

The Role of MHC Class I And Class II in Adaptive Immunity

Name: Hamid Hussain Wani Email: hamidwani44@gmail.com

Affiliation: Saraswati college of pharmacy, SGC Group, Gharuan-140413, Mohali, Punjab, India

ABSTRACT

Adaptive immunity depends on the major histocompatibility complex (MHC) proteins presenting antigens. Before being presented, peptides must be created from proteins that are either channelled or manufactured by the cell's own translational machinery.

entering the vesicular system of endo-lysosomes. Following a thorough search in secondary lymphatic organs, a sustained contact between a T cell receptor and particular pMHC complexes ultimately causes T cells to multiply and develop a particular cellular immune response. The structural characteristics of the binding groove of each unique MHC allele variant significantly influence the peptide repertoire that MHC proteins display after processing. Furthermore, by encouraging the binding of high-affinity antigens, two peptide editors—tapasin for class I and HLA-DM for class II—help to shape the peptidome that is shown. The mechanism of the catalysed peptide exchange for MHC class I and class II proteins is still up for debate, despite the abundance of biochemical and structural data, and it is unclear why some MHC allelic variants are more vulnerable to peptide editing than others. According to recent research, protein intermediate states have a significant impact on MHC allele-specific peptide presentation. This suggests that MHC dynamics have a significant impact on the occurrence of immunodominance and the emergence of autoimmune disorders.

Despite the different roles that MHC classes I and II play in adaptive immunity, we highlight the commonalities between their dynamics in this review of recent work that describes them from a theoretical and experimental point of view.

Keywords: HLA, protein dynamics, peptide exchange, tapasin, HLA-DM, major histocompatibility complex, antigen presentation, and adaptive immunity

INTRODUCTION

Our immune system depends on two classes of major histocompatibility complex (MHC) molecules, MHC class I and class II, which present antigens to functionally different T cell populations. Nevertheless, nothing is known about the cause of this crucial MHC class difference. Each of the class I and class II major histocompatibility complex (MHC) groups is a multigene family formed by gene duplications and subsequent diversifications, with

different individuals with different roles. By delivering antigens to T cells, the traditional MHC class I and class II molecules serve essential roles in our immune system. T cell receptors (TCRs) on CD8+ T cells receive peptide antigens from conventional MHC class I molecules, while classical MHC class II molecules provide peptide antigens.

responses to CD4+ T cells' TCR. Following their contact with the MHC molecular complex and peptide antigen, CD8+ T cells are crucial for the target's destruction.

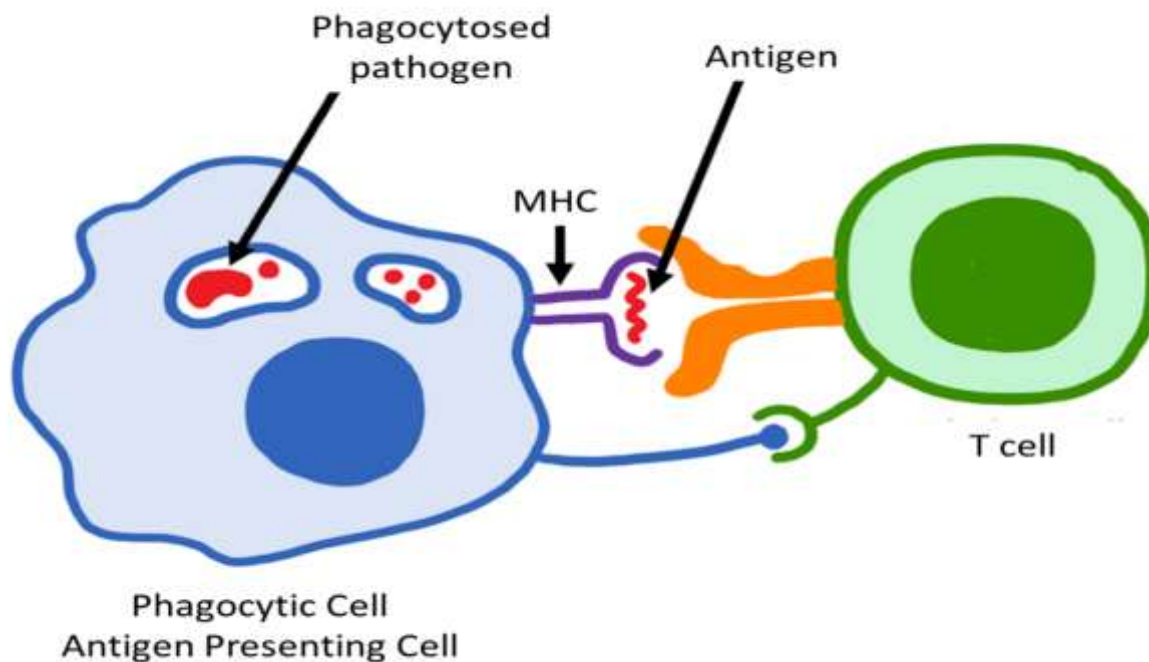
cells (such as tumour cells or virus-infected cells), but CD4+ T lymphocytes are essential for supporting or controlling immune cells that present antigens, such as B lymphocytes, which have the capacity to produce antibodies. Therefore,

there is a clear correlation between the MHC class divergence and our fundamental immunological processes. Though MHC research has been conducted for decades, there has been little advancement in our knowledge of the cause of this crucial MHC class difference.

Because they show antigens, Major Histocompatibility Complex (MHC) proteins are essential for adaptive immunity. Proteins must be converted into peptides before they can be shown. The translational machinery of the cell can either produce or channel these proteins enters the system of endo-lysosomes. After a protracted search in secondary lymphatic organs, a T cell receptor's prolonged engagement with particular pMHC complexes ultimately causes T cells to multiply and launch a particular cellular immune response.

The structural characteristics of the binding groove of each unique MHC allele variant significantly influence the peptide repertoire that MHC proteins display after processing. Moreover, two peptide editors—HLA-DM for class II and tapasin for class I—

II—promote the binding of high-affinity antigens, which helps to shape the peptidome that is shown. The mechanism of the catalysed peptide exchange for MHC class I and class II proteins is still up for debate, despite the abundance of biochemical and structural data, and it is unclear why some MHC allelic variants are more vulnerable to peptide editing than others.



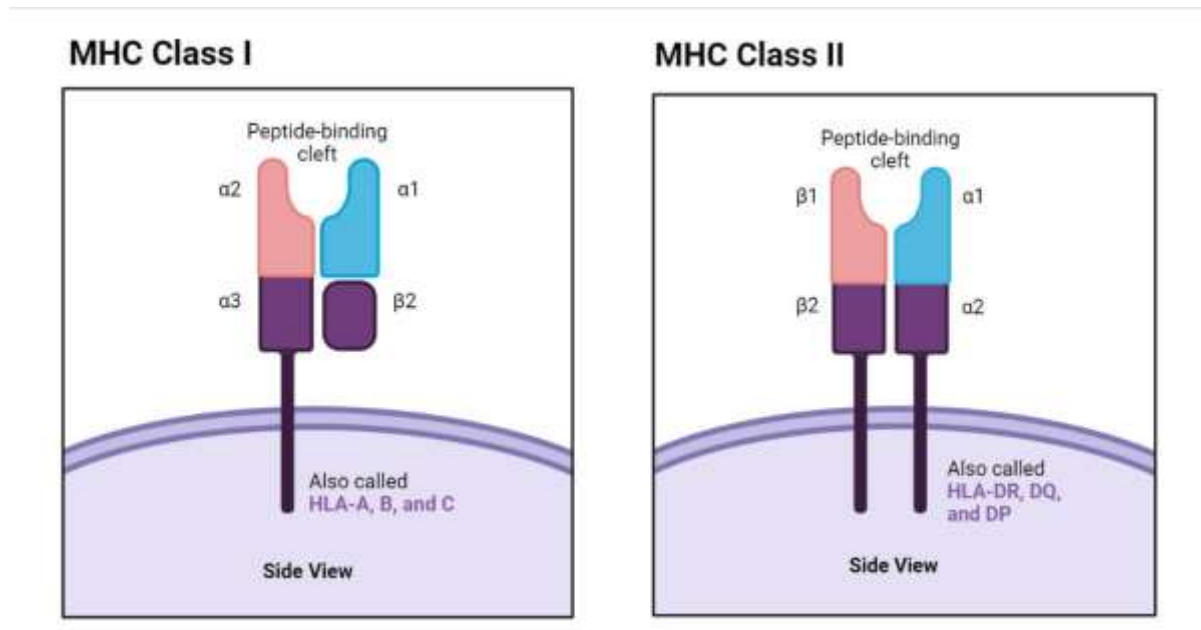
Antigen presentation. The purple complex in the image's centre is the Major Histocompatibility Complex (MHC). It has delivered the antigen for the APC's surface to display. T cell attachment and activation are facilitated by MHC (green).

Structure and Types of MHC

There are two primary classes of MHC molecules: Class I and Class II. Despite having different shapes and roles, both classes serve the same purpose in presenting antigens to T lymphocytes.

- **MHC Class I:** Nearly all nucleated cells express these molecules. They give CD8⁺ cytotoxic T cells endogenously produced peptides, usually from intracellular pathogens like viruses. A beta-2 macroglobulin chain and a heavy alpha chain make up an MHC Class I molecule. The groove for binding peptides is formed by the alpha chain.
- **MHC Class II:** Professional antigen-presenting cells (APCs), such as dendritic cells, macrophages, and B cells, are the main carriers of these molecules. They expose CD4⁺ helper T lymphocytes to exogenously generated peptides,

which are usually obtained from external pathogens. The alpha and beta chains of MHC Class II molecules each contribute to the peptide-binding groove.



MHC molecules that are not classical (HLA-E, HLA-G, and CD1)

The non-classical MHC-Ib family (e.g., HLA-E, HLA-G) and CD1 molecules, in addition to the classical MHC class I and II molecules, have specific functions in immune modulation and antigen presentation. While CD8 T cells are presented with peptides by classical MHC-I, these molecules have limited polymorphism and bind distinct ligands:

Through the CD94/NKG2A/B inhibitory receptor, HLA-E delivers leader peptides generated from classical MHC-I to natural killer (NK) cells, preserving NK cell tolerance to healthy cells (Braud et al., 1999).

In order to decrease immune responses and promote fetal-maternal tolerance, HLA-G, which is expressed in immunologically privileged locations such as the placenta, binds to leukocyte immunoglobulin-like receptors (LILRB1/2) on NK cells and macrophages (Adams & Luoma, 2013).

CD1 molecules bridge the gap between innate and adaptive immunity by presenting lipid antigens, such as mycobacterial glycolipids, to non-traditional T cells, such as NKT cells.

Beyond peptide presentation, these non-classical molecules broaden MHC's functional repertoire by highlighting their functions in immune evasion, tolerance, and reactions to non-protein antigens.

MHC's Function in Immune Responses

The immune system's capacity to differentiate itself from others and mount effective defences depends heavily on MHC molecules.

- Activation of T lymphocytes the peptide-MHC complex on the surface of APCs is recognized by T-cell receptors (TCRs), which then attach to it. The activation and development of T cells into effector cells depend on this recognition. After identifying peptides presented by MHC Class I, CD8⁺ T cells develop into cytotoxic T lymphocytes, which destroy infected cells. After differentiating into helper T cells in response to peptides presented by MHC Class II, CD4⁺ T cells mobilize other immune cells to help coordinate the immune response.
- Immune Surveillance: The immune system can keep an eye on the condition of cells thanks to MHC molecules. An immune response can be triggered by any modifications to the repertoire of presenting peptides, including those resulting from infection or cancer. This procedure is essential for identifying and removing cells that are transforming into cancerous cells or harbouring intracellular infections.

Intersection: Connecting Intracellular and Extracellular Immunity

Cross-presentation, in which foreign antigens (from viruses, malignancies, or vaccinations, for example) are shown on MHC class I molecules to activate CD8⁺ T lymphocytes, is a crucial deviation from the traditional MHC-I pathway. Immune surveillance against pathogens that do not directly infect APCs is made possible by this mechanism, which is mostly carried out by specialized dendritic cells (DCs) (Joffre et al., 2012).

- **Cytosolic Pathway: Mechanistic Pathways:**

The conventional peptide-loading complex (PLC) loads internalized antigens onto MHC-I after they are carried from endosomes to the cytosol and broken down by proteasomes.

For instance, CD8α⁺ DCs cross-present tumour antigens.

- **The Vascular Pathway:**

Endosomes or phagosomes process antigens, which are then loaded onto MHC-I without being broken down by proteases.

Example: Antigens produced from apoptotic cells are presented.

The Roles of MHC Molecules in Adaptive Immune Responses

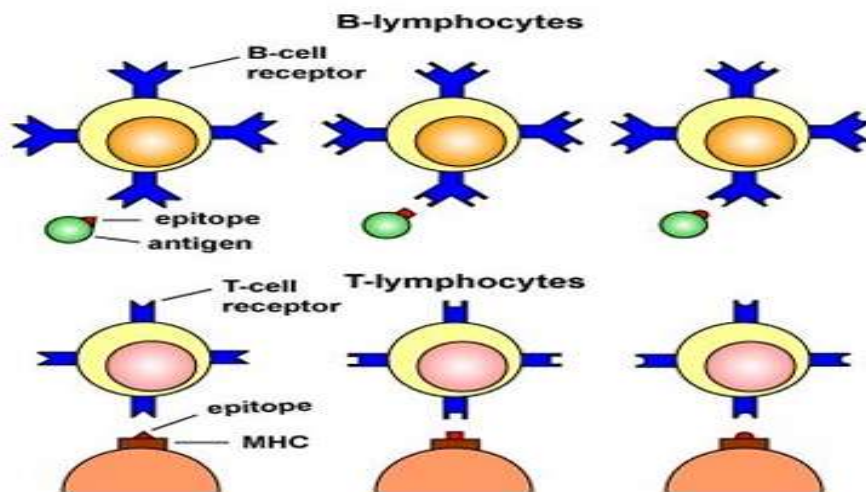
T-lymphocytes can distinguish between self and non-self by recognizing antigen epitopes thanks to MHC molecules. The T-cell receptors (TCRs) on T-lymphocytes can only identify epitopes, which are usually short chains of amino acids termed peptides, after they have been joined to MHC molecules. This is in contrast to B-cell receptors on B-lymphocytes, which can directly bind epitopes on antigens.

With many variants for each gene, the MHC genes are the most polymorphic in the human genome. A person expresses the alleles inherited from each parent because the MHC genes are co-dominantly expressed. This maximizes the quantity of MHC molecules that bind peptide for T-lymphocyte presentation. Furthermore, every MHC molecule has the capacity to bind at several distinct peptides, including both foreign and self-peptides. MHC molecules fall into two classes: MHC-I and MHC-II.

- T8 cells are presented with epitopes by MHC-I molecules.
- T4 cells are presented with epitopes by MHC-II molecules.

Both innate and adaptive immune responses result in the production of cytokines, which raise the expression of MHC molecules. MHC-I molecules are expressed more when cytokines like interferon-alpha, interferon-beta, interferon-

gamma, and tumour necrosis factor are present, whereas interferon-gamma is the primary cytokine that increases the expression of MHC-II molecules.



B- and T-lymphocytes have receptors on their surface that are specific to epitopes. B-cell receptors on B-lymphocytes can directly identify epitopes on antigens. T-lymphocytes possess TCR molecules, which only identify epitopes once they have been attached to bodily cells via MHC molecules.

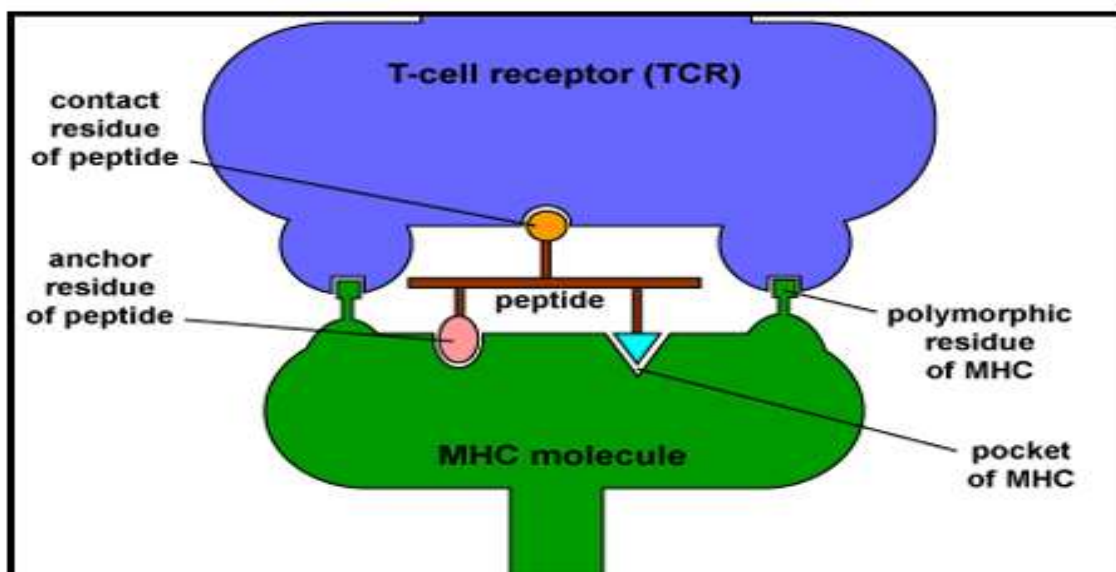
MHC-I compounds

The purpose of MHC-I molecules is to help the body identify tumour and contaminated cells so that cytotoxic T lymphocytes, or CTLs, can eliminate them. Effector defence cells called CTLs are produced from naive T8 lymphocytes. MHC-I molecules consist of:

- the body's nucleated cells.
- have a deep groove that is capable of binding peptide epitopes, usually from endogenous antigens and ranging in length from 8 to 11 amino acids.
- Give naive T8 lymphocytes and cytotoxic T lymphocytes with complementary-shaped T-cell receptors, or TCRs, MHC-I/peptide complexes.
- Certain antigen-presenting dendritic cells have the ability to cross-present foreign epitopes through the mechanism of antigens to MHC-I molecules, which will thereafter be presented to uninformed T8 cells.

Human cell cytosol contains proteins called endogenous antigens. The following are examples of endogenous antigens:

- a. proteins generated by viruses during their replication;
- b. proteins generated by intracellular bacteria, such as Chlamydias and Rickettsias, during their replication;
- c. Antigen-presenting cells and other proteins that have escaped into the cytosol from phagocytes' phagosomes;
- d. Cancer cells' tumour antigens; and
- e. Self-peptides from host cellular proteins.



A complementary T-cell receptor is bound by an MHC molecule with bound peptides. This diagram demonstrates how a T cell receptor (TCR) on a T lymphocyte's surface can identify one residue of an MHC molecule's bound peptide epitope and two polymorphism residues of an MHC molecule.

Cylindrical organelles known as proteasomes break down viral, bacterial, or tumour proteins into a range of peptide epitopes during the replication of viruses and intracellular bacteria within their host cell as well as during the replication of tumour cells. Proteases also break down the body's own cytosolic proteins into peptides.

Following their attachment to a groove of MHC-I molecules, these peptide epitopes are subsequently carried to the cell's surface, where they are recognized by a complementary-shaped T-cell receptor (TCR) and a CD8 molecule, which functions as a co-receptor on the surface of either a cytotoxic T-lymphocyte (CTL) or a naive T8-lymphocyte. The MHC molecule and the foreign peptide antigen are both recognized by the TCRs.

However, self-peptides attached to MHC-I are not recognized by TCRs. Normal cells are therefore not targeted and eliminated. To activate naive T8-lymphocytes, dendritic cells attach endogenous antigen epitopes to MHC-I molecules and present them to the cells.

A complementarily shaped TCR/CD8 on the surface of a naive T8-lymphocyte can recognize an MHC-I molecule with a bound peptide on the surface of antigen-presenting dendritic cells to start cell-mediated immunity. As will be covered later, some dendritic cells are also capable of cross-presenting foreign antigens to MHC-I molecules.

MHC-II compounds

Maintaining self-tolerance and initiating successful immune responses depend on class II Major Histocompatibility Complex (MHC-II) molecules presenting peptide antigens. The thymus's selection stage of T cell maturation marks the start of immunological tolerance to antigens shown on MHC-II molecules, which persists in the periphery. For positive selection in the thymus, CD4 T cells must engage with self-ligands supplied by MHC-II molecules. Additionally, tonic stimulation by MHC-II-peptide complexes in the periphery is necessary for CD4 T cell survival.

The development of T cells with T cell receptor specificities that are overtly reactive to the self is inhibited during the thymus's negative selection phase, while cells with borderline reactivity are guided into the CD4 T regulatory lineage.

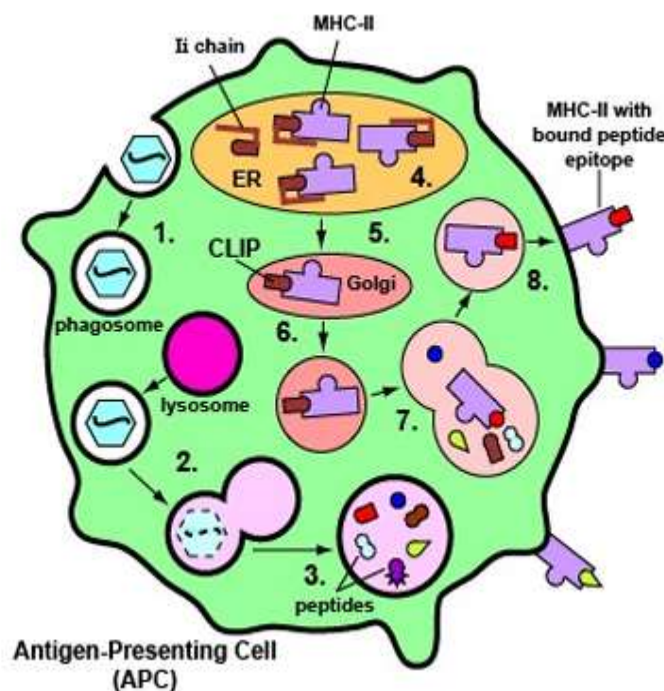
When antigen-presenting cells (APCs) release peptides that notify the adaptive immune system to launch a focused defence against invasive pathogens, a peripheral immune response is triggered. APC type, maturation status, and external environment all affect the entry of both foreign and self-antigens into the endo/lysosomal route, proteolytic processing, and peptide selection for presentation. Therefore, these parameters determine the MHC-II immunopeptidome, which is the set of peptides presented by MHC-II molecules.

MHC-II molecules are made to help T4 cells distinguish between self and non-self by recognizing foreign antigen epitopes. The molecules of MHC-II are

- ✱ produced by APCs, or antigen-presenting cells, which include B-lymphocytes, dendritic cells, and macrophages.
- ✱ have a deep groove that can bind peptide epitopes, usually from exogenous antigens, that are 10–30 amino acids long, but ideally 12–16 amino acids long. The peptides interact with the groove all the way along their length.
- ✱ Give naive T4 lymphocytes or effector T4 lymphocytes with a complementary shaped T cell receptor, or TCR, MHC-II/peptide complexes.
- ✱ Certain antigen-presenting dendritic cells have the ability to cross-present endogenous antigen epitopes to MHC-II molecules such that they can subsequently be presented to naive T4-lymphocytes.

Exogenous antigens, which include bacteria, fungi, protozoa, and free viruses, are antigens that enter the body from outside sources. Through phagocytosis, these foreign antigens get into B-lymphocytes, dendritic cells, and macrophages. A phagosome absorbs the microorganisms and subsequently merges with lysosomes. The phagolysosome becomes acidified after this union.

The phagolysosome's proteases are then activated by acidification, allowing the microbe's protein antigens to be broken down into a number of small peptides. Following their attachment to MHC-II molecules, these peptide epitopes are subsequently carried to the antigen-presenting cell's (APC) surface.



Certain infections, including *Leishmania*, *Mycobacterium leprae*, and *Mycobacterium tuberculosis*, can proliferate in macrophage endocytic vesicles without being eliminated by lysosomes. However, T4-effector lymphocytes known as T1 cells can activate these macrophages, which then employ intravesicular proteases to break down the pathogens' proteins into

peptides to be presented to passing MHC-II molecules en route to the cell surface.

Here, a complementarily shaped T-cell receptor and a CD4 molecule, a co-receptor, on the surface of a T4 lymphocyte can identify the MHC-II molecules with associated peptides. The cells the body utilizes to control humoral immunity and cell-mediated immunity are called T4-lymphocytes.

References

1. Janeway's Immunobiology – Murphy K, Weaver C. *Janeway's Immunobiology*. 9th ed. Garland Science; 2016.
2. Cellular and Molecular Immunology – Abbas AK, Lichtman AH, Pillai S. *Cellular and Molecular Immunology*. 10th ed. Elsevier; 2021.
3. Kuby Immunology – Punt J, Stranford SA, Jones PP, Owen JA. *Kuby Immunology*. 8th ed. W.H. Freeman; 2019.
4. Roitt's Essential Immunology – Delves PJ, Martin SJ, Burton DR, Roitt IM. *Roitt's Essential Immunology*. 13th ed. Wiley-Blackwell; 2017.
5. Immunobiology – Janeway CA Jr. et al. *Immunobiology*. Garland Publishing; 2001.
6. Lehninger Principles of Biochemistry – Nelson DL, Cox MM. *Lehninger Principles of Biochemistry*. 8th ed. W.H. Freeman; 2021.
7. Harper's Illustrated Biochemistry – Rodwell VW et al. *Harper's Illustrated Biochemistry*. 32nd ed. McGraw-Hill; 2021.
8. Medical Microbiology – Murray PR, Rosenthal KS, Pfaller MA. *Medical Microbiology*. 9th ed. Elsevier; 2020.
9. Robbins and Cotran Pathologic Basis of Disease – Kumar V, Abbas AK, Aster JC. *Robbins and Cotran Pathologic Basis of Disease*. 10th ed. Elsevier; 2021.
10. Basic Immunology – Abbas AK, Lichtman AH. *Basic Immunology*. 7th ed. Elsevier; 2023.
11. Braud VM, Allan DS, O'Callaghan CA, et al. HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C. *Nature*. 1998;391:795–799.
12. Adams EJ, Luoma AM. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. *Annu Rev Immunol*. 2013;31:529–561.
13. Joffre OP, Segura E, Savina A, Amigorena S. Cross-presentation by dendritic cells. *Nat Rev Immunol*. 2012;12(8):557–569.
14. Neefjes J, Jongsma MLM, Paul P, Bakke O. Towards a systems understanding of MHC class I and MHC class II antigen presentation. *Nat Rev Immunol*. 2011;11:823–836.
15. Blum JS, Wearsch PA, Cresswell P. Pathways of antigen processing. *Annu Rev Immunol*. 2013;31:443–473.
16. Rock KL, Reits E, Neefjes J. Present yourself! By MHC class I and MHC class II molecules. *Trends Immunol*. 2016;37(11):724–737.
17. Cresswell P. Assembly, transport, and function of MHC class II molecules. *Annu Rev Immunol*. 1994;12:259–293.
18. Wearsch PA, Cresswell P. The quality control of MHC class II peptide loading. *Curr Opin Cell Biol*. 2008;20(6):624–631.
19. Jensen PE. Recent advances in antigen processing and presentation. *Nat Immunol*. 2007;8(10):1041–1048.
20. Germain RN. MHC-dependent antigen processing and peptide presentation. *Cell*. 1994;76(2):287–299.
21. Klein J, Sato A. The HLA system. First of two parts. *N Engl J Med*. 2000;343:702–709.
22. Klein J, Sato A. The HLA system. Second of two parts. *N Engl J Med*. 2000;343:782–786.

23. Bjorkman PJ, Parham P. Structure, function, and diversity of class I major histocompatibility complex molecules. *Annu Rev Biochem.* 1990;59:253–288.
24. Brown JH, Jardetzky TS, Gorga JC, et al. Three-dimensional structure of the human class II histocompatibility antigen HLA-DR1. *Nature.* 1993;364:33–39.
25. Madden DR. The three-dimensional structure of peptide-MHC complexes. *Annu Rev Immunol.* 1995;13:587–622.
26. Yewdell JW, Bennink JR. Immunodominance in major histocompatibility complex class I-restricted T lymphocyte responses. *Annu Rev Immunol.* 1999;17:51–88.
27. Wieczorek M, Abualrous ET, Sticht J, et al. Major histocompatibility complex (MHC) class I and MHC class II proteins: conformational plasticity in antigen presentation. *Front Immunol.* 2017;8:292.
28. Townsend A, Bodmer H. Antigen recognition by class I-restricted T lymphocytes. *Annu Rev Immunol.* 1989;7:601–624.
29. Unanue ER, Turk V, Neeffjes J. Variations in MHC class II antigen processing and presentation in health and disease. *Annu Rev Immunol.* 2016;34:265–297.
30. Parham P. *The Immune System.* 5th ed. Garland Science; 2021.
31. Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell.* 7th ed. Garland Science; 2022.
32. Lodish H, Berk A, Kaiser CA, et al. *Molecular Cell Biology.* 9th ed. W.H. Freeman; 2021.
33. Delves PJ, Roitt IM. The immune system. *N Engl J Med.* 2000;343:37–49.
34. Murphy K. *Janeway's Immunobiology.* Garland Science; 2017.
35. Kindt TJ, Goldsby RA, Osborne BA. *Kuby Immunology.* 6th ed. W.H. Freeman; 2007.
36. Peakman M, Vergani D. *Basic and Clinical Immunology.* 2nd ed. Churchill Livingstone; 2009.
37. Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol.* 2010;125:S3–S23.
38. Male D, Brostoff J, Roth DB, Roitt I. *Immunology.* 9th ed. Elsevier; 2020.
39. Goldsby RA, Kindt TJ, Osborne BA. *Immunology.* 5th ed. W.H. Freeman; 2003.
40. Parkin J, Cohen B. An overview of the immune system. *Lancet.* 2001;357(9270):1777–1789.