Journal of the Minnesota Academy of Science

Volume 51 | Number 1 Article 4

1985

The Immunology of Transplantation

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ABSTRACT A number of life-threatening diseases, such as kidney failure, diabetes, and certain kinds of coronary heart disease, can be cured by organ transplantation. However, despite decades of research, graft rejection remains a very real threat to the organ transplant recipient. In attempting to develop methods that interfere with the graft rejection process, scientists have uncovered a remarkably complex system of cellular interactions that allows the total destruction of a transplanted organ while leaving the recipient's own organs untouched. This ability to distinguish *self* from *non-self* is achieved through intercellular communication involving cell-to-cell contact and the release of a number of communication molecules. This tangled web of cellular interactions is the focus of a great deal of scientific interest since the solution to the graft rejection problem lies in our ability to understand it. In addition, the cellular interactions that produce graft rejection may serve as a model to help us better understand cellular communication in general.

Introduction

Organ transplantation is rapidly becoming a routine therapeutic procedure for the reversal of a number of life-threatening diseases. Kidney transplants, the most prevalent and successful form of organ transplantation, now result in one-year graft survival rates of 70% to 80% for cadaver grafts and over 90% for living related donors (1). More than 200 kidney transplants are performed each year at the University of Minnesota Hospitals, which have the largest and most comprehensive organ transplant program in the world. In addition, liver, heart, bone marrow, pancreas, lung, cornea, middle ear, and heart/lung transplants have been performed at this center and others with increasing success. Despite these strides, transplant patients must live with the constant threat that their new life-saving organ will be rejected. During the rejection process, the cells of the transplanted organ are recognized as foreign by the recipient's immune system and are subsequently attacked and destroyed.

Under normal circumstances, it is in our best interest to have foreign cells eliminated from our bodies. Our constant temperature, electrolyte balance, and nutrient supply make us superior incubators for a wide variety of infectious microorganisms, which would quickly invade and overcome our bodies without the immune system standing guard. Unfortunately, the immune stystem does not use *harmfulness* as a criterion for recognition but rather *foreignness*. Because the cells of another individual are foreign, they are subject to the same recognition and attack as the microorganisms the immune system evolved to handle.

Beyond advances in surgical techniques and organ preservation, then, an integral component of transplantation therapy involves attempting to thwart the ability of the recipient's immune system to either recognize or attack the newly transplanted organ. Efforts in this area include donor-recipient matching, in which the genetic foreignness of the donor tissue is minimized, and the development of agents that suppress the recipient's immune system. Unfortunately, with a suppressed immune system, the recipient becomes vulnerable to opportunistic infections that can be life threatening. A new generation of immunosuppressants is being developed that attempts to suppress only those components of the immune system that cause graft rejection while sparing those components that fight infection. However, these agents are not perfectly able to accomplish this task and are not without side effects.

The real answer to the problem of rejection lies in our ability to better understand the process by which grafts are rejected. This enormously complex process remains only partially understood despite four decades of research. The problem can be divided into two major questions:

1) How does the immune system recognize transplanted tissue as foreign? and

2) Once recognition has occurred, how does the immune system attack and destroy the foreign graft?

Because graft rejection requires both of these processes, preventing the immune system from doing either would ensure graft survival.

Recognition of Transplanted Tissue as Foreign

The immune system uses foreignness as the sole criterion for recognition and destruction of a cell. The effective elimination of pathogenic microorganisms requires a system that is capable of killing living cells. Yet, our own cells must be spared this destruction. Therefore, the immune system must be able to differentiate *self* from *non-self*. This is accomplished by the system's inability to recognize and respond to any molecule that is a legitimate component of its own body. Thousands of proteins and other molecules are floating free in the body or are embedded in the outer membranes of cells. During fetal development, the immune system is exposed to these molecules and becomes unable to respond to them. This tolerance of self extends only to those molecules present during fetal life or shortly thereafter (2). All other molecules, if presented to the immune system in the right fashion, will be recognized as foreign and attacked. For example, since microorganisms have surface molecules very different from ours, they are easily recognized and destroyed.

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Leukocytes

The immune system is embodied in the white blood cells, called leukocytes, and closely related cells. The immune response is a complex set of interactions between a foreign molecule, called an antigen, and the leukocytes. Lymphocytes, macrophages, and dendritic cells are the principal leukocytes involved in the immune response to transplanted tissue.

The immune response begins when a surface receptor on a lymphocyte combines with the antigen for which it is specific. Each lymphocyte has a specific type of surface receptor with a shape that is complementary to just one antigen. The binding of the surface receptor and the antigen causes the lymphocyte to begin rapidly dividing or proliferating. Once stimulated by antigen, the various types of lymphocytes can perform their specific roles in the process of antigen elimination. In addition, some of these lymphocytes "remember" this encounter and, if presented with this antigen again, respond more rapidly and extensively. This memory for past encounters is the basis for immunization against disease.

Glycoprotein Markers

Normally, the immune system serves us well. However, when an organ is transplanted, the immune system turns its exquisitely sensitive and deadly power to recognize and destroy foreignness toward the newly grafted tissue. Special glycoproteins on the surface of cells are the molecules by which the cells of the graft are recognized as foreign. Many of the surface proteins on human cells are identical from person to person. For instance, the membrane channel for sodium is probably the same molecule in all members of the human species. However, there is a set of glycoproteins present on most cells of the body that is unique to each individual of the species. These *membrane markers* are encoded by an area on chromosome 6 called the major histocompatibility complex (MHC) (reviewed 3-5). This complex, assumed to be present in all mammalian species, is called the HLA region (human leukocyte antigens) in humans, and in the mouse — most often used for investigations in this area — it is called the H-2.

In both species there are at least three extremely polymorphic, codominant loci within this area coding for the Class I antigens — membrane-bound glycoproteins that are present on almost all cells of the body (6). The Class I antigens are encoded by the K, D, L, and R regions in the mouse and the A, B, and C regions in the human (Figure 1) (7, 8). It has been estimated that each of these loci may have up to 100 alleles, making it rare for any two people to be identical at all three of the known human loci unless they are identical twins. Because the Class I antigens are on most of the cells of the body, transplanted tissue bears molecules that are foreign to the recipient's immune system.

A second area within the major histocompatibility complex codes for glycoproteins that are found only on the surface of lymphocytes, macrophages, dendritic cells, and a limited number of other cells types (9-11). These polymorphic, membrane-bound glycoproteins, called Class II antigens, can be recognized as foreign by the recipient's immune system but also probably play a key role in the interactions between the various components of the immune system that make the immune response possible (12). Class II antigens are encoded by the I region of the mouse and the D region of the human (Figure 1).

Foreignness, then, is present in two forms in transplanted tissue. The cells of the graft itself, for instance, kidney and liver cells, carry foreign Class I antigens. Plus, any transplanted lymphocytes, macrophages, or dendritic cells bear foreign Class II antigens. These cells are very likely to be transplanted in a graft because they reside in the fluid compartment bathing all the cells of the body. When they are transplanted with a graft, they are called *passenger leukocytes*.

Presentation of soluble antigen by adherent cells

The fact that transplanted tissue is foreign to the recipient's immune system is only the beginning of a story that takes a rather complex turn at this point. It has been apparent since the early 1970s that foreignness alone is not enough to trigger an immune response. The antigen also must be presented by an immune system cell which, until recently, was believed to be the macrophage. Rosenthal, et al., used *in vitro* methods to demonstrate that lymphocytes would not proliferate in the presence of soluble antigen (as opposed to membrane-bound antigen) unless the antigen was associated with adherent cells (13, 14). (Adherent cells are leukocytes that will adhere to glass or plastic.) It is now known that the adherent population, originally thought to be entirely composed of macrophages, also includes dendritic cells, which are probably more potent antigen presenters than macrophages (11, 15).

Further investigation (16, 17) revealed that the major histocompatibility complex plays a significant role in the presentation of soluble antigen by adherent cells in the following way: The immune system has memory for antigens it has encountered before. When an antigen is encountered for the first time, a primary response occurs in which lymphocytes become primed and memory is induced. When the identical antigen is encountered again, a secondary response occurs, which includes lymphocyte proliferation. A secondary response will produce much more proliferation if soluble antigen is presented in association with an adherent cell of the same MHC type as the one which initially presented the antigen. For example, if antigen is presented in association with a type A adherent cell in the primary response, a strong secondary response will occur only if that antigen is presented on a type A adherent cell again. If it is presented on a type B adherent cell, the response will be poor. In other words, the lymphocytes responding in this system remember not only the antigen but also the major histocompatibility complex antigens on the surface of the cell presenting the antigen. This phenomenon is called *MHC restriction*. Current evidence suggests that the Class II antigens, found on the surface of both macrophages and dendritic cells, are the MHC products involved in the presentation of soluble antigen (12).

Thus, the MHC glycoprotein membrane markers on the cell surface are probably involved in the presentation of antigen and in the interactions of the cells of the immune system. They also are involved in the recognition phase of graft rejection. Apparently, the presence of donor Class II antigen-bearing dendritic cells is necessary for the recognition of foreignness in transplanted tissue. Evidence for this comes from a number of sources. One *in vitro* method, the mixed leukocyte reaction (MLR), tests the ability of lymphocytes to recognize foreign MHC antigens and to respond by proliferating. In this test, leukocytes from one individual are mixed with leukocytes from a second, MHC non-identical (allogeneic) individual. Normally each set of leukocytes would see the other as foreign and would proliferate. "A" would respond to "B," and "B" would respond to "A." To test only one of these responses at a

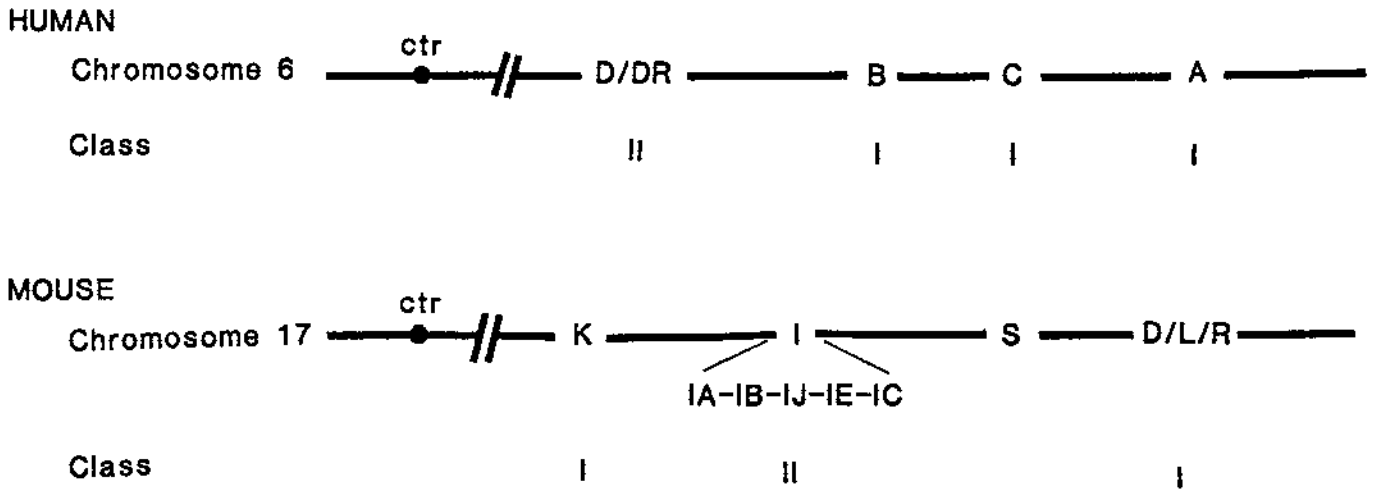

Figure 1. Genetic map of the major histocompatibility complex of humans and mice. The Class I antigens, present on the surface of all cells, are encoded by the A, B, and C regions in the human and the K, D, L, and R regions in the mouse. The Class II antigens, found on certain cells of the immune system, are encoded by regions D/DR in humans and the I region in mice.

time, the leukocytes from individual "A" are treated with chemicals or irradiation to prevent their proliferation. The "A" cells, then, are the stimulator cells. The leukocytes from individual "B" remain untreated and are the responders in this system. Recognition of the foreign MHC antigens on the stimulator cells is manifested by the proliferation of the responding cells. When dendritic cells are specifically removed from the stimulating leukocyte population, the proliferation of the responding cells is significantly reduced. Further, the addition of a small number of stimulator dendritic cells reconstitutes the proliferation (17).

Numerous studies *in vivo* indicate that if transplanted grafts are purged of their passenger leukocyte population, which includes dendritic cells, either by a pre-transplant period in tissue culture that is differentially toxic to leukocytes (18-20) or by direct elimination of Class II antigen-bearing cells (21), graft survival is significantly enhanced. Further, when leukocytes of donor origin are injected into recipients bearing a surviving graft, the graft is usually subsequently rejected (22). Thus, the presence of donor or stimulator dendritic cells appears to be a prerequisite for graft rejection and MLR proliferation.

It is unclear from these investigations whether the elimination of Class II antigen-bearing cells prolongs graft survival through the elimination of MHC incompatible Class II antigens or through the elimination of the dendritic cells on which they reside. In studies using strains of mice which differed from one another only in very limited areas of the MHC, it was found that if the donor and recipient are Class I mismatched but identical at Class II, graft rejection still occurs (23). Therefore, Class II incompatibility is not necessary for graft rejection but the presence of cells bearing Class II antigens is. These findings are consistent with previous work indicating the importance of Class II bearing dendritic cells in antigen presentation. Although the exact role played by dendritic cells in graft rejection is not known, because they appear to be essential to the graft rejection process, their elimination would make grafts "invisible" to immune detection while leaving the functioning part of the grafted tissue unharmed. Anti-Class II antibodies are currently available that can specifically kill these passenger cells.

There is another interesting twist to this story that complicates matters considerably — the minor histocompatibility loci. The major histocompatibility complex is only one of many genetic regions that cause graft rejection. The *minors*, as they are called, cause a slower rejection if they are mismatched, but they can ultimately lead to the loss of a functioning graft.

Studies indicate that the minor antigens must be presented in association with the major histocompatibility antigens in the same fashion as soluble antigen or MHC antigens (24). Further, researchers have found that if passenger dendritic cells share the major histocompatibility antigens with the graft but do not share the minor antigens, they can still present the minors as foreign and precipitate graft rejection. However, if the dendritic cells do not share the major histocompatibility antigens with the graft, they cannot present the graft's minor antigens and rejection does not occur (25). Therefore, if the removal of dendritic cells from grafts becomes a viable method for prolonging graft survival, it is very important that the donor and recipient be mismatched as far as possible. Once the graft is in place, recipient dendritic cells will invade it and take up residence in it. If they have the same MHC as the graft (i.e., if the donor and recipient are matched by tissue typing), they may be able to present the minor histocompatibility differences to the recipient's immune system and precipitate rejection. It would be an ironic twist if the tissue typing systems established to ensure the closest possible match between donor and recipient are used in the future to ensure the greatest mismatch or a mismatch at the specific locus responsible for antigen presentation.

Destruction of the Transplanted Organ

Infiltration by leukocytes

The sequence of events that causes graft rejection begins with the presentation of the graft's foreign MHC antigens to the recipient's leukocytes, which are continually traveling through all the organs of the body. These stimulated leuko-

cytes migrate to local lymph nodes where they rapidly divide and become capable of destroying the graft. When these anti-graft *effector cells* are released from the local lymph nodes into the blood, they return to the transplanted graft, recognize the foreign MHC antigens that originally stimulated their development, and destroy the graft cells bearing these antigens. Once in the graft, they secrete substances that cause a general inflammatory response in which non-specific leukocytes are attracted to the area (26).

Consequently, graft rejection is characterized by the infiltration of the graft by leukocytes. Analysis of the appearance and surface markers of these cells has identified them as predominantly lymphocytes and macrophages. Further analysis of the lymphocytes reveals the presence of both major lymphocyte subpopulations: the B-lymphocyte (B-cell) and the T-lymphocyte (T-cell) (27). B-lymphocytes cause cellular destruction by secreting antibodies — large proteins that bind to the surface markers on foreign cells — marking them for destruction by macrophages. Although B-cells make antibodies against foreign grafted tissue (28), this antibody-mediated form of destruction probably plays, at most, a minor role in the typical graft rejection process. A now classic experiment demonstrated this: When antibodies against a skin graft were injected into an animal bearing the graft, the antibodies did not cause the graft to be rejected (29).

The T-lymphocytes found in rejecting grafts can be further divided into two distinct subpopulations based on the presence of specific surface markers: the T-helper (T_H) cells and the T-cytotoxic (T_C) cells (27). The early investigations of the role of each of these cells in graft rejection involved the use of the mixed leukocyte reaction (MLR) described above plus an additional test called the CML (cell-mediated lympholysis). After a leukocyte population is stimulated to proliferate in an MLR, the cells are transferred to a dish containing target cells, which share the MHC antigens of the stimulator cells. Radioactive chromium has been introduced into the cytoplasm of these target cells. If the stimulated leukocytes can kill the target cells, the radioactive chromium is spilled into the culture medium and can be detected. If the leukocytes cannot kill the targets, no radioisotope is released.

Through the use of these two tests, it was found that T-helper cells proliferated during the MLR but were unable to kill target cells in the CML, while T-cytotoxic cells did not proliferate during the MLR but were able to kill target cells (30). It was also found that if T-helper cells were removed from the population before stimulation in the MLR, the ability of T-cytotoxic cells to kill target cells in the CML was significantly reduced (31). Therefore, as their name implies, T-helper cells help T-cytotoxic cells to become capable of killing target cells.

For a number of years the MLR and CML were seen as *in vitro* correlates of graft rejection. It was assumed that T-cytotoxic cells actually destroyed the graft with the help of T-helper cells. As investigations of this system continued, an additional division of labor between these two cell populations became apparent. Investigators found that T-helper cells respond to differences in Class II antigens, and T-cytotoxic cells respond to differences in Class I antigens (32). It was hypothesized that T-helper cells were stimulated by Class II differences in the graft to proliferate and help the T-cytotoxic cells become capable of killing the graft. The T-cytotoxic cells required two signals for their activation: the Class I antigens on the surface of the stimulating cells and a signal from the stimulated T-helper cells.

Although the T-cytotoxic cells present in a rejecting graft are capable of killing target cells bearing the same MHC antigens as the graft (33), they are not the only killers in the population. Non-specific cellular destruction, especially apparent in the later stages of graft rejection (34), may be mediated by macrophages (35). In a type of immune reaction called a delayed-type hypersensitivity reaction (DTH), macrophages are induced to become potent killers by factors secreted by T-helper cells (or T_{DTH} cells which, to date, cannot be distinguished from T-helper cells).

There is growing evidence that the delayed-type hypersensitivity reaction may play a major role in graft destruction (36). Some of the most compelling evidence comes from studies in which rats and mice bearing viable MHC disparate grafts were deprived of their own immune systems by irradiation and then repopulated with T-helper cells, T-cytotoxic cells, or the two subsets together. Researchers found that reconstitution with both subsets or T-helper cells alone caused graft rejection while reconstitution with T-cytotoxic cells did not (37). Although we must exercise caution in interpreting these results (38), growing evidence indicates that the T-cytotoxic cell is not the only effector cell involved in graft destruction, and that the macrophage, activated by the T-helper cell, may play a major role (39, 40).

Cellular communication

Regardless of the mechanism, communication between the cells of the immune system is a necessary prerequisite for destruction of the graft. Dendritic cells must communicate with responding cells during the antigen recognition process. Similarly, T-helper cells must communicate with T-cytotoxic cells, macrophages, and even B-lymphocytes in the process whereby these cells become actively engaged in graft destruction. This communication probably involves some direct cell-to-cell contact mediated by the surface glycoproteins of the MHC. The cells also communicate through the release of soluble factors which have been shown to enhance the graft rejection process (41). For instance, T-helper cells secrete a factor called interleukin-2 (IL-2), which is required to generate the killing ability of the T-cytotoxic cell. This is presumably because it binds to specific receptors on the T-cytotoxic cell's membrane, giving this cell the signal it needs to become a killer (42). Additional evidence indicates that the presentation of antigen by the dendritic cell induces T-cytotoxic cells to become responsive to interleukin-2 (43).

The immensely complex process by which grafts are rejected provides an exciting model for cellular interaction in general. The use of cell-to-cell contact and soluble factors as a way of communicating may be a widespread method used by many types of cells in multicellular organisms. Indeed, it has been found that some non-immune cellular interactions appear to be controlled by the genes of the major histocompatibilty complex or by genes that are near the complex on the chromosome (44).

Summary: A Model

A simplified outline of the process of graft rejection is presented in Figure 2. The process begins with the presentation of foreign MHC antigens by a stimulator cell, probably a dendritic cell, which bears Class I and Class II MHC antigens. T-helper cells, T-cytotoxic cells, and B-lymphocytes are all stimulated by this antigen presentation. The T-helper cell is stimulted by the Class II antigens, the T-cytotoxic cell by the Class I antigens, and the B-lymphocyte by both. Before they

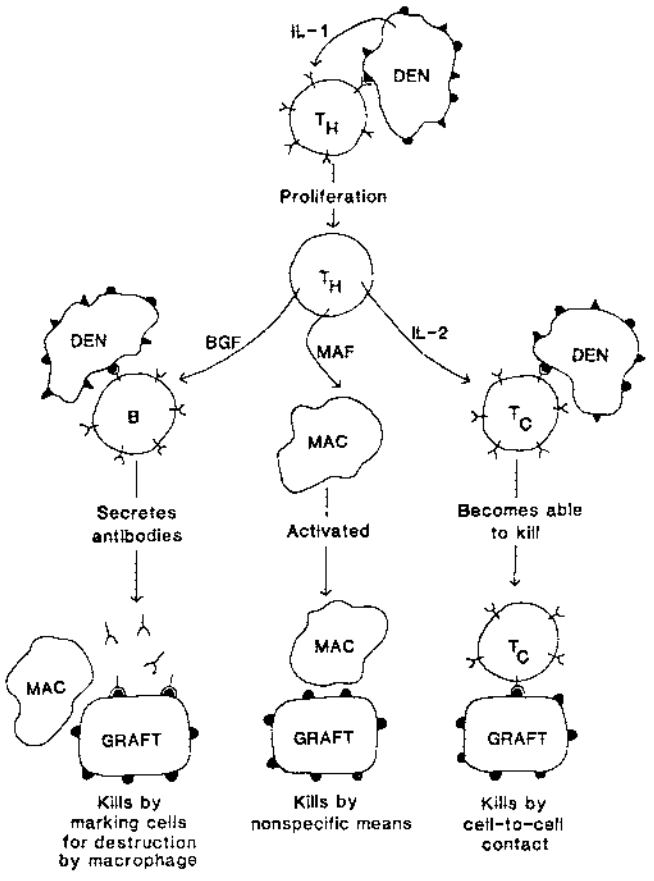

Figure 2. A model for the cellular interactions producing graft rejection. T_H = T-helper cell; T_C = T cytotoxic cell; MAC = macrophage; B = B lymphocyte; DEN = dendritic cell; IL-1 and IL-2 = Interleukin 1 and 2; MAF = macrophage activating factor; BGF = B cell growth factor; ● = Class I surface antigens; ▲ = Class II surface antigens.

can respond, however, each needs a second signal. The T-helper cell receives its second signal in the form of a soluble factor, called co-stimulator by Lafferty (45), which the dendritic cell secretes when the T-helper cell binds to it. This soluble factor is very possibly interleukin-1. Once it has received both signals, the T-helper cell rapidly divides and secretes a second soluble factor, interleukin-2. This factor provides the second signal to the T-cytotoxic cell, which can then develop the ability to kill by cell-to-cell contact cells bearing the original Class I antigens.

In addition to interleukin-2, stimulated T-helper cells also release macrophage activating factors, which cause macrophages to become active, though non-specific, killers. The T-helper cells also secrete B-cell growth factors, which cause stimulated B-lymphocytes to develop into cells that secrete antibodies. The antibodies can then bind to the Class I antigens on the surface of the graft cells and mark them for specific destruction by an activated macrophage.

We are just beginning to clearly define the details of these cellular interactions. As investigations continue and more of these interactions are understood, our power to interfere with this process without harming the graft recipient will increase dramatically. There is hope that we can develop procedures through this research that will make organ transplantation a therapeutic alternative for the treatment of many life-threatening diseases.

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