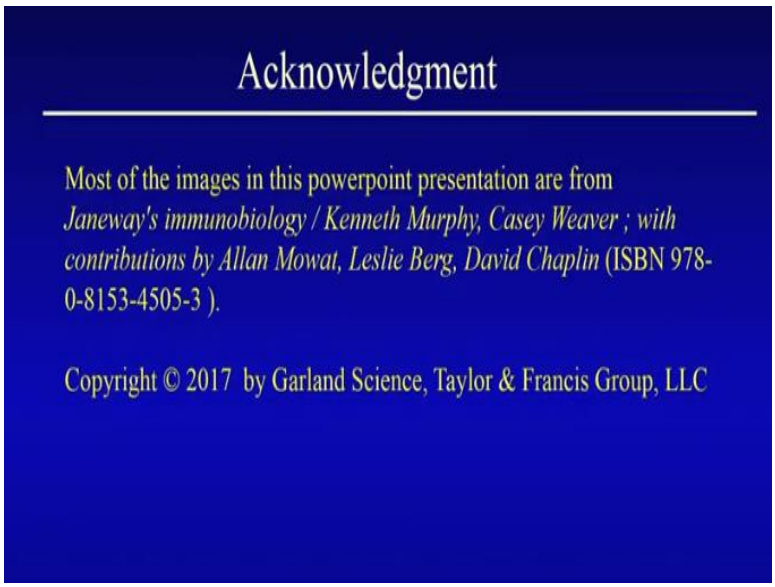
Immunology
Prof. Sudip Kumar Ghosh
Department of Biotechnology
Indian Institute of Technology-Kharagpur

Lecture - 54
Transplantation or Graft vs. Host Reaction

Welcome you all. So today as we have discussed in the last lecture that we are going to talk about transplantation or kind of graft versus host reaction okay.

(Refer Slide Time: 00:31)



So and as usual this slide also contain many images from the Janeway immunology book. And today what we are going to discuss is like if you transplant any organ or a part of one's body to another person, what happen our adaptive immune system are rejecting it, not every cases but most of the cases, okay. So immune system when developed, there is no question of this kind of transplantation.

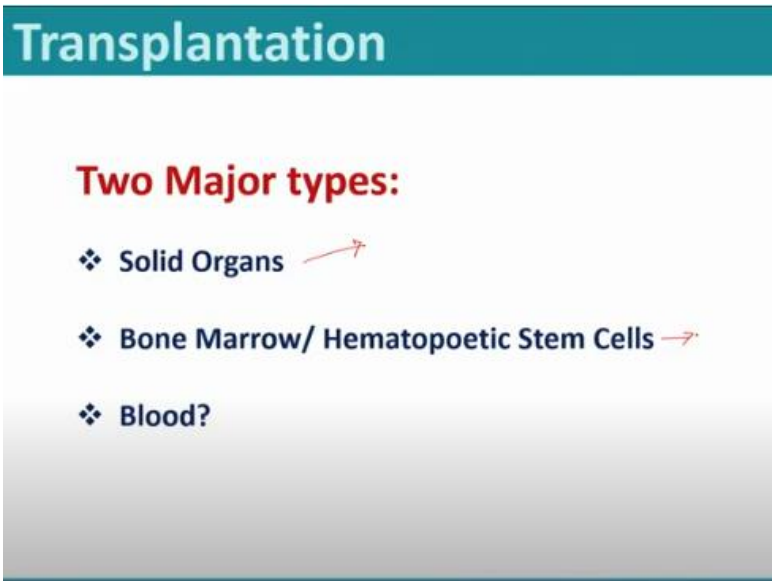
But somehow our immune system developed the adaptive immunity against anything foreign. Foreign means, even if it is human to human, immune system do not agree with that. So they find it foreign and do the adaptive immune response. And as a result, what happen if we transplant any organ like you know many of you know or most of you know or heard about like kidney transplantation, cornea transplantation, heart transplantation okay, skin transplantation.

So for many reason, we have to do. This is a very important medical aspect, like the transplant and our immune system is really causing problem and that is one of the major reason like why we have to understand the immunology and could extend so that we can overcome or manipulate the immune system in such a way so that we can do this thing very easily.

Now, I mean whatever we had the situation like 10, 15 years back or 20 years back, it is much better now. We will see why it is better, for what reason it is better. Transplantation is much more common today and success rate is very high. But still immune system is working in its own way, okay.

So what is the major parameter or what is the major thing that immune system is going to do with the transplant organ and why immune system reject it and how it is going to reject. We will go just briefly or as much as possible within this limit.

(Refer Slide Time: 02:45)



So there are two major types of transplantation. One is solid organs. Solid organs means kidney, heart brain, okay? And second one is the bone marrow or hematopoietic stem cells, in case of particularly the leukemia, if you consider. So in solid organ it is, in solid organ it is you can say kidney, heart, brain. And in bone marrow hematopoietic stem cells, we are mostly do like in case of leukemia or the blood cell cancer.

So to change like if there is having any blood cancer, what happen? The bone marrow cells get transformed and they are producing a single type of cell, lot of a huge amount. So if you have to change this, we can change this by a good bone marrow or the hematopoietic stem cells in the bone marrow so that, that person individually can produce the correct cells.

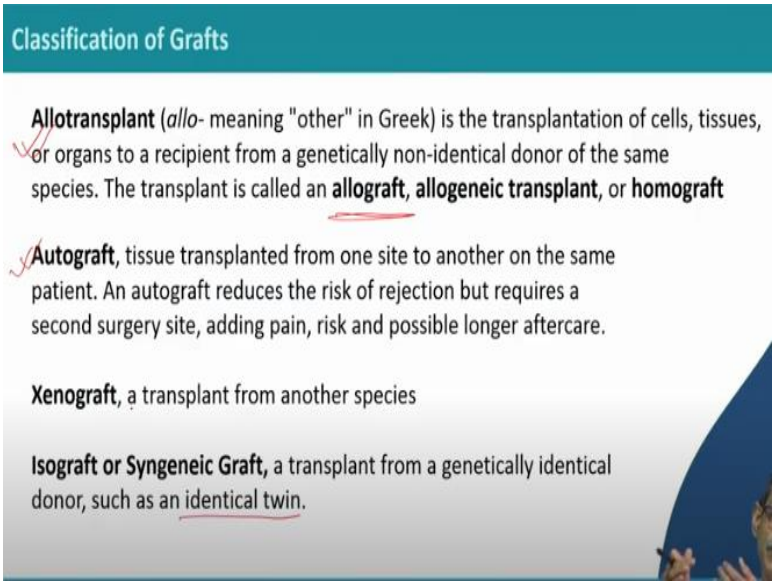
And in case of somebody some person kidneys somehow not working, then we need to transplant the kidney and in some cases heart. So that that individual every other organs are perfectly alright. But kidney is not working. So whole body is going to collapse with time. So just to or liver transplantation. So any kind of organ from one particular person or the donor to the recipient, is called transplantation.

And in that case, how immune system reacts we will see. And the another thing is blood. Blood is also tissue, right? So if we transplant blood do we call it transplantation? No, normally we call blood transfusion. Is also a tissue but it is not as complicated as the other organ. Blood has only four type that you know A, B, AB and O. And another factor is Rh factor, Rh plus and minus.

So if you and matching these blood groups is very simple and straightforward. So when you transfuse blood, it is very easy and simple tester there. We just match the group and the Rh positive or Rh negative and then we can transfuse. But even after that if a person continuously transfuse with different person's blood, sometimes what happen antibody against RBC or RBC membrane protein has developed.

So reaction is there, but it is still much better. So it do not consider it as other organ transplantation, but we call it transfusion. But it is also a tissue when we transfer and this is the earliest one which is solved long time back, right. And you know who discovered this blood grouping also received a Nobel Prize and that we do not care that much like kidney or other solid organs or the stem cells.

(Refer Slide Time: 05:48)



So what actually causing this problem and what kind of graft so is possible. So if we go for classification of graft, we depending on that, we say allo transplant, okay. Allo transplant or allograft. What is that? It is the transplantation of cells or tissue or the organ to a recipient from genetically known identical donor. But the same species like human to human if we transfer them, but we are not genetically identical.

No two individuals are genetically identical except the, if you see the last one the isograft or syngeneic graft, that is genetically identical donor means identical twin, okay. Identical twin, what is identical twin? Twin can form two way. Like two egg can fertilized by two different sperm. So basically there are two independent they are genetically different.

But if one egg fertilized by one sperm, and that zygote divided into two and then two individual happen or the twin born, they will be identical. That is called identical twin. So they are genetically basically identical because form one cell divided to two cell. That two cell from two individuals. So in that case, we call it isograft or syngeneic graft.

Otherwise any two individual even the offspring or parent, anybody is very close, very related, but they are not genetically identical okay, particularly in a particular set of genes that we are going to come. So in that case we the graft we call allograft, or allogeneic graft and the transplant we call allo transplant. What is autograft?

Autograft means if tissue transplanted from one part of the body to other part of the body, okay same individual.

Like it happen when many times we do that for the artery, okay heart operation. We do that for skin like if there is any part of the exposed part of the body get burned, then we transplant the skin from other part of the body which is normally covered. So skin will develop there, the scar will not be visible. So we do it. In that case it is autograft. But earlier days, people used to think about the xenograft.

Xenograft means part of the body or the organ from different species like pig to human, monkey to human that is called xenograft. So there are four different kind of grafts are there. But normally what happen? If I mean it is not always possible to have the isograft or the identical twin as a donor, right. Autograft is common, if necessary we can have.

But most of the transplantation that we have you must have heard like okay, kidney donor, a person is looking for a kidney donor. That means, we need another person to give the organ and that in that case we. So most of the cases we see in the transplantation is allograft transplantation, okay. Autograft is still more than this identical twin.

But now it is there are lot of attempt was made and people are still trying to modify xenograft just to modify the other organism's organ in such a way so that we can transplant. There are a lot of recombinant technology thing is there and you already know complement, right. So if any other specie's organ transplant into our body, what will happen? Our complement will find them foreign and little help of antibody that will kill all the organ.

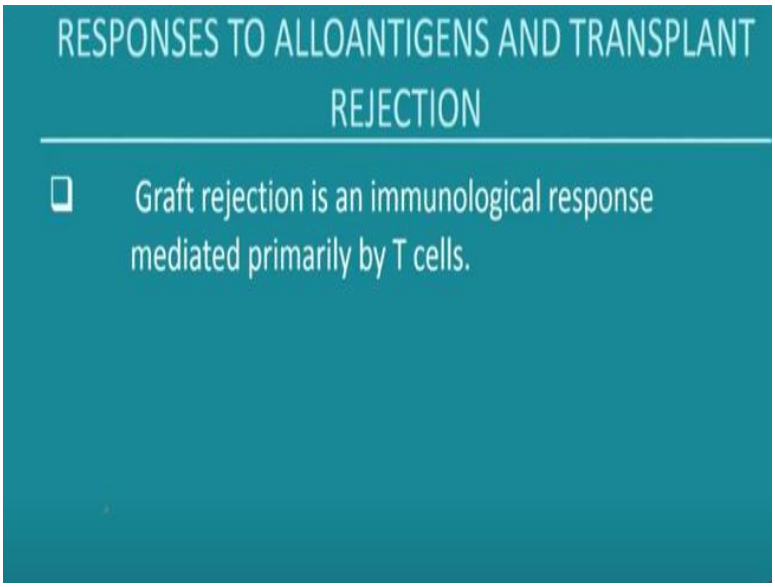
So now what people are trying to put the inhibitor of complement which is already say you already know that our blood also along with the complement protein also have some protein which inhibit their function so that our complement should not harm our own cell. So if that inhibitor protein, you make a transgenic animal, so that that animal will express the inhibitor protein of human. So what will happen?

That organ if you transplant at least complement will not do any harm, okay complement will not create any problem. So this way people are trying. Another way people are trying which you might have heard and do not have much scope, but just to tell the briefly like tissue engineering okay. So people are trying to get the cell from individual and make the tissue in the lab, so that that organ can be transplanted.

So if I can make a liver from my liver cells or any other kind of stem cells in laboratory, so that liver will be basically almost similar or identical with my liver. So if I can make liver outside by tissue engineering that liver I can transfer. So it is not that easy like I cannot make a kidney in the lab so easily. But skin, the research on skin development or artificial skin development is much in progress and it is almost in a good shape.

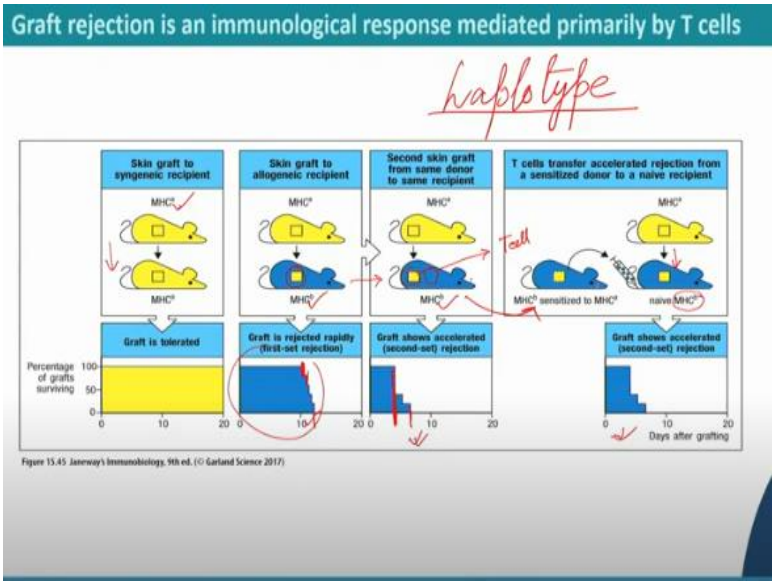
So that maybe in near future there are some but not exactly like our skin, but very close to our skin is already developed in the laboratory. So from myself skin has been developed, that skin can be transplanted. So we do not have to cut skin from other part of the body, okay.

(Refer Slide Time: 11:43)



What actually rejecting or what actually responsible for that graft rejection? The graft rejection is an immunological response completely and is mediated primarily by T cells, okay. You know T cell is a very important component of the adaptive immune response. So T cells, how it is discovered?

(Refer Slide Time: 12:03)



It is discovered it was first in how this transplantation is discovered? It is long back in the 1930s when one scientist in England was trying to transplant tumor from one mice to another mice, okay. And what was found that the tumor from one of one mice is rejected in some other mice. So that time conclusion was like, this tumor progression depends on genetic variability.

You will did not know because immunology was not progressed that much and also other information was not there. And eventually it was found that this is by T cells and not only T cells alone and there is another set of complex gene, which now we know it is MHC the major histocompatibility. From name you can understand. Histamines tissue, I told you earlier already.

Histamines tissue and compatibility. That means, some genes are responsible which is highly polymorphic which are responsible for compatibility of the two tissues from donor and recipient. And this function how it is different we know. So far what we discussed that, if you remember the T cell lectures, we discussed about MHC restriction. So our T cell normally does not recognize for an MHC.

That is for 95% of the cell or maybe little more, but a very good population of T cells present in our immune system, which are alloreactive. Alloreactive means, which can recognize other's MHC. That was not discussed much. But these alloreactive T cells are the major concern for this rejection. As soon as one organ transplant to another body 95% or little more than that will not do any harm.

But that 4, 5% alloreactive T cells are going to recognize the foreign. And as soon as they recognize a foreigner if it is a cytotoxic T cell, they will kill it, okay. So we will come. But how it was first discovered, the T cell is the major responsible for this rejection, this is the experiment. What it was done. Say they are normally, one more information I should add.

Normally what you say the one set of allele of MHC, which is coming from single parent. Suppose father and mother, one set will come from father, another set will come from mother. And I already told you that they are codominant, okay, that both will express. So one set that we inherit from our father or mother is known as haplotype okay. So remember and we check what is this means.

So one set that we receive from either of the parents, either from mother so I have or all of us have two haplotype. One exactly the mother another from father, okay. And this combination because we cannot say how many genes are there, so many polymorphism. So normally a particular type or one set or two haplotype set containing mouse suppose it is MHC a, okay MHC a. Another is MHC b, okay.

So two mice they are genetically different. So instead of saying where the differences are, how many differences, we group them MHC a type. That means all MHC a type mice are identical in one type. MHC b is different. MHC c is different. I am not going all the details like what are the difference. Just for the time being assume MHC c is one type MHC b is another type, okay.

So if you transfer skin from MHC a to MHC a type, MHC a to MHC a type graft is not rejected, okay. It is kind of auto, okay. They are exactly same, it is like identical. It is normally we find it only in breed mice, okay. In breed mice, they are genetically almost identical. But now if you do the similar experiment with MHC a to MHC b what will happen?

Within 10 to 15 days, within 10 to 15 days it will be rejected. You see this different stair like thing is that means this graft means some mice I mean rejected at these days, some group is these days. Because you cannot do experiment with one mice only.

When you do this kind of experiment you have to maintain a minimum number so that you can suppose you do it with one mice and at the very 10th or 11th day it dies.

So I cannot conclude that all mice will have the same thing. So we have to do a minimum number so that I can do statistics to get a good result or the reliable result. So maybe 9 mice or maybe 15 mice. So what we see that some mice die at this 11 days. Someone at 12, someone 13, someone 14 something like that, okay. So this stair is like that. So you see within 2, 3 days within 2, 3 days most of the mice rejected their skin, clear.

So now if you take the same mice which is suppose you transplant one part and you see this is transplanted here and it is rejected. So you thought something might be wrong, because when you are doing the experiment first time what will happen? Maybe something is wrong. So okay let us try. So you take the same mice and transplant again from the same donor another part of the body, okay.

You see it is little left, okay. It is little it was initially it was here now it is here. You see what happen the graft rejection is much more accelerated. It is much before like 5 to 6 days or 7 days within that and most of them die here or the rejected the graft is rejected not die. Graft is rejected here and one or two are here okay, maximum. So what happen initially it took 12 days or 13 days.

Same mice if you transplant again within 6, 7 days it reject the graph. It is so people thought that it is very similar to your primary infection and primary immunization and secondary immunization. That means if any adaptive response, if it happens successively the first time it take little more time and next time it take less time. So the antibody concentration goes up. If you remember that similar thing happen.

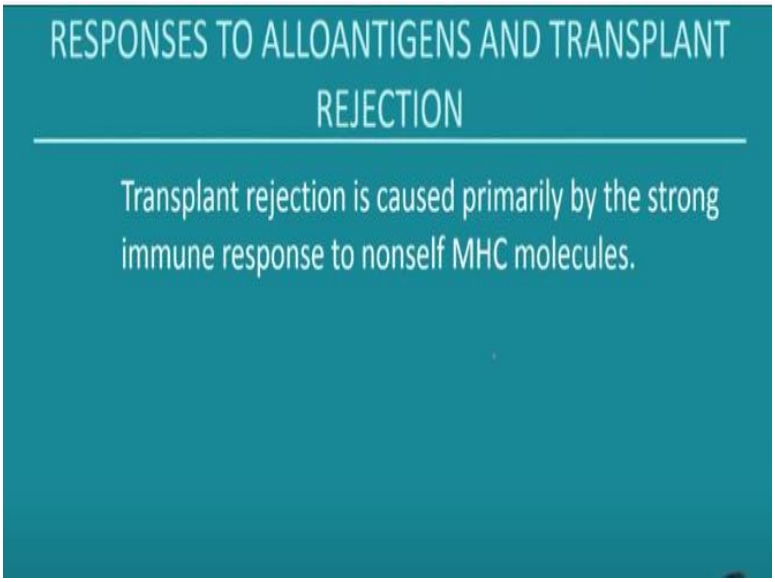
Like initially immune system need more time to understand that some foreign thing came, okay some foreign thing came so it is here. But same mice took much less time, okay. So then they realized what could be the problem, I mean what is there. So they did many experiment. But after that what is this effective one is that you assume the similar thing. Suppose you have this mice, okay.

You isolate T cell from there. So this is this one. So this mice and this mice is same, which is already sensitized. Either this one or this one is fine. It is already sensitized, okay. So T cell is activated. Now what you have what happen? If you do this experiment, so if you take a fresh MHC b, which is not transplanted before and one donor MHC a if you transplant this it is supposed to react like this. It should take 10 to 12 days, right.

But what you do? In addition to that transplant, you isolate the T cell from the sensitized mice, purify it, and then inject the T cell, both are MHC b but one was sensitized. That means transplantation happened before. Isolate T cell, inject. What happen? You see the similar reaction, okay. That means, even if it is the first time getting the transplanted part of the skin, but in addition to that it is also getting sensitized T cell which is accelerating the whole process.

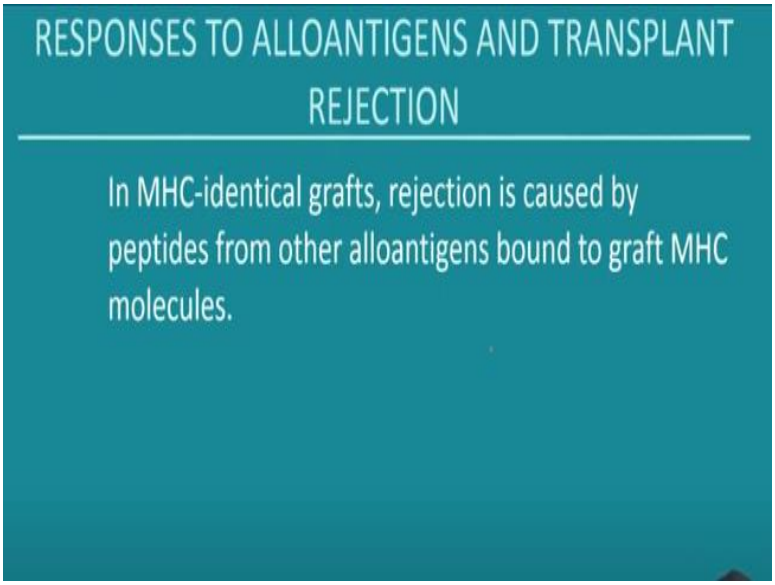
So what I can say very simple way that T cell is one of the important factor which is contributing this graph rejection, okay. This T cell is the one of the important factor or primarily the T cell is responsible for graft rejection.

(Refer Slide Time: 21:12)



Next, transplant rejection is caused primarily by the strong immune response to nonself MHC molecule. That I just told before like there are alloreactive T cells, which can recognize the MHC molecules of nonself.

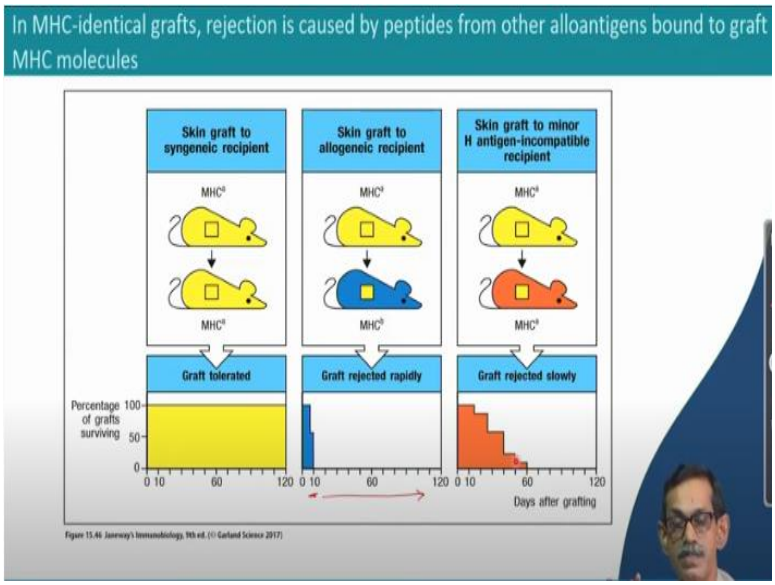
(Refer Slide Time: 21:32)



That is whatever came is not mine, okay. But what happen if it is MHC identical? If it is MHC identical, then it should not do this graft rejection, but what happen in MHC identical also in some cases, this rejection is caused but slowly, okay. I am repeating again. MHC identical, but not exactly like the inbred allo to allo, no. They are both are MHC a, but some part is not exactly identical.

Then it can cause or it will reject the graft, but not as fast as what we just see in the MHC and MHC b type. It will take longer time, okay.

(Refer Slide Time: 22:25)



It will take longer time like MHC a to MHC a okay this scale is this particular scale is changed. You see it is also in the 10 days okay. So it is not like before. It was before it was little far I mean, just a minute, before it was here okay. So the scale changed. So

do not be confused like that. So MHC a to MHC a complete match, okay. It is a syngeneic recipient. Syngeneic means completely identical, there is no variation.

So there will be no graft rejection, it is graft will be tolerated. So body will not figure out this is come from somebody else. MHC a to b that we just discussed. Within 10, 15 days it will reject the graft, okay. But what will happen MHC a to MHC a, but they are not they are MHC's are identical, but rest of the part is not identical. What is going to happen? It is also going to reject but it will take longer time.

In case a to b is 10 days, but both are MHC a okay donor and acceptor or donor and the recipient, but here MHCs are identical. So it is taking longer time. That means T cell is responsible that we know. If T cell is responsible definitely MHC will play a major role, okay. And while studying all this thing what I said the first time how they figured out that transplantation is not successful in one mice to another mice.

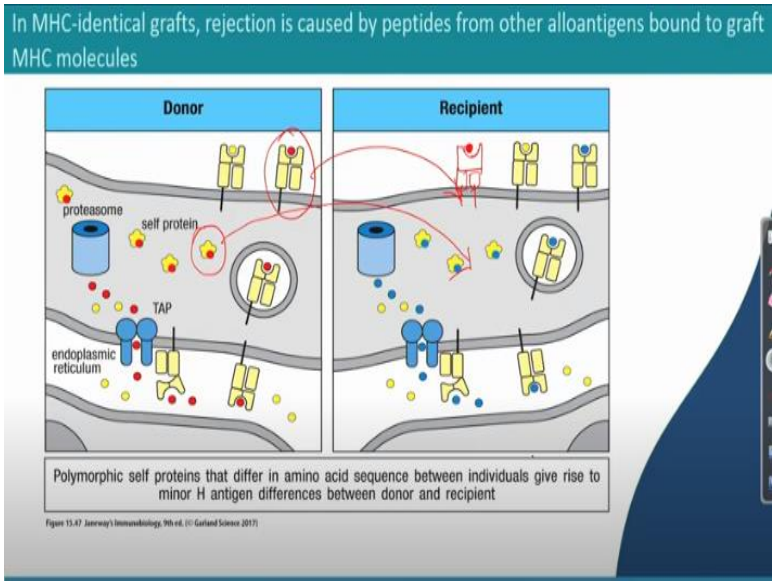
While transferring this tumor in 1930 it took long time like 15, 20 years it took to understand that MHC is the responsible and the first MHC was reported in 1958, okay 1958. It is not like hundreds of years, it is and after that lot of work, different history. And if you want to know MHC and development of this, you just what you can do is you can just type history of MHC, history of MHC in net.

There are lot of good sites are there where series wise their discovery, who are the scientist, what they did, how it is progressively discovered? It is nicely you can find in different sites in the net, okay. It is nicely written. So 1958 it was first discovered like okay human has some gene, which is polymorphic and initially it was named as MAC, okay. So he isolated the blood from three individual patient and the first letter of their first name was M, A and C.

That is how MAC and later it was named as HLA. And this what we are seeing here that MHC a to MHC a when it is coming and it is rejecting. Suppose, all are identical. Or one thing, I am just giving you a simple example. Suppose, one male is donating the organ and a female is receiving, right. So there is a difference in our chromosome. We have the male has Y chromosome, which is not present in female.

So any gene present in Y chromosome may be different in case of female, right. Male gene Y, but that is the reverse is not true. Because both male and female both has X, okay. So these kind of minor changes in the protein are possible. I am just giving a very straightforward example. The Y specific proteins which is not present in female can make a difference which our body can figure out or the immune system can figure out this is for it, okay. How?

(Refer Slide Time: 26:35)



So this is a very nice I like this cartoon for to where it is very simple way it is explained like what is this called. It is called actually minor antigen, okay. It is called minor antigen, minor H antigen actually. You know major histocompatibility that H and it is a minor. What is happen? Hope you remember this slide, remember this picture.

So normally all the proteins are degraded through proteasome in the cytoplasm and they transport through TAP and then fit into the MHC molecule, MHC 1. So if you remember the antigen processing, suppose two protein of two individuals are almost identical, you see the yellow part okay, yellow part. That means these protein are almost identical, but there is small segment which is red here another is blue here, okay.

So this red and blue are the very small difference. So if this is donor, so donor cell protein will also be chopped and processed, it will not do any immune response, but it will process and be presented. So both yellow and red part will go to the surface. So

yellow will be there and red will be there. So this is donor, okay. Donor will not create any problem, but if you transfer this thing and in recipient what is there, yellow and blue.

So what will happen if you give some organ or some part of the donor's thing say kidney or anything, this will go right, this part will go. So what will happen if this protein are expressed in recipient body, so there will be another MHC thing, so what we actually see is this one will also be here okay. So along with this blue, yellow there will be one red also okay, red one also, red one also.

So this red part which is not present in the recipient are coming from donor. So it is so minute so immune system will take longer time to identify that this is foreign, okay. If it is major problem it immediately within seven, eight days it can figure it out. But if there is a minute difference and that yellow and red is not that big. Maybe one or two amino acid is different, not much okay.

So finding that small difference will take long time and that is why instead of 10 days, it is taking 60 days. But ultimately, our body will recognize that whatever way you try to convince me I will not. I can figure it out that okay I have small and you the donor thing or the organ that I received has a small difference and that is called minor H antigen. So in MHC identical graft also rejection may happen because of the alloantigen bound to the graph. Okay?

So today, I mean in this lecture, we are going to stop and next lecture, we are going to figure it out some more points. Okay. So till then, bye.