Transplantation

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Transplantation is the introduction of biological material - organs, tissue, cells, fluids - into an organism.

We can distinguish 3 critical relationships between the transplanted material and the recipient.

syngeneic transplants - from genetically identical individuals, usually the same individual *(these are similar to grafts between identical twins or isogenic strains of experimental animals)*

allogeneic transplants - from one individual to another of the same species

xenogeneic transplants - between individuals of different species.

Unsurprisingly syngeneic transplants do not usually generate any immunological problems.

But allogeneic and xenogeneic transplants are almost always destroyed by immunological processes unless some action is taken to impair the immunological process.

Basically therefore transplantation presents 2 key problems:

Genetic variation between donor and recipient.

Immunological recognition of the variation.

Genetic variation between donor and recipient

Genetic variation between individuals that results in protein sequence differences is at the heart of the transplant problem.

Average number of proteins whose sequence varies from one individual to another is greater than a few hundred, possibly as high as several thousand.

Obviously the variation is even greater between individuals from different species.

Even if identical at the MHC, transplants between individuals are likely to be rejected due to minor histocompatibility loci.

In the mouse there are about 50 such loci, in humans probably more.

The key distinction is that individually these minor H loci are less 'strong' and in particular the strength varies between allelic differences.

Immunological recognition of the variation

Genetic differences between donor and recipient are only of significance in transplantation if they cause incompatibility.

Almost ubiquitous in allogeneic transplants is immunological rejection.

Early experimental work on allotransplantation in mice identified a very clear distinction between one chromosomal region and the remainder of the genome.

Non-identity at this special region always led to very rapid rejection of the transplanted tissue, even if this was the only genetic difference between the donor and recipient.

This region was therefore termed the Major Histocompatibility Complex (MHC).

This region exists in all vertebrates and it is highly polymorphic, so that in a population 2 individuals will almost certainly differ at this region unless they are monozygotic.

Recognition and rejection mechanisms

There are 3 basic types of 'recognition' which allows the host to know that the transplanted tissue is foreign.

recognition by antibody

recognition of foreign MHC by T cells (direct recognition)

recognition of minor H loci by T cells (Indirect recognition)

These recognitions may lead to very different time scales of destruction of the transplanted cells/tissue and trigger distinct effector mechanisms.

There are 3 types of rejection:

Hyperacute rejection

Acute rejection

Chronic rejection

Hyperacute rejection

This type of rejection occurs very rapidly, resulting in necrosis of the transplanted tissue within minutes or a few hours of contact.

It always results from the reactivity of the donor cells with pre-existing antibody.

The most common situation in which this occurs is in ABO blood group incompatible transplants.

Acute Graft Rejection

This is the main immunological barrier to allotransplantation.

It is caused by T cell recognition of the transplanted tissue.

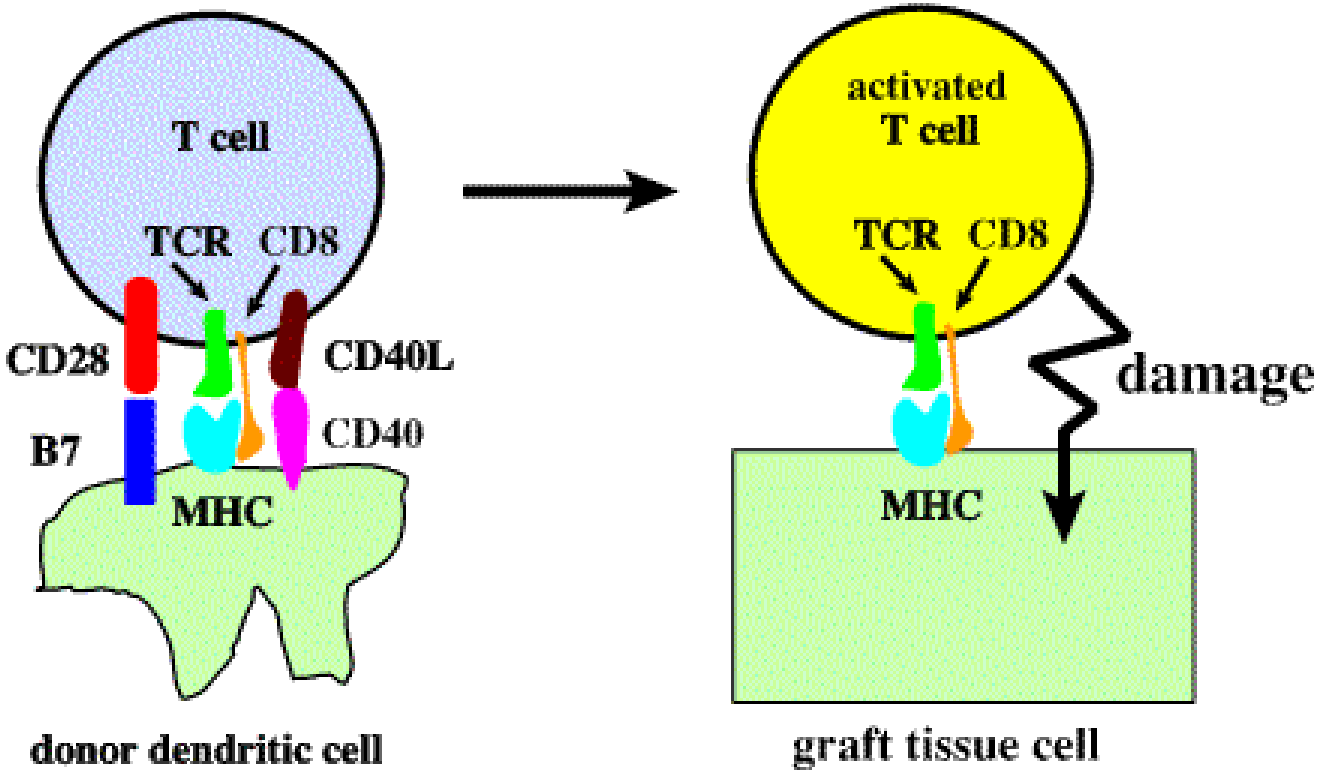
It is not a significant problem in red cell transfusion because the cells survive only short periods and human RBC do not express MHC antigens.

There are 2 quite distinct modes of recognition:

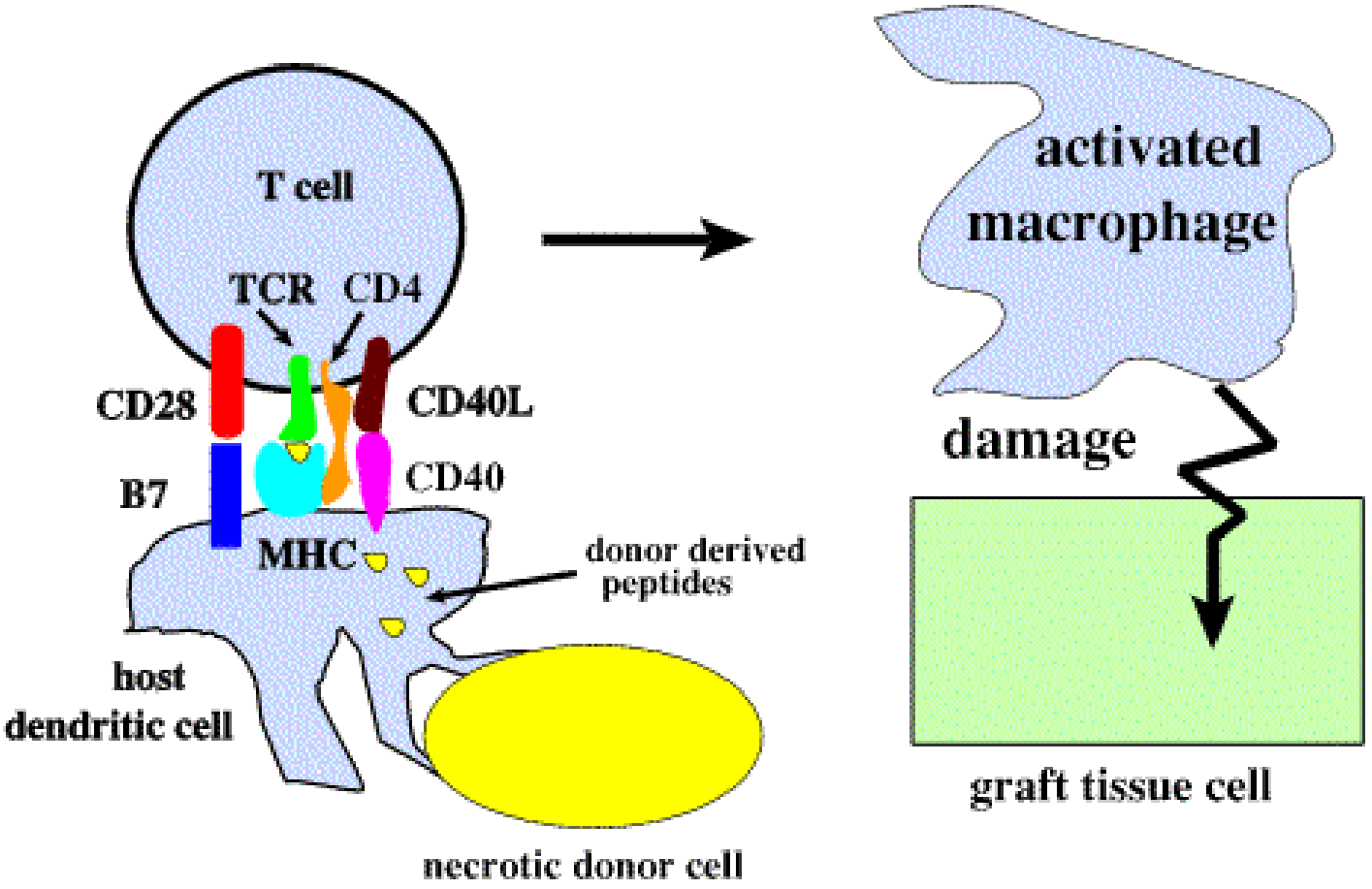
Direct recognition of allo MHC.

Indirect recognition of minor transplantation antigens.

Direct recognition of donor MHC molecules



Indirect recognition of minor H antigens



MHC identical grafts are still rejected acutely by T cell dependent mechanisms.

Minor transplantation antigens are proteins which vary in sequence and where one (at least) of the allomorphs is found in a peptide which binds to the MHC of the recipient.

Properties of minor antigens

Rejection is slower than for MHC.

It is additive, so that many minor differences combine to give rapid rejection.

Rejection times (in experimental grafts) are more variable and strength is allele specific.

Chronic rejection

Considerable progress in the management of acute rejection has been made.

In contrast, essentially there is no significant improvement in treatment of long-term loss of transplanted organs through chronic rejection.

Possibly in part this is because the mechanism(s) of chronic rejection are still obscure.

Particular transplant situations

Privileged sites

Transplants at certain anatomical sites are generally accepted without any immune rejection.

The most important of these is the cornea.

The absence of lymphatic drainage is probably the critical common factor.

Immunosuppression

It is essential to clinical transplantation.

“Standard" regime varies for different tissue/organs.

Kidney transplants involves combination therapy with 3 different sorts of drug.

Steroids - given for systemic immunosuppressive effects, complex mechanism of action
e.g. prednisolone

Cytotoxic substances - lead to cell death, esp. on entry into cell cycle
e.g. azathioprine

Immunosuppressive substances - targeting cell signalling pathways in lymphocytes

e.g. cyclosporin A; others include FK506, rapamycin

The immunosuppressive drug needs to be maintained indefinitely.

Many novel treatments are in development, particularly antibodies blocking surface molecules critical in T cell activation e.g B7-1,2 (CTLA4-Ig) ; anti-CD40L

Currently licenced biotherapeutic treatments used to treat graft rejection include

anti-CD3 monoclonal antibodies
anti-CD25 monoclonal antibodies (CD25 is a component of the receptor for IL2, a major growth factor for T cells)