

BIO-479 Exercise 8

# Lecture 11 Recapitulation

# Genetic Basis of Histocompatibility

- Regarding the expression and inheritance of Human Leukocyte Antigens (HLA), which of the following statements is correct?
- 1, MHC Class I molecules are expressed exclusively on the surface of professional Antigen-Presenting Cells (APCs) such as dendritic cells and macrophages.
- 2, Due to the co-dominant expression of MHC genes, a heterozygous individual typically expresses six distinct MHC Class I isoforms on the surface of their nucleated cells.
- 3, The high degree of polymorphism in the MHC locus is generated by somatic recombination of gene segments within the individual's somatic cells.
- 4, MHC Class II molecules present peptides to CD8+ Cytotoxic T Lymphocytes (CTLs) to initiate the adaptive immune response.

# Genetic Basis of Histocompatibility

- A recipient receives a kidney transplant from a sibling. Genetic testing confirms that the donor and recipient are HLA-identical (perfectly matched for both MHC Class I and Class II alleles). Despite this, the graft is slowly rejected in the absence of immunosuppression. What is the primary immunological mechanism driving this rejection?
- 1, Hyperacute rejection caused by pre-existing natural IgM antibodies against donor blood group antigens.
- 2, Direct allorecognition, where recipient T cells bind with high affinity to the intact, donor-derived MHC molecules.
- 3, Indirect recognition of minor histocompatibility antigens, which are peptides derived from polymorphic self-proteins differing between the siblings.
- 4, Loss of tolerance due to the donor kidney lacking expression of inhibitory MHC Class I molecules (Missing Self hypothesis).

# Genetic Basis of Histocompatibility

- Regarding the inheritance and genetic organization of the Major Histocompatibility Complex (MHC), which of the following statements accurately explains why a sibling is often the preferred living donor?
- 1, Because MHC genes are located on different chromosomes, they segregate independently, increasing the statistical likelihood of a random match among siblings to nearly 75%.
- 2, The set of MHC alleles present on a single chromosome is tightly linked and inherited as a unit (haplotype); therefore, there is a 25% probability that a sibling will share both haplotypes and be fully HLA-identical to the recipient.
- 3, Siblings are preferred solely because they share "Minor Histocompatibility Antigens," whereas MHC identity is irrelevant due to the universal suppression of Class I molecules on kidney tissue.
- 4, MHC alleles are prone to high rates of somatic hypermutation; thus, family members are less likely to have diverged genetically compared to unrelated donors.
- 5, A sibling has a 50% chance of being fully HLA-identical (2-haplotype match) and a 50% chance of being a complete mismatch (0-haplotype match).

# Direct vs. Indirect Allorecognition

- In the context of "Direct Allorecognition," which of the following best characterizes the interaction between the recipient's immune system and the donor graft?
- 1, Recipient CD4+ T cells process donor MHC proteins into peptides and present them on their own self-MHC Class II molecules.
- 2, The response is characterized by a remarkably high frequency of responding T cells (up to 10%), as many clones can cross-react with the intact allogeneic MHC molecule.
- 3, This pathway is the primary driver of chronic rejection, resulting in gradual vessel occlusion and fibrosis over a period of years.
- 4, The activation of T cells in this pathway requires the donor cells to be stripped of their surface proteins, leaving only the peptide backbone visible to the recipient.
- 5, This mechanism is exclusively mediated by B cells producing isohemagglutinins against donor endothelial antigens.

# Direct vs. Indirect Allorecognition

- A specific limitation exists regarding CD8+ Cytotoxic T Lymphocytes (CTLs) activated via the "Indirect Allorecognition" pathway. Which of the following statements accurately describes this limitation?
- 1, CTLs activated via this pathway undergo immediate apoptosis due to the absence of co-stimulation from donor Dendritic Cells.
- 2, These CTLs are specific for donor peptides presented by recipient MHC molecules; therefore, they cannot directly bind to and lyse the graft cells, which express *donor* MHC.
- 3, Indirectly activated CTLs switch phenotypes to become regulatory T cells (Tregs), thereby suppressing the immune response rather than promoting rejection.
- 4, The Indirect pathway exclusively activates CD4+ T cells and is incapable of generating any CD8+ CTL response under any circumstance.
- 5, These CTLs can only recognize donor cells if the donor cells have been infected by a virus that downregulates MHC Class I expression.

# Direct vs. Indirect Allorecognition

- In the case of Indirect Allorecognition, what is the specific complex that triggers T-cell activation?
- 1, The recipient's TCR binds to an intact allogeneic (donor) MHC molecule expressed on the surface of a donor dendritic cell.
- 2, The recipient's TCR binds to a donor-derived peptide presented by a donor MHC molecule.
- 3, The recipient's TCR binds to a self (recipient) MHC molecule that is presenting a peptide derived from the processing of a donor MHC molecule.
- 4, The recipient's TCR recognizes carbohydrate side chains on donor endothelial cells, independent of any MHC molecule.
- 5, The donor's TCR recognizes host peptides presented on host MHC molecules.

# Effector Mechanism and Pathology of Rejection

- A patient undergoes a cardiac transplant. Within minutes of restoring blood flow to the graft, the organ becomes cyanotic and mottled. A rapid biopsy reveals widespread thrombosis and neutrophil infiltration within the graft vasculature. Which of the following best describes the origin of the specific effector molecules responsible for triggering this "Hyperacute" pathology?
- 1, They are high-affinity IgG antibodies produced by memory B cells that were primed during a previous viral infection that shared peptide homology with the donor MHC.
- 2, They are "natural" IgM antibodies, that cross-react with ABO antigens expressed on the donor endothelium.
- 3, They are acute-phase proteins (such as C-reactive protein) synthesized by the recipient's liver in response to the surgical inflammatory stress.
- 4, They are autoantibodies directed against ischemic neo-antigens exposed on the recipient's own endothelial cells during surgery.

# Effector Mechanism and Pathology of Rejection

- Chronic rejection remains the major cause of late graft failure and is histologically distinct from acute rejection. Which of the following molecular mechanisms best explains the unique pathological feature of "vessel occlusion" observed in chronic rejection?
- 1, The massive release of perforin and granzymes by CD8+ CTLs leads to the widespread apoptosis of endothelial cells and immediate vascular collapse.
- 2, Complement activation by alloantibodies leads to the formation of the Membrane Attack Complex (MAC) and lysis of the vascular wall.
- 3, Secretion of cytokines by CD4+ T cells stimulates the proliferation of vascular smooth muscle cells and fibroblasts, leading to intimal thickening and fibrosis.
- 4, Ischemia-reperfusion injury during transplantation causes a permanent metabolic defect in the graft endothelium, preventing vasodilation.

# Immunosuppressive Pharmacology

- Tacrolimus (FK506) and Sirolimus (Rapamycin) are potent immunosuppressive drugs that share the ability to bind to the intracellular immunophilin FKBP12. Despite this shared binding partner, their downstream effects on T-cell activation are fundamentally different. Which of the following statements accurately describes the molecular mechanism of the Sirolimus-FKBP12 complex?
- 1, It binds to the Mammalian Target of Rapamycin (mTOR) Complex 1, inhibiting the kinase activity required for Signal 3 (cytokine-driven proliferation) transduction and cell cycle progression from G1 to S phase.
- 2, It forms a ternary complex with Calcineurin, inhibiting its phosphatase activity and thereby preventing the nuclear translocation of the transcription factor NFAT. **FK506**
- 3, It competitively inhibits the binding of Interleukin-2 (IL-2) to the high-affinity IL-2 receptor alpha chain (CD25) on the surface of activated T cells. **Basiliximab**
- 4, It acts as an antimetabolite by inhibiting inosine monophosphate dehydrogenase (IMPDH), thus depleting the guanosine nucleotides necessary for DNA synthesis. **Mycophenolate Mofetil**
- 5, It enters the nucleus and binds to Glucocorticoid Response Elements (GREs), repressing the transcription of pro-inflammatory cytokine genes such as IL-1 and IL-6. **Corticosteroids**

- Consider a laboratory experiment using two inbred mouse strains: Strain A (H-2a) and Strain B (H-2b). These strains are crossed to produce an F1 (H-2a/b) hybrid generation. Which of the following experimental outcomes is genetically and immunologically correct?
- 1, A skin graft transferred from an F1 hybrid mouse to a parental Strain A mouse will be accepted because the recipient shares the 'a' haplotype.
- 2, T cells isolated from an F1 hybrid mouse will proliferate vigorously when cultured with irradiated APCs from Strain A in a Mixed Lymphocyte Reaction (MLR).
- 3, A skin graft transferred from a parental Strain B mouse to an F1 hybrid mouse will be accepted because the F1 recipient recognizes both 'a' and 'b' MHC molecules as “self”
- 4, A skin graft transferred from Strain A to Strain B will be rejected slowly because the rejection is driven solely by Minor Histocompatibility Antigens in this scenario.
- 5, Re-grafting a Strain B mouse with Strain A mouse skin (after it has already rejected a primary Strain A graft) will result in “first-set” rejection kinetics due to T-cell exhaustion

- Graft-versus-Host Disease (GVHD) is a major complication of Hematopoietic Stem Cell Transplantation (HSCT). Based on the pathophysiology described in the lecture, which of the following sequences best represents the "Recipient Conditioning" and "Donor T cell Activation" phase that initiates this disease?
- 1, Donor B cells produce antibodies against the recipient's ABO blood group antigens, leading to widespread complement activation and hemolysis.
- 2, Ischemia during the transplant procedure causes the donor stem cells to express "Missing Self" markers, triggering an attack by recipient Natural Killer (NK) cells.
- 3, Pre-transplant radiation/chemotherapy damages the recipient's intestinal mucosa, allowing bacterial LPS to trigger the release of pro-inflammatory cytokines (TNF-alpha, IL-1) that activate donor T cells.
- 4, The recipient's regulatory T cells (Tregs) become hyperactive and suppress the donor's immune system, preventing the engraftment of the new bone marrow.
- 5, Chronic stimulation of donor CD8+ T cells by recipient Minor Histocompatibility Antigens leads to the formation of fibrotic plaques in the recipient's coronary arteries (Allograft Vasculopathy).

- A patient awaiting a kidney transplant undergoes immunological risk assessment. The results are:  
1) Microcytotoxicity Cross-match is NEGATIVE. 2) One-way Mixed Lymphocyte Reaction (MLR) with the donor shows a very high Stimulation Index (high radioactive thymidine uptake). How should these results be interpreted clinically?
- 1, The negative cross-match indicates the absence of pre-formed antibodies, ruling out Hyperacute Rejection; however, the high MLR suggests a significant MHC Class II mismatch, predicting a strong T-cell mediated Acute Rejection response.
- 2, The high MLR indicates that the recipient has high titers of "Natural Antibodies" (IgM) against the donor, making Hyperacute Rejection inevitable despite the negative cross-match.
- 3, The results are contradictory; a negative cross-match is impossible if the MLR is high, as both tests measure exactly the same effector mechanism (CD8+ cell lysis).
- 4, The high MLR proves that the donor and recipient are HLA-identical siblings, but the negative cross-match suggests that the donor has a viral infection.
- 5, The patient can proceed with transplantation without any immunosuppression, as the negative cross-match is the only predictor of long-term graft survival.