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Continuous Medical Education

Immunobiology of transplantation

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INTRODUCTION

Current knowledge of the response to an allograft is based on our understanding of the immune response to any exogenous antigen (Figure 1). The key cells involved in the immune response to an allograft are dendritic cells, macrophages, and lymphocytes. Lymphocytes can be divided into a number of functional populations. The thymus-derived (T) lymphocytes can be broadly divided into helper T lymphocytes (T_H or CD4+), characterized by the expression of the CD4 molecule, and cytotoxic T lymphocytes (T_C or CD8+), characterized by the expression of the CD8 molecule. Bone-marrow-derived (B) lymphocytes differentiate into plasma cells which produce antibody in response to antigen stimulation. The T_H cells can be further subdivided into T_{H1} and T_{H2} lymphocytes based on the pattern of cytokines produced by the cells. T_{H1} cells produce IL-2 and γ-interferon, while T_{H2} cells produce IL-4 and IL-10[1]. These two subpopulations of T_H lymphocytes have the capacity to regulate each other's activity.

REGULATION OF THE IMMUNE RESPONSE

Role of the antigen-presenting cell

The interaction between T lymphocytes and antigen-presenting cells involves multiple T cell surface molecules and their counter-receptors expressed by antigen-presenting cells. As depicted in Figure 1, the receptors can be divided into five functional categories, including 1) the antigen-specific T cell receptor, 2) the CD4 or CD8 coreceptors, 3) the accessory or adhesion molecules, 4) the costimulatory molecules, and 5) the cytokine receptors. Relevant to transplantation, inhibition of T cell interactions with antigen-presenting cells has been shown to prolong graft survival, and there are either clinical or experimental studies showing increased survival by blocking each of the five categories of receptors[2-4]. The most successful example to date has been the monoclonal antibody OKT3, which recognizes the CD3 complex associated with the T cell receptor.

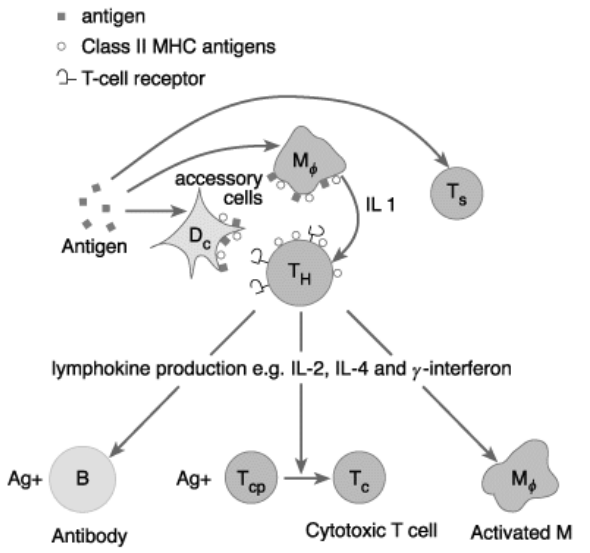

Figure 1. The immune response to an antigen. Antigen is presented to the T_H cell by the antigen-presenting cells of the host, either macrophages (Mφ) or dendritic cells (Dc). The antigen -presenting cells of the host must share the same Class II antigens with the helper T cells for the antigen to be recognized (MHC restriction). Once triggered, the helper T cell produces a number of lymphokines, such as IL-2 which is necessary for the maturation of the cytotoxic-T-cell precursor (TCP) to the mature TC cell, IL-4 which is required for the growth and differentiation of B lymphocytes into antibody-producing cells, and γ-interferon which has a number of effects including induction of major histocompatibility complex class II molecules on many different types of tissue. Furthermore, suppressor T cells (TS), which can damp down this response at several levels, may be activated (Quoted from Morris, 1994)[5].

T cell receptor recognition of antigen

Antigen specificity is determined by the T cell receptor, which recognizes processed antigen in the form of short peptides bound to an MHC molecule[6].

CD4+ and CD8+ T cell subsets

The two major subsets of T cells, the CD8+ cytotoxic T cells and CD4+ T helper cells, recognize the processed antigen on MHC class I and II, respectively. Class I MHC molecules are expressed by essentially all eukaryotic cells

except red blood cells and oocytes. In contrast, class II MHC molecules are expressed primarily on antigen-presenting cells, including dendritic cells, B cells, and macrophages. In addition, some cells, such as endothelial cells, express class II molecules after stimulation with lymphokines, such as IFN-γ[7].

Although not directly involved in antigen recognition, the CD4 and CD8 coreceptors bind to nonpolymorphic regions of the MHC molecules. Thus, the specificity of class I versus class II recognition is determined by whether a T cell expresses CD4 or CD8 in conjunction with the specificity of the T cell receptor. In addition, CD4 and CD8 increase the avidity of the T cell interaction with the antigen-presenting cell and are involved in signal transduction[8]. Blockade of the CD4 molecule on T helper cells has potent immunosuppressive effects in human cadaveric renal transplants[9].

Accessory molecules

A large number of T cell surface molecules originally termed adhesion molecules have been shown to increase the avidity of the interaction with the antigen-presenting cell. However, some of these receptors have also been shown to transduce signals and thus are more appropriately called accessory molecules. For example, CD2 stimulation has been shown to induce T cell activation[10].

T cell activation

T lymphocytes perform many regulatory and effector functions during an immune response. The activation of a T cell requires at least two signals[11]. One signal is transduced by the antigen-specific T cell receptor when it recognizes processed antigen bound to an MHC molecule on the surface of an antigen-presenting cell. The second signal is mediated by a costimulatory molecule that is independent of antigen. The best characterized costimulatory molecule is CD28, which is constitutively expressed on the surface of essentially all CD4+ and approximately 50% of CD8+ peripheral T lymphocytes[12]. CD28 binds a family of counter-receptors termed B7, which are expressed by antigen presenting cells. After activation, another costimulatory molecule termed CTLA4 is expressed by the T cell and binds B7 with a greater affinity than CD28[6].

Lymphokines and lymphokine receptors

T cell activation and proliferation are also modulated by soluble lymphokines, which bind to lymphokine receptors, such as the IL-2 receptor (IL-2R). Signaling through the T cell receptor and CD28 costimulatory molecule is sufficient to activate the T cell to produce and secrete IL-2; however, these signals alone are not sufficient to promote T cell proliferation. In fact, blockade of the IL-2R α-chain causes T cell arrest at the G1/S phase of the cell cycle[11]. Monoclonal antibodies to the IL-2R have been shown to be immunosuppressive in both animal models and clinical trials with the anti-Tac monoclonal antibody[3,13].

T_{H1} and T_{H2} cell subsets

The two subsets of CD4+ T cells defined in terms of cytokine production are the T_{H1} and T_{H2} subsets. Both subsets produce some lymphokines, such as IL-3 and granulocyte-macrophage colony-stimulating factor, whereas each subset produces a predominant set of lymphokines. The T_{H1} subset preferentially produces IL-2, IFN-γ, and TNF-α. In contrast, the T_{H2} subset preferentially produces IL-4, IL-5, IL-6, and IL-10. The net effect of producing each cytokine profile is differential regulation of the immune response. The T_{H1} subset is considered proinflammatory, promoting delayed -type hypersensitivity (DTH) reactions and cytotoxic T lymphocyte expansion. The T_{H2} subset is considered a helper of B cells[6].

In summary, cell-cell interactions between T cells and antigen-presenting cells can be divided into five classes of receptors. Examples of each class of receptor (antigen-specific T cell receptor, CD4 or CD8 coreceptor, costimulatory molecules, accessory molecules, and lymphokine receptors) are shown in Figure 1. Therapeutic or experimental manipulation of members of each class of receptor has been shown to prolong graft survival. The most effective in clinical studies to date has been the anti–T cell receptor monoclonal antibody OKT3[2,14-16].Experimental studies investigating the effect of blocking the costimulatory receptors have been particularly promising. The major benefit of this approach is that blockade of costimulation during the initial phases of transplantation may induce graft-specific tolerance without producing nonspecific immunosuppression[6].

GRAFT REJECTION

Mechanisms of rejection

The four syndromes of graft rejection are frequently overlapping and not totally distinct in clinical practice. Similarly, the classic categories

of cellular (lymphocyte) and humoral (antibody) mechanisms of rejection are now known to be interrelated[6].

Antibody-mediated rejection

The role of antibody in hyperacute rejection has been clearly established from multiple observations. First, there is a direct correlation between the existence of a positive pretransplant crossmatch, which detects anti–MHC class I antibody, and the development of hyperacute rejection[17]. Second, antigraft antibodies can be eluted from donor kidneys after hyperacute rejection. Third, the passive transfer of antigraft antibodies in experimental models can provoke hyperacute rejection. The most controversial is the role of antibody in chronic dysfunction. Because of the scanty cellular infiltrate in most cases of chronic rejection, it has been proposed by some authors that the process is mediated by antibody[6].

T cell–mediated rejection

In clinical transplantation, the role of T cells has been confirmed by the dramatic effects of anti–T cell antibodies, including OKT3, antithymocyte globulin, and antilymphocyte globulin; the effectiveness of which is often limited by the side effects of nonspecific immunosuppression[6].

Although T cells are most likely necessary to initiate both acute and chronic graft dysfunction, the relative contribution of the different T cell subsets has not been clearly elucidated. There is now substantial evidence that the "cytotoxic" CD8+ T cell subset can also produce lymphokines, including IL-2 and IFN-γ, at levels sufficient to promote autocrine growth. Thus, in some circumstances, CD8+ T cells can provide their own help and function independently of the CD4+ subset. Conversely, the "helper" CD4+ T cell subset can have cytotoxic effector function and mediate target cell lysis without the involvement of the CD8+ subset. Understanding these concepts, it is not surprising that either the CD4+ or CD8+ T cell subset can mediate graft rejection independently of the other subset[18,19].

An analysis of the role of lymphokines in graft rejection favors the hypothesis that the T_{H1} subset is the major mediator of acute graft rejection. In models of transplantation, the switch from a T_{H1}-type to a T_{H2}-type response has been shown to diminish acute rejection[20].

Delayed-type hypersensitivity-mediated rejection (DHT)

The DTH response is regulated by the CD4+ T cell; however, the effector cells are most likely macrophages and possibly CD8+ cytotoxic T cells. Consequently, the effector mechanisms may involve immunologically nonspecific mediators, including IFN-γ and TNF-α. Evidence that the DTH response is involved in acute graft rejection is based on a correlation between graft rejection and the ability to generate DTH responses to the same antigenic challenge[21].

Natural killer cell-mediated graft rejection

Natural killer cells are frequently identified in the infiltrating cells during acute graft rejection; however, the role of graft cell lysis by natural killer cells remains unknown[6].

Clinical syndromes of rejection

On the basis of the pathologic process and the kinetics of the rejection response, the rejection of renal allografts is commonly divided into four clinical syndromes: hyperacute, acute, accelerated, and chronic rejection.

Hyperacute rejection

Hyperacute rejection occurs within minutes to hours. A graft that initially becomes pink after vascular re-anastomosis rapidly becomes mottled, ischemic, and anuric. Histologic analysis shows fibrin and platelet thrombi, fibrinoid necrosis of the vessel walls, and usually the absence of a mononuclear cell infiltrate[22]. During hyperacute rejection, preformed antibodies bind to graft antigens on the vascular endothelium of the donor kidney. The antigens recognized by the antibodies can be HLA antigens (usually HLA class I), the AB blood group antigens, or the poorly defined endothelial or monocyte antigens. Specific antibodies, complement-mediated damage, and deposition of fibrin are the most important pathogenic effectors. Accurate pretrans-plantation blood and tissue typing can prevent most cases of hyperacute rejection; however, occasional cases of hyperacute rejection occur because of the endothelial or monocyte antigens, which cannot be evaluated by current methods of tissue typing[6].

Acute rejection

Episodes of acute rejection commence 5 to 7 days after transplantation and occur with decreasing frequency after 3 months. However, acute rejection can occur months to years after transplantation, frequently associated with the

withdrawal of immunosuppressive medications. Acute rejection is characterized by mononuclear cell infiltrates of the interstitium, which is composed predominantly of lymphocytes[6].

Most studies indicate that the major regulators of acute rejection are T lymphocytes[18,23]. Consistent with these observations, most episodes of acute rejection after renal transplantation can be reversed with immuno-suppressive agents directed at T lymphocytes, including high-dose cortico-steroids and the OKT3 monoclonal antibody. However, the clinical diagnosis of acute rejection is not homogeneous and in some cases probably involves a combination of both cellular and humoral mechanisms including cell-mediated cytotoxicity by CD8+ cytotoxic T cells, DTH reactions induced by CD4+ T cells, and in some cases antibody-mediated damage[24].

Accelerated rejection

Aggressive episodes of rejection occurring within 5 to 6 days after transplantation and differentiated from hyperacute rejection by the lack of an immediate onset are termed accelerated rejection and are thought to be caused by prior sensitization to antigens expressed by the graft. The kinetics of accelerated rejection are consistent with a memory or secondary immune response. Prior exposure to the donor graft antigens has been attributed to blood transfusions, pregnancy, and previously rejected grafts. The most important risk factor for accelerated rejection is clearly prior allograft loss[25]. The principal finding on pathologic examination is fibrinoid necrosis of the small vessels[26], which is consistent with a recipient antibody–mediated process. However, there is evidence that cell-mediated immunity may be responsible for some cases of accelerated rejection[6].

Chronic dysfunction

Most cases of graft loss due to rejection occur within the first 3 to 6 months after transplantation; however, a steady rate of attrition continues months to years after transplantation and is commonly attributed to chronic rejection, which is more appropriately termed "chronic dysfunction" because of the multifactorial pathogenesis of decreased function. Evidence that this process is, at least in part, immune mediated is based on the observation that the half-life of renal allografts in HLA-identical grafts is 25 years compared with 8 years with cadaveric donors. However, the immune mechanisms of chronic rejection remain poorly understood. Biopsy results usually show a mild to moderate lymphocyte infiltration that is inconclusive in terms of supporting a cell-mediated process. In some cases, graft-specific antibodies have been detected[27]. Thus, the role of cellular versus humoral mechanisms remains undetermined. The best predictive factor for chronic rejection is the occurrence of episodes of acute rejection.

Table1. Methods of immunosuppression in clinical use.

Method	Mechanism
Cyclosporine/ FK-506	Blocks NFAT activation in T cells and transcription of IL-2 and other cytokine genes.
Rapamycin	Blocks IL-2 signaling; causes T cell cycle arrest
Mycophenolate mofetil	Blocks lymphocyte nucleotide synthesis and cell activation
Corticosteroids	Blocks macrophage cytokine production
Anti-CD3	Enhances clearance of T cells or blocks surface CD3 function
Anti-CD25	Blocks IL-2 activation of T cells; clearance of T cells; clearance of activated T cells

IL-2: interleukin-2, NFAT: nuclear factor of activated T cells (Quoted from Abbas et al, 2000)[28].

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