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Immune response to viral infections

- The immune system is the body's natural ability to defend against pathogens (e.g. viruses, bacteria) and resist infections
- Two types of immunity are:
  - **innate immunity** and
  - **adaptive immunity**

Innate immune response

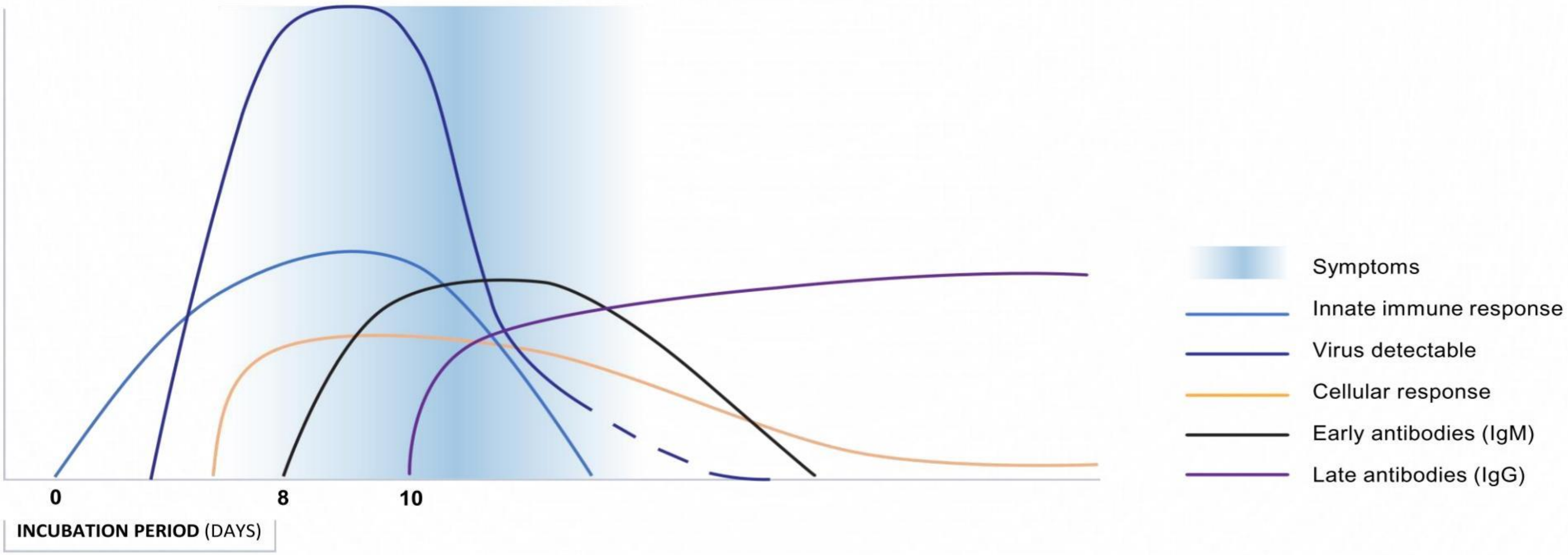
- First line of defence
- General immediate response to ANY infection
- Innate immune response cells secrete interferons[1] and other chemicals (cytokines)
- Interferons interfere with virus replication
- The innate response activates the adaptive immune response[2]

Adaptive immune response

- Second line of defence
- Specific response to the infection
- Starts after 6 - 8 days
- Involves two types of white blood cells
  - **T cells** (cellular response)
  - **B cells** (antibody response)

Immune response to viral infections

The innate immune response is immediate, whereas the cellular and antibody response usually starts after 6 to 8 days



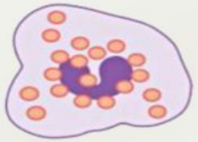
Innate immune response

- When a virus enters the body, **cells can recognize markers** present on the virus
- This results in non-specific antiviral activity
- **Cells of the innate system** (such as macrophages, neutrophils, dendritic cells and others) **are activated to remove pathogens and foreign cells** from the body and activate the adaptive immune response

Cells involved in the innate immune response

Macrophage
Phagocytic cell that consumes foreign pathogens; Stimulates response of other immune cells

Neutrophil
First responder at site of infection. Most common type of white blood cells. Releases toxins that kill bacteria and recruits other immune cells to site of infection



Natural killer cell
Kills virus infected cells and tumor cells

Dendritic cell
Presents antigen on its surface, thereby triggering the adaptive immune response

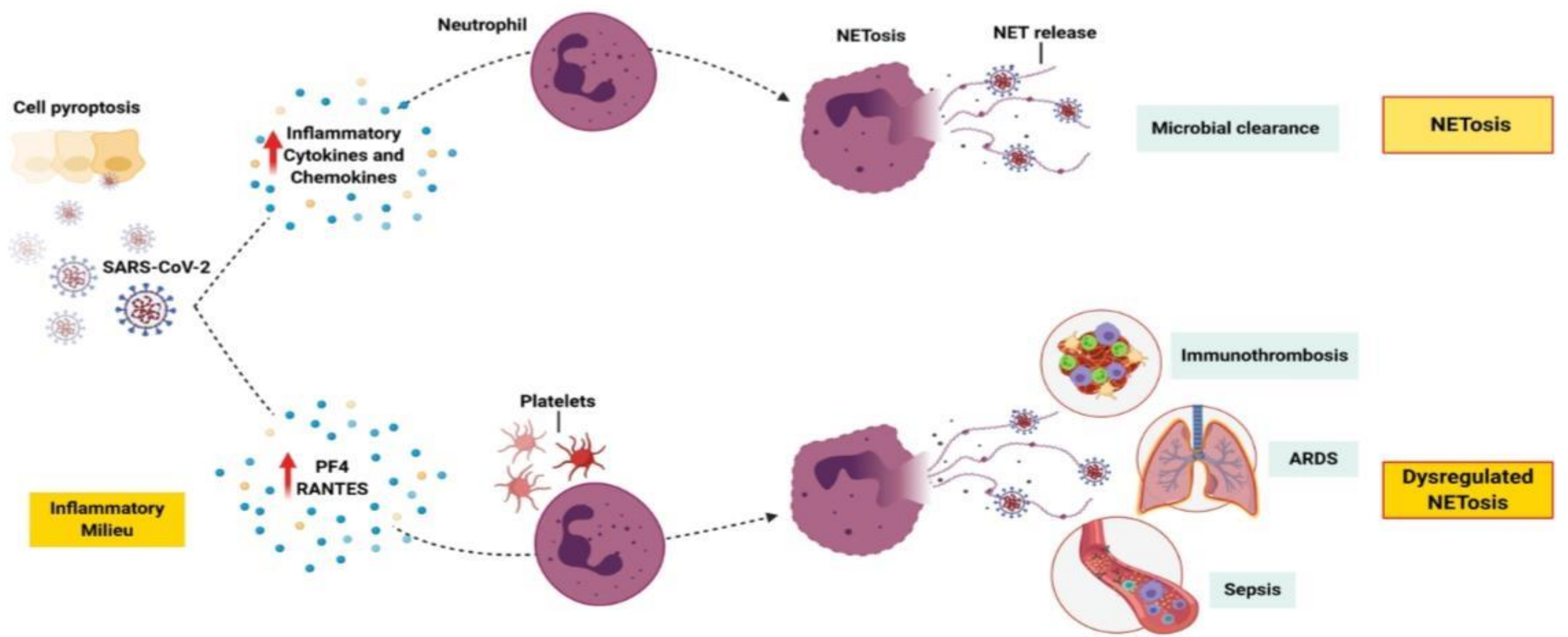
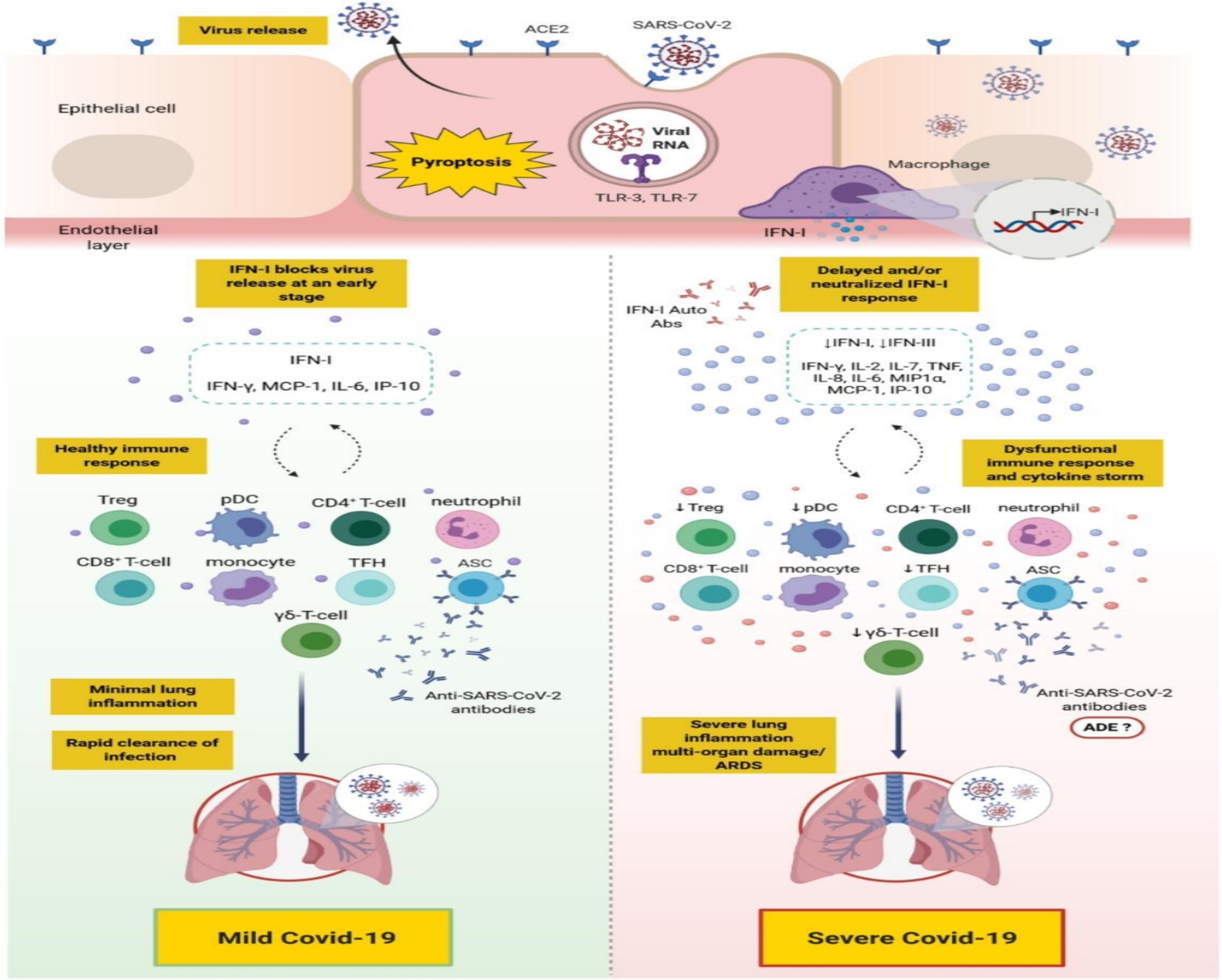


Figure 1 NETosis in severe Covid-19. SARS-CoV-2 infection and pyroptosis triggers the release of inflammatory cytokines and chemokines, which leads to the recruitment of neutrophils and other immune cells. Activation of neutrophils triggers NETosis, and the release of NETs to trap and kill the virus. However, a dysregulation in this process might lead to an increase in PF4 and RANTES, both of which are known to trigger NETosis. Activated platelets play a major role in NET-mediated tissue damage, and pathogenic immunothrombosis. In addition, NETosis contributes towards sepsis and ARDS.

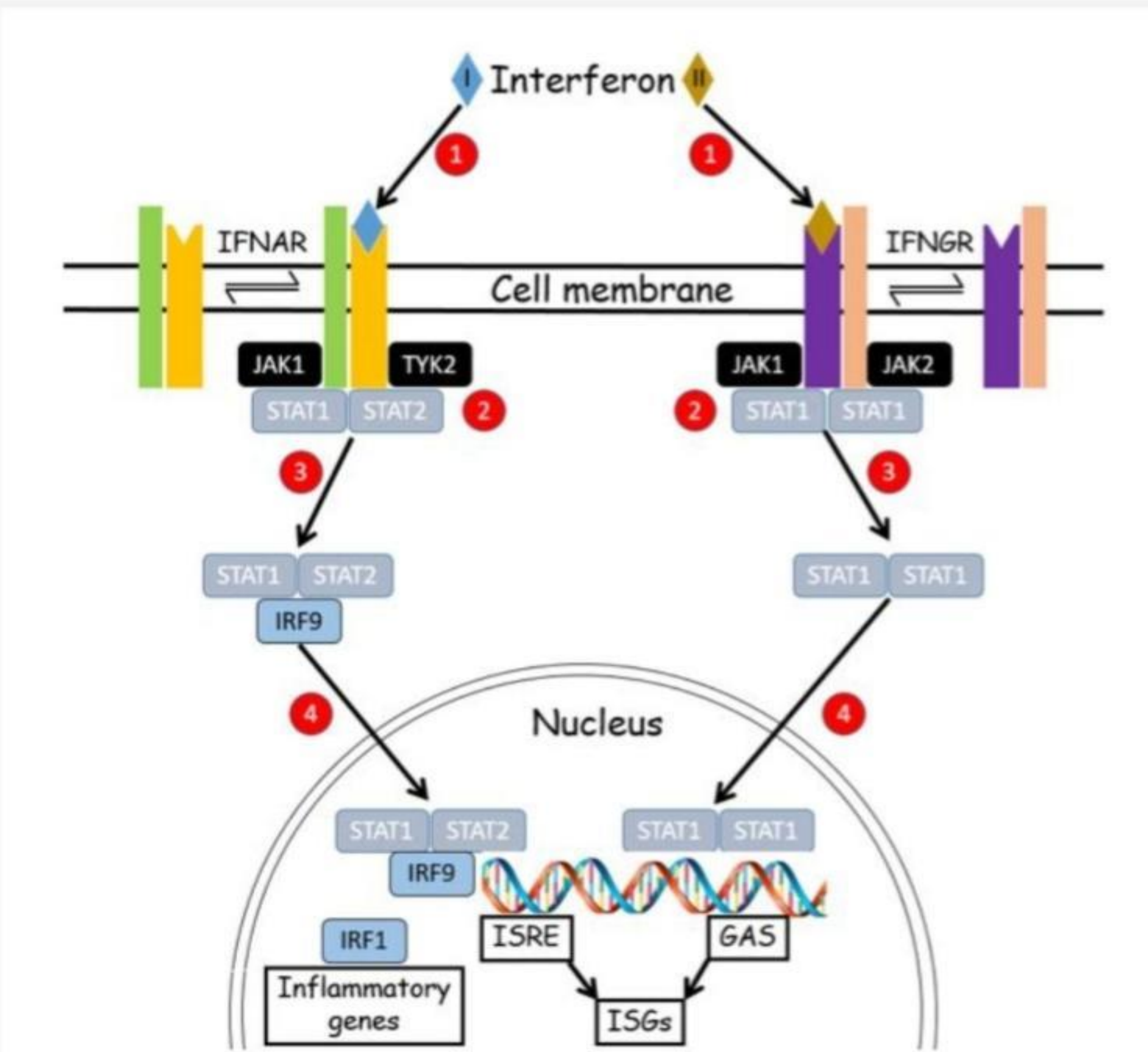
Note: This figure was created with BioRender.com.

Abbreviations: ARDS, acute respiratory distress syndrome; NET, neutrophil extracellular trap; PF4, plasma platelet factor 4; RANTES, regulated on activation, normal T-cell expressed and secreted; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



Virus release
ACE2
SARS-CoV-2
Epithelial cell
Pyroptosis
Viral RNA
TLR-3, TLR-7
Macrophage
IFN-I
IFN-I
Endothelial layer
IFN-I blocks virus release at an early stage
IFN-I
IFN-γ, MCP-1, IL-6, IP-10
Healthy immune response
Treg
pDC
CD4⁺ T-cell
neutrophil
CD8⁺ T-cell
monocyte
TFH
ASC
γδ-T-cell
Minimal lung inflammation
Rapid clearance of infection
Anti-SARS-CoV-2 antibodies
Mild Covid-19
Delayed and/or neutralized IFN-I response
IFN-I Auto Abs
↓IFN-I, ↓IFN-III
IFN-γ, IL-2, IL-7, TNF, IL-8, IL-6, MIP1α, MCP-1, IP-10
Dysfunctional immune response and cytokine storm
↓Treg
↓pDC
CD4⁺ T-cell
neutrophil
CD8⁺ T-cell
monocyte
↓TFH
ASC
↓γδ-T-cell
Anti-SARS-CoV-2 antibodies
ADE ?
Severe lung inflammation multi-organ damage/ ARDS
Severe Covid-19

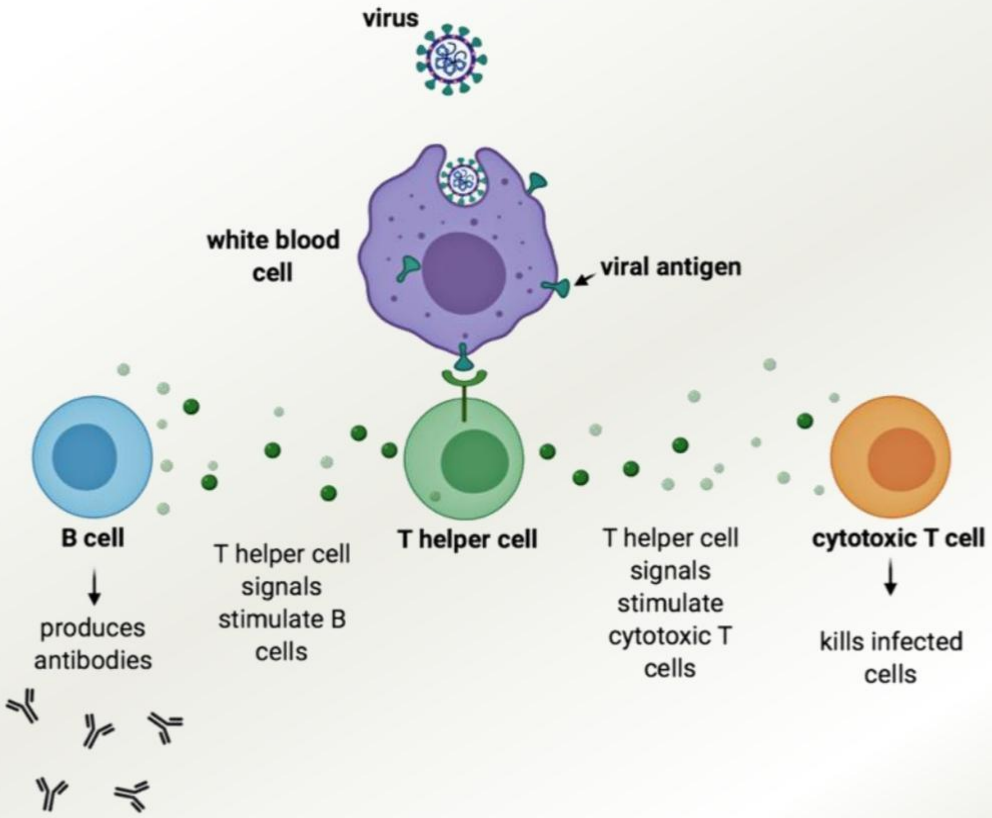
- Interferons, released from secretory cells, bind to receptors in the cell membrane.
- They activate JAK-STAT pathways.
- After phosphorylation by Janus and tyrosine kinases, STAT molecules bind to interferon regulatory factors (IRFs) and enter the nucleus.



Adaptive immune response: T cells

T cells (cellular response)

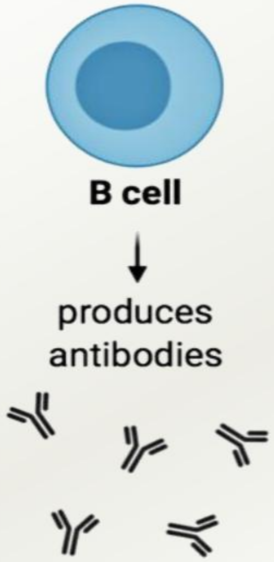
- **T cells recognize cells that are infected with a specific virus** and rapidly increase in number to tackle the infection
- Types of T cells:
  - **CD4+ helper T cells** bring in other cells of the immune system and stimulate B-cells to produce antibodies specific to that virus
  - **CD8+ cytotoxic T cells** kill the cells in which the virus is multiplying and help to slow down or stop the infection



Adaptive immune response: B cells

B cells (antibody response)

- **B cells produce antibodies** that are specific to the virus
- **IgM antibodies** are produced first and disappear after a few weeks
- **IgG antibodies** are produced at the same time or a couple days later, and titres (levels) usually remain for months or years



Memory cells

- **Once the infection is over**, the T cells and B cells decline in number, but some cells will remain (memory cells)
- Memory cells respond rapidly if they come in contact with the same virus again, killing the virus and accelerating an antibody response

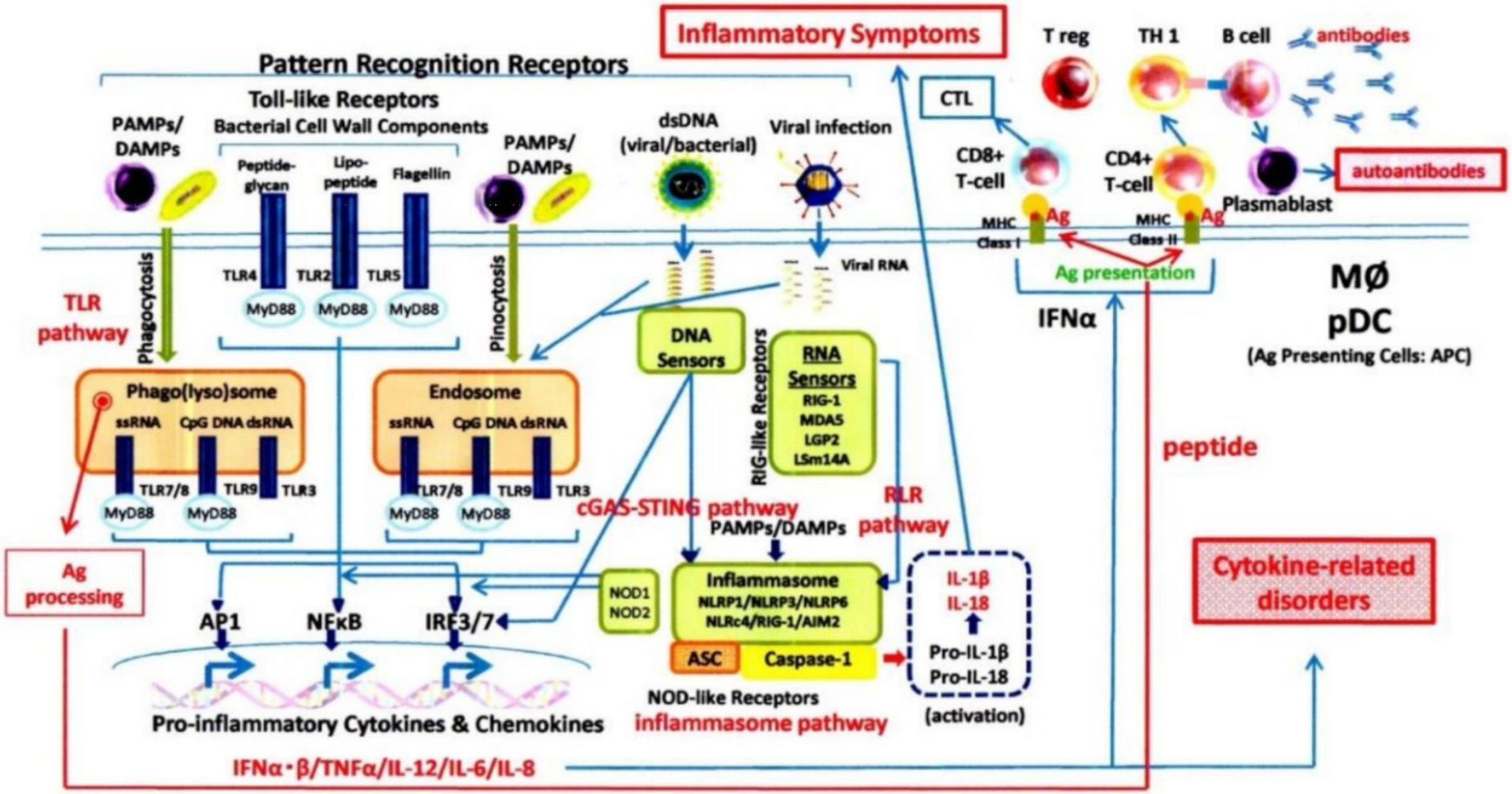
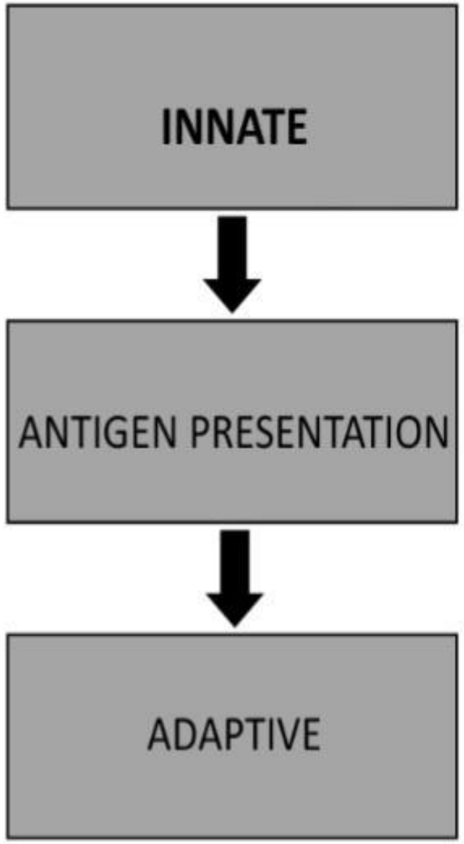


Figure 1. The innate immune system and acquired immune system.

Brief Review of Immunology

- **Innate:**
  - Early response
  - Recognizes **general, non-specific** pathologic stimuli
  - No "memory"

- **Adaptive:**
  - **Delayed** response
  - Humor and cellular components
  - Responds to specific, pathogenic antigens
  - Generate immunological memory

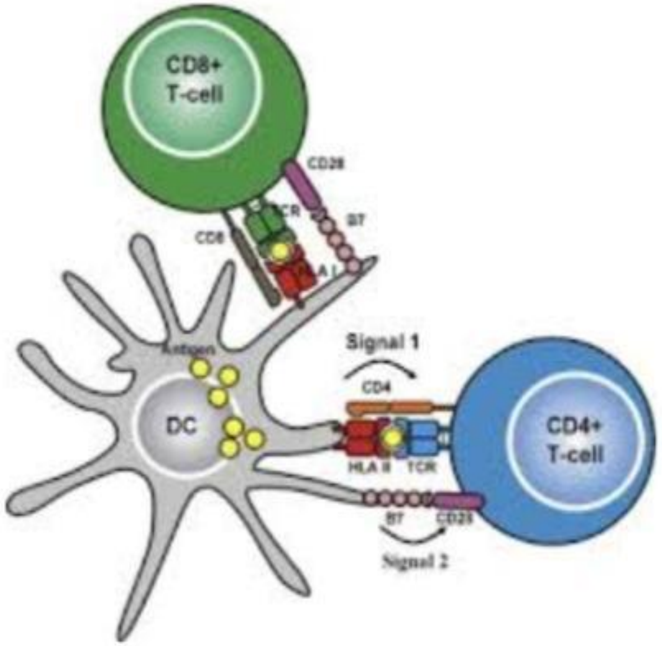


Brief Review of Immunology

<u>Cytotoxic T-cells</u> (CD8) directly kill nucleated cells expressing specific peptide-MHC Class I complex

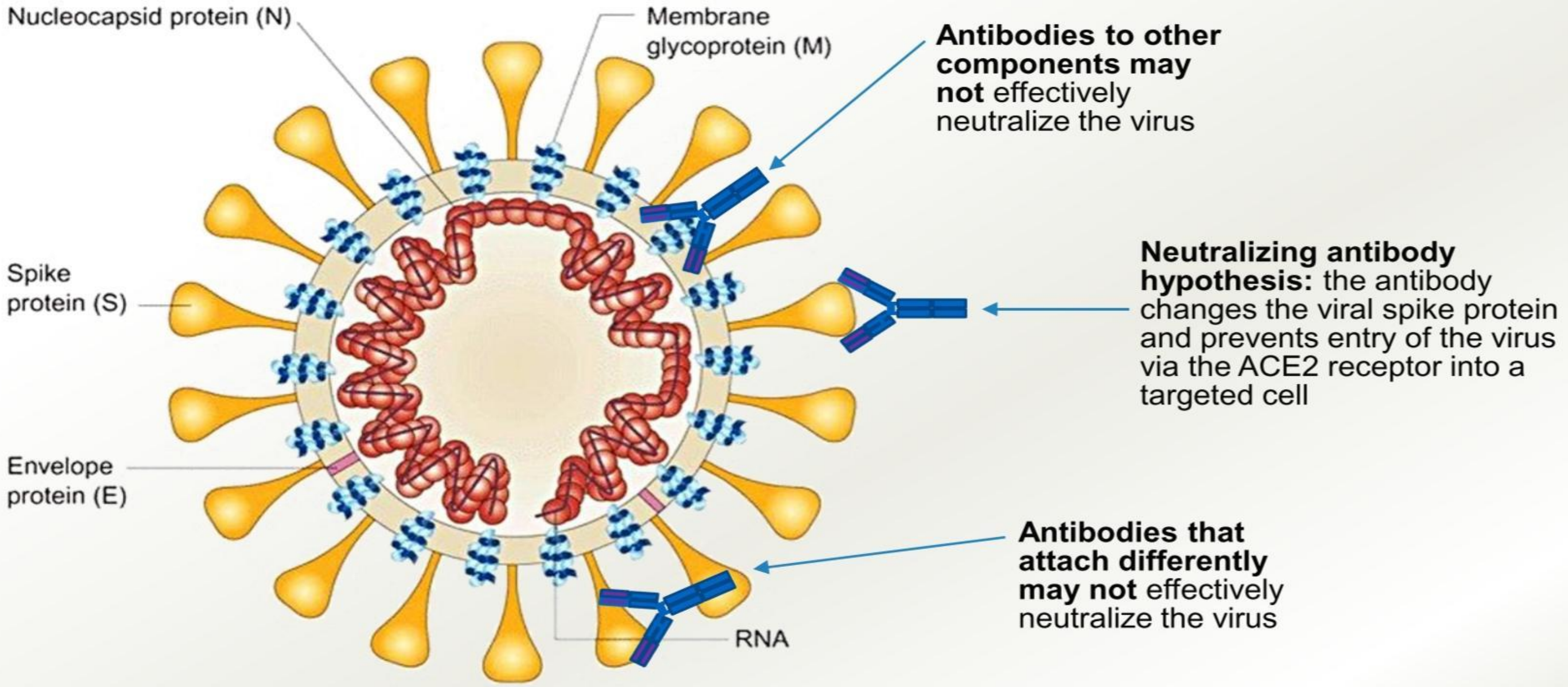
<u>Helper T-cells</u> (CD4) coordinate the immune response, release cytokines, and promote B-cell antibody class switching

<u>B-cells</u> are primarily responsible for antibody production



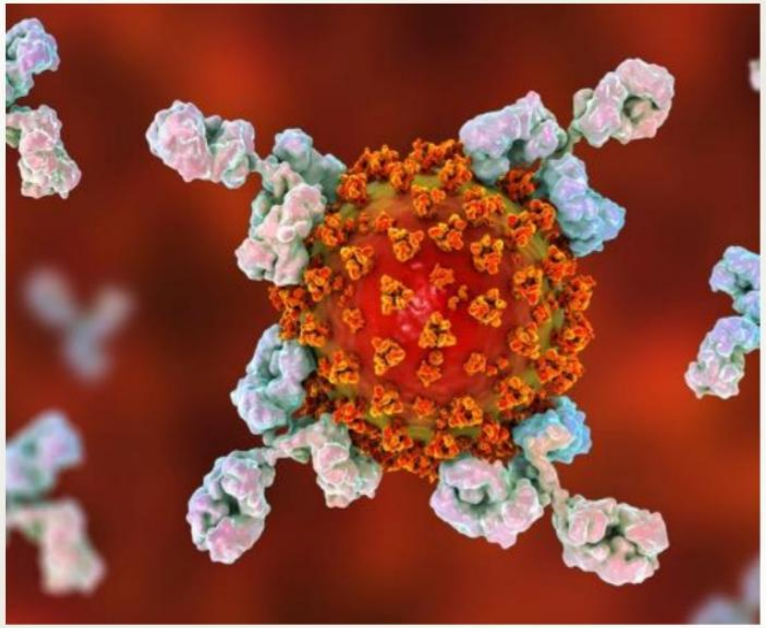
Neutralizing antibodies bind to viral proteins

Components of the SARS-CoV-2 virus



Antibody response to SARS-CoV-2

- **Most COVID-19 patients who recover have antibodies** to SARS-CoV-2 detectable in their blood
- Most COVID-19 patients develop antibodies about 1-3 weeks after symptoms appear. Many patients start to recover during this time.
- **Patients who have had more severe disease appear to have higher levels of neutralizing antibodies.** While, patients who had mild or asymptomatic COVID-19 have lower levels of neutralizing antibodies.
- Several studies* show that antibodies **remain for several months in individuals who tested positive**, for example a study of more than 30,000 individuals with mild to moderate COVID-19 found that neutralizing antibody titres persisted for at least 5 months after SARS-CoV-2 infection



T cell response to SARS-CoV-2

- It is possible that in persons with **low levels of neutralizing antibodies**, the innate immune response and the T cell response clears the virus
- Some studies show that persons exposed to SARS-CoV-2 may develop virus-specific T cell responses without detectable circulating antibodies
  - ➢ This may mean that persons who have had mild COVID-19 or were asymptomatic can generate memory T-cell responses to prevent recurrent infection in the absence of antibodies
- Some T cells in persons without exposure to SARS-CoV-2 have been found to cross-react with SARS-CoV-2 (possibly due to prior exposure to other coronaviruses)
  - ➢ This may mean that persons with reactive T-cells will get less severe disease if exposed to SARS-CoV-2

Re-infection of SARS-CoV-2

- Generally, a person who recovered from a viral infection is protected against a new infection
- It is not yet known how long protection will last after a SARS-CoV-2 infection
- To date, re-infection with SARS-CoV-2 seems rare but several cases of repeat SARS-CoV-2 infection have been reported
- Preliminary results from the *SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN)* study conclude that **past SARS-CoV-2 infection reduces the risk of re-infection by 83% for at least 5 months** and that **fewer than 1% of 6,600 study participants who had COVID-19 were re-infected**

SIREN
SARS-CoV2 Immunity & Reinfection Evaluation

SARS-CoV-2 variants & re-infection

- **Changes in the virus genomic sequence**, called mutations, **can make prior immunity less effective** (e.g. as with the influenza virus)
- Recently, several SARS-CoV-2 variants have emerged that involve genetic mutations of the spike protein
- Studies are ongoing to investigate if some of these variants can evade the immune response to a previous SARS-CoV-2 infection and make people more vulnerable to re-infection
- In lab experiments, one of the mutations present in the variants identified in South Africa and Brazil has helped the virus evade antibodies generated after an initial infection
- In Brazil, studies are ongoing to determine if a new variant called P.1 may lead to more cases of re-infection

Thank You,
Any Questions?