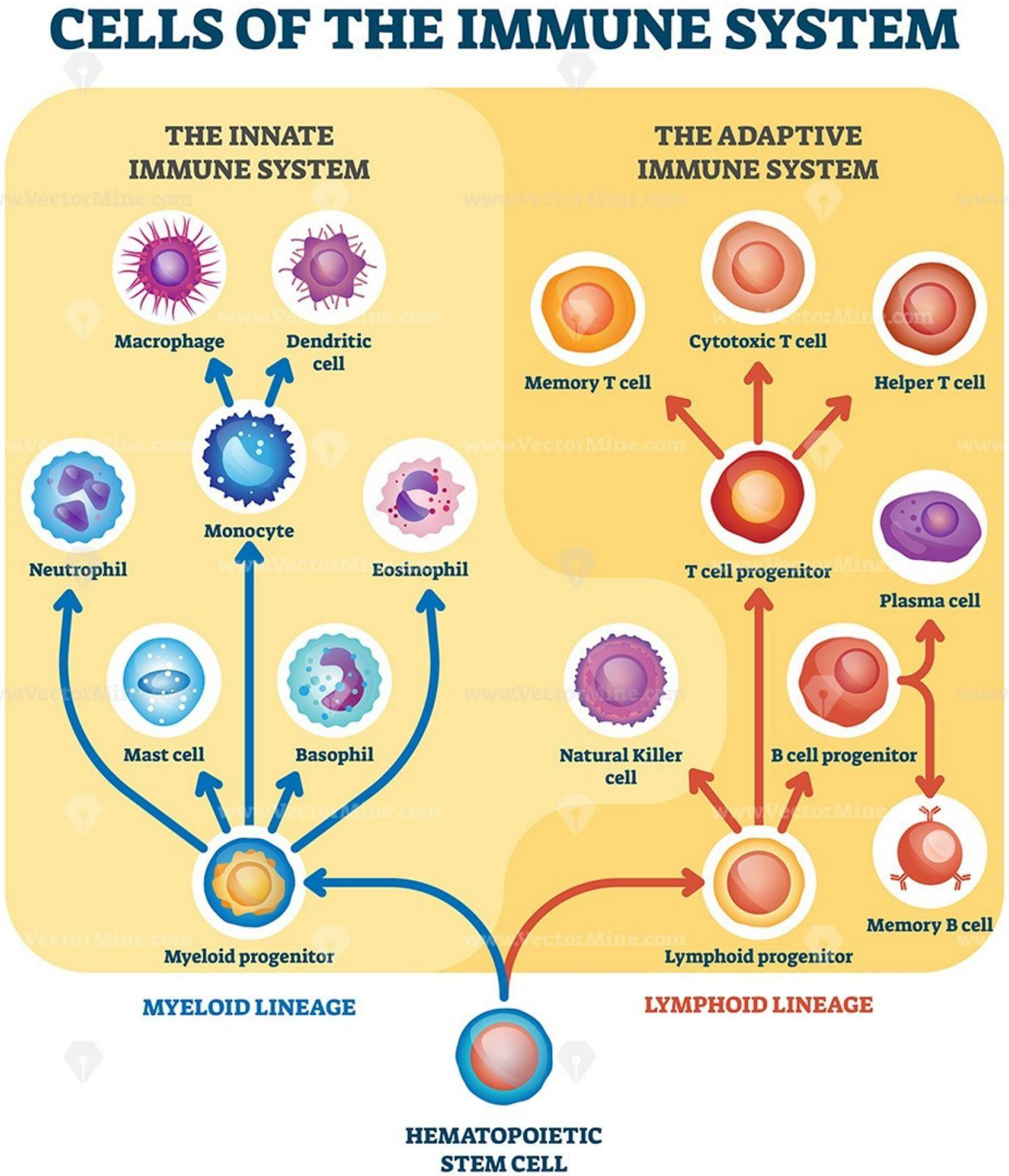
Antiviral Immune Response

Cells of immune system

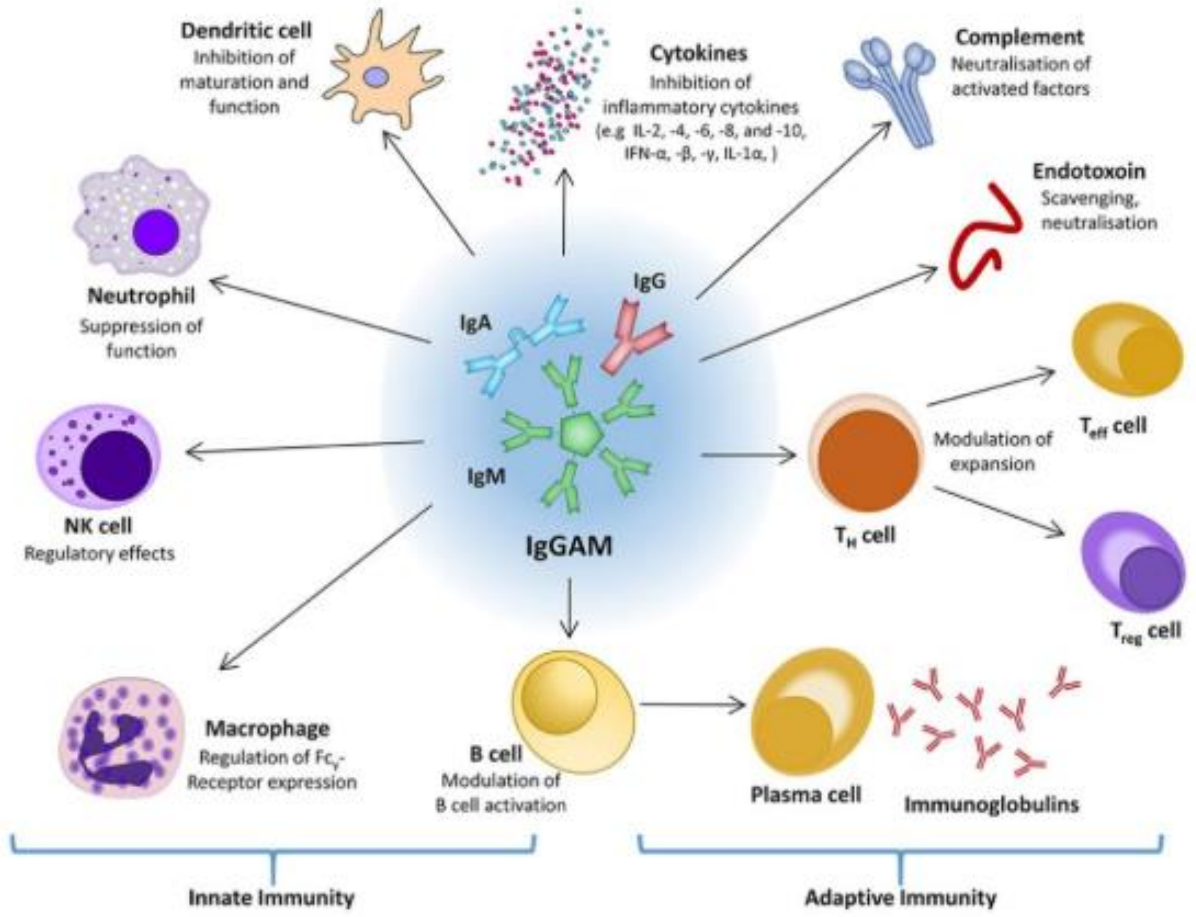
- **Natural Killer cells**
- **Lymphocytes**
  - T-lymphocytes
  - B-Lymphocytes, plasma cells
- **Monocytes, Macrophage**
- **Granulocytes**
  - neutrophils
  - eosinophils
  - Basophils



https://www.dreamstime.com/immune-system-cells-vector-illustration-labeled-educational-division-scheme-anatomical-explanation-diagram-lymphoid-cell-image176769982

Molecules of Immune system

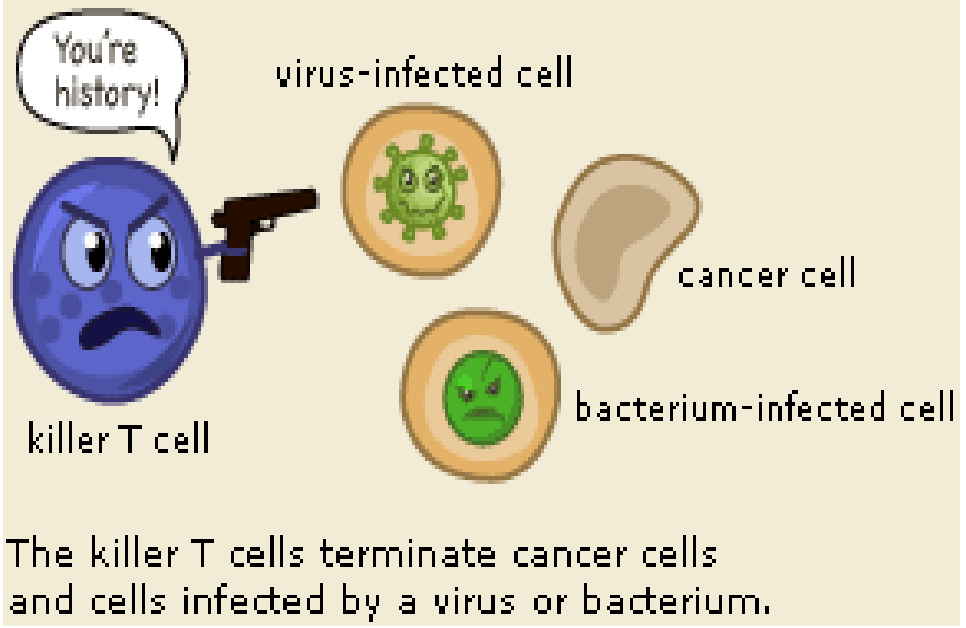
- Antibodies
- Complement
- Cytokines
- Interleukines
- Interferons



Addissouky, T. A.,et al. (2024). Towards personalized care: Unraveling the genomic and molecular basis of sepsis-induced respiratory complications.

Natural Killer cells

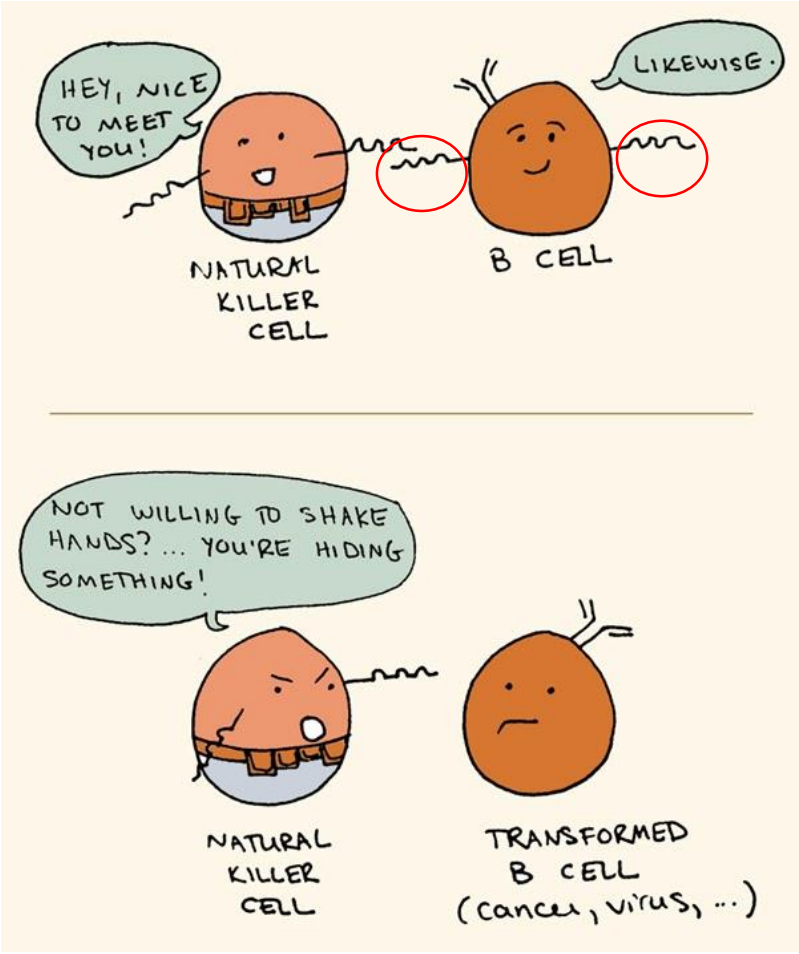
- They're also a type of lymphocyte like B- and T-lymphocyte
- Important part of the innate immune system
- NK cells have the ability to destroy virus /bacteria infected cells (Intracellular pathogens) and cancer cells.
- These cells do not show antigen specificity and work independently of the presence of antibodies.



http://media.acc.qcc.cuny.edu/faculty/nursingdept/softchalk4/softchalk42.html

NK cells differentiate choose cells to kill ?

Following virus infection in host cells, changes occur in the synthesis and presentation of MHC-I proteins.
NK cells can take advantage of this change to differentiate virus-infected cells.



Uninfected cell / Normal cell

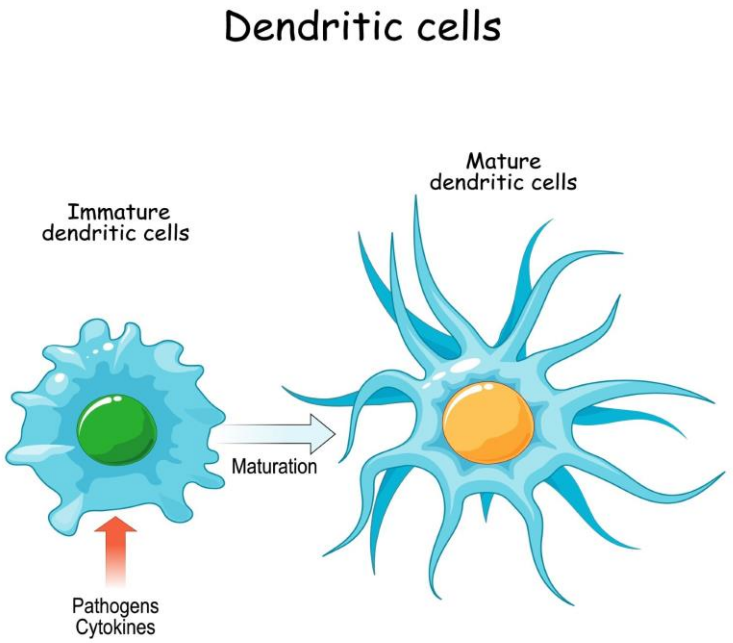
Microbe infected cell / cancer cell

Some cell surface proteins are missing

https://knowyourscience.blogspot.com/2013/

Dentritic cells

- Dendritic cells, which receive foreign antigens by phagocytosis, quickly reach the lymph nodes and present the antigens to T lymphocytes through the MHC-II protein.
- All 3 cells (dentritic cells, monocyte and macrophage) have receptors to which the complement and Fc region of immunoglobulins can bind.
- In this way, immunocomplexes (virus particles bound with antibodies) in circulation or tissues can be phagocytosed easily



Dendritic cells. Image Credit: Designua / Shutterstock
https://www.news-medical.net/health/What-are-Dendritic-Cells.aspx

Monocytes and Macrophages

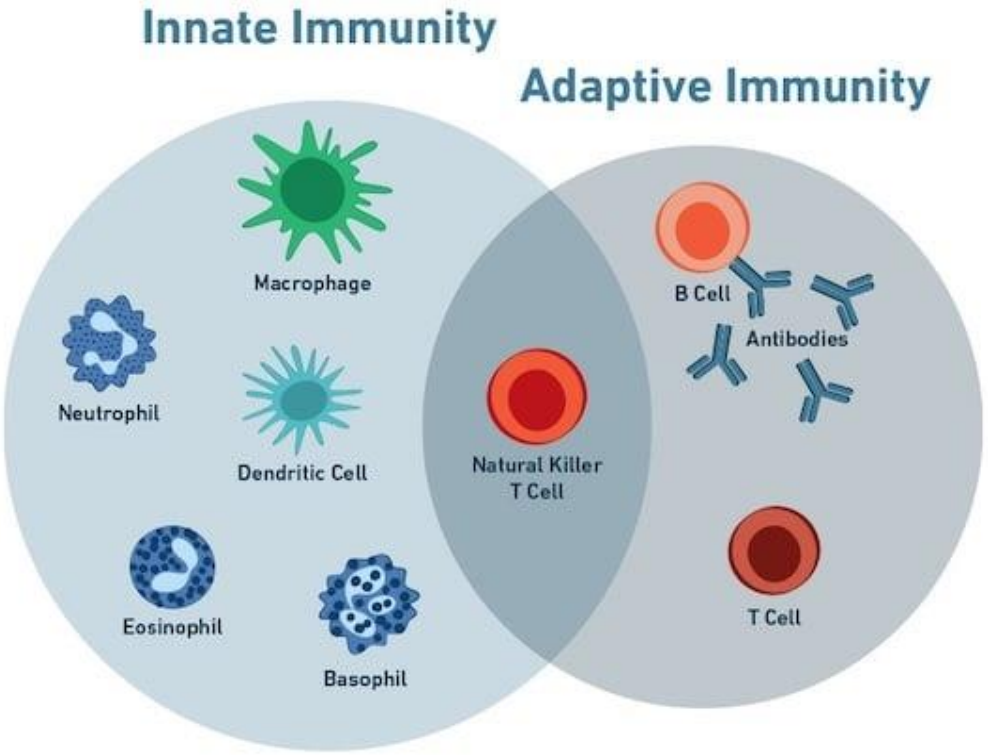
- Monocytes (~5% of WBCs)
- They migrate into the tissues and become Macrophages

"Big eaters"

- Phagocytosis of microbes in tissue
  (neutrophils are present only in blood)
- Antigen presentation
(Macrophages have MHC-II receptor)

HOST IMMUNE CONTROL MECHANISMS

- The most important factor that restricts the proliferation of the virus in the host is the host's protection mechanisms.
- The immune system is composed of two broad types of cellular defenses referred to as the innate immune response and the adaptive immune response.



https://blog.cellsignal.com/immunology-overview-how-does-our-immune-system-protect-us

Immune System

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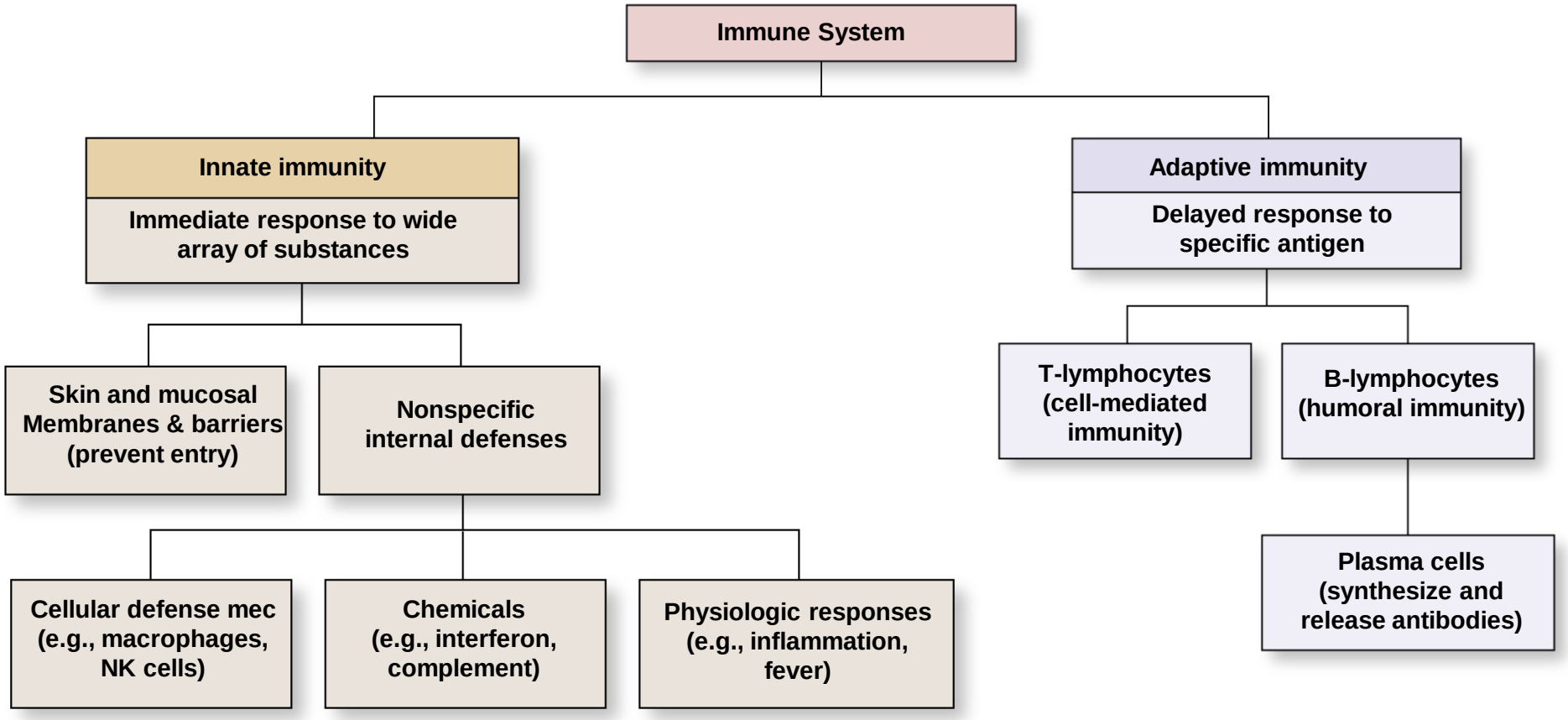


Innate immunity

Microorganisms that overcome natural barriers encounter cells and molecules that are readily available in the body, work without discrimination between microorganisms, and are a part of the immune system. The protection provided by mechanisms using these cells is called innate immunity.

- first line of immune response
- relies on mechanisms that exist before infection

Based on genetic

Relies on already formed components

Rapid response: within minutes of infection

Not specific

same molecules / cells respond to a range of pathogens

Has no memory

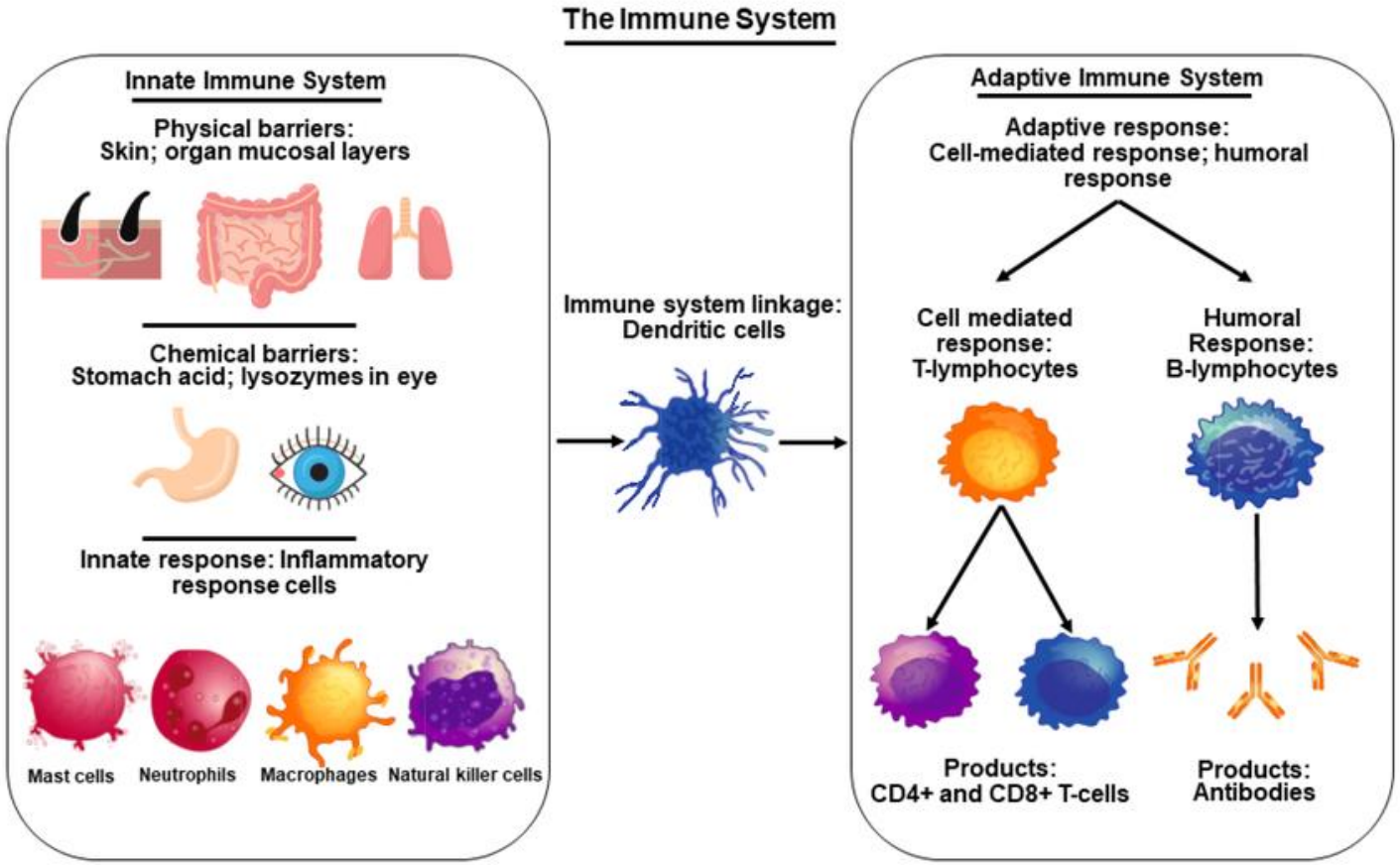
same response after repeated exposure

Adaptive Immunity

The body's other defense system is stimulated after foreign factors enter the body, it specifically recognizes the molecules of these factors and becomes stronger every time it encounters these factors. This is called Adaptive immunity.

- Second line of response (if innate fails)
- relies on mechanisms that adapt after infection
- handled by T- and B- lymphocytes
- one cell determines one antigenic determinant

These two immune mechanisms work together

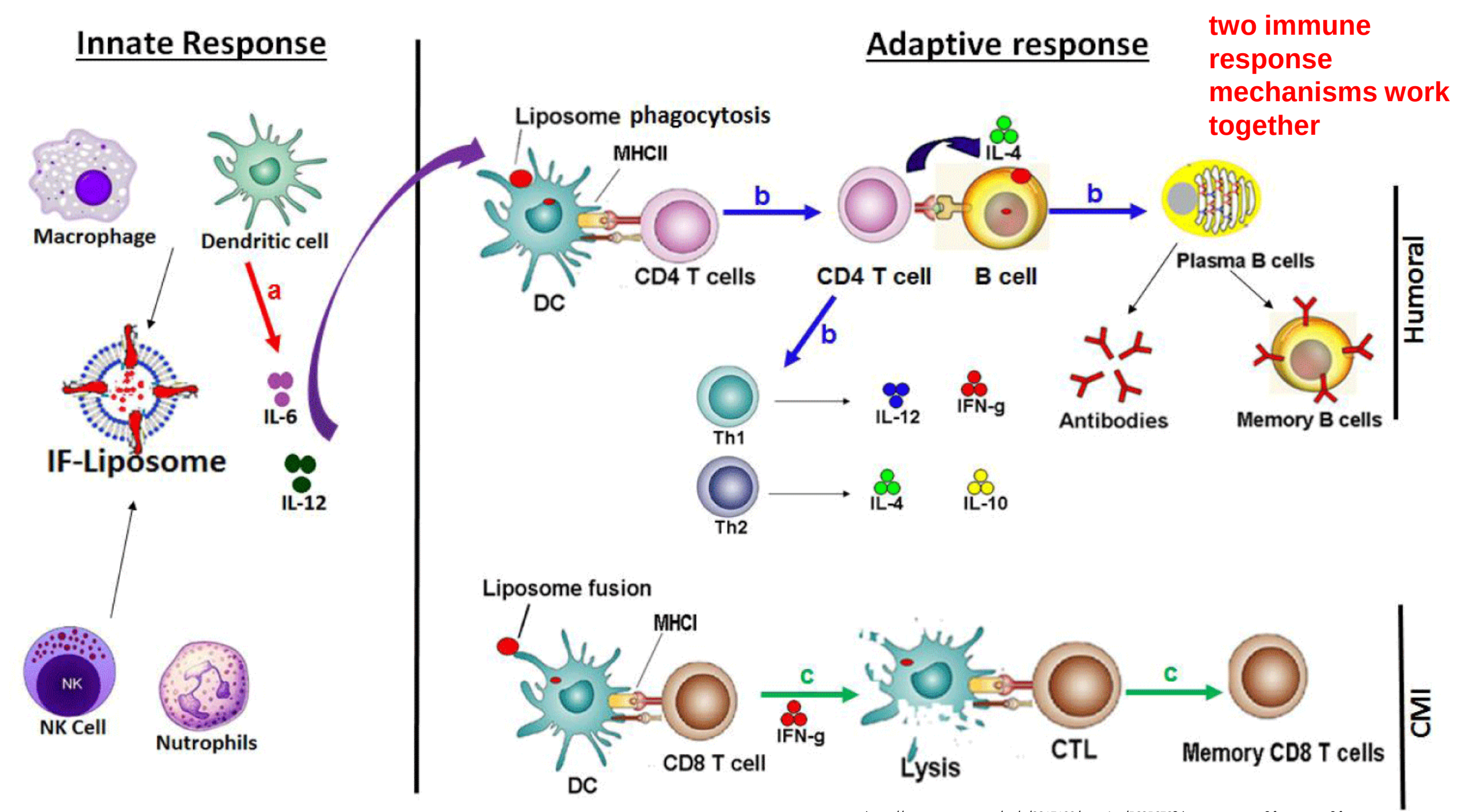


- The innate immune system is composed mainly of physical and chemical barriers, and an initial inflammatory response made up of mast cells, neutrophils, macrophages, and natural killer cells.
- The adaptive immune response works through B- and T-lymphocytes creating a specialized and learned immune response to specific pathogens through antibodies and CD4+ and CD8+ cells.
- The adaptive and innate components are connected through dendritic cells that allow for the activation of the adaptive response once the innate system has recognized a threat to that organism.

Manna, Pulak & Gray, Zackery & Reddy, P. Hemachandra. (2022). Healthy Immunity on Preventive Medicine for Combating COVID-19. Nutrients. 14. 1004. 10.3390/nu14051004.

Table 1: Differences between Innate and Adaptive Immunity

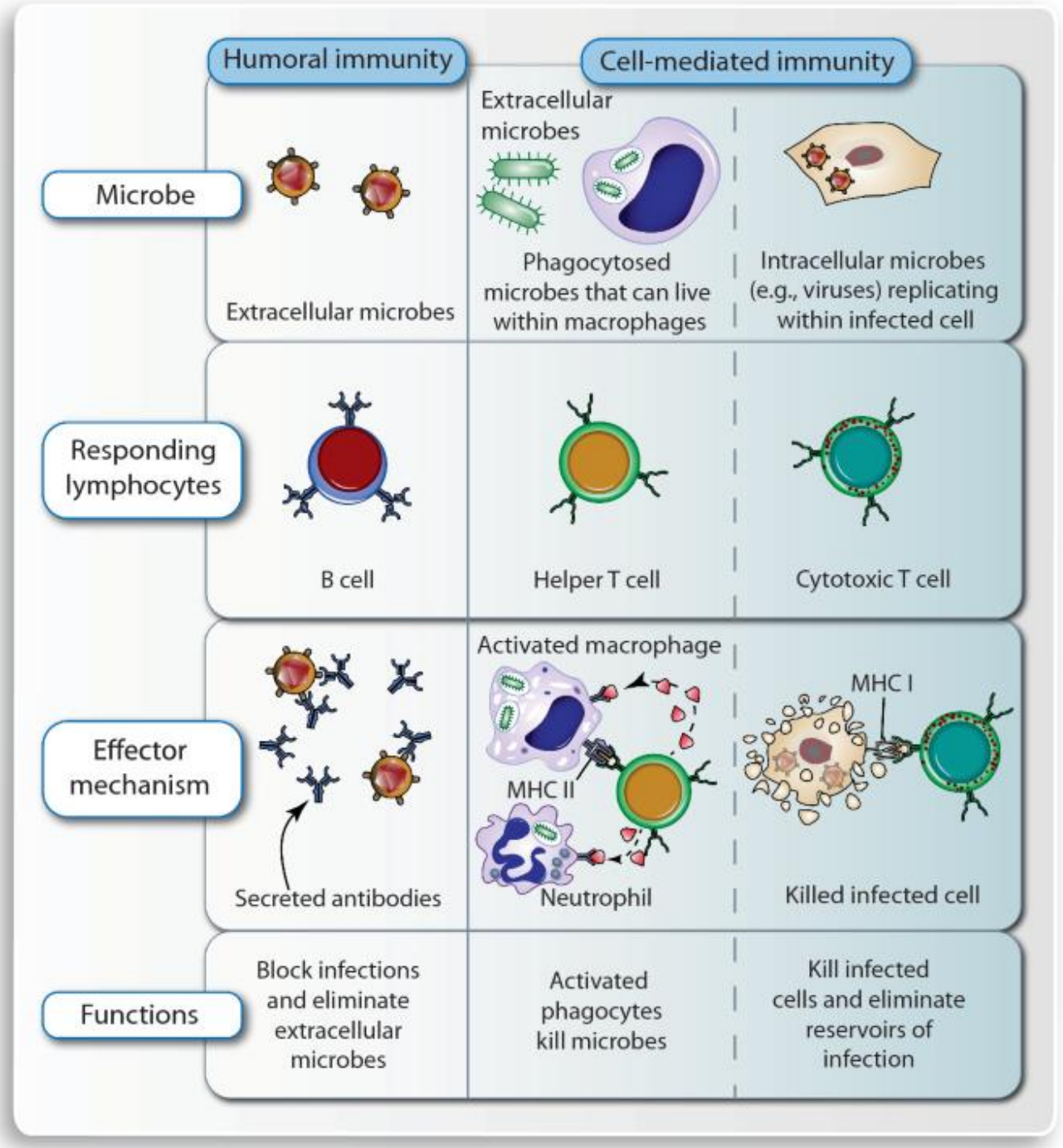
Feature	Innate Immunity	Adaptive Immunity
Cells involved	Dendritic leukocyte, Natural killer cells, Mast cell, Granulocytes/ Macrophages, Basophils, etc.	Killer CD8+ T-cells, Helper CD4+ T-cells, B-cells, Antigen presenting cells, etc.
Molecules involved	Cytokines, Complement cells, Interferon, Acute phase reactants/ proteins	Antibodies, Cytokines
Receptors	Germline encoded	Encoded in gene segments
	No somatic rearrangement	Somatic rearrangement necessary
	Non-clonal distribution	Clonal distribution
Action time	Immediate effector activation	Delayed effector activation
Response	Rapidly occurs (0-6 h ours)	Occurs over days to weeks
Order of defence	It is the first line of defense of immune system	Action against pathogens that are able to evade or overcome innate immune defense
Immunological memory	None	Confer Immunological memory
Types of Immune response	Inflammation, Complement mediated killing, Phagocytosis	Antibodies generation, microbial destruction by Helper T cells and Cytotoxic T cells
Subsequent exposure	Immune response does not get alter on repeated exposure	Immune response get improves with subsequent exposure
Reason behind immune evasion	Caused by pathogenic virulence	Caused by mutation of the recognized antigen
Allery or hypersensitivity reaction	None	Immediate and delay hypersentivity
Potency	Lower	Higher
Physio-anatomicalcal barriers	Skin, Mucous membranes, Temp, pH, chemicals, etc	Lymph nodes, spleen, mucosal associated lymphoid tissue
Functions	(a) Recruiting immune cells to site of infection; (b) Activation of complement cascade to identify antigens; (c) Identification & removal of foreign substances present in organs, tissues, blood and lymph; (d) Activation of adaptive immune system through antigen presentation; (e) Acting as physical & chemical barrier to infectious agents.	(a) Recognition of specific "non-self" antigens during the process of antigen presentation; (b) Generation of responses that are tailored to maximally eliminate specific pathogens or infected cells; (c) Development of immunological memory, through memory B cells and memory T cells.



https://www.goconqr.com/en/p/9817133/question/5685678?dont_count=true&frame=true&fs=true

Adaptive immunity

Humoral and cell-mediated adaptive immunity. The adaptive immune system can be distinguished into a humoral part, which is mediated by antibodies secreted by B cells (**left**), and a component represented by T_H cells coordinating the action of other immune cells (**center**) and cytotoxic T cells destructing infected and transformed cells (**right**).



Carlberg, C., Velleuer, E. (2022). Adaptive Immunity and Antigen Receptor Diversity. In: Molecular Immunology. Springer, Cham. https://doi.org/10.1007/978-3-031-04025-2_3

Adaptive Immun response

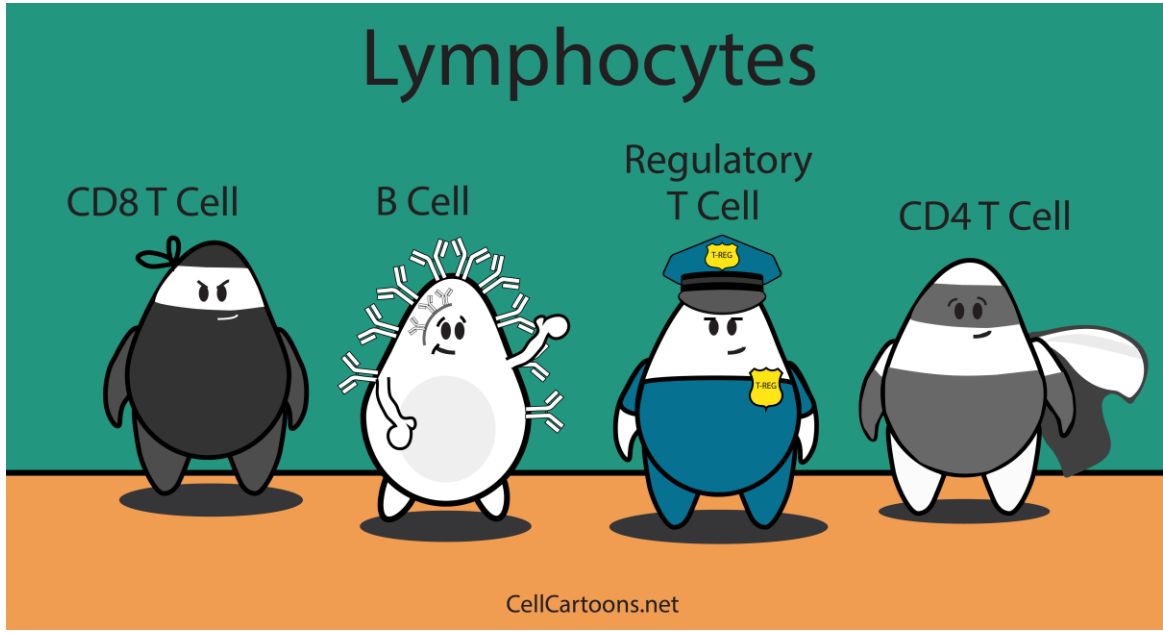
- these components develop with time
- Lymphocytes (B, T): Are major players in the immune response but other cells and participants in the innate system work cooperatively
- Identifies, attacks, and reinforces immunity to a specific pathogen

- Based upon resistance acquired during life
- Relies on genetic events and cellular growth
- Responds more slowly, over few days
- Is specific
  - each cell responds to a single epitope on an antigen
- Has anamnestic memory
  - repeated exposure leads to faster, stronger response

Adaptive immunity: mechanisms

- Humoral immune response (HI)
  - B-lymphocytes
  - mediated by antibodies
  - eliminate extra-cellular microbes

  and their toxins
- Cell-mediated immune response (CMI)
  - T-lymphocytes
  - eliminate intracellular microbes that survive within phagocytes or other infected cells



1. Humoral immune response (HI)

a- Virus neutralization

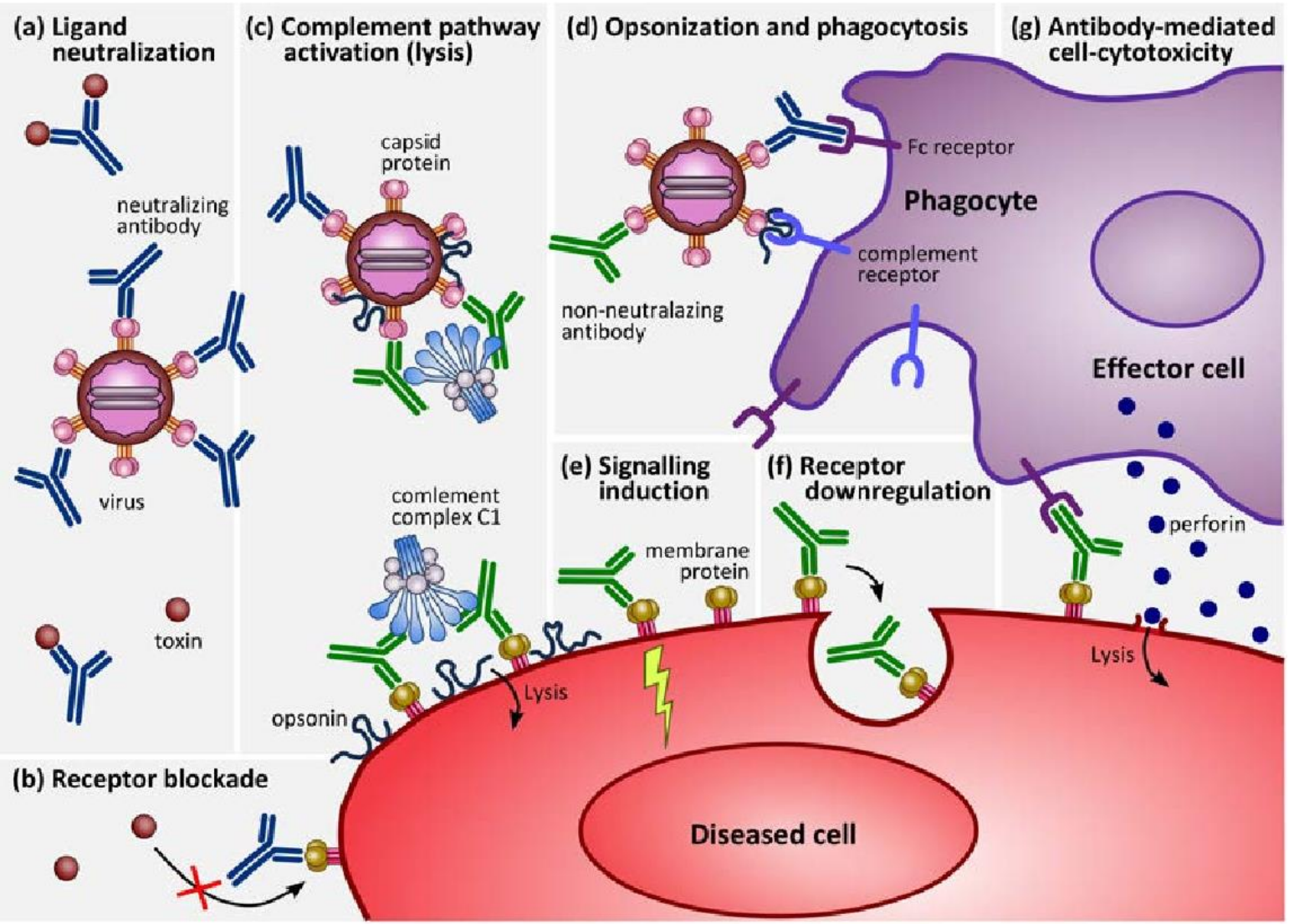
- During viremia periods of infections (if any),
- Antibodies neutralize the virus, preventing them from binding to sensitive cell receptors.
  - Eg. PI-3, distemper, pestivirus inf.
- In superficial viremic infections (influenza), secretory IgAs neutralize viruses on mucosal surfaces.

b- Antibodies directly destroy free viral particles in the following ways:

i- Virus aggregation and opsonization

ii- Complement-mediated lysis

* Both mechanisms also act in virus-infected cells.



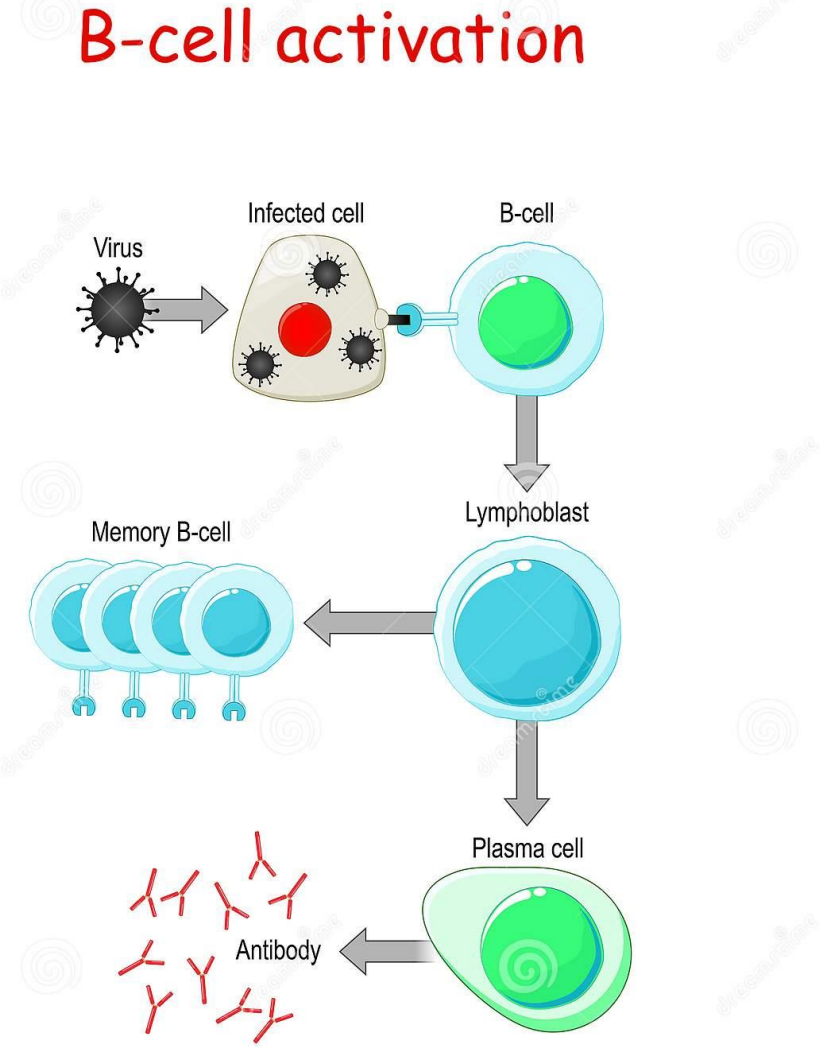
Schematic illustration of the main biological roles of IgG.

- (a) Ligand neutralization: IgG bind a toxin or a virus thus preventing it from activating their cognate cell receptors and penetrating cells.
- (b) Receptor blockade: IgG act as antagonists by inhibiting a cell receptor.
- (c) Complement pathway activation: IgG activate complement mediated lysis and opsonization.
- (d) Opsonization and phagocytosis: the pathogen is digested by phagocytes that are recruited by IgG (via the Fc fragment) and opsonins.
- (e) Signalling induction: IgG induce cascade reactions (active signals) that alter cellular fates.
- (f) Receptor downregulation: binding of cell surface receptors by IgG result in their internalization (thus limit the receptors that can be activated).
- (g) Antibody-mediated cell cytotoxicity: effector cells recruited by IgG secrete proteins that contributes to the lysis of the cell.

Martin, N. (2014). Colloidal stability and folding of antibodies in the presence of chaperone-like poly(acrylate) derivatives : role of hydrophobic and electrostatic interactions.

Humoral immune response

1. B lymphocytes recognize specific antigens
   - proliferate and differentiate into antibody-secreting plasma cells
2. Antibodies bind to specific antigens on microbes; destroy microbes via specific mechanisms
3. Some B lymphocytes evolve into the resting state - memory cells



dreamstime.com
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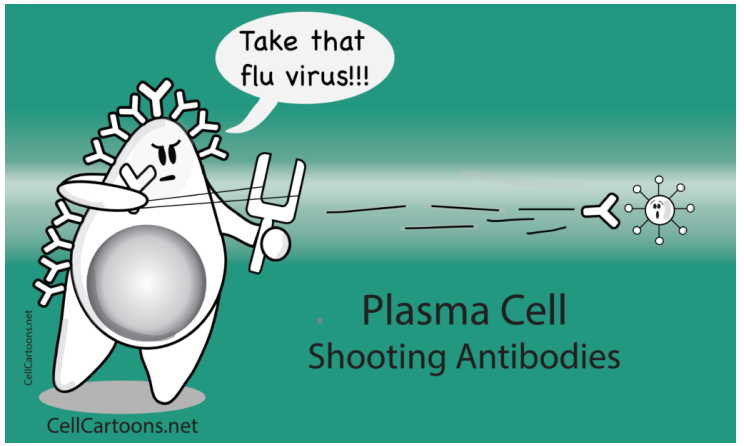
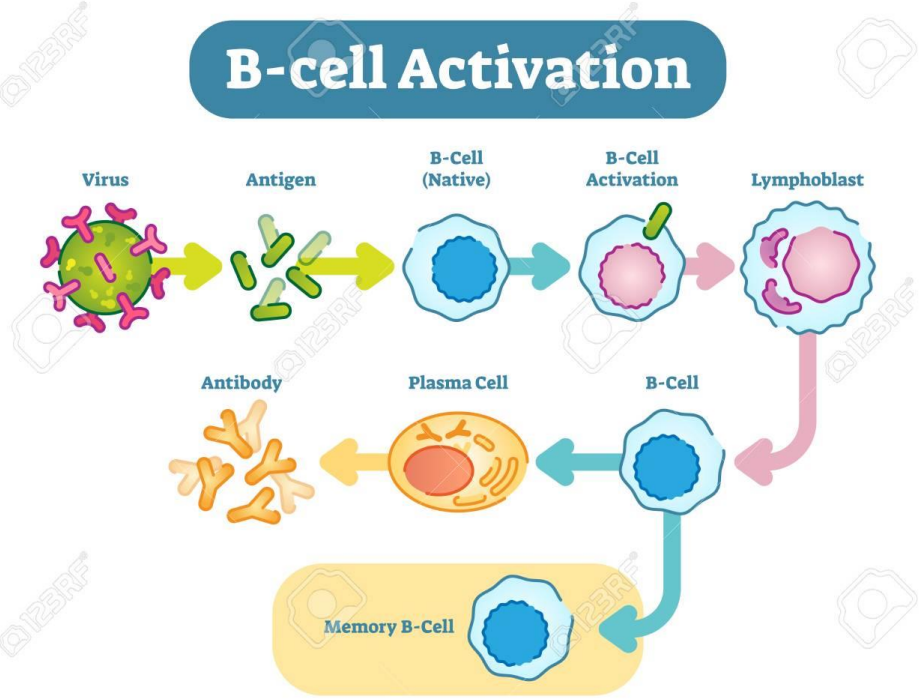
B lymphocyte

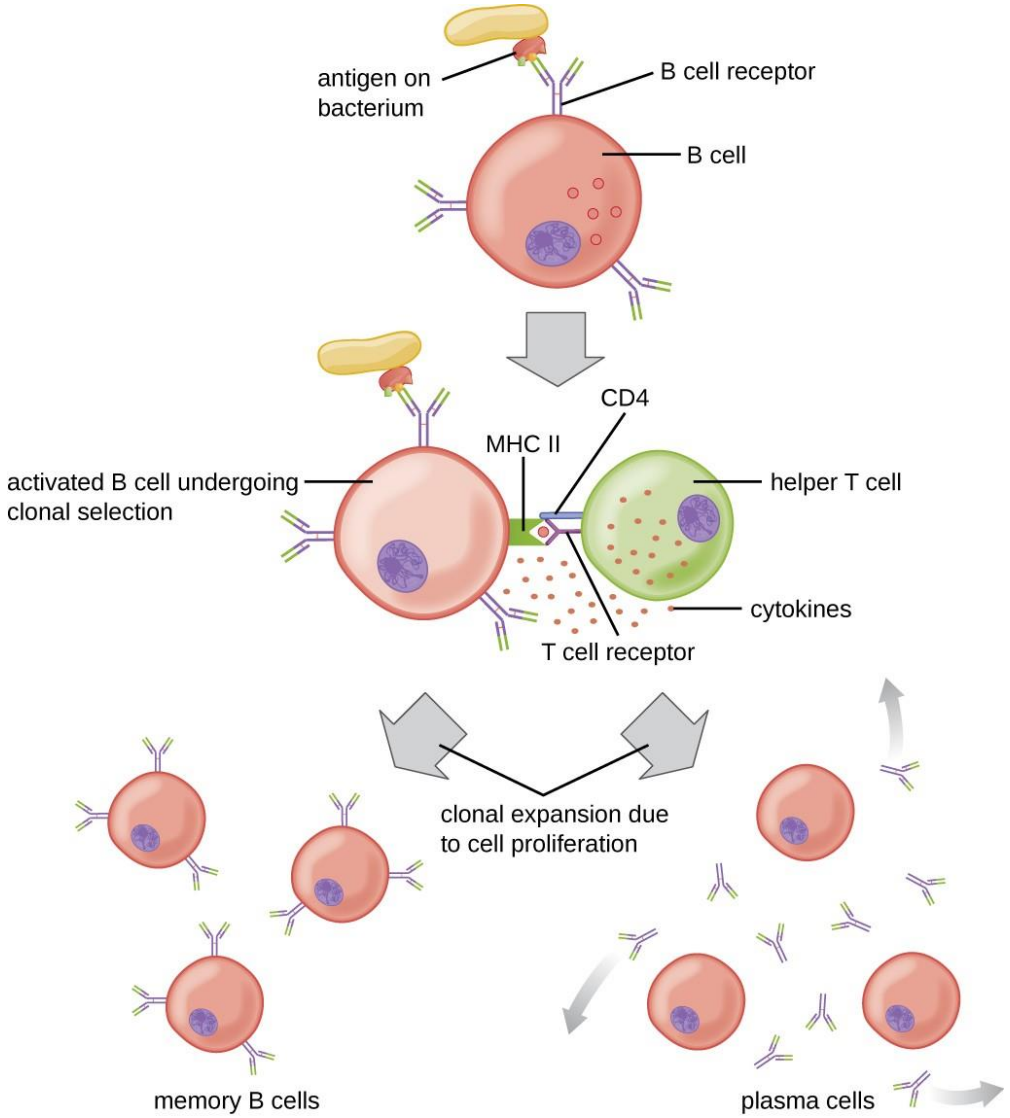


- These cells originate from bursa fabricius in poultry and bone marrow in mammals.
- While T lymphocytes can only recognize antigens presented by MHC, B lymphocytes can naturally recognize and bind antigens with their slg receptors.
- Therefore, it is possible that B lymphocytes can be stimulated directly with virus particles or viral antigens.



https://www.dreamstime.com/b-cells-also-known-as-lymphocytes-type-white-blood-cell-lymphocyte-subtype-function-humoral-immunity-image108044193

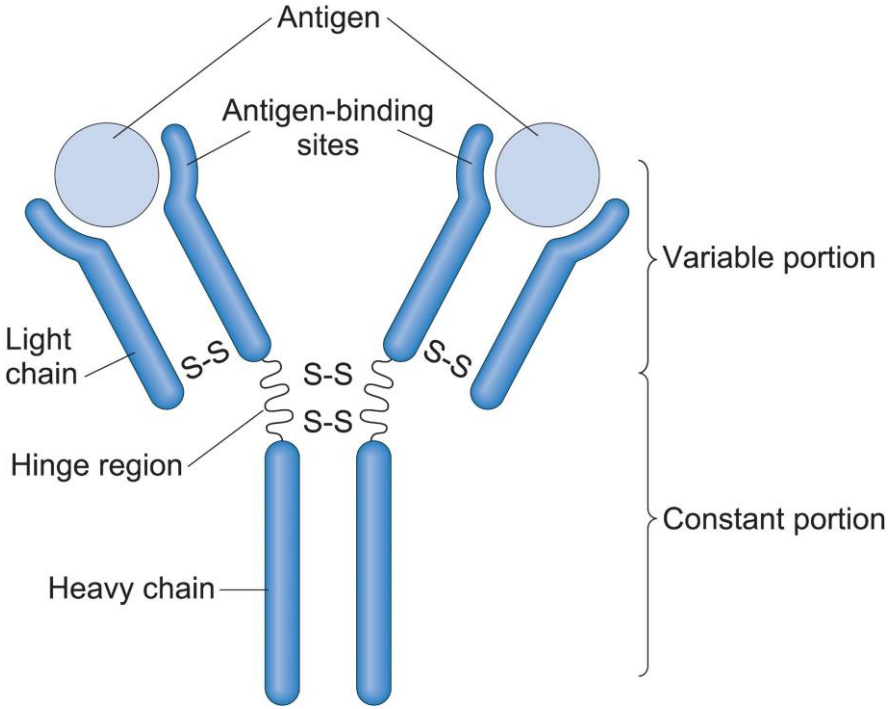
- On the other hand, B lymphocytes firstly need regulatory signals from T cells in order to proliferate, start synthesizing antibodies and then transform into memory cells.
- Thus, humoral immune response can begin.
- Each activated B lymphocyte synthesizes antibodies that are specific for a single epitope.



https://courses.lumenlearning.com/suny-microbiology/chapter/b-lymphocytes-and-humoral-immunity/

Antibodies (immunoglobulins)

- Belong to the gamma-globulin fraction of serum proteins
- Y-shaped or T-shaped polypeptides
  - 2 identical heavy chains
  - 2 identical light chains
- Five kinds of antibodies
  - IgG, IgM, IgA, IgD, IgE



https://www.news-medical.net/life-sciences/The-Structure-of-an-Antibody.aspx

Image Credit: periyanayagam/Shutterstock.com

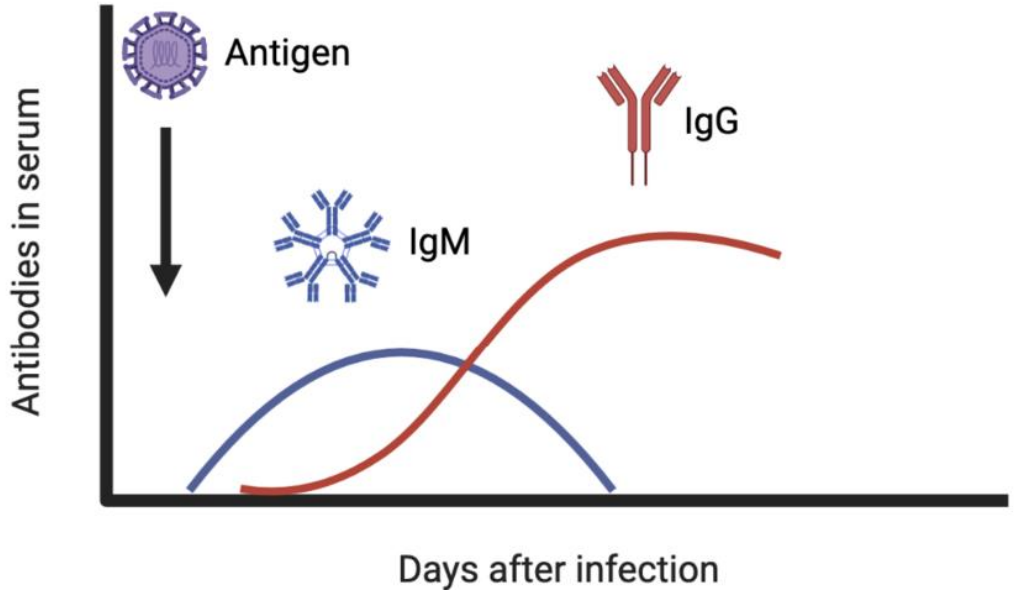
IMMUNGLOBULIN CLASSES IN MAMMALS

1. Immunoglobulin G (IgG-gamma):

- It is the Ig class found in the highest concentration in the blood (70-80%).
- Since it is the smallest Ig class, it passes through the vein more easily than other classes.
- The most important thing is that it inactivates and neutralizes microbes. It occurs intensively in the secondary immune response.
- It has a dimer structure.

2. Immunoglobulin M (IgM-mu):

- It is the immunoglobulin class found in the second highest concentration (5-15%).
- It is the largest class of immunoglobulins.
- IgM is the first class of immunoglobulins formed during the primary immune response. In the secondary immune response, IgM is replaced by IgG.
- It has a pentamer structure.



da Silva, Priscilla & Reis, José & Rodrigues, Marcio & Mesquita, João. (2023). Serological Cross-Reactivity in Zoonotic Flaviviral Infections of Medical Importance. Antibodies. 12. 18. 10.3390/antib12010018.

3. Immunoglobulin A (IgA-alpha):

- It is a class of immunoglobulins that are found in low concentrations (5-15%) in the blood, but the majority are released to mucosal surfaces.
- They bind to microorganisms on the mucosal surface and neutralize toxins.
- It has a dimer structure.

4. Immunoglobulin E (IgE-epsilon):

- It is the Ig class found in the lowest concentration (0.005-2%) in the blood.
- It is the most important Ig class involved in reactions against parasites and allergic reactions.

5. Immunoglobulin D (IgD-delta):

- Its main function is to work as an antigen receptor on B cells. It is present on the B cell at the same time as IgM.

5 Types of Antibodies

Antibodies or immunoglobulins (Ig) are Y-shaped proteins that recognize unique markers (antigens) on pathogens.

IgA

Secreted into mucous, saliva, tears, colostrum. Tags pathogens for destruction.

IgD

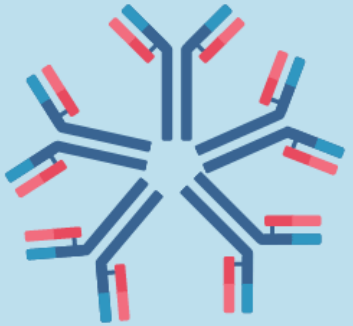
B-cell receptor. Stimulates release of IgM.

IgE

Binds to mast cells and basophils. Allergy and antiparasitic activity.

IgG

Binds to phagocytes. Main blood antibody for secondary responses. Crosses placenta.



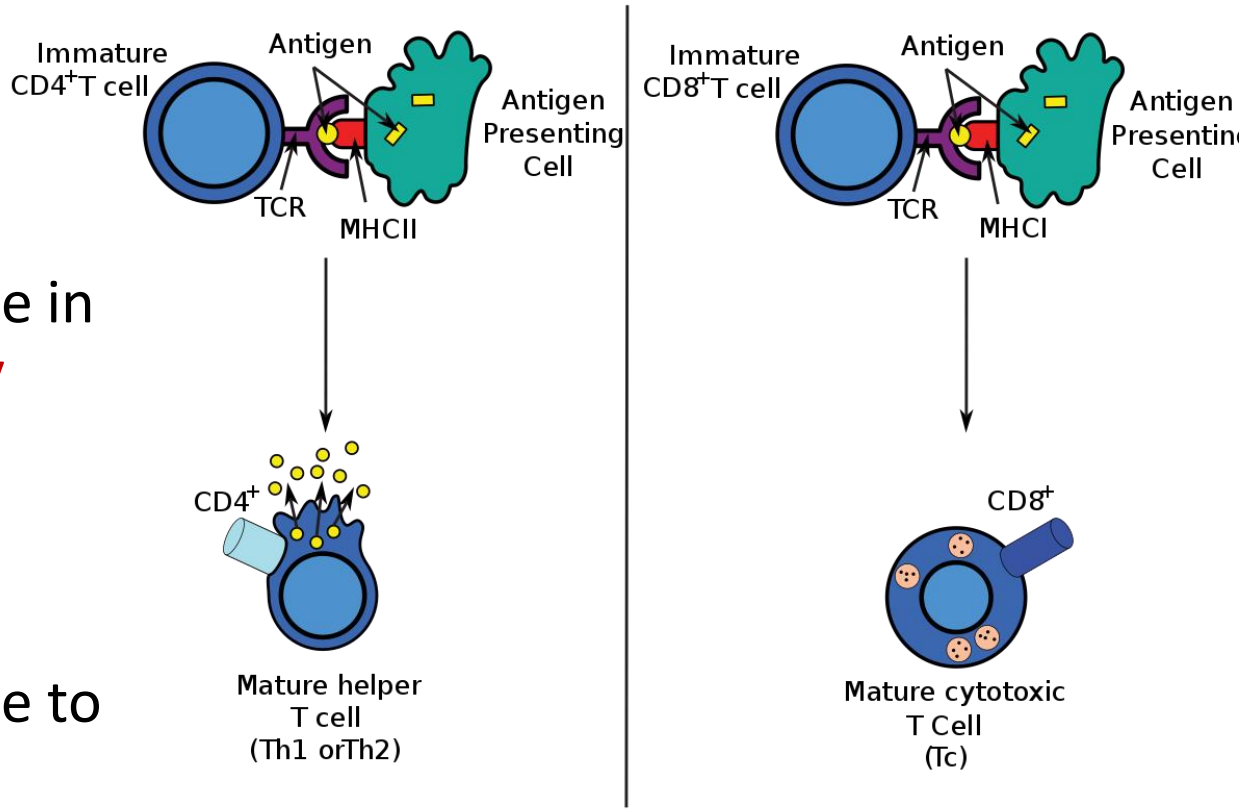
IgM

Fixes complement. Main antibody of primary responses. B-cell receptor. Immune system memory.

https://sciencenotes.org/types-of-antibodies-and-their-functions/

2. Cell-mediated immune response (CMI)

1. T lymphocyte (T-cell)
   - recognizes peptide antigen on macrophage in association with major histo-compatibility complex (MHC) class
   - identifies molecules on cell surfaces
   - helps body distinguish self from non-self
2. T-cell goes into effectors cells stage that is able to kill infected cells

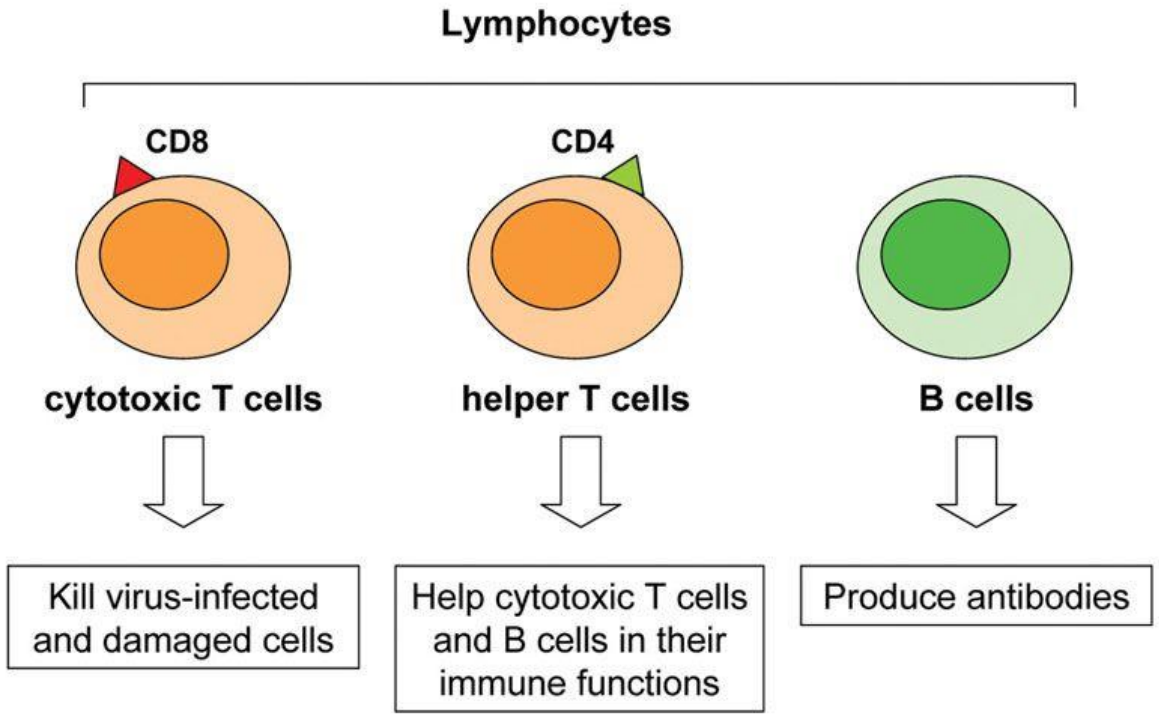


https://en.wikipedia.org/wiki/Antigen_presentation

T lymphocyte

- These cells, which need the thymus for their maturation, take part in the regulation of the immune response.
- **Therefore, functionally, there are 2 types of T lymphocytes:**

- helper T- lymphocytes (CD4+) Th cells
  - CD4+ T cells activate phagocytes to kill microbes
- cytotoxic T-lymphocyte (CD8+) CTLs
  - CD8+ T cells destroy infected cells containing microbes or microbial proteins

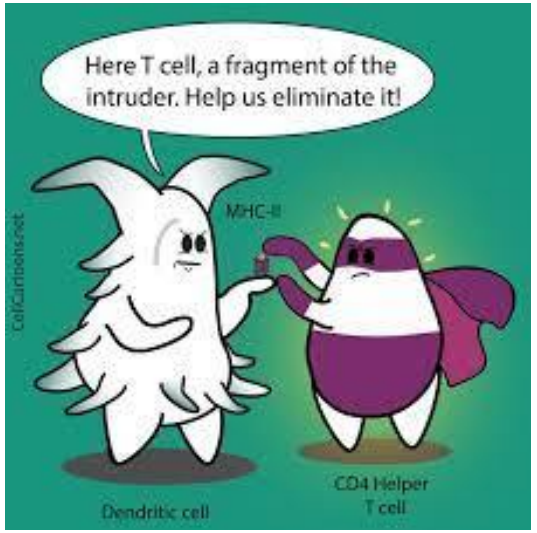


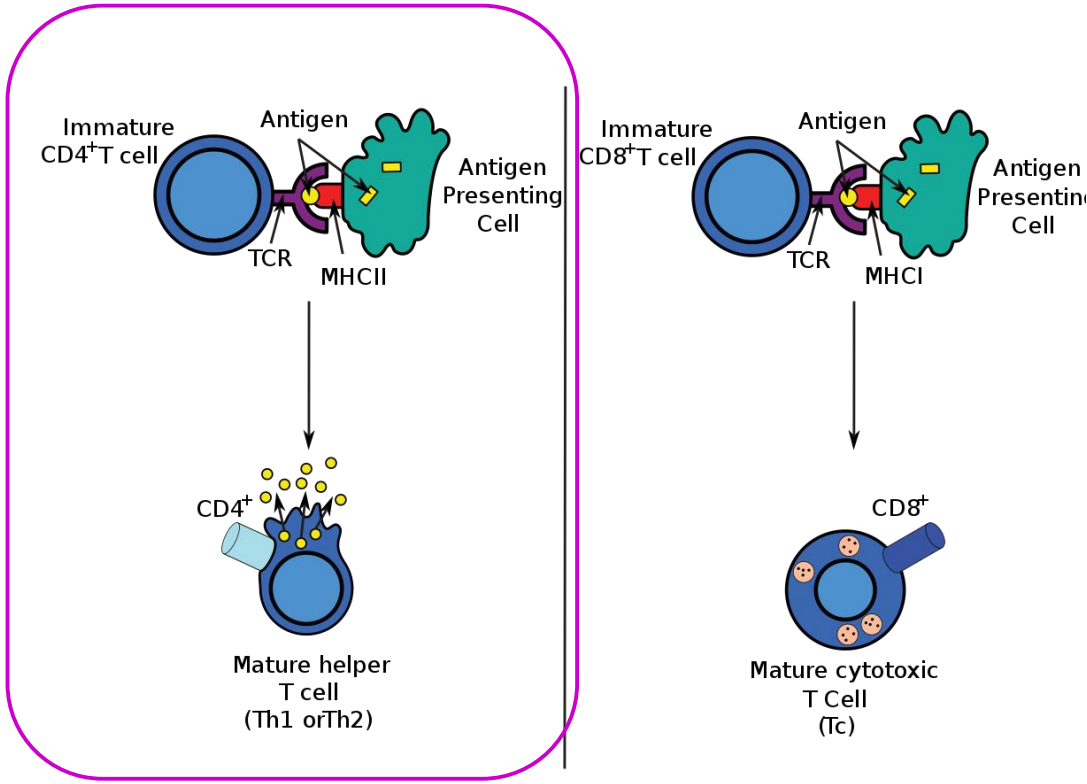
Three types of lymphocytes involved in the immune response against infectious agents in the human body. (Diagram: Dr Ignacio Romero) https://demo.oppia-mobile.org/media/courses/cd3-et/01_15073_en.html

1. Helper T lymphocytes (Th)

- They have CD4 molecules on their surface. They recognize viral antigens presented by MHC-II receptors on the surface of antigen-presenting cells.
- They stimulate other cells that play a role in the immune response with the cytokines they secrete. ie,
  - B lymphocytes begin to synthesize antibodies, Tc cells gain a cytotoxic character.
- There are 2 types of helper T lymphocytes, Th1 and Th2.

These regulate the immune response with the release of different cytokines, initiate the inflammatory reaction and play a role in hypersensitivity reactions.

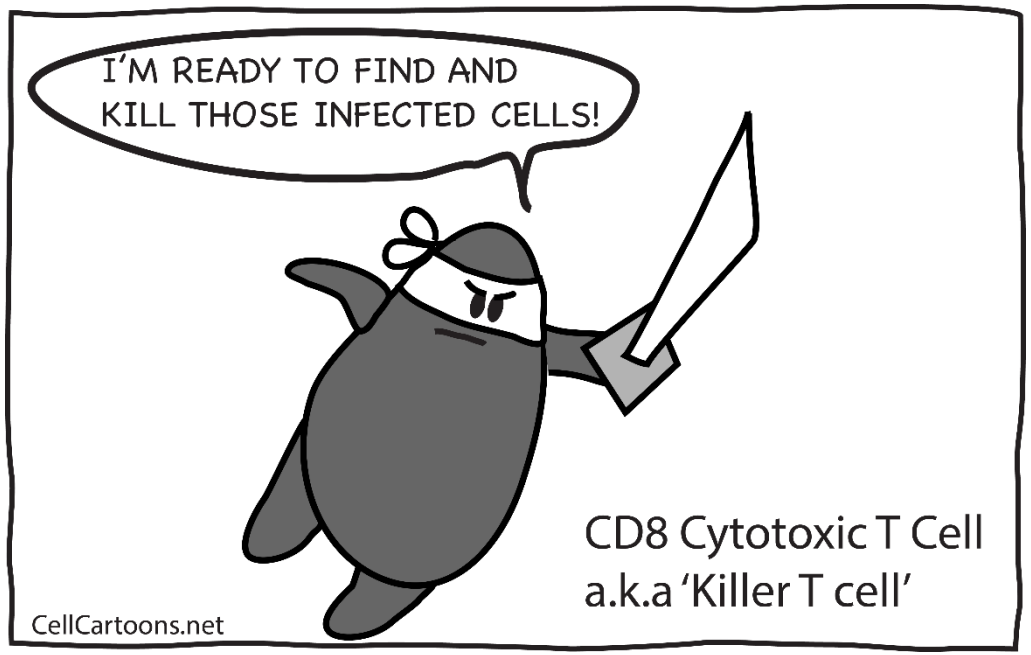


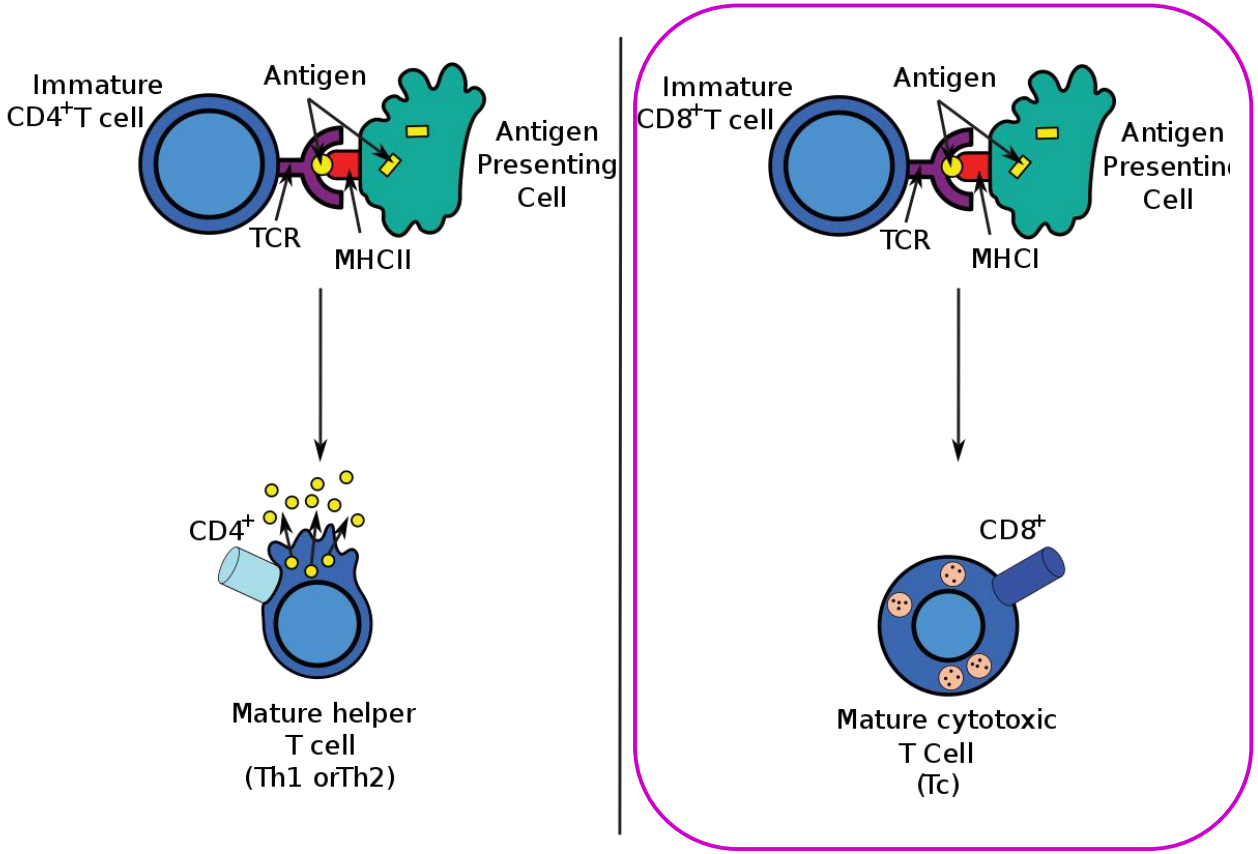


https://en.wikipedia.org/wiki/Antigen_presentation

2. Cytotoxic T lymphocytes

- They have T cell receptors (TCR) carrying viral antigens presented by MHC-I molecules on the surface of infected cells along with CD8 molecules on the surface.
- Thus, activated cytotoxic T lymphocytes provide lysis of virus-infected cells.





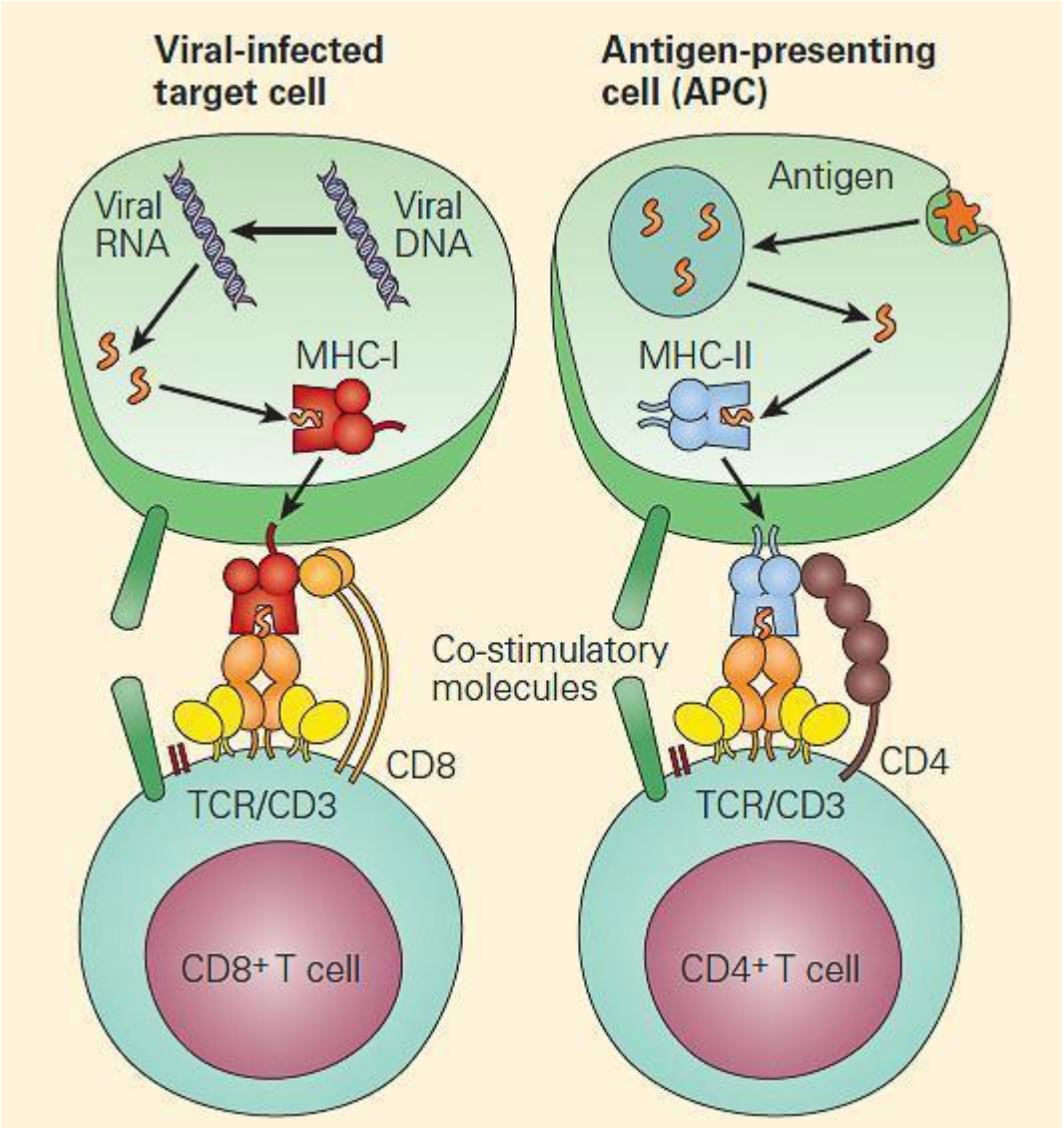
https://en.wikipedia.org/wiki/Antigen_presentation

CMI shows its effect on the virus-infected cell as follows:

- NK-cells destroy virus-infected cells in the early infection period before the formation of antibodies
- CTLs kill virus-infected cells that display viral antigens with MHC-I
- Th-cells stimulated by viral antigens release cytokines. Cytokines stimulate and activate macrophages to kill virus-infected cells.
- Antibody-dependent cell-mediated cytotoxicity (ADCC):
  - Antibodies bind to the virus-infected cell surface and enable these cells to be lysed by NK cells, macrophages and polymorphs.

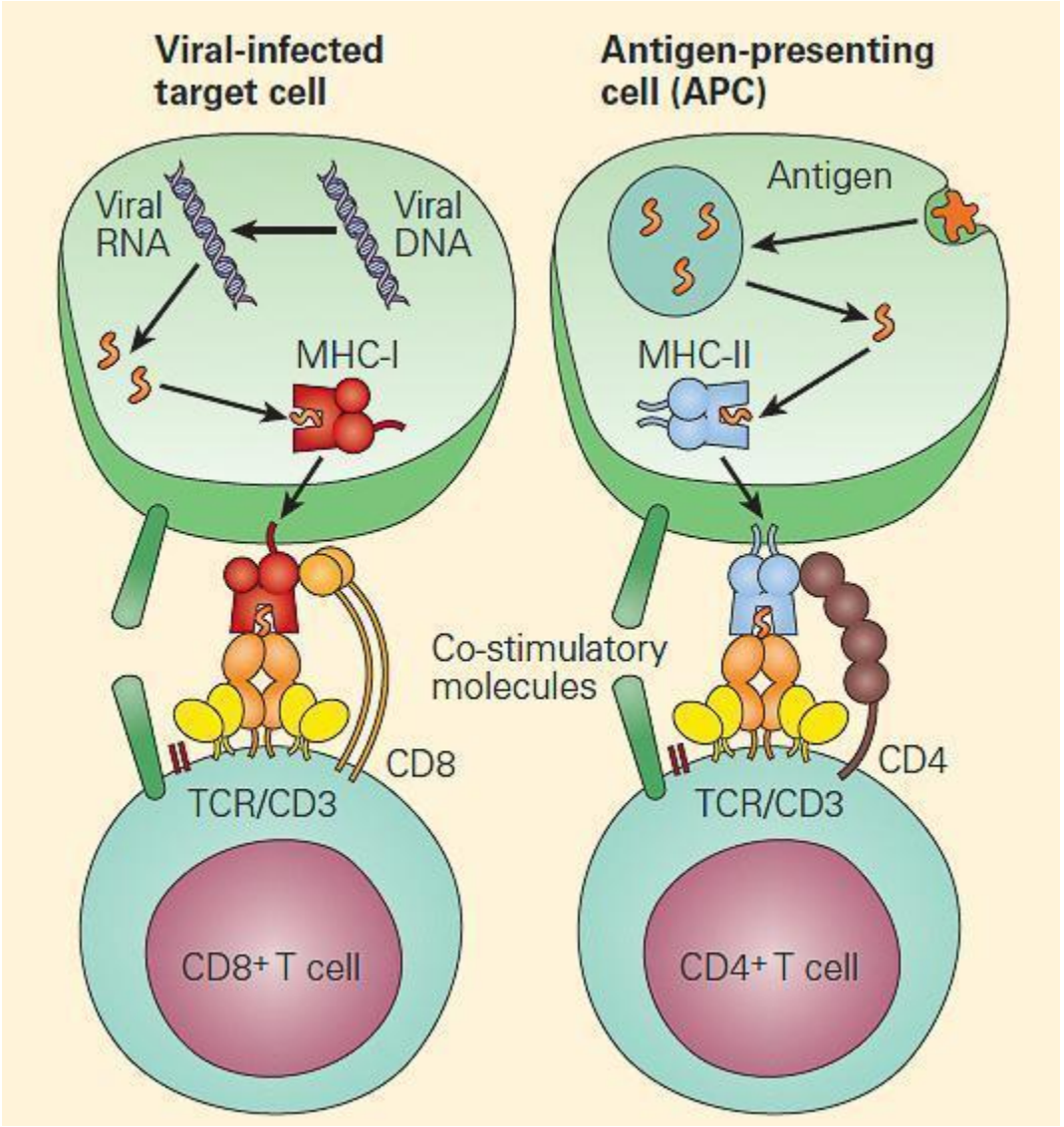
Viral Immun response

- A significant portion of the infectious virus particles entering the organism are phagocytosed and destroyed by macrophages before reaching the sensitive cells that they will infect.
- Short chain viral proteins formed after degradation in macrophages are presented to lymphocytes on the macrophage surface via MHC-II proteins.



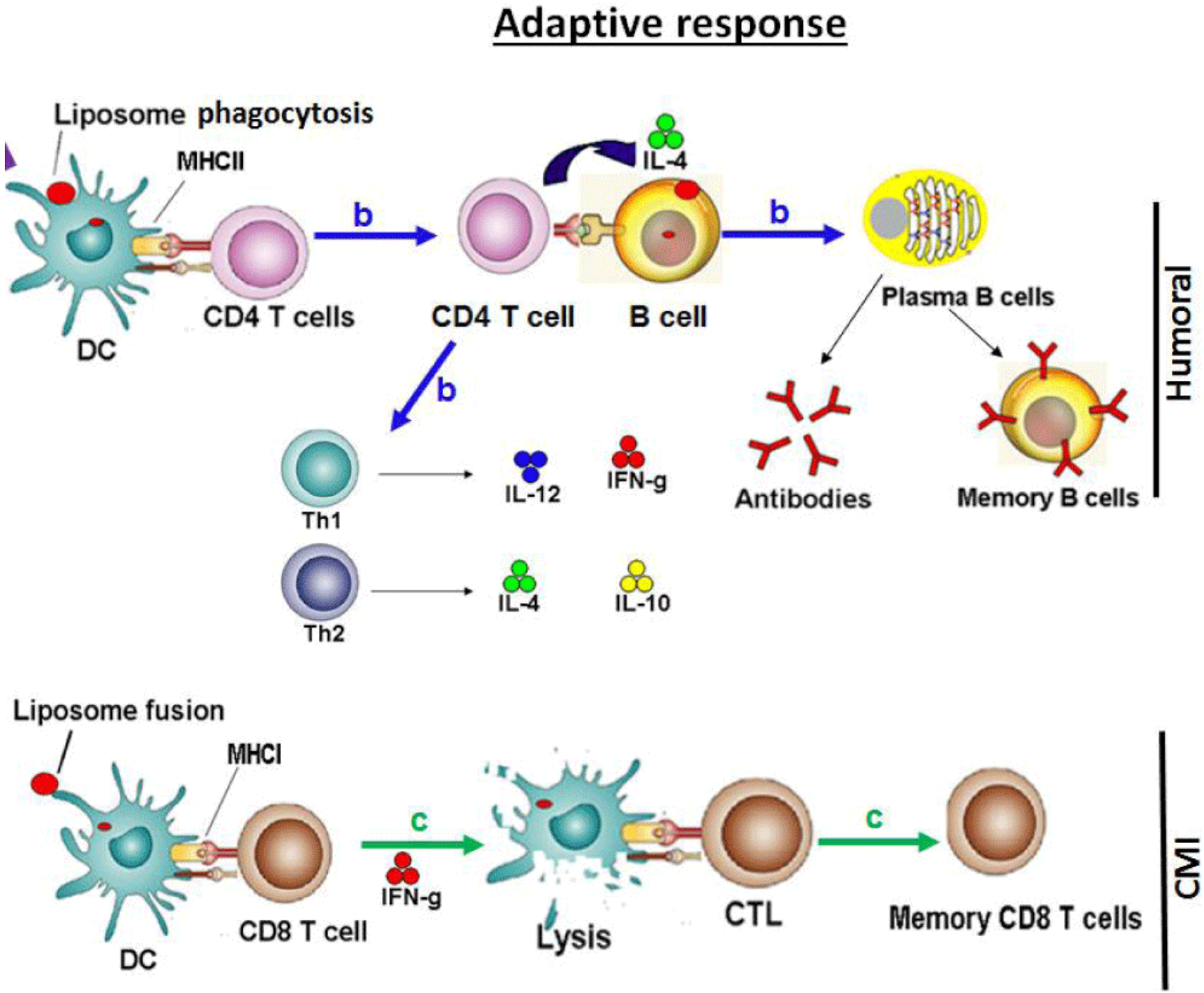
[Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012]

- The complex presented on the macrophage surface (MHC-II and viral antigen) is detected by helper T lymphocytes (CD4) and Th1 lymphocytes proliferate and begin to release lymphokines.
- These lymphokines enable circulating monocytes to migrate to the site of infection as well as proliferate and transform into active macrophages.
- Activated macrophages show high levels of chemotaxis, phagocytic properties, and the ability to degrade antigens.



[Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012]

- Th2 lymphocytes perform the secretion of a different lymphokine group.
- These lymphokines especially affect B lymphocytes bound to antigen, allowing them to multiply and transform into antibody-synthesizing plasma cells.
- Plasma cells formed in the early stages of the humoral response are short-lived and synthesize IgM class antibodies.
- At the next stage, affinity maturation occurs and longer-lived plasma cells and memory cells originating from high affinity B lymphocytes are formed.
- When viruses are intracellular, killing of virus-infected cells by cytotoxic T cells is the only possibility to eliminate the microbes. Therefore, the main function of cytotoxic T cells is the surveillance of the body for possible virus-infected cells. However, virus-infected cells can only be detected and eliminated by cytotoxic T cells, when peptides originating from viral proteins are presented by MHC-I proteins.



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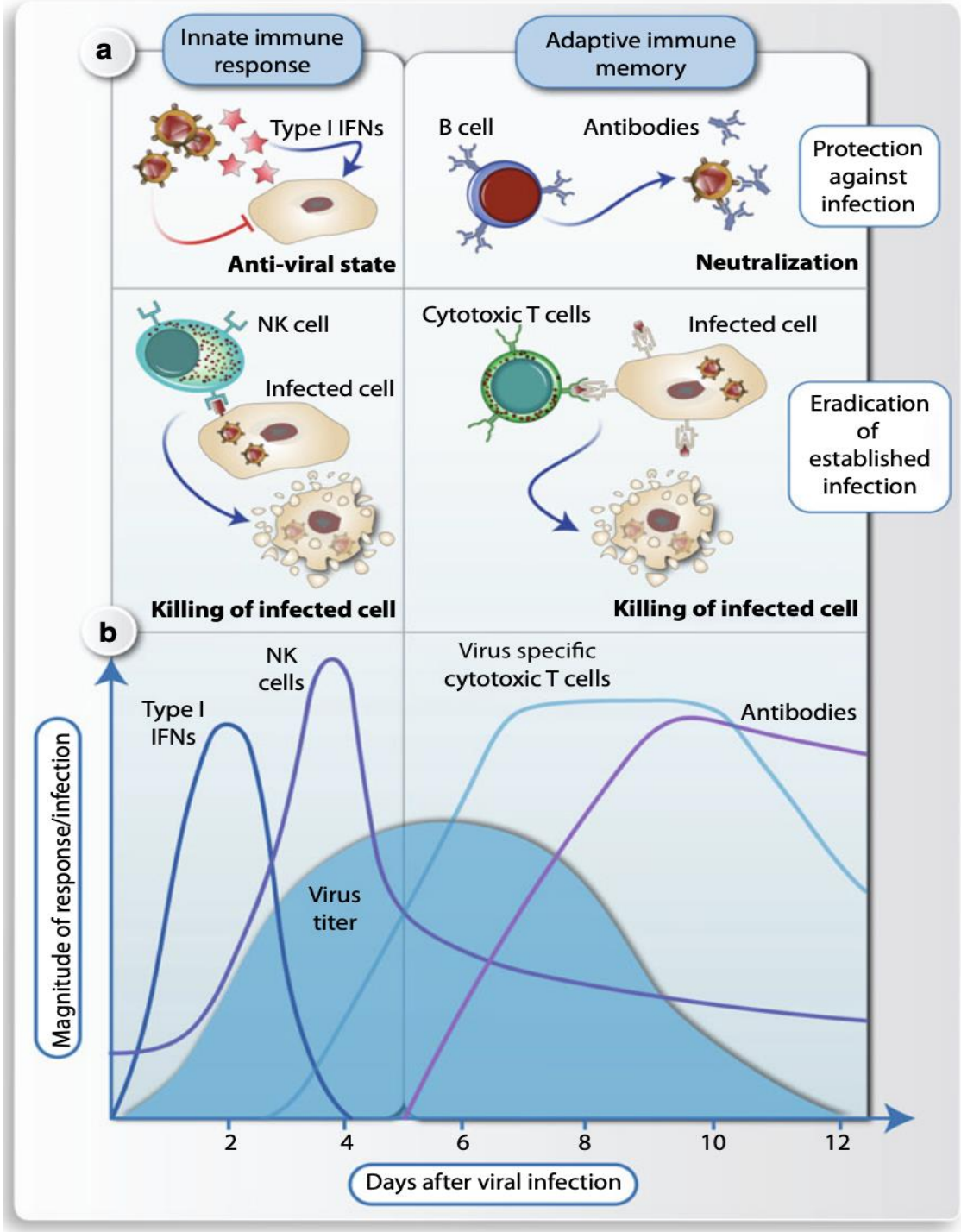

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