CYTOKINE

Cytokines – Monokines - Lymphokines Interleukins and Interferons

Cytokines

Properties of Cytokines

Cytokines are small secreted proteins which mediate and regulate immunity, inflammation, and hematopoiesis. They must be produced de novo in response to an immune stimulus. They generally (although not always) act over short distances and short time spans and at very low concentration. They act by binding to specific membrane receptors, which then signal the cell via second messengers, often tyrosine kinases, to alter its behavior (gene expression). Responses to cytokines include increasing or decreasing expression of membrane proteins (including cytokine receptors), proliferation, and secretion of effector molecules.

Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action).

It is common for different cell types to secrete the same cytokine or for a single cytokine to act on several different cell types (pleiotropy; see the table below.) Cytokines are redundant in their activity, meaning similar functions can be stimulated by different cytokines. Cytokines are often produced in a cascade, as one cytokine stimulates its target cells to make additional cytokines. Cytokines

can also act synergistically (two or more cytokines acting together) or antagonistically (cytokines causing opposing activities).

Their short half life, low plasma concentrations, pleiotropy, and redundancy all complicated the isolation and characterization of cytokines. Searches for new cytokines is now often conducted at the DNA level, identifying genes similar to known cytokine genes.

Cytokine Activities

Cytokine activities are characterized using recombinant cytokines and purified cell populations in vitro, or with knock-out mice for individual cytokine genes to characterize cytokine functions in vivo. Cytokines are made by many cell populations, but the predominant producers are helper T cells (Th) and macrophages.

The largest group of cytokines stimulates immune cell proliferation and differentiation. This group includes Interleukin 1 (IL-1), which activates T cells; IL-2, which stimulates proliferation of antigen-activated T and B cells; IL-4, IL-5, and IL-6, which stimulate proliferation and differentiation of B cells; Interferon gamma (IFNg), which activates macrophages; and IL-3, IL-7 and Granulocyte Monocyte Colony-Stimulating Factor (GM-CSF), which stimulate hematopoiesis.

Other groups of cytokines include interferons and chemokines. Interferons IFNa and IFNb inhibit virus replication in infected cells, while IFNg also stimulates antigen-presenting cell MHC expression. Chemokines attract leukocytes to infection sites. Chemokines have conserved cysteine residues that allow them to be assigned to four groups. The groups, with representative chemokines, are C-C chemokines (RANTES, MCP-1, MIP-1a, and MIP-1b), C-X-C chemokines (IL-8), C chemokines (Lymphotactin), and CXXXC chemokines (Fractalkine). Some cytokines are predominantly inhibitory. For example, IL-10 and IL-13 inhibit inflammatory cytokine production by macrophages.

Helper T cells have two important functions: to stimulate cellular immunity and inflammation, and to stimulate B cells to produce antibody. Two functionally distinct subsets of T cells secrete cytokines which promote these different activities. Th1 cells produce IL-2, IFNg, and TNFb, which activate Tc and macrophages to stimulate cellular immunity and inflammation. Th1 cells also secrete IL-3 and GM-CSF to stimulate the bone marrow to produce more leukocytes. Th2 cells secrete IL-4, IL-5, IL-6, and IL-10, which stimulate antibody production by B cells.

T cells are initially activated as Th0 cells, which produce IL-2, IL-4 and IFNg. The nearby cytokine environment then influences differentiation into Th1 or Th2 cells. IL-4 stimulates Th2 activity and suppresses Th1 activity, while IL-12 promotes Th1 activities. Th1 and Th2 cytokines are antagonistic in activity. Th1 cytokine IFNg inhibits proliferation of Th2 cells, while IFNg and IL-2 stimulate B

cells to secrete IgG2a and inhibit secretion of IgG1 and IgE. Th2 cytokine IL-10 inhibits Th1 secretion of IFNg and IL-2; it also suppresses Class II MHC expression and production of bacterial killing molecules and inflammatory cytokines by macrophages. IL-4 stimulates B cells to secrete IgE and IgG1. The balance between Th1 and Th2 activity may steer the immune response in the direction of cell-mediated or humoral immunity. (See The Big Picture: Immunity to Infection.)

Cytokine Receptors

Cytokines act on their target cells by binding specific membrane receptors. The receptors and their corresponding cytokines have been divided into several families based on their structure and activities. Hematopoietin family receptors are dimers or trimers with conserved cysteines in their extracellular domains and a conserved Trp-Ser-X-Trp-Ser sequence. Examples are receptors for IL-2 through IL-7 and GM-CSF. Interferon family receptors have the conserved cysteine residues but not the Trp-Ser-X-Trp-Ser sequence, and include the receptors for IFNa, IFNb, and IFNg. Tumor Necrosis Factor family receptors have four extracellular domains; they include receptors for soluble TNFa and TNFb as well as membrane-bound CD40 (important for B cell and macrophage activation) and Fas (which signals the cell to undergo apoptosis). Chemokine family receptors have seven transmembrane helices and interact with G protein. This family includes receptors for IL-8, MIP-1 and RANTES. Chemokine receptors CCR5 and CXCR4 are used by HIV to preferentially enter either macrophages or T cells.

Hematopoietin cytokine receptors are the best characterized. They generally have two subunits, one cytokine-specific and one signal transducing. An example is the GM-CSF subfamily, where a unique a subunit specifically binds either GM-CSF, IL-3, or IL-5 with low affinity and a shared b subunit signal transducer also increases cytokine-binding affinity. Cytokine binding promotes dimerization of the a and b subunits, which then associate with cytoplasmic tyrosine kinases to phosphorylate proteins which activate mRNA transcription. GM-CSF and IL-3 act on hematopoietic stem cells and progenitor cells and activate monocytes. With IL-5, they also stimulate eosinophil proliferation and basophil degranulation. All three receptors phosphorylate the same cytoplasmic protein. Antagonistic GM-CSF and IL-3 activities can be explained by their competition for limited amounts of b subunit.

The IL-2R subfamily of receptors for IL-2, IL-4, IL-7 , IL-9, and IL-15 have a common signal-transducing g chain. Each has a unique cytokine-specific a chain. IL-2 and IL-15 are trimers, and share an IL-2R b chain. Monomeric IL-2R a has low affinity for IL-2, dimeric IL-2R bg has intermediate affinity, and trimeric IL-2R abg binds IL-2 with high affinity. IL-2R a chain (Tac) is expressed by activated but not resting T cells. Resting T cells and NK cells constitutively express low numbers of IL-2R bg. Antigen activation stimulates T cell expression of high affinity IL-2R trimers as well as secretion of IL-2, allowing autocrine stimulation of T cell proliferation in an antigen-specific manner. Antigen specificity of the immune response is also maintained by the close proximity of antigen-

presenting B cells and macrophages with their helper T cells, so that cytokines are secreted in the direction of and close to the membrane of the target cell. X-linked severe combined immunodeficiency (X-scid) is caused by a defect in IL-2R family g chain, which results in loss of activity from this family of cytokines.

Cytokine activity can be blocked by antagonists, molecules which bind cytokines or their receptors. IL-1 has a specific antagonist that blocks binding of IL-1a and IL-1b to their receptor. During immune responses, fragments of membrane receptors may be shed and then compete for cytokine binding. Microbes also influence cytokine activities. For example, Vaccinia virus (Smallpox and Cowpox) encodes soluble molecules which bind IFNg, while Epstein-Barr virus (Infectious Mononucleosis) encodes a molecule homologous to IL-10 that suppresses immune function in the host.

The TNF receptor family molecules CD40 and Fas bind cell surface ligands on effector T cells: CD40L and FasL. CD40 is expressed on B cell and macrophage plasma membranes. T cell CD40L binding to B cell CD40 stimulates B cell proliferation and isotype switching. T cell CD40L binding to macrophage CD40 stimulates macrophages to secrete TNFa and become much more sensitive to IFNg. T cell FasL binding to Fas leads to the activation of caspase proteases that initiate apoptosis of the cell expressing membrane Fas. Activated lymphocytes express Fas, so that FasL-positive Tc cells can regulate the immune response by eliminating activated cells. An immune deficiency disease linked to expression of a mutant Fas is characterized by over-proliferation of lymphocytes.

Interleukin

Interleukins are a group of cytokines (secreted signaling molecules) that were first seen to be expressed by white blood cells (leukocytes, hence the -leukin) as a means of communication (inter-). The name is something of a relic though (the term was coined by Dr. Paetkau, University of Victoria); it has since been found that interleukins are produced by a wide variety of bodily cells. The function of the immune system depends in a large part on interleukins, and rare deficiencies of a number of them have been described, all featuring autoimmune diseases or immune deficiency.

Interferons (IFNs)

Interferons (IFNs) are natural proteins produced by the cells of the immune system of most vertebrates in response to challenges by foreign agents such as viruses, parasites and tumor cells. Interferons belong to the large class of glycoproteins known as cytokines. Interferons are produced by a wide variety of cells in response to the presence of double-stranded RNA, a key indicator of viral infection. Interferons assist the immune response by inhibiting viral replication within host cells, activating natural killer cells and macrophages, increasing antigen presentation to lymphocytes, and inducing the resistance of host cells to viral infection. When the antigen is presented to matching T and B cells, those

cells multiply and strategically and specifically wipe out the foreign substance. That is why antigen presentation is so important to the immune response.

Types of interferon

There are three major classes of interferons that have been described for humans according to the type of receptor through which they signal:
Interferon type I: All type I IFNs bind to a specific cell surface receptor complex known as the IFN-α receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains. The type I interferons present in humans are IFN-α, IFN-β and IFN-ω.[1]
Interferon type II: Binds to IFNGR. In humans this is IFN-γ.
Interferon type III: Signal through a receptor complex consisting of IL10R2 (also called CRF2-4) and IFNLR1 (also called CRF2-12)

Viral induction of interferons

All classes of interferon are very important in fighting RNA virus infections. However, their presence also accounts for some of the host symptoms, such as sore muscles and fever. They are secreted when abnormally large amounts of dsRNA are found in a cell. dsRNA is normally present in very low quantities. The dsRNA acts like a trigger for the production of interferon (via Toll Like Receptor 3 (TLR 3), a pattern recognition receptor of the innate immune system which leads to activation of the transcription factor IRF3 and late phase NF kappa Beta). The gene that codes for this cytokine is switched on in an infected cell, and the interferon synthesized and secreted to surrounding cells.

As the original cell dies from the cytolytic RNA virus, these thousands of viruses will infect nearby cells. However, these cells have received interferon, which essentially warns these other cells that there's a wolf in the flock of sheep. They then start producing large amounts of a protein known as protein kinase R (or PKR). If a virus infects a cell that has been “pre-warned” by interferon, the PKR is indirectly activated by the dsRNA (actually by 2'-5' oligoadenylate produced by the 2'-5' oligoadenylate-synthetase which is produced due to TLR3 activation), and begins transferring phosphate groups (phosphorylating) to a protein known as eIF-2, a eukaryotic translation initiation factor. After phosphorylation, eIF2 has a reduced ability to initiate translation, the production of proteins coded by cellular mRNA. This prevents viral replication and inhibits normal cell ribosome function, killing both the virus and the host cell if the response is active for a sufficient amount of time. All RNA within the cell is also degraded, preventing the mRNA from being translated by eIF2 if some of the eIF2 failed to be phosphorylated.

Furthermore, interferon leads to upregulation of MHC I and therefore to increased presentation of viral peptides to cytotoxic CD8 T cells, as well as to a change in the proteasome (exchange of some beta subunits by b1i, b2i, b5i - then known as the immunoproteasome) which leads to increased production of MHC I compatible peptides.

Interferon can cause increased p53 activity in virus infected cells. It acts as an inducer and causes increased production of the p53 gene product. This promotes apoptosis, limiting the ability of the virus to spread. Increased levels of transcription are observed even in cells which are not infected, but only infected cells show increased apoptosis. This increased transcription may serve to prepare susceptible cells so they can respond quickly in the case of infection. When p53 is induced by viral presence, it behaves differently than it usually does. Some p53 target genes are expressed under viral load, but others, especially those that respond to DNA damage, aren't. One of the genes that is not activated is p21, which can promote cell survival. Leaving this gene inactive would help promote the apoptotic effect. Interferon enhances the apoptotic effects of p53, but it is not strictly required. Normal cells exhibit a stronger apoptotic response than cells without p53.

Additionally, interferon has been shown to have therapeutic effect against certain cancers. It is probable that one mechanism of this effect is p53 induction. This could be useful clinically: Interferons could supplement or replace chemotherapy drugs that activate p53 but also cause unwanted side effects.[2].Some of these side effects can be serious, severe and permanent.

Immunosuppression - Transplantation

Transplantation and rejection

- Rejection of transplantation tissues occurs because the immune system of the recipient recognizes and responds to foreign (tissue) histocompatibility antigens expressed on the graft.
- The histocompatibility antigens that are most important are those encoded by the major histocompatibility complex (MHC).
- T lymphocytes can directly recognize and respond to foreign MHC molecules.
- Activated T-helper cells make lymphokines which drive the activation of many
- different effector mechanisms of graft destruction.
- Lymphokines also act upon the graft to increase the expression of MHC molecules and adhesion molecules, making the graft more susceptible to rejection.
- Graft rejection responses can be reduced by matching of donor and recipient MHC molecules, especially to for MHC class II molecules.
- Specific immunosuppression will be used in the future, inactivating only those lymphocyte clones which cause graft rejection.

The immunobiology of transplantation is important for many reasons, in terms of both its impact on our understanding of immunological processes and its application in the development of clinical transplantation. It was the study of

mouse skin-graft rejection that led to the discovery of the major histocompatibility complex (MHC) molecules, which function in the presentation of antigens to T cells. T cells are pivotal in transplant rejection, and much of our knowledge of T cell physiology and function, of self tolerance and autoimmunity, and of the role of the thymus in T cell destruction, is derived from studies of transplantation. Last, but not least, transplantation of tissues is very important clinically. The need to prevent transplant rejection has led to the development and use of new tolerance of the grafted tissues. These approaches also have a more general application in the treatment of various immune disorders, such as immune-mediated tissue damage in hypersensitivity and autoimmunity.

In clinical practice, organs are transplanted to make good a functional deficit (Figure-1). Unless the donor and recipient are genetically identical, the graft antigens will elicit an immunological rejection response. Transplantation can stimulate all of the various active mechanisms of humoral and cellular immunity, both specific and non-specific. This is a consequence of the recognition by the recipient's T cells of large numbers of foreign and 'neo-self' peptides associated with the foreign MHC molecules on the grafted cells and of graft-derived peptides bound to self MHC Figure-8). Also, a transplant can activate all the regulatory mechanisms that control immune responses causing a state of unresponsiveness to the graft. Hence, transplantation immunology encompasses virtually all aspects of immune function.

BARRIERS OF TRANSPLANTATION

Transplantation barriers can be described in terms of the genetic disparity between the donor and the recipient: grafts can be categorized as autografts, isografts, allografts or xenografts (Figure-2). Autografts from one part of the body to another are not foreign and therefore do not elicit rejection. Similarly, isografts between isogeneic (genetically identical) individuals, such as monozygotic (identical) twins or mice of the same inbred strain, do not express antigens foreign to the recipient and so do not activate a rejection response. The allograft is the common clinical transplant, where one person donates an organ to a genetically different individual. In this case the graft is llogeneic (i.e. between members of the same species, having allelic variants of certain genes). The cells of the allograft will express alloantigrafts which are recognized as foreign by the recipient.

The maximal genetic disparity is between members of different species, and a xenograft across such a xenogeneic barrier is generally rapidly rejected, either by naturally occurring IgM antibodies in the recipient or by a rapid cell-mediated rejection (see below). If they are treated to reduce their immunogenicity, tissue xenografts that would otherwise be non-viable, such as pig skin, blood vessels or valves, can be grafted to man. Despite this, attempts to transplant whole organs from animal to man have been spectacularly unsuccessful, although some success has been achieved in xenografting between animal species. If the immunological problems of xenografting can be overcome, the use of animal donorscould alleviate the worldwide shortage of human organs for transplantation. Nevertheless, various non-immunological problems remain,

including donor organ size, physiological differences, transmission of animal diseases and the ethics of xenografting.

HISTOCOMPATIBILITY ANTIGENS Histocompatibility antigens are the targets for rejection

The antigens primarily responsible for rejection of genetically different tissues are known as histocompatibility (i.e. tissue compatibility) antigens and the genes coding for these antigens are referred to as histocompatibility genes. There are more than 30 histocompatibility gene loci, and they cause rejection at different rates. Of these, alloantigens encoded by the genes of the MHC induce particularly strong reactions; these are the molecules that present antigens in a formk recognizable to T cells – all vertebrate species have an MHC. In mice the MHC is called H-2, while in man it is known as the human leucocyte intigaen (HLA) system. The products of allelic variants of the other histocompatibility genes individually cause weaker rejection responses and are consequently known as minor histocompatibility antigens; these antigens are normal cellular constituents. None the less, combinations of several minor antigens can elicit strong rejection responses (Figure-3).

MHC haploypes are inherited from both parents and are co-dominantly expressed

The genes of the MHC are subject to simple Mendelian inheritance and are co-dominantly expressed. In other words, each individual has two 'half-sets' (haplotypes) of genes, one haplotypes are expressed equally, so that each cell in the offspring has both maternal and paternal MHC molecules on its surface (Figure-5).

MHC molecules are expressed on transplanted tissues ad induced by cytokines

MHC molecules are not equally distributed on all cells of the body. Class I molecules are normally expressed on most nucleated cells (and on erythrocytes and platelets in some species), while class II molecules are restricted to antigen-presenting cells (APCs, e.g. dendritic cells and activated macrophages), B cells and, in some species, activated T cells and vascular endothelial cells. The expression of MHC on cells is controlled by cytokines: interferon-γ (IFNγ) and tumor necrosis factor (TNF) are powerful inducers of MHC expression on many cell types which would otherwise express MHC molecules only weakly. As will be seen, this is important in graft rejection.

THE LAW OF TRANSPLANATION

The transplant situation is unique in that foreign MC molecules can directly activated T cells. Conventional T cell responses against foreign proteins require that such antigens are processed into peptides and presented on the surface of the recipient's APCs in association with MHC molecules.

Host-versus-graft responses cause transplant rejection

The overriding consideration for organ allograft rejection is whether the graft carries any antigens that are not present in the recipient. This principle of host-versus-graft reactions is illustrated in Figure-6.

Graft-versus-host reactions result when donor lymphocytes attack the graft recipient

A special situation occurs in bone-marrow transplantation, in which graft-versus-host disease (GVHD) is induced by immunologically competent T cells being transplanted into allogeneic recipients which are unable to reject them. This inability may be due to the genetic differences between the donor and recipient, or because of a lack of immunocompetence (through immunity or immunsuppression) of the recipient. In this situation, the immunocompetent T cell transplanted with the bone marrow can attack the recipient (Figure-7). GVHD is a major complication of bone-marrow transplantation, causing severe damage, particularly to the skin and intestine, and is avoided by careful typing, removal of mature T cells from the graft and the use of immunosuppressive drugs.

THE ROLE OF T LYMPHOCYTES IN REJECTION T-cells are pivotal in graft rejection

Rodents born without a thymus (congenitally athymic or 'nude') have no mature T cells and cannot reject transplants. The same is true of normal rats or mice from which the thymus is removed in the neonatal period, before mature T cells are released to the periphery. Likewise, adult thymectomy (AT) of rats or mice (to stop the production of T cells), followed by irradiation (to remove existing mature T cells) and bone marrow (BM) transplantation (to restore haemopoiesis) produces 'ATx.BM recipients' which have no T cells and cannot reject grafts.

In any of these animals (nudes, neonatally thymectomized or ATx.MB), the ability to rejects grafts is restored by the injection of T cells from a normal animal of the same strain. Thus T cells are necessary for rejection. This does not imply that antibodies, B cells or other cells play no part. Indeed, antibodies cause graft damage and macrophages may be involved in inflammatory reactions in grafted tissue.

Rejection responses have a molecular basis in the TCR-MHC interaction

Via their T-cell receptors (TCRs), the T cells involved in rejection recognize donor- derived peptides in association with the MHC antigens expressed on the graft. As we already know, the structure of the T cell receptor (TCR) (see Figure-13) is such that T cell can only 'see' peptide antigens when they are associated with MHC molecules, and this MHC restriction is imposed by positive selection in

the thymus (see Figure-8). So, to understand the involvement of T cells in rejection, we need to examine the difference between recipient and graft MHC molecules and how such differences effect the range of antigens presented to the recipient's TCR.

Different MHC molecules have similar structures but different peptide-binding grooves

The structure of different MHC molecules are almost identical, with the overall shape consisting of two α helices lying on a β-pleated sheet stop two immunologlobulin-like domains which sit on the cell membrane. Between the α helices is a deep groove into which peptides can be bound. The part of the MHC molecule that is important in T cell recognition is the outer surface of these α helices, which is highly conserved between different MHC molecules.

The significant amino-acid sequence differences between two MHC molecules – comparing, for example, A2 and Aw68 allelic variants of the HLA-A antigen – lie deep in the groove between the α helices, not on the outer surface contacted by the TCR (see Figure-7). Hence, for T cell recognition, the principal difference between MHC molecules is in the shape and charge of the peptide-binding groove, and this governs which peptides can be bound and in what orientation they are presented to TCRs (see Figure-11 and 12).

Graft and host MHC molecules present different peptides

In the normal physiological situation, the MHC groove is occupied by peptides derived from normal cellular constituents by intracellular degradative pathways. Thymic tolerance mechanisms ensure that T cell recognition of these self peptide-self MHC complexes, which would lead to autoimmunity, does not occur. However, when cells are infected (with virus, for example), the normal cell-derived peptides are replaced by peptides of foreign origin, as is the case of 'professional' APCs. T cells then respond to these foreign peptides in association with self MHC molecules.

However in the case of a genetically distinct transplanted tissue a third situation arises. A different array of peptides is presented on the cell surface because of the different shape and charge of the peptide-binding sites of the graft MHC molecules. This allows binding, not only of peptides derived from the foreign MHC and minor allelic histocompatibility antigens, but also peptides of host molecules which do not bind to self MHC and which therefore have not induced tolerance (Figure-8). This leads to the expression on transplanted APCs of a very large number of novel antigens which can be recognized by the recipient's T cells. This so-called 'direct' mode of antigen presentation is supplemented by the direct recognition of graft peptides bound by self MHC. It is not surprising therefore that up to 10% of an individual's T cells may respond to these antigens originating from the engrafted tissue.

T-helper (TH) cells and lymphokines are involved in rejection

The role of T-helper (TH) cells in rejection

Injecting T cells of the CD4+ subpopulation (TH cells) into nude or ATx.BM recipients leads to acute skin-graft rejection. Naïve, unsensitized CD8+ T cells (Tc cells) are unable to do this, but when CD8+ T cells are mixed with a very low number of CD4+ T cells, or are presensitized to graft antigens (i.e. taken from animals which have already rejected a graft), rapid graft destruction is then seen. Treating recipients with monoclonal anti-CD4+ antibodies (Figure-9) confirms the importance of TH cells in rejection.

TH cells are activated by APCs derived from bone marrow and carrying MHC class II molecules. The APCs activating rejection can come from either the donor or the recipient. Those of donor origin are present in the graft as 'passenger leucocytes' (interstitial dendritic cells) and they cause 'direct' activation of the recipient's TH cells. Those of recipient origin are located in draining lymphoid tissues and acquire antigen that is shed from the transplant, and present it to the recipient's TH cells to cause 'indirect' activation. Direct activation is a more powerful stimulus to rejection than the so-called indirect route (Figure-10). Thus passenger cells may have a strong influence on graft survival (Figure-11).

The role of lymphokines in rejection

In addition to the role of CD4+ TH cells, a multiplicity of immunological mechanisms including lymphokines are involved in the process of rejection. The overall picture is show in Figure-12.

The most important lymphokines in cellular rejection are interleukin-2 (IL-2), which is required for activation of Tc cells, and IFNγ, which induces MHC expression, increases APC activity, activates large granular lymphocytes and, in concert with lymphotoxin, activates macrophages.Macrophages, in turn, release TNFα, an important mediator of graft damage. (Note: the mixture of INFγ and lymphotoxin was formerly known as macrophage activating factor or MAF.).

Lymphokines (IL-4, -5 and -6) are also required for B-cell activation, leading to the production of anti-graft antibodies. These antibodies fix complement and cause damage to the vascular endothelium, resulting in haemorrhage, platelet aggregation within the vessels, graft thrombosis, lytic damage to cells of the transplant, and the release of the pro-inflammatory complement components, C3a and C5a.

Not all parts of the graft need to be attacked for rejection to occur. The critical targets are the vascular endothelium of the microvasculature and the specialized parenchymal cells of the organ, such as renal tubules, pancreatic islets of Langerhans or cardiac myocytes.

IFNγ can cause vascular endothelial cells to express high levels of class II MHC molecules, and can induce the expression of class I and II molecules on

parenchymal cells, which usually express little or none of these. This upregulation of MHC expression on cells of the graft can provoke greater stimulation of the rejection response and provide a greater number of target molecules within the graft for antibodies and activated cells.

Lymphotoxin and IFNγ also upregulate the expression of adhesion molecules on vascular endothelium, these are required for the adhesion of blood-borne leucocytes to the walls of blood vessels prior to their migration across the endothelium into the tissues.

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