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Historical Review

Immunology of Hepatic Allograft Rejection and Specific Aspects of Immunosuppression: Historical Review

Ayman Zaki Azzam*

Faculty of Medicine, Alexandria University, Alexandria, Egypt

***Corresponding Author:** Ayman Zaki Azzam, Faculty of Medicine, Alexandria University, Alexandria, Egypt.

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Liver transplantation has become a recognized and effective form of therapy for patients with end-stage liver disease [1].

The transplantation of an organ from a member of one species into a member of the same species (allo-transplantation) elicits an allogenic (non-self) immune response directed at the foreign antigens expressed on the donor organ tissues [2]. This immune response can be part of the innate immune system or the adaptive immune system [3]. The former system reflects the evolutionary experience of our species with the environment. It consists of antibodies, complement, natural killer (NK) cells, macrophages, and neutrophils [4]. The adaptive immune response reflects a finely tuned specific responses orchestrated by macrophage T-and B-cell interactions [5]. The main targets of the adaptive response are the major histocompatibility complex (MHC) antigens designated as human leukocyte antigens (HLA) in man [6]. In addition, immune responses are directed toward minor histocompatibility antigens, which are derived from other polymorphic molecules that differ between donor and recipient [7].

Rejection has been divided into hyperacute, acute and chronic types [8] (Table 1) Hyperacute responses occur within minutes to hours. They are antibody and complement mediated and are generally irreversible [9]. Acute rejection is cell mediated. It occurs over a period of days to months and can be reversed using a variety of currently available drugs [10]. Chronic rejection generally occurs over a span of months. It is unresponsive to current therapy and continues to be a source of graft loss [11].

Type	Time of onset	Mechanism	Clinical outcome
Hyperacute	Minutes to hours	Anti-α-Gal, complement, platelets, thrombosis	Fatal
Acute	Days to weeks	T cells, macrophages, natural killer cells, B cells	Reversible
Chronic	Weeks to years	T cells, B cells, macrophages	Irreversible

Table 1: Hepatic allograft rejection.

Immune mechanisms

As a part of the host's immune responses, there are both innate and adaptive immune responses. Innate immunity has evolved over time to deal with noxious agents in a rapid manner. In general these responses consist of both humoral (antibody, complement, coagulation) and cellular elements (neutrophils and macrophages) [4]. In contrast, a second learned or adaptive immune response has evolved that deals with the recognition of specific antigens via T- and B-cell receptors [5]. Both systems are involved in transplantation. With harvesting of an organ, leading to damage from ischemia and perfusion, the innate immune system is evoked [12]. In classic transplantation rejection, the adaptive immune system is activated, which leads to cellular and humoral immunity (rejection) directed against transplantation antigens in a highly selective manner [5].

Relationship between injury and rejection

During the process of organ harvesting, tissue injury occurs, which leads to the expression of molecules not normally expressed on the surface of tissues [13]. These "neo" antigens can elicit three types of immune responses. The first is the initiation of innate responses that consists of both cellular and humoral elements, including neutrophils, macrophages, cytokines, complement, and coagulation proteases. The second and third responses constitute the adaptive immune response leading to production of specific T- and B-cell repertories (Table 2).

Type	Components	Target
Innate immunity	Macrophages, neutrophils, complement, coagulation cascade, NK cells, antibodies	Bacteria, xenoantigens
Adaptive immunity	T cells (T_H1, T_H2, CTL), B cells, macrophages, dentritic cells, chemokines, cytokines	Viruses, alloantigens

Table 2: Components of host immune response.

NK, natural killer; CTL, cytotocic T lymphocyte

The cell-mediated immunity

In general, recipient T cells (CD4) recognize donor HLA class II antigens in the transplanted organ and are subsequently activated to proliferate, differentiate, and secrete cytokines [14]. These cytokines further increase the expression of HLA class II antigens on the vascular endothelium, stimulate B cells to produce high-titered and high-affinity antibodies against the allograft, and arm cytotoxic T cells, macrophages and NK cells.

The nature of the alloantigen

The MHC locus on chromosome 12 encodes for molecules that are the primary target for the alloresponse [15]. The MHC encodes for two major classes of proteins: HLA class I and HLA class II. Class I molecules are expressed on the surface of all nucleated cells in the body, although at different densities, whereas class II molecules are exclusively expressed on B cells and cells of the macrophage lineage. Class II expression can be unregulated in a number of cell types, including the vascular endothelium, epithelium, and T lymphocytes.

MHC class II molecules present exogenous antigens to CD4+ T helper cells, leading to their activation as measured by cytokine production and the production and secretion of antibodies by B cells. In contrast, endogenous antigens are presented in concert with MHC class I molecules to cytotoxic CD8+ T cells, resulting in elimination of viruses and tumor cells [16]. The MHC is highly polymorphic, allowing for collective immunity against pathogens.

Antigen presenting cells

Allograft presentation is accomplished by only a few specialized antigen-presenting cells (APCs). These APCs include dentritic cells, macrophages, B cells, and endothelial cells [17]. The most distinguishing feature of APCs is their unique display of costimulatory adhesions molecules. The adhesion molecules serve as ligands for counter-receptors on T cells. In addition to the expression of costimulatory molecules, other factors that influence APC function are the immune status of the responding T cell (naïve versus memory) and proinflammatory mediators that may be present at the site of APC-T cell contact [18].

When T cells encounter antigenic peptides displayed by component APCs, they are activated to produce lymphokines, which allows them to acquire cytolytic activity and ultimately to proliferate. In general, CD4+ T cells survey peptides displayed by MHC class II molecules, whereas CD8+ T cells survey peptides displayed by MHC class I molecules. Proinflammatory cytokines such as IL-4 and interferon-γ influence the result of T-cell activation, including the pattern of cytokines secreted and the activity of cytolytic T cells.

Direct and indirect allorecognition

It has been proposed that two distinct routes of allorecognition exist [17]. In the first, the direct pathway, T cells recognize intact allo-MHC antigens on the surface of circulating donor cells. In the second, the indirect pathway, T cells recognize processed alloantigens in the context of self antigen-presenting cells [19].

The T-cell response that results in early acute cellular rejection is caused mainly by the direct allorecognition pathway. T cells derived from the direct pathway constitute as many as 5% to 10% of the total T-cell peripheral pool. This strong response is due to the high density of MHC molecules on the donor graft and the large number of different peptides.

In the indirect pathway, donor alloantigens are shed from the graft, ingested by host antigen-presenting cells, and presented to CD4+ T cells. These activated T helper cells then secrete cytokines

and provide necessary signals for the growth and maturation of effector cytotoxic T cells and B cells. Indirect presentation is important in maintaining and amplifying the rejection response, especially in chronic rejection [20].

T-cell recognition

The T cell receptor (TCR)

Antigen specificity in allograft rejection is provided by clonally restricted T- cell receptors [21].

Coreceptors (CD4 and CD8)

CD4 binds to the β_2 segment of the MHC class II molecules, whereas CD8 interacts with the α_3 segment of class I molecules. Both CD4 and CD8 bind to cytoplasmic tyrosine kinase Lck, which brings Lck into close proximity with the TCR complex, where it acts early in the signal transduction pathway of activation of T cells. Later in the activation process, the CD4/Lck complex is anchored to TCR complex. This process increases the avidity of the TCR-MHC interaction and increases the signaling process. CD45 is critical to T–cell receptor signaling.

T-cell activation

Following the engagement of the TCR, tyrosine phosphorylation of many proteins occur. Phosphorylation of phospholipase C-γ-1 increases its activity and induces cleavage of phosphatidylinositol bisphosphate, which leads to the production of the second messengers inositol 1, 4, 5-trisphosphate and diacylglycerol. Inositol 1, 4, 5-trisphosphate induces a sustained in intracellular calcium, whereas diacylglycerol activates protein kinase C. These two signals together induce and activate DNA binding factors needed for IL-2 gene transcription. The rise in intracellular calcium activates a calcium-dependant serine-threonine phosphatase, calcineurin, which modifies the constitutively expressed nuclear factor of activated T cells (NF-AT), dissociating its inhibitor (I-κB) and thus allowing it to translocate to the nucleus, where it induces transcription of IL-2. Cyclosporine and tacrolimus (FK506) bind to cytoplasmic proteins (immunophilins), which bind to calcineurin and inhibit its activation, thus preventing NF-AT cell function and IL-2 transcription [22].

Costimulation

For maximal IL-2 production by T cells, antigen-presenting cells must also provide costimulatory signals. There are a number of costimulatory molecules on APCs. The major costimulatory actively necessary for proliferation of T cells by IL-2 appears to be mediated by the interaction of CD28 on the T-cell surface with its ligands, members of the B7 family on APCs [23]. Engagement of the TCR in the absence of this costimulatory signal fails to induce an immune response, results in a state of anergy, and prevents transplant rejection [24]. In humans, more than 95% of resting $CD4^+$ cells and 50% of resting $CD8^+$ cells express CD28. Following activation, the expression of CD28 is markedly increased. CD28 is structurally homologous to the cytolytic T-lymphocyte antigen 4 (CTLA-4). The expression of CTLA-4 is restricted to activated T lymphocytes and delivers a negative second signal modulating T-cell activation.

T-cell differentiation

Once an allograft interacts with a T-cell receptor, activation of genes leads to the development of differentiated effector T cells. The protooncogenes c-myc and c-fos are transcribed rapidly following T-cell activation. The products of these early-activation genes in concern with the effects of ongoing signal transduction initiate the next wave of gene activation, including the transcription of IL-2 and the IL-2 receptor.

Subsequently, additional cytokines, including IL-3, IL-4, IL-5, IL-6, and interferon-γ, are produced. In response to these cytokines, and in particular IL-2 and IL-4, T cells take on differentiated functions that include immunoregulation and cytotoxisity. The genes coding for granzymes, perforins, and chemokines such as RANTES are then generated over the next 4 to 6 days. Within 7 to 14 days, late-activation molecules are produced, including the integrin supergene family.

CD4 T cells and cytokines

Activated $CD4^+$ T cells secrete an array of cytokines that modulate and amplify the immune response. $CD4^+$ T cells have been subdivided into T_H1 and T_H2 $CD4^+$T cells depending on the pattern of cytokine production. T_H1 cells predominately produce IL-2 and interferon-γ, whereas T_H2 cells produce IL-4, IL-5, IL-6, and IL-10 [25]. T_H1 and T_H2 cells develop from a common precursor (T_H0) and can crossregulate each other. Interferon-γ inhibits the production of T_H2 cells, whereas IL-4 and IL-10 inhibit the production of $T_H1$cells.

CD8 Tcells and cytotoxicity

$CD8^+$T cells, also known as cytotoxic T lymphocytes (CTLs), are able to kill cells of an allograft either by the secretion of granzymes and perforins or by the induction of apoptosis through the Fas/Fas ligand pathway [26].

Within activated CTLs are a number of cytolytic granules that contain a variety of cytolytic proteins, such as perforin, a complement-like protein, as well as a family of serine proteases called granzymes [27]. Perforins polymerize in the target cell membrane to produce large pores, leading to osmotic lysis of the cells.

Granzymes are thought to induce apoptosis by deregulating normal control processes within the cell. Both granzyme B and perforin transcripts are expressed in acute cellular rejection [28].

Leukocyte-endothelial cell interaction

The migration of leukocytes across the endothelium into the allograft can be divided into four distinct phases: tethering, triggering, tight adhesion, and transendothelial cell migration. Cellular adhesion molecules are cell surface glycoproteins involved in cell-cell and cell-matrix interactions. These molecules are critical for leukocyte adhesion to the endothelium transmigration, binding to target cells, and cytotoxicity. These main family members of the cellular adhesion molecules participate in immune and inflammatory processes: the immunoglobulin gene superfamily, integrins, and selectins [29].

The initial tethering of leukocytes to endothelium is mediated by the selectin family [30]. The rapid turnover of the selectins allows leukocyte-endothelial cell interaction to occur and can lead to further activation and tight adhesion.

Strong adhesion of leukocytes to the endothelium is mediated by intergrins [31]. Chemokines (chemoattractant cytokines) increase cell adhesion by activating the intergrins on circulating leukocytes. Five intergrins have been implicated as being important in lymphocyte-endothelial cell interactions: LFA-1, which binds intercellular adhesion molecule 1(ICAM-1) and ICAM-2 on endothelium, and VLA-4 which binds VCAM-1.

After integrin-mediated attachment is established, leukocytes can then migrate through the endothelium and basement membrane to enter the tissue. This transmigration process is dependent on integrins and chemokines. At the same time, T cells secrete metalloproteases that digest the basement membrane, thus allowing cells to enter the tissue.

Release of inflammatory cytokines from macrophages, including IL-1, TNF-α and interferon-γ, induces changes in endothelium such as increased expression of MHC class II molecules, including E-selectin and ICAM-1 [32].

Hepatic allograft rejection

Immune targets and responses

Rejection of the transplanted liver is traditionally classified into three types: hyperacute, or antibody-mediated, rejection; acute, or cellular, rejection; and chronic, or ductopenic, rejection. Each form reflects mobilization of a different pathway within the immune response and offers a distinct immunotherapeutic challenge. The hepatic allograft, however, is relatively resistant to progressive injury related to rejection, and organ loss attributable to drug-resistant rejection remains an uncommon occurrence following engraftment.

Hyperacute rejection

Antibodies reactive with donor antigens can have many different effects on an allograft: they can destroy it, enhance its survival, or have no effect on the function of an allograft [33]. The final determinants include the class, titer and specificity of the anti-donor antibodies, the timing of the response; the density and distribution of target antigens in the organ [34] and possibly, on the source of complement.

Humoral rejection of the liver has recently been defined [35] as a relatively uncommon form of allograft injury and subsequent dysfunction, primarily mediated by antibody and complement, occurring immediately (hyperacute) or during the first week (acute) after transplantation. The antibodies are either preformed antibodies or represent anti-donor antibodies that developed after transplantation. Humoral rejection, antibody mediated rejection and hyperacute rejection are considered as acceptable synonyms [35].

Antibodies directed at antigens expressed on the vascular endothelium are potentially the most destructive, since vascular injury interferes with the blood supply [33]. Antibodies included in this group are those reactive with the major ABO blood group and class

I MHC antigens, detectable in conventional blood typing and lymphocytotoxic crossmatch tests, respectfully.

The critical event in the effector phase of the humoral rejection appears to be antibody binding to the endothelium and subsequent complement fixation and activation. This results in direct endothelial damage, the formation of platelet-fibrin thrombi, initiation of the clotting cascade, subsequent microvascular thrombosis and arterial vasospasm, all of which act in concern to ruin the microvasculature, impair blood flow and eventually cause hemorrhagic necrosis.

Hyperacute rejection (HAR), a rare form of hepatic allograft rejection, is thought to be the result of the interaction of preformed recipient antibodies with transplanted liver. Either preexisting antibodies exist in sufficient titers to produce massive necrosis, or a brief stimulus by donor antigen is sufficient to stimulate preprogrammed B cells to generate an immediate rise in titer [36]. When present, HAR becomes evident within hours to days of transplant surgery, resulting in hepatocyte necrosis that leads to rapid allograft failure. The only effective treatment is urgent retransplantation [37].

The initial liver histopathology demonstrates sinusoidal congestion and hemorrhage [38]; subsequent examination reveals hepatocyte loss, largely mediated through ischemic injury [39]. Microvascular thrombosis is not generally recognized on routine histologic examination. The recipient antibodies produce damage through binding to endothelial cells, triggering activation and deposition of complement and activating the coagulation cascade. Massive fibrin deposition occurs, which, coupled with the production of vasospastic polypeptides, results in ischemia and further hepatocyte injury, ultimately resulting in organ failure with profound coagulopathy and hepatic encephalopathy [40]. Upregulation of endothelial cell adhesion molecule expression also occurs, promoting infiltration of leukocytes and increasing local cytokine release.

HAR is recognized to occur during liver transplantation in humans in two situations: with ABO-incompatible grafts and in the presence of preformed, donor-specific, lymphocytotoxic antibodies [41]. These antibodies, which reacts against allogenic HLA class I antigens, play an important pathogenic role in renal allograft rejection; however, their role in liver transplantation is less certain. For this reason, and because of practical considerations, crossmatch results have largely been ignored in liver transplantation [42]. The well-known resistance of the liver to humoral rejection has provided important insights about the pathophysiology of humoral rejection. Secretion of soluble MHC class I antigens by the liver, Kupffer cell phagocytosis of cytotoxic antibodies, complement, immune complexes and activated platelet aggregates; the dual hepatic blood supply through the hepatic artery and portal veins and the unique hepatic sinusoidal microvasculature, which is devoid of a conventional basement membrane [43] have all cited as explanations for the liver's ability to withstand the impact of pre-formed anti-donor antibodies much better than other organs.

ABO incompatible

The first signs of serious liver injury often develop in the operating room after vascular re-anastomosis and before abdominal closure [44]. The liver usually reperfuses uniformly and produces bile, but within minutes or hours becomes hard and swollen before bile flow slows or stops altogether. An inordinate need for platelets and difficulty in achieving hemostasis signal the initiation of an intrahepatic consumptive coagulopathy [45]. However, the intraoperative events are rarely serious enough to abort the procedure or undertake immediate retransplantation. An unexplained rise in liver injury tests during the first several posttransplant days, refractory thrombocytopenia, hypocomplementemia and symptoms signal the possibility that humoral rejection is occurring [45]. At this point, hepatic angiography is often obtained to investigate the cause of the unexplained allograft dysfunction. In the typical case, it shows segmental narrowing, or a "sausage-like" appearance [44] and/or diffuse luminal narrowing with poor peripheral filling. These are signs indicative of immunologically-mediated arterial vasospasm.

Unfortunately, in conventionally treated recipients of ABO incompatible organs the marked rise transaminases is followed in 60%-70% of cases by synthetic function failure, subsequent wound site bleeding and other systemic signs of hepatic failure, that necessitate retransplantation [44]. Those that survive the early insult are more prone to the development of biliary tract strictures late after transplantation [46].

ABO compatible

Lymphocytotoxic antibodies in general, cause less serious injury than the isoagglutinins [45]. In addition, the ability of various lymphocytotoxic antibodies to effect graft damage greatly varies, which appears to be related to the antibody titer, specificity and class [45]. The IgG class reportedly cause the most damage [45].

In general, the higher the titer of IgG anti-MHC antibodies detected on the routine crossmatch before transplantation [47] the more likely the patient will encounter significant difficulties during and after the operation [45].

If allograft failure does not occur in a positive crossmatch patient, acute rejection, manifest as cellular infiltration of the liver, usually becomes evident within 5-7 days of transplantation [48]. This makes the cause of injury and dysfunction more obvious. If the allograft survives the early post-operative injury, long term sequela of an early humoral insult from isoagglutinins or lymphocytotoxic antibodies can include: biliary sludge and structuring with obstructive cholangiopathy, and obliterative arteriopathy and loss of small bile ducts, or chronic rejection [49].

The International Panel suggests that the minimal diagnostic criteria are: rapid onset liver dysfunction with histologic features of ischemic necrosis and predominantly neutrophilic infiltrates, in the absence of other clearly defined causes of ischemia or infarction. The diagnosis is strengthened if neutrophilic or necrotizing arteritis is present, if immunoglobulin deposits can be demonstrated in the liver, and if preformed anti-donor antibodies are found. Technical and preservation-related causes of ischemia infarction should be reasonably excluded [35].

Acute rejection

Acute rejection (AcR), also known as cellular or reversible rejection, is typically first seen 5 to 7 days following transplantation; the majority of episodes occur within 90 days of transplant surgery [50]. Depending on whether protocol liver biopsies are carried out, AcR is seen up to 75% of liver transplant recipients [51]. Although the clinical presentation is quite varied, it is typically characterized by a rise in the canalicular enzymes (alkaline phosphatase, γ-glutamyltransferase) and bilirubin, with a less substantial increase in the aminotransferases. It may, however, present as jaundice with significant transaminase elevations. Diagnosis is by liver biopsy, with three characteristic findings noted on histopathological examination: (a) portal infiltration with expansion of the triads with a variety of cells, including predominantly lymphocytes; (b) bile duct invasion and injury; and (c) portal venous endophlebitis [52].

AcR is usually responsive to intravenous steroids alone or in conjunction with OKT3 and rarely results in graft loss. Steroid- and OKT3- unresponsive cases may benefit from switching cyclosporine to tacrolimus (or vice versa).

The targets of activated lymphocytes in AcR are the bile duct epithelial cells (BEC) and the endothelium of the veins and arteries within the liver. Direct hepatocyte involvement appears to be uncommon, particularly early. The portal infiltration contains activated lymphblastoid cells, both T cells and B cells, plasma cells, and, in lesser numbers, all other leukocyte populations. $CD4^+$ cells are prominent and are thought to be the primary source of cytokines, which then acts to upregulate HLA expression, increase cytotoxic T lymphocyte differentiation, and increase alloantibody production [53]. In the early phase of AcR, HLA class I-specific alloreactive T cells predominate; a mixture of class I-specific and class II –specific T cells is present in later phases [54].

Normal hepatocytes constitutively express small amounts of HLA class I antigens, while exhibiting virtually no class II antigen expression [55]. This pattern is also seen in BEC and endothelial cells. During early episodes of AcR, HLA class I and II expression are both enhanced [56]. The mechanism of cell injury and death in AcR appears to be via accelerated apoptosis. The incidence of apoptotic hepatocytes roughly parallels the severity of acute rejection, although their injury probably occurs through indirect mechanisms. However, injured bile duct epithelial cells also display ultrastructural changes consistent with apoptosis, and it has been proposed that BEC apoptosis is predominant mechanism of cell injury and death in AcR, whereas hepatocyte apoptosis assumes primary importance in chronic rejection [57].

Chronic rejection

Chronic rejection (CR), often labeled with more useful term ductopenic rejection, is first seen a few weeks following transplantation, and may be diagnosed years later [58]. It is characterized by an ischemic injury to the bile ducts resulting in duct paucity, and is often considered one of the many “disappearing duct” syndromes [59]. Liver biochemistry is typically cholestatic, with little evidence

of necroing flammatory activity. Response to therapy is variable and usually poor, and the disease progresses, often indolently, to allograft failure that necessitates retransplantation. Fortunately CR is uncommon.

An infiltrate is often noted early in CR, composed predominantly of activated CD8+T lymphocytes. As duct necrosis evolves and duct paucity develops, the infiltrate resolves. A vasculopathy is also present, with intimal thickening and total or subtotal occlusion of hepatic arterial branches, resulting in ischemic loss of BEC. This may not be apparent on routine liver biopsy because it may involve ducts that are located somewhat remotely from the affected portal triads. Thus, duct loss results from a combination of duct-specific immune responses and arterial ischemic injury [60]. Hepatocytes may be specifically targeted.

A number of risk factors for CR have been proposed. The majority of patients who go on to develop CR have had an episode of AcR. Other studies, however, have shown that a single episode of AcR, if adequately treated, may actually have a protective effect and improve long-term graft survival [61]. Clearly, retransplantation for CR is a significant risk factor for a subsequent development of further CR, lending credence to the notion that it is the recipient, rather than the donor, factors that predominate.

Immunosuppressive drugs

The immunosuppressive therapeutic regimens are intended to concurrently suppress the patient immune response to the transplanted allograft while preserving an adequate functional immunity to prevent the development of opportunistic infection and malignancy. The immunosuppressant agents have a narrow therapeutic window, and the patients frequently experience serious complications from overimmunosuppression or suffer from acute and chronic graft rejection from underimmunosuppression [62]. Continued development of immunosuppressive agents with greater immunopotency and specificity, and improved safety profiles, together with the development of improved immune monitoring methods, offers great promise in the management of the liver transplant recipient.

Corticosteroids are powerful anti-inflammatory agents that have been used to suppress the harmful effects of immune responses of autoimmune or allergic origin as well as those induced by graft rejection [30]. They were the first immunosuppressive agents used in solid organ transplant therapy, and they remain a cornerstone of many immunosuppressive regimens. Low doses of prednisone are a key component of maintenance post transplantation immunotherapy, whereas larger doses of both prednisone and methyl prednisolone are often used as first-line treatment for acute allograft rejection.

The precise mechanisms for steroid-induced immunosuppression have not been fully elucidated. The immunosuppressive properties of steroids are related to their ability to suppress antibody and complement binding and to reduce the synthesis of key immunomodulating cytokines, such as interleukin (IL)-2 and interferon-γ [63]. Additionally, steroids inhibit macrophages secretion of IL -1, a key element in antigen presentation and initiation of cute allograft rejection [64].

There are a number of adverse effects associated with their use, however, including fluid retention, weight gain, bone mineral loss, diabetes mellitus, and thinning of the skin. These agents continue to remain a mainstay in induction immunotherapy as well as in treatment of acute cellular rejection. They remain as one of the few agents that affect antigen presentation and macrophage activation.

Two cytotoxic agents commonly used as immunosuppressive agents are azathioprine (Imuran) an antimetabolite that acts as a purine analog, which is incorporated into cellular DNA and inhibits purine nucleotide synthesis and metabolism [64] and mycophenolate mofetil (CellCept). Both of these agents interfere with DNA synthesis and have their major pharmacologic effects on dividing cells, such as T and B lymphocytes. Thus acting early during the proliferative phase of cell cycle, inhibiting primary cell-mediated and humoral responses. The use of azathioprine is limited by a range of toxic effects on tissues in the body, which have in common the property of continuous cell division. These effects include decreased immune function, leucopenia, anemia, thrombocytopenia [65], damage to gastrointestinal epithelium [66] and hair loss. Mycophenolate mofetil is a more selective inhibitor of purine synthesis [67]. Its site of action is to inhibit inosine monophosphate dehydrogenase (IMPDH), an enzyme necessary for de novo purine synthesis in lymphocytes [68]. Its selectivity to lymphocytes results in fewer side effects than the use of azathioprine, but gastrointestinal toxicity (diarrhea), leucopenia, and thrombocytopenia have limited its usefulness.

The systematic study of products from bacteria and fungi has led to the development of new immunosuppressive agents, including cyclosporine A, a cyclic decapeptide derived from the fungus Tolypocladium inflatum Gams [69], tacrolimus (FK506) [70], a macrolide derived from the filamentous bacteria Streptomyces tsukabaensis, and rapamycin, a macrolide derived from Streptomyces hygroscopicus [71]. Cyclosporine A and tacrolimus block T-cell activation [72]. These include IL-2, whose synthesis by T cells is am important growth signal for T lymphocytes. The mechanism of action of cyclosporine A and tacrolimus is now well understood. Each binds to a different group of immunophilins: Cyclosporine A binds to the cyclophilins and tacrolimus to the FK-binding proteins (FKBP). These immunophilinis are peptidyl-prolyl cis-trans isomerases. The immunophilin-drug complexes inhibit the Ca2+-activated serine-threonine phoshatase calcineurin, which, once activated following T-cell receptor binding, dephosphorylates the cytosolic component of the transcription factor NF-AT, allowing it to migrate to the nucleus, where it induces transcription of the IL-2 gene [72].

Both Neoral (a microemulsion of cyclosporine A) and tacrolimus are effective immunosuppressive agents, but they have major toxicity profiles related to a narrow therapeutic window (efficacy dose versus toxicity dose). Trough levels for tacrolimus and C2 (levels 2 hours postadministration) for cyclosporine [73] have been used for monitoring these agents.

Rapamycin (sirolimus), like tacrolimus, binds to the FKBP family of immunophilins. However, the rapamycin-immunophilin-complex has no effect on calcineurin activity but instead blocks signal transduction pathway triggered by the ligation of IL-2 to the IL-2 receptor. It also inhibits lymphocyte proliferation driven by other growth factors, including IL-4 and IL-6.Recent evidence has suggested that rapamycin inhibits translation initiation by preventing formation of the cap structure present at 5` end of all cellular RNAs [74].

Antibodies and antlymphocyte preparations

Interfere with the immune response in a more specific way. Antilymphocyte preparations may be polyclonal or monoclonal.

Polyclonal antilymphocyte preparation

These may be antilymphocyte serum (ALS), antilymphocyte globulin (ALG), or antithymocyte globulin (ATG). These polyclonal preparations contain antibodies with much wider spectrum of activity than the monoclonal preparations. Although they are very effective, the risks of infection and, later, of malignancy are high.

Antibodies to the T-cells receptor

CD3, the T-cell receptor, plays a crucial rule in T-cell interactions and antigen recognition. Blockade of this receptor prevents signal transduction. Administration of antibodies to CD3 is effective in the treatment of established rejection.

OKT3

Is a monoclonal preparation containing antibodies directed against CD3.This agent is effective in lowering the total lymphocyte count and in the prevention and treatment of acute liver allograft rejection. Side effects include pyrexia, chest pain diarrhea wheezing, tachycardia, and hypertension. In addition, aseptic meningitis may affect up to 30% of recipients.

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Volume 2 Issue 4 June 2019