteria itself, from this bacterium. So now this DC, which is presenting antigen through this MHC, will help our T cell to learn what kind of information is present in this bacteria. As a result, our T cell will learn how to make a specific type of weapon, a specific type of reagent, so that we can fight against this bacterium.



This weapon is, particularly, an antibody. I will be discussing this in some other lecture. But anyway, these are the steps showing how the transition from innate to adaptive immune response happens. So, that is all. During the next lecture, I will be discussing our adaptive immune response, but remember, this innate response is very important at the very beginning and prevents the growth of these microbes. But at some point, when it cannot tackle them properly, it needs help from our adaptive immune system, which can completely clear the infection. Particularly in this context, you should try to understand that macrophages and dendritic cells, although they are part of our innate immune

response, are the linkers. They are linking between the innate and adaptive immune response. As you can see, they are directly engulfing and phagocytosing those microbes. That is true. That way, they are reducing the number. At the same time, they are digesting those microbes, making small peptides, and presenting them on their surface to teach adaptive immune cells in our body how to make different substances of adaptive immune response to clear the infection. That is why macrophages and dendritic cells link between innate and adaptive immune response. That is all. Thank you very much.

REFERENCES

1. Janeway's Immunology (9th Edition)

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