Welcome to the FIT Board Review Corner, prepared by Sarah Spriet, DO, and Tammy Peng, MD, senior and junior representatives of ACAAI’s Fellows-In-Training (FITs) to the Board of Regents. The FIT Board Review Corner is an opportunity to help hone your Board preparedness.

Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 17 (pages 359-369): Transplantation Immunology
Prepared by Kristen Dazy, MD, Scripps Clinic Medical Group, San Diego (California)

1. Which term best describes the type of graft which is transplanted between individuals of different species?
   a. Autologous graft
   b. Syngeneic graft
   c. Allogenic graft
   d. Xenogeneic graft

2. What is the primary molecule responsible for the strong rejection reaction seen in allogenic transplants?
   a. Major histocompatibility complex (MHC)
   b. Minor histocompatibility antigens
   c. Natural killer cells
   d. Host T cell receptor

3. Allogenic MHC molecules of a graft can be presented for recognition by the recipient’s T cells in two fundamentally different ways. Which of the following terms describes the process in which T cells of a graft recipient recognize intact, unprocessed MHC molecules in the graft?
   a. Transferred recognition
   b. Direct recognition
   c. Indirect recognition
   d. Uptake recognition

4. Indirect presentation of an alloantigen largely results in recognition by CD4+ T cells because the antigen is acquired by host APCs primarily through the endosomal vesicular pathway and is therefore presented by class II MHC molecules. Some antigens of phagocytosed graft cells appear to enter the class I MHC pathway of antigen presentation and are indirectly recognized by CD8+ T cells. Which of the following terms best describes this phenomenon of activation of CD8+ T lymphocytes?
   a. Autophagy
   b. Cross-trafficking
   c. Cross-presentation
d. Cross-immunity

5. Where does the majority of the activation of alloreactive T lymphocytes take place?
   a. Donor graft
   b. Donor lymphatic vessels
   c. Recipient lymph nodes
   d. Spleen

6. Which of the following molecules is found on APCs and serves as a costimulator of alloreactive T cells?
   a. B5
   b. B6
   c. B7
   d. B8

7. What is the name of the test that has been used clinically in the past to predict T cell-mediated graft rejection?
   a. Mixed lymphocyte reaction
   b. Graft versus host reaction
   c. Transplantation test
   d. Agglutination test

8. What is the primary mechanism of graft rejection once alloreactive T cells are stimulated via the indirect pathway?
   a. Cytotoxic T lymphocyte-mediated killing of graft cells
   b. Cytokine-mediated inflammation
   c. Antibody-mediated inflammation
   d. Immune complex-mediated inflammation

9. Hyperacute rejection begins within minutes to hours after transplantation and is mediated by which of the following mechanisms?
   a. T lymphocyte-mediated killing of graft parenchymal cells
   b. Fibroblast occlusion of blood vessels
   c. Immune complex deposition
   d. Preexisting antibodies to donor endothelial antigens

10. Which of the following is an example of hyperacute rejection?
    a. ABO blood group incompatibility
    b. HLA mismatch
    c. Graft vs. host disease
    d. Transfusion-related acute lung injury
Answers
A graft transplanted between individuals of different species is called a xenogeneic graft (or xenograft) and the molecules that are recognized as foreign on xenografts are called xenoantigens. The other answers described other types of transplanted grafts between the same individual (autologous), between two genetically identical individuals (syngeneic), and between two genetically different individuals of the same species (allogenic).

Transplants of most tissues between any pair of individuals, except identical twins, will be rejected because MHC molecules are so polymorphic that no two individuals inherit the same ones. The role of MHC molecules as the antigens that cause graft rejection is a consequence of the nature of T cell antigen recognition. Minor histocompatibility antigens typically induce weaker or slower rejection reactions than do MHC molecules but their relevance in clinical solid organ transplantation is uncertain.

In the case of direct recognition, intact MHC molecules displayed by cells in the graft are recognized by recipient T cells without a need for processing by host antigen presenting cells (APCs). A likely explanation is that T cell receptors (TCRs) have an inherent specificity for MHC molecules regardless of whether they are self or foreign. In the case of indirect recognition, allogenic MHC molecules from graft cells are taken up and processed by recipient APCs and peptide fragments of these allogenic MHC molecules are bound and presented by self MHC molecules.

This phenomenon is an example of cross-presentation or cross priming (see also Fig. 6-20), in which dendritic cells ingest antigens of another cell (i.e. the graft), and present these antigens on class I MHC molecules to activate (prime) CD8+ T lymphocytes.

It is believed that donor APCs migrate to regional recipient lymph nodes and present unprocessed allogenic MHC molecules to the recipient’s T cells (direct pathway). Host dendritic cells may also migrate into the graft, pick up graft alloantigens, and transport these back to the draining lymph nodes where they are displayed (indirect pathway). The connection between lymphatic vessel in allografts and the recipient’s lymph nodes is not made surgically and is likely established by growth of new lymphatic channels in response to inflammatory stimuli produced during grafting.

In addition to recognition of alloantigen, costimulation of T cells primary by B7 molecules on APCs is important for activation alloreactive T cells. Blocking this costimulation may therefore serve as a therapeutic strategy to inhibit graft rejection.

The response to alloreactive T cells to foreign MHC molecules can be analyzed in an in vitro reaction called the mixed lymphocyte reaction (MLR). The MLR was previously used clinically as a predictive test of T cell-mediated graft rejection, and as an in vitro model of graft rejection. Studies of the MLR were among the first to establish the role of class I and class II MHC molecules in activating distinct populations of T cells.
8. B, pages 367-368
Only CTLs that are generated by direct allorecognition can kill graft cells, whereas both CTLs and helper T cells generated by either direct or indirect alloantigen recognition can cause cytokine-mediated damage to grafts. CLTs that are generated by the indirect pathway are self MHC restricted and will not be able to kill the foreign graft cells because these cells do not express self MHC allogeneic peptides. Therefore, when T cells are stimulated by the indirect pathway, the principle mechanism of rejection is not CTL-mediated killing of graft cells but inflammation caused by the cytokines produced by the effector T cells.

Hyperacute rejection is characterized by thrombotic occlusion of the graft vasculature and is mediated by preformed antibodies in the host circulation that binds to donor endothelial antigens and activates complement which then promotes a number of changes within the graft endothelium to promote intravascular thrombosis.

10. A, pages 368-369.
The best known example of hyperacute rejection due to preexisting alloantibodies are those directed against the ABO blood group antigens expressed on red blood cells. This is seen in hemolytic disease of the newborn when the fetus has type A or B blood and is born to a mother with type O blood. Maternal alloantibodies directed against A and B antigens cross the placenta and result in direct hemolysis of the newborn’s red blood cells.
Review Questions

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By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 17 (pages 370-380): Transplantation Immunology
Prepared by Erin Kempe, MD, Nationwide Children’s Hospital, Columbus (Ohio), and Kara Wada, MD, Nationwide Children’s Hospital, Columbus (Ohio)

1. Histologic examination of a kidney allograft undergoing acute rejection would exhibit which of the following:
   a. CD4+ T cells
   b. Neutrophil infiltration
   c. Smooth muscle cell proliferation in blood vessels
   d. Thrombotic occlusion of graft vasculature

2. Matching which HLA type is most important for predicting the survival of kidney allografts?
   a. HLA-A
   b. HLA-C
   c. HLA-DP
   d. HLA-DQ

3. Hyperacute rejection of allografts is mediated by incompatibility of which antigen class?
   a. ABO blood group antigens
   b. HLA-A alleles
   c. HLA-DQ alleles
   d. RH antigens

4. Calcineurin inhibitors can be effective immunosuppressive medications for the prevention of graft rejection through which of the following mechanisms:
   a. Accumulation of metabolic toxins that kill lymphocytes
   b. Inhibition of mTOR
   c. Inhibition of NFAT activation
   d. Upregulation of IL-2 transcription

5. Individuals with the Bombay blood group lack which of the following antigens?
   a. H antigen
   b. O antigen
   c. Rh antigen
   d. Sialyl Lewis X

6. Acute transplant rejection can be treated by various modalities. Which treatment and mechanism are paired correctly?
   a. Anti-thymocyte globulin – depletes circulating T cells by activating complement or opsonizing for phagocytosis
   b. Anti-CD25 antibodies – bind to the IL-2 receptor and stimulate IL-2 signaling
   c. Anti-CD52 antibodies – deletes central B cell populations
   d. CTLA4-Ig – binds to CD28 on T cells preventing their interaction with APCs.
7. Which statement is most true about allograft rejection?
   a. Chronic rejection is always preceded by episodes of acute rejection.
   b. Arterial occlusion due to smooth muscle cell proliferation is dominant lesion in acute
      rejection.
   c. Acute rejection is managed by rapidly intensifying the immunosuppressive regimen and
      is more reversible than chronic rejection.
   d. Chronic rejection is characterized by Cd deposition in the vessels.

8. Which immunosuppressant drug inhibits growth factor mediated T cell proliferation by binding
   to FKBP and inhibits mTOR?
   a. Tacrolimus
   b. Sirolimus
   c. Mycophenolate mofetil
   d. Azathioprine

9. Graft versus host disease a serious and known complication of hematopoietic stem cell
   transplant and characterized by:
   a. Grafted T cells recognizing host alloantigens.
   b. A lack of involvement by NK cells
   c. A reaction against major histocompatibility antigens
   d. A minor cause of mortality among bone marrow transplant recipients

10. A first-time mother comes into your practice. She is worried because she is Rhesus antigen
    negative and read about erythroblastosis fetalis. What should you tell her?
    a. If the baby’s father is Rhesus antigen negative she will still need an anti-RhD antibody
       injection.
    b. She should be concerned about the development of erythroblastosis fetalis with her
       current pregnancy.
    c. Erythoblastosis fetalis is mediated by IgM antibodies.
    d. Erythoblastosis fetalis can be prevented by administration of an anti-RhD antibody
       injection within 72 hours of birth for the first Rh positive baby.
Answers

1. A, page 370, Figure 17.9.
Acute rejection can be cell-mediated through alloreactive CD4+ T cells, or antibody-mediated through the effects of alloantibodies binding to alloantigens on vascular endothelial cells. Hyperacute rejection is mediated by pre-formed alloantibodies binding to endothelial antigens resulting in thrombotic occlusion of the vasculature. Neutrophilic infiltration can sometimes be seen. Chronic rejection is mediated by intimal smooth muscle cell proliferation and fibrosis.

Matching HLA-A, HLA-B, and HLA-DR are most important for kidney allograft survival.

Hyperacute rejection occurs due to incompatible ABO blood group antigens, and is performed for most types of transplantation. HLA typing is done for grafts that can survive outside the donor for longer periods of time, such as in renal transplantation, and can help improve graft survival. Rh typing is important in prevention of erythroblastosis fetalis.

4. C, pages 372-373, Figure 17.11.
Calcineurin inhibitors such as cyclosporine and tacrolimus, block IL-2 dependent proliferation of T cells by preventing calcineurin activation of NFAT. Rapamycin exerts a similar effect by inhibiting mTOR which is required for transcription of other proteins important for cell survival and proliferation. Immunosuppressants like mycophenolate mofetil and azathioprine exert their effects through production of toxic antimetabolites.

The Bombay blood group occurs in patients who are unable to produce A, B, and H blood group antigens. This phenotype is seen in patients with LAD type 2.

ATG depletes circulating T cells, anti-CD25 binds to the IL-2R and blocks IL-2 signaling, anti-CD52 depletes peripheral T and B cells. CTLA4 antibody binds to B7 on APCs preventing them from interacting with CD28 on T cells.

Chronic rejection develops insidiously during months or years and may or may not be preceded by episodes of acute rejection. Arterial occlusion due to smooth muscle cell proliferation is dominant lesion in chronic rejection. Acute antibody mediated rejection is characterized by C4d deposition.

8. B, Figure 17-11.
Sirolimus (rapamycin) inhibits growth factor mediated T cell proliferation by binding to FKBP. FKBP then binds to and inhibits mTOR thus blocking proliferation.

GVHD is characterized by grafted T cells recognizing and damaging host alloantigens. NK cells are thought to play an important role in acute GVHD. The reactions occur against the minor histocompatibility antigens and GVHD is the principal cause of mortality among BMT recipients.
Erythroblastosis fetalis is a potentially lethal condition that occurs when Rh negative mothers become sensitized to Rhesus factor by an Rh positive baby typically at that time of delivery. Subsequent Rh positive babies can then develop RBC destruction via anti-Rh antigen IgG antibodies that cross the placenta. This is prevented by administration of an anti-RhD antibody injection within 72 hours of birth for the first Rh positive baby.