Wellcome Film Project

Cell-Mediated Immune Response

Uptodate: Immunology, Part 5

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Black-and-white

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<**Opening titles**>

<**Professor John Turk to camera**

In the last talk, you were told about humoral antibody response, which is mediated by immunoglobulin molecules. These, as you remember, are produced by B-lymphocytes which transform and differentiate into plasma cells. Now, the other half of the immune response is known as the cell-mediated immune response. And here we're dealing with effector T cells.

<**Turk over diagram showing possible changes arising from bone marrow lymphocytes**>

Now, as you remember, the bone marrow lymphocyte can either become a B-lymphocyte under bursa influence, or can become a T-lymphocyte under thymus influence. And antigen can stimulate T-lymphocytes to proliferate and differentiate into sensitised lymphocytes, and these are the cells that react and cause rejection of

antigen in the cell-mediated response. Or, as part of an allergic reaction, what is known as delayed hypersensitivity.

<**Turk to camera**>

Now delayed hypersensitivity or cell-mediated immune responses can be involved in a number of immunological processes. And we can go through these and find out the extent of cell-mediated immunity. Quite a large proportion of all immunological reactions involve cell-mediated immunity in one way or another.

<**Turk over series of tables listing delayed hypersensitivity reactions to microbial protein antigens**>

The first group that I'd like to talk to you about are the delayed hypersensitivity reactions to microbial protein antigens. These include the tuberculin reaction, the pseudo Schick reaction to diphtheria toxoid, the reaction of immunity to vaccinia virus and other delayed hypersensitivity reactions to fungal antigens and to protozoal antigens. In addition, one has delayed hypersensitivity reactions to serum protein antigens as shown in the next chart which occur following small doses of foreign antisera. Then one has insect bites, contact sensitivity to simple chemicals and the reactions behind homograft rejection, and then cellular immunity to certain bacteria, such as mycobacteria or brucella, against fungi, protozoa and viruses.

Cell-mediated immunity is also involved in collaboration with humoral antibody in the development of organ-specific autoimmune lesions, such as those that occur in Hashimoto's thyroiditis or to allergic encephalitis, aspermatogenesis and adrenalitis. And one of the most important mechanisms that cell-mediated immune processes are involved in is the immunological surveillance mechanisms against tumours.

<**Turk to camera, then over series of tables comparing tuberculin and Arthus reactions; to camera sporadically in between**>

To understand the mechanism of delayed hypersensitivity, most people have studied the tuberculin reaction and the tuberculin reaction is taken as the prototype of all cell-mediated immune reactions. One might compare the tuberculin reaction, as an example of cell-mediated immunity, with the Arthus reaction as an example of an immunological reaction, an allergic reaction that is produced by humoral antibody.

The tuberculin reaction takes 24 to 48 hours to develop, whereas the Arthus reaction takes 4 to 8 hours to develop. The time course of the tuberculin reaction, the prolonged time that it takes for the reaction to occur is due to the time it takes for lymphocytes to accumulate in the, at the site of antigen reaction. Whereas in the Arthus reaction, when one injects a foreign serum protein, there is antibody already in the extra cellular fluid.

In addition, these reactions differ in their macroscopic appearance. The tuberculin reaction is an erythematous indurated reaction, whereas the Arthus reaction is associated with oedema and haemorrhage. And microscopically the reactions differ because the tuberculin reaction is mainly a mononuclear cell infiltrate, whereas the Arthus reaction has mainly a polymorphonuclear leukocyte[1] infiltrate.

Finally, these reactions differ in the way that one can passively sensitise an animal or a person. The Arthus reaction, because it's mediated by antibodies contained in serum, can be transferred passively – Arthus sensitivity can be transferred passively by serum. But the tuberculin reaction, being mediated by the specifically sensitised lymphocytes, needs to be transferred by suspensions of lymphoid tissue.

00:06:51:00

<**Turk, seated, to camera, points to a chart to his right and moves the pieces around on it**>

[1] Spelt leucocyte in the table referred to. I am using the recognised spelling for this series of transcriptions for continuity.

Now, to understand the actual mechanism of sensitisation I would like to go over to this chart here.

All immune reactions can be thought of as somewhat like a nervous reflex arc with an afferent limb and an efferent limb. And the lymph node is rather like the ganglion in the centre. The afferent limb involves the phase of recognition of that which is foreign, and this is followed by the phase of proliferation of lymphocytes and then the phase of rejection of that which is foreign. Or, in the case of an allergic reaction, the release of pharmacological agents causing the actual reaction in the skin or tissues.

Now in the cell-mediated immune reaction, what happens is that a lymphocyte coming from the periphery will recognise that which is foreign in skin (whether it is the application of a contact sensitising agent or the transplantation of a skin allograft) and then will pass down to the central lymphoid tissue where it'll find the right milieu for proliferation.

Now one can look a little bit more closely at lymphoid tissue and one can see the process of proliferation which occurs at the latent period of 4 days which occurs between first contact with antigen and the time when the animal becomes sensitive. Now, if we look in this next chart at a diagram of a lymph node, we can see that it has certain structural features that are common to all lymphoid tissues.

<**Turk over illustration of lymph node, uses indication stick**>

It has a medulla with medullary cords where we find B-lymphocytes and plasma cells. It has lymph follicles and germinal centres, again B cell area; but it has a large area of diffuse lymphoid tissue where the T cells are found, and this is called the paracortical area or the thymus-dependent area because it contains cells; it contains lymphocytes which are dependent on thymus integrity in late foetal and neonatal life. And this can be shown in the first histological section that I want to show you; […]

<**Turk over histogram of lymph node with depleted T-lymphocytes**>

[…] this is of a lymph node where T-lymphocytes have been depleted and you can see the medulla on your left-hand side, well-populated with B-lymphocytes and plasma cells, and out in the periphery the germinal centres and lymph follicles populated with B-lymphocytes. But in the centre to the right you see the depleted area where the T-lymphocytes had occurred, and this type of histological appearance occurs in animals that have been thymectomised neonatally, in babies born without a thymus and in animals or people treated with anti-lymphocyte serum.

00:10:26:00

<**Turk over illustration of lymph node showing proliferation of lymphocytes, then autoradiographs of the same**>

Now, proliferation, as I said, of lymphocytes as part of the cell-mediated immune response occurs in this paracortical area, and we can see this histologically by looking at the lymphocytes, and we see that they transform into large blast cells, which in this picture are covered with little speckles because this is an autoradiograph showing that the lymphocytes, the blast cells, have taken up tritiated thymidine prior to division. And if we look later we can see which type of cells they have divided into and you can see they've divided into other cells which are morphologically indistinguishable from T-lymphocytes. So this is the picture of T-lymphocyte proliferation occurring as part of a cell-mediated immune response.

<**Turk over diagram comparing cell-mediated immunity with humoral antibody production**>

Now, if we compare the lymphoid pattern, the lymphoid tissue pattern, that occurs in cell-mediated immunity with that which occurs in humoral antibody production, we can see, we can gear this over to relatively pure cell-mediated immunity in contact sensitivity in which case there is proliferation of lymphocytes in the T-lymphocyte area but no activity in the B-lymphocyte area. On the other hand, in pure, in relatively pure humoral antibody production which occurs during the intradermal injection of pneumococcal polysaccharide, one gets marked B-lymphocyte proliferation and

plasma cell formation in the medulla and large germinal centres formed. But in most immune responses there is both a cell-mediated immune response and humoral antibody response. And when one immunises with protein antigens, bacteria, and so forth, one gets both germinal centres, plasma cells and proliferation of T-lymphocytes in the paracortical area.

So, this process of lymphocyte proliferation is part of the latent period during the development of the cell-mediated immune response and this can be shown to […]

<**Turk over graph showing peaks of lymphocyte proliferation, then returns to earlier chart with movable pieces**>

[…] reach its peak 4 days after sensitisation; the day before the animal or the person may show the earliest signs of cell-mediated immunity, the earliest signs of allograft rejection, the earliest signs of contact sensitivity or the earliest signs of tuberculin sensitivity. And when the person has shown this, has developed sensitivity, then this phase of proliferation in the local lymph node begins to decrease,

And at that time, one can see that there are lymphocytes capable of reacting with antibody in the periphery, causing its rejection, but also capable of going to other areas of lymphoid tissue where they can carry on the proliferation process so that the draining lymph node is not necessary any more.

Now when the lymphocyte goes out and reacts with antigen in the periphery to cause its rejection, it causes the release of pharmacological agents. And this is shown in the next chart in the next type slide that we have.

<**Turk over tables and slides showing the effects of the release of pharmacological agents and their subsequent biological activities**>

Reaction with antigen, and this, you see we get the release of soluble substances from the lymphocyte, pharmacological mediators which are called lymphokines, and

these can have a direct effect on macrophages and cause the initiation of inflammatory reactions.

Now these substances are of molecular weight, approximately 40,000, and they have a number of biological activities which are shown in the next slide. There is skin reactive factor, what we call migration inhibitory factor, a lymphotoxin capable of causing damage to target cells in culture – cancer cells and such like, and also other factors such as a mitogenic or blastogenic factor.

If we take the pharmacological agents released from lymphocytes by specific antigen and inject them into an animal, we get the production of a reaction very much like a tuberculin reaction. And this is shown in the next slide. On the left hand side you see one of these reactions that has occurred following the injection of the pharmacological agents released from specifically sensitised lymphocytes by specific antigen.

But as I mentioned, these also cause the inhibition of migration of macrophages from capillary tubes. And this is shown in the next picture where, on the left-hand side, you can see that one gets, in culture one can get a fan of macrophages normally growing out of a capillary tube (this is very much enlarged). On the right-hand side you see the growth of macrophages in the presence of the pharmacological agents released from specifically sensitised lymphocytes by antigen. You can see the macrophages are here inhibited from migrating.

<**Turk to camera**>

Now this tends to cause the macrophages to accumulate at the site of a delayed hypersensitivity or cell-mediated immune reaction. But also these macrophages can cause the killing of intracellular organisms as part of a cell-mediated immune process. And so one is involved in 2 phases of macrophage activity: the inhibition of macrophage function and then one has the phase of increased macrophage function.

00:17:10:00

Now if one looks at macrophages in tissue culture – can I have the next picture?

<**Turk over slides and graph describing how macrophages function in tissue culture**>

Yes, this shows the macrophages in normal tissue culture, stabilised culture of macrophages. Now, 1 hour after adding the lymphokine preparation, the pharmacological agent released from lymphocytes, one can see in the next picture that the macrophages are rounded off and inhibited from moving. But then, at a later stage, the macrophages tend to become activated again, take on the appearance of epitheloid cells, they may palisade, and they cause the rejection of intracellular bacteria that they have ingested.

Now one can follow enzyme function of these macrophages and this is shown in the next chart, here. In the early phase when one has the rounding off of the macrophages, one sees there's decreased enzyme activity and then this is followed at a later phase by marked increase in enzyme activity which parallels the difference in morphological appearance of the macrophages and their ability to begin to destroy intracellular organisms.

<**Turk to camera**>

Now up to this point we've discussed cell-mediated immunity as though it was just a T cell effector mechanism and we haven't really mentioned the possibility that there might be interaction between other cells, possibly B cells, and T cells in the mechanism of such a response. We know in the humoral antibody response that a T cell response is very important in the augmentation of the subsequent B cell response and humoral antibody production. Recently, we've been able to investigate the interaction between other cells, possibly B cells, and T cells in the production of a cell-mediated immune response. What we are looking for in such a situation may not be the augmentation but the modulation, or damping down of the T cell response, by suppressor cells, possibly of the B cell class.

00:20:04:00

<**Turk over illustration of rat as a contact sensitivity model, then a table is superimposed over it**>

If we go and look at this diagram that we have here of the actual mechanism of sensitisation in a contact sensitivity model, what I'm talking about will come a little bit clearer. In contact sensitivity, in fact, there are two things happening. There is the fixation of the contact sensitiser[2] to the skin, but there also is diffusion of soluble antigen down to the spleen and other areas of lymphoid tissue.

Now there's no doubt that the antigen fixed in the periphery stimulates the T-lymphocytes to proliferate in the draining lymph node and we've looked at that in the previous part of our discussion. But also, the soluble antigen can come down to the spleen and other areas of lymphoid tissue and stimulate the proliferation of B-lymphocytes and possibly other lymphocyte types. If one was to eliminate B-lymphocytes from a system without affecting T-lymphocyte proliferation, then one might be able to investigate the possible way in which B-lymphocytes or suppressor cells might interact with T-lymphocytes in the actual phase of the immune response.

Now this is shown in the superimposed diagram that we have here, and you can see that in a normal situation we've denoted the resultant skin reactivity of a normal animal to a contact sensitiser as 2+, and we say that this is the result of the interaction between 4+ effector T-lymphocytes and 2- suppressor B-lymphocytes. Now, in this system we can eliminate the suppressor element by pre-treating animals with the drug cyclophosphamide which doesn't affect the ability of the T-lymphocytes subsequently to proliferate. And the resultant reactivity of the animal is as we have denoted 4+. And we can return the suppressor element by transfusing spleen cells from animals that have been sensitised without being pre-treated with cyclophosphamide back into the cyclophosphamide pre-treated animal.

[2] Spelt as sensitizer in the programme. English spelling has been used for continuity.

Now, the transfer of lymph node cells, draining lymph node cells especially, doesn't return the suppressor element; in fact, adds to the effector element as shown in the 4th line. And we can reproduce the effect of the cyclophosphamide in removing the suppressor element, by splenectomy 4 days after sensitisation in normal animals. As you see, in this particular diagram, that we have demonstrated that there is a population of suppressor cells that is capable of modulating the effector T-lymphocytes, and keeping a balance to maintain homeostasis between B-lymphocytes and T-lymphocytes. Such a homeostatic mechanism is very important because if one is able, in a clinical situation, to remove the suppressor element, then one might be able in this way to enhance effector T-lymphocytes in a situation where this may be of value, such as in the elimination of tumour cells in patients with cancer. At the moment, however, this is very much a laboratory model and is not yet directly applicable to the clinical situation.

<**Turk, seated, refers to earlier chart with movable pieces**>

Now to recapitulate, the cell-mediated immune response mediated by T-lymphocytes can be considered, as we showed in this chart over here, as a 3 phase phenomenon. The phase of recognition of that which is foreign, followed by the augmentation of the immune response by the proliferation of T-lymphocytes, which can then pass out into the periphery, react with the foreign antigen and cause its rejection by the production of this population of pharmacological agents derived from lymphocytes, known as lymphokines.

<**Turk to camera**>

These agents act by activating macrophages which can eliminate intracellular organisms, play a role in graft rejection and can also produce the inflammatory reaction that is typical of delayed hypersensitivity, the allergic type of reaction that we associated with cell-mediated immunity.

As in every situation, an allergic reaction may be considered a result of local tissue damage occurring in the vicinity of a rejection process of that which is foreign due to

the spill over of pharmacological agents which are released as part of the rejection process.

<**End credits**>