BUNĚČNÁ IMUNITA

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Wikipedie

Imunitní odpověď proti virům je nedílnou součástí funkce imunitního systému, na které se podílí jak vrozená, tak adaptivní složka imunity.

Z přirozené imunitní odpovědi se jedná především o interferony I. typu, jejichž signalizační dráhy jsou spuštěny přes receptory rozpoznávající molekulární vzory (pattern recognition receptors): Toll-like receptory
NOD-like receptory
RIG-like receptory

Z adaptivní imunitní odpovědi jsou to NK buňky a cytotoxické CD8+ T lymfocyty.

British Society for immunology

Immune responses to viruses

Via cytotoxic cells

When a virus infects a person (host), it invades the cells of its host in order to survive and replicate. Once inside, the cells of the immune system cannot 'see' the virus and therefore do not know that the host cell is infected. To overcome this, cells employ a system that allows them to show other cells what is inside them – they use molecules called **class I major histocompatibility complex proteins** (or **MHC class I**, for short) to display pieces of protein from inside the cell upon the cell surface. If the cell is infected with a virus, these pieces of peptide will include fragments of proteins made by the virus.

A special cell of the immune system called a **T cell** circulates looking for infections. One type of T cell is called a **cytotoxic T cell** because it kills cells that are infected with viruses with toxic mediators. Cytotoxic T cells have specialised proteins on their surface that help them to recognise virally-infected cells. These proteins are called **T cell receptors** (**TCRs**). Each cytotoxic T cell has a TCR that can specifically recognise a particular antigenic peptide bound to an MHC molecule. If the T cell receptor detects a peptide from a virus, it warns its T cell of an infection. The T cell releases **cytotoxic factors** to kill the infected cell and, therefore, prevent survival of the invading virus

Cytotoxické T lymfocyty s pomocí NK buněk kontrolují virové infekce a nádory

British Society for immunology

Immune responses to viruses

Via interferons

Virally infected cells produce and release small proteins called **interferons**, which play a role in immune protection against viruses. Interferons prevent replication of viruses, by directly interfering with their ability to replicate within an infected cell. They also act as signalling molecules that allow infected cells to warn nearby cells of a viral presence – this signal makes neighbouring cells increase the numbers of MHC class I molecules upon their surfaces, so that T cells surveying the area can identify and eliminate the viral infection as described above.

Cytotoxické T lymfocyty s pomocí NK buněk kontrolují virové infekce a nádory

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Immune responses to viruses

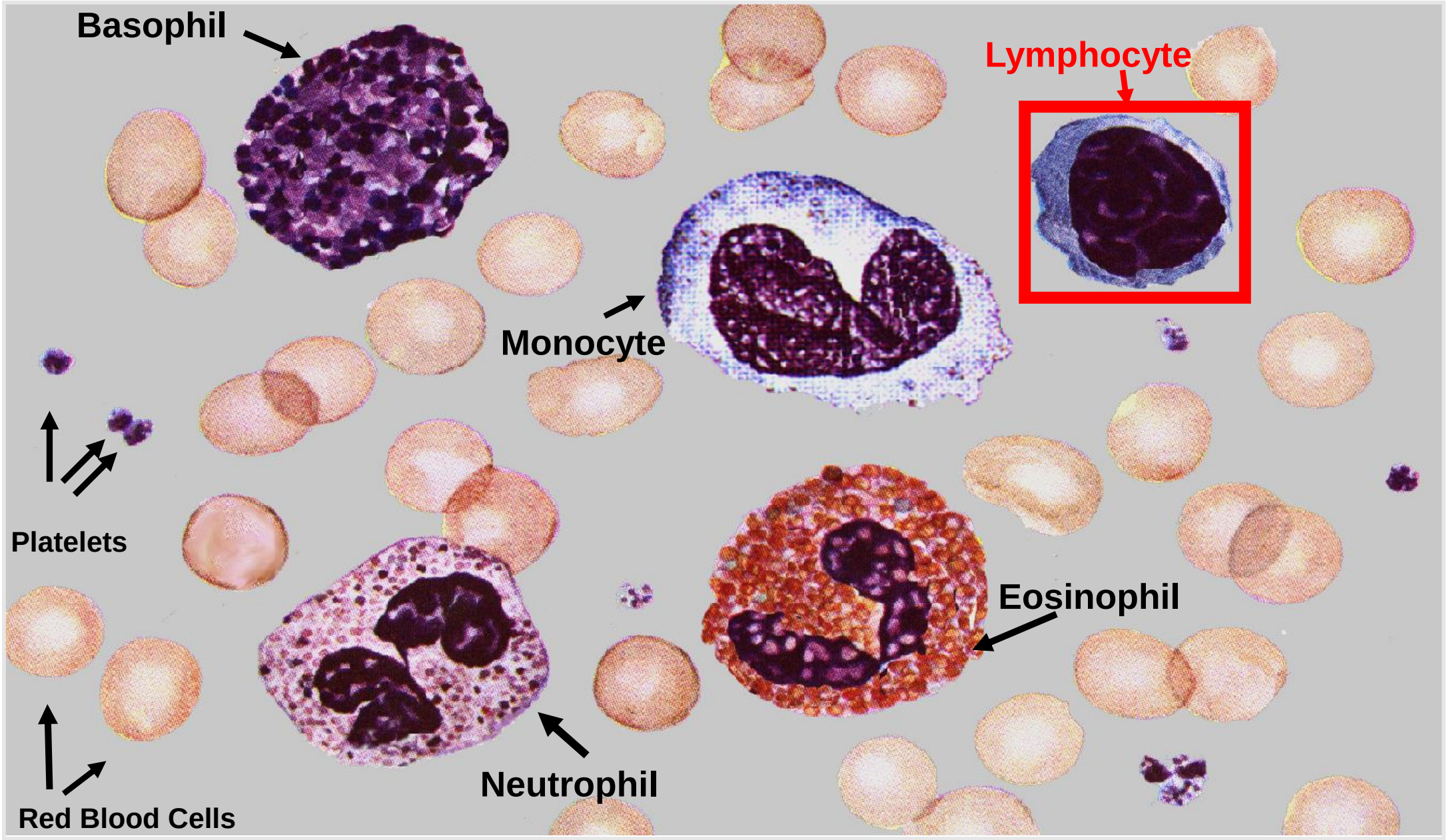
Via antibodies

Viruses can also be removed from the body by **antibodies** before they get the chance to infect a cell. Antibodies are proteins that specifically recognise invading pathogens and bind (stick) to them. This binding serves many purposes in the eradication of the virus:

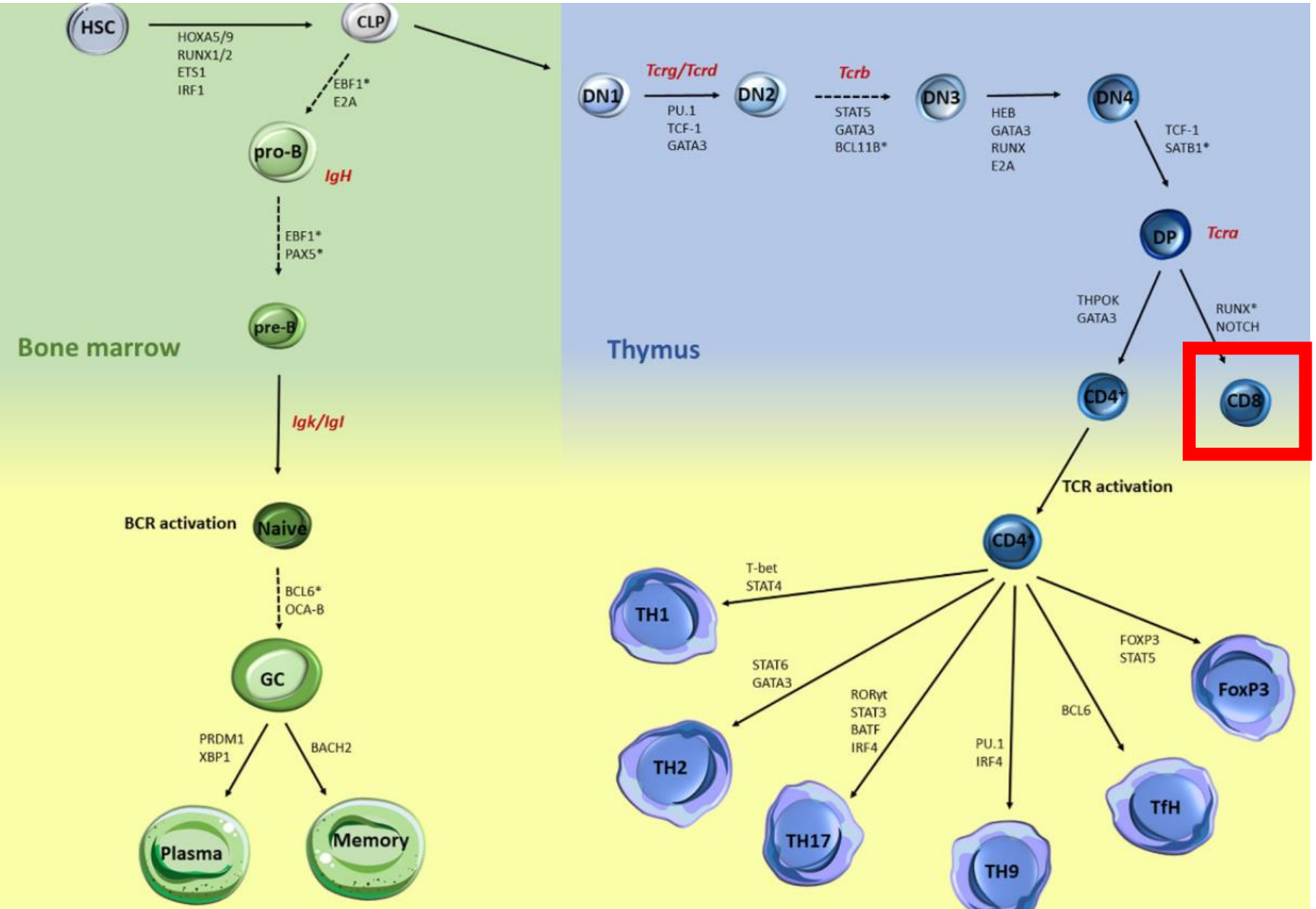
- Firstly, the antibodies neutralise the virus, meaning that it is no longer capable of infecting the host cell.
- Secondly, many antibodies can work together, causing virus particles to stick together in a process called **agglutination**. Agglutinated viruses make an easier target for immune cells than single viral particles.
- A third mechanism used by antibodies to eradicate viruses, is the activation of phagocytes. A virus-bound antibody binds to receptors, called Fc receptors, on the surface of phagocytic cells and triggers a mechanis known as **phagocytosis**, by which the cell engulfs and destroys the virus.
- Finally, antibodies can also activate the complement system, which opsonises and promotes phagocytosis viruses. Complement can also damage the envelope (phospholipid bilayer) that is present on some types o virus

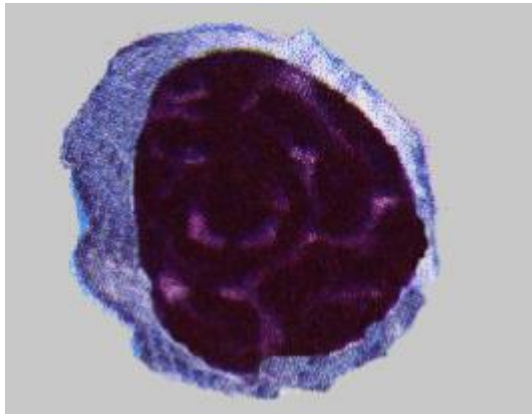
Cytotoxické T lymfocyty s pomocí NK buněk kontrolují virové infekce a nádory

Cellular immunity = Cell-mediated immunity ?



B and T Lymphocytes = Adaptive Immunity

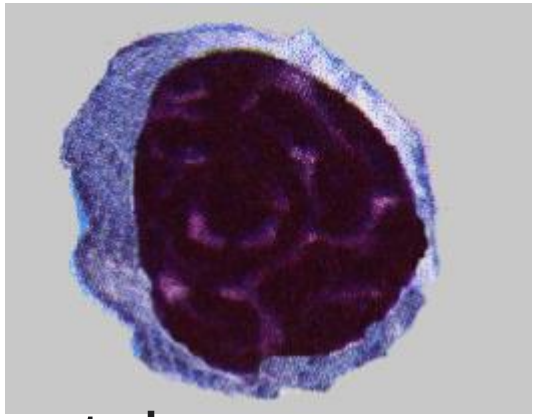




NK cells

are an “exception”, probably representing the first try to develop QC of somatic cell content

Adaptive immunity exists in Vertebrates



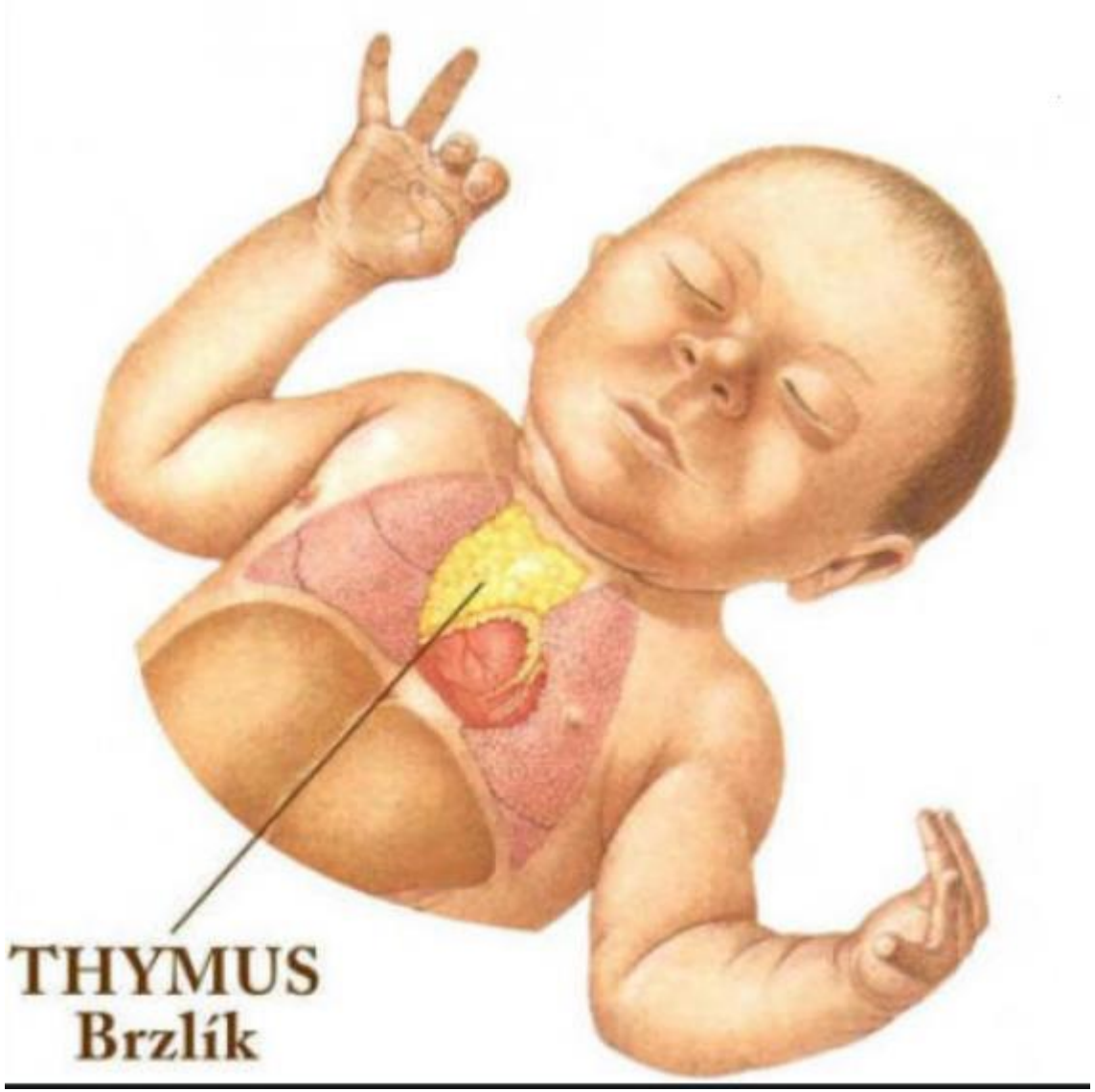
Lymphocytes:

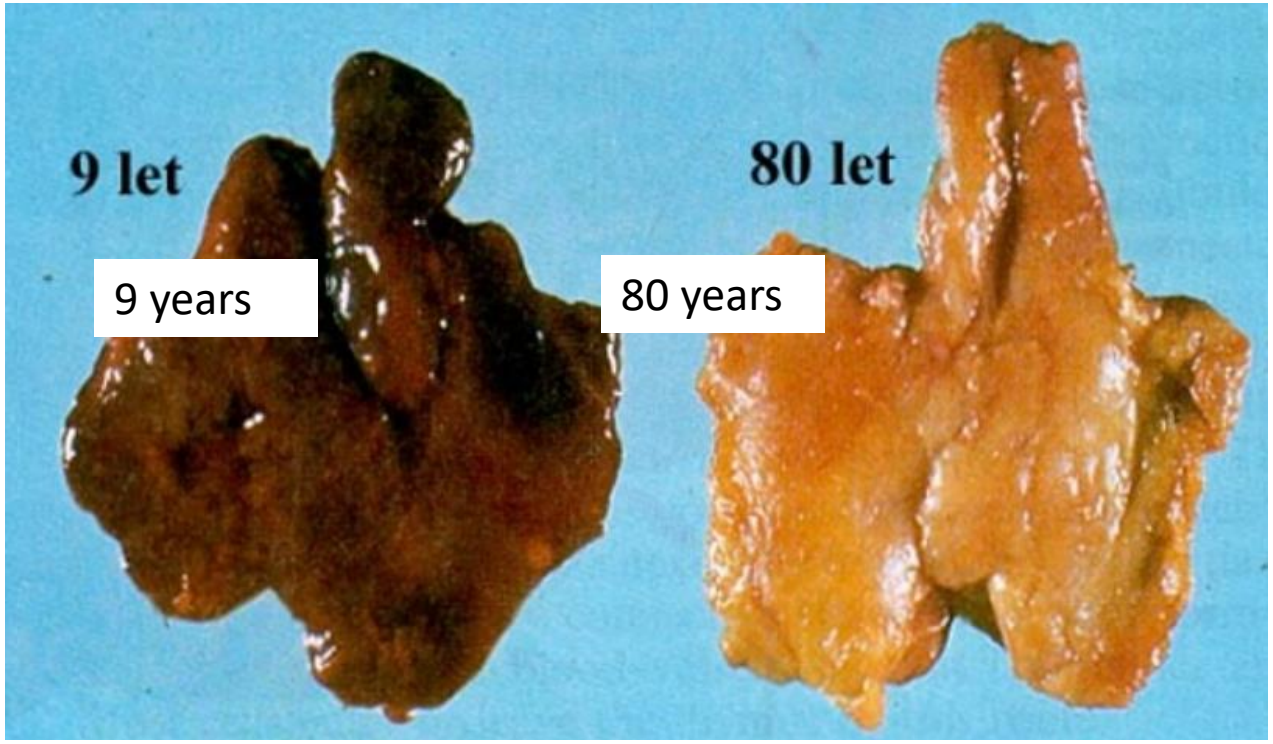
NK cells: kill somatic cells that are defective in antigen (protein fragment = peptide) presentation (missing self)

T-cells: kill somatic cells that bear „unknown“ protein fragments (peptides) on their surface – viral, oncogenic and transplanted material. A subset of T-cells (CD4+) is involved in immune system regulation, which also includes antibody formation. **The other CD8+ subset** is dedicated to quality control of protein synthesis – seek and kill.

B-cells: under precisely controlled conditions costume their randomly generated antibodies to perfectly fit to foreign “soluble” material

Thymus

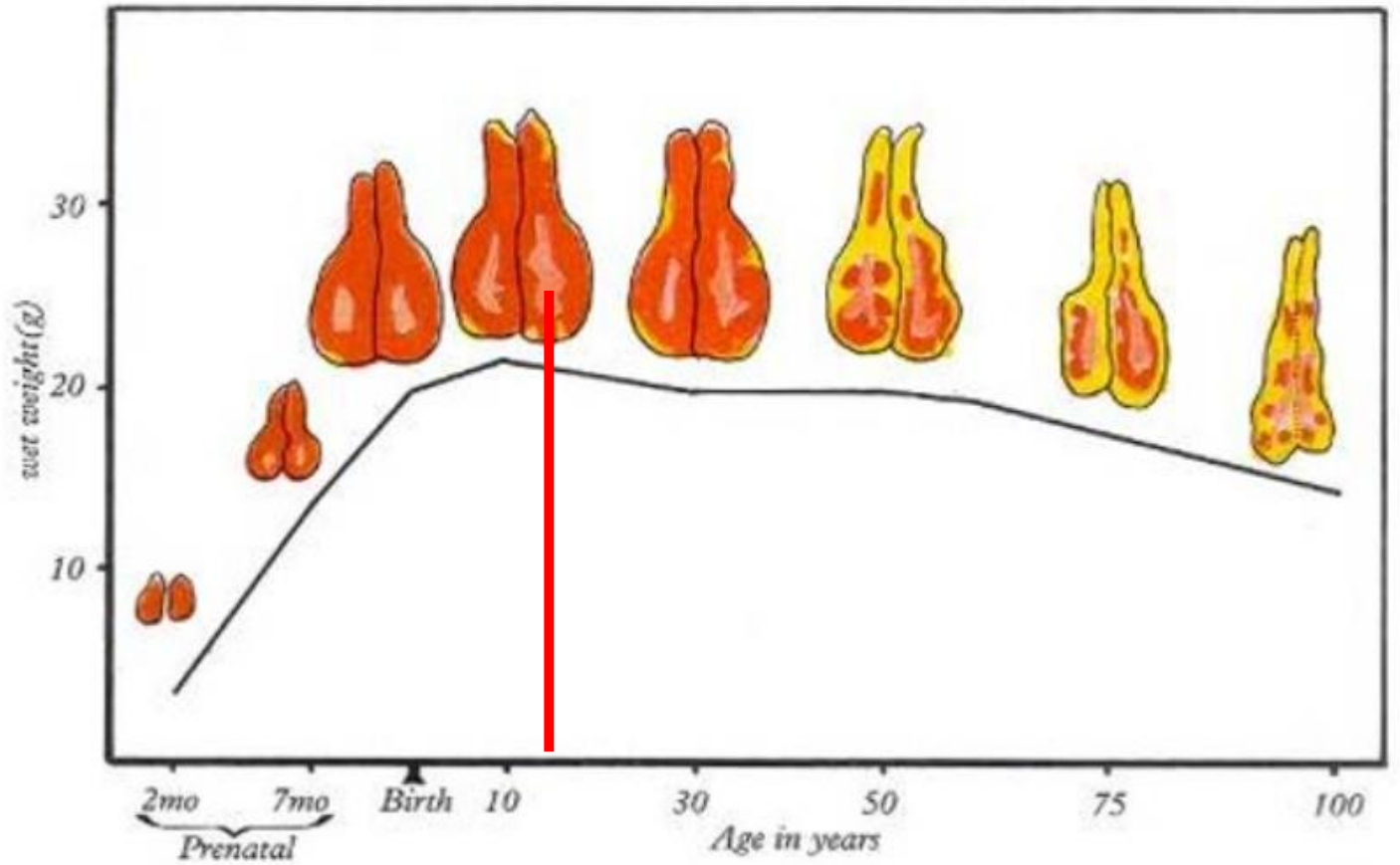




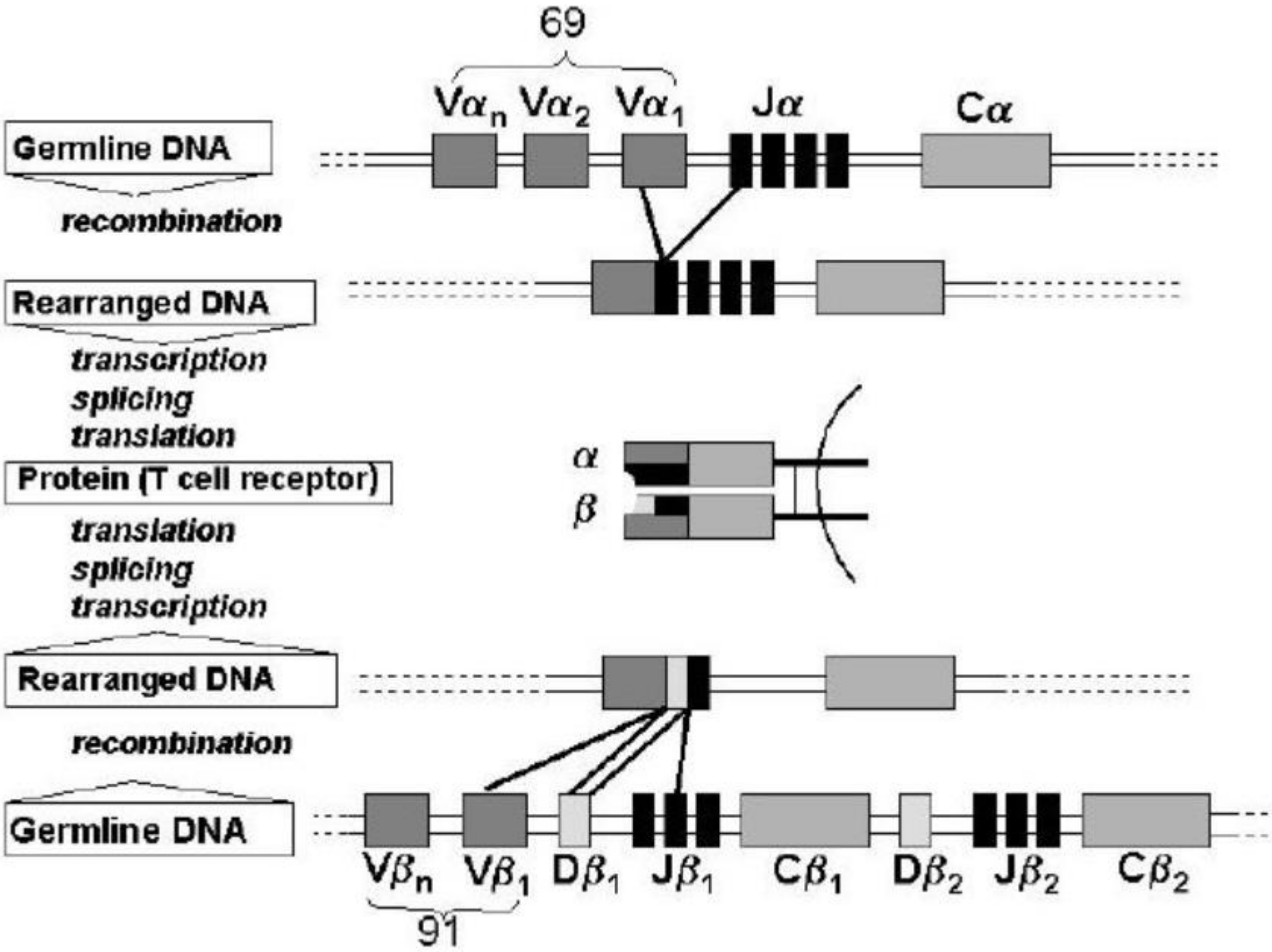
Thymus

- Starts its function in the 10th week of intrauterine development
- Mass in newborns: 15 - 25 g (0.5 až 1 % of body mass).
- Maximum relative size at the age of 3 years, in 12-year old childern - 35 g.

In puberty, involution of the thymus begins. Why?
T-cell production takes a lot of material and energy,
For 1 functional T-cell in the body, 99 „trainees“ will die.



T cell receptor rearrangement (formation)



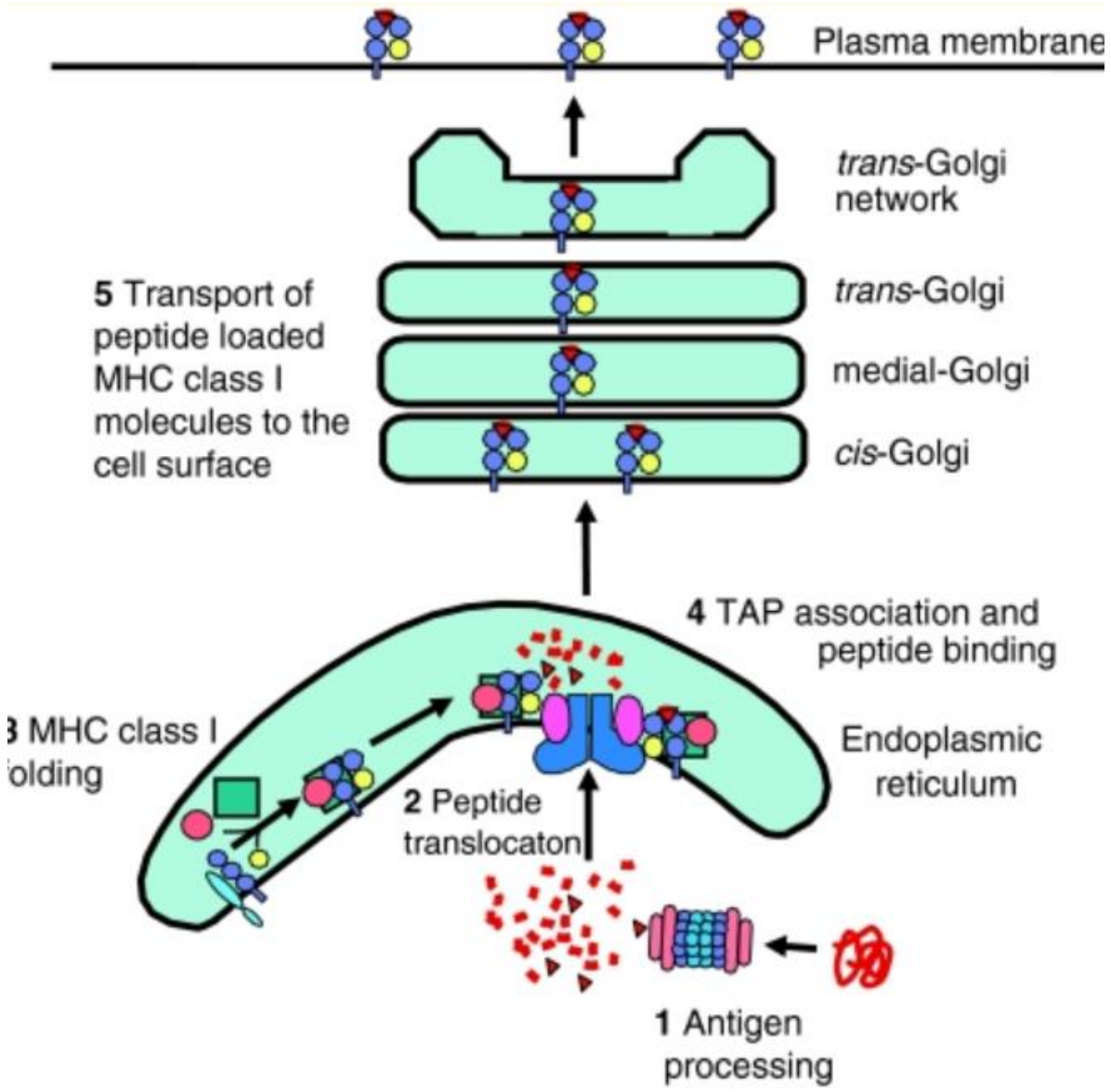
T cell development and maturation in the thymus

T-cell precursors arrive to thymus from bone marrow. In the cortex they make their receptors (TCR). And many of them die after randomly due to non-productive rearrangement. When rearranged genes are „readable“, thymocytes are tested for the capability of recognizing individual’s cells (positive selection). In medulla, the cells are tested for the ability to recognize self antigens. Thise that can feel anything die as they could represent a danger (autoimmunity). It has been estimated that less than 1 % of thymocyte “trainess” leave the thymus with one and the only task – to kill somatic cells bearing a foreign protein fragment peptide) on their surface.

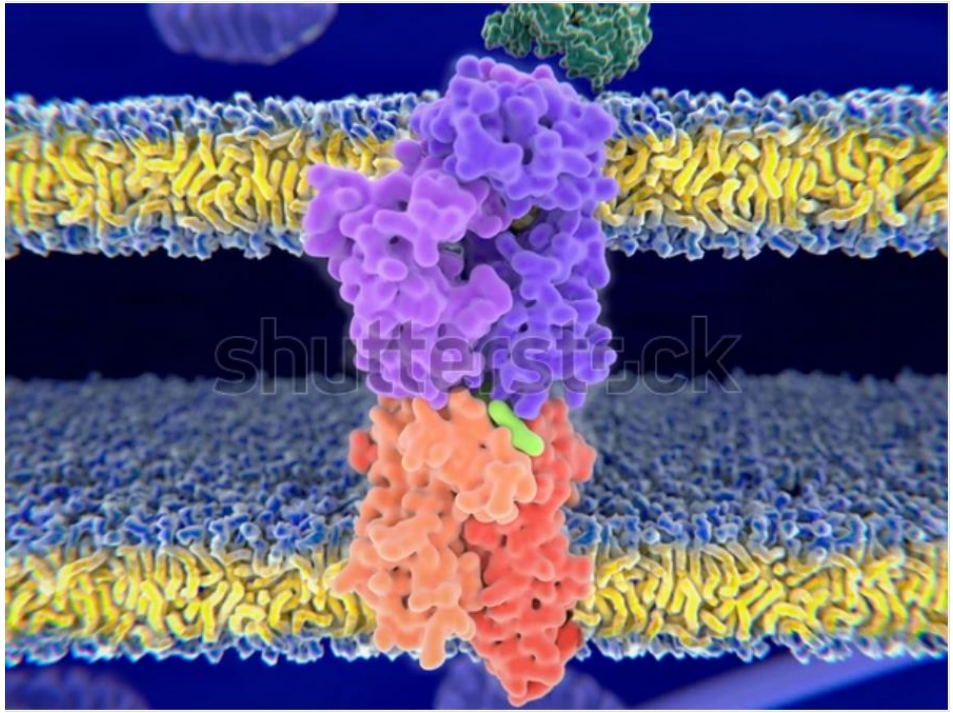
The process of thymocyte selection makes perfect killers for the expense of a lot of energy and material losses.

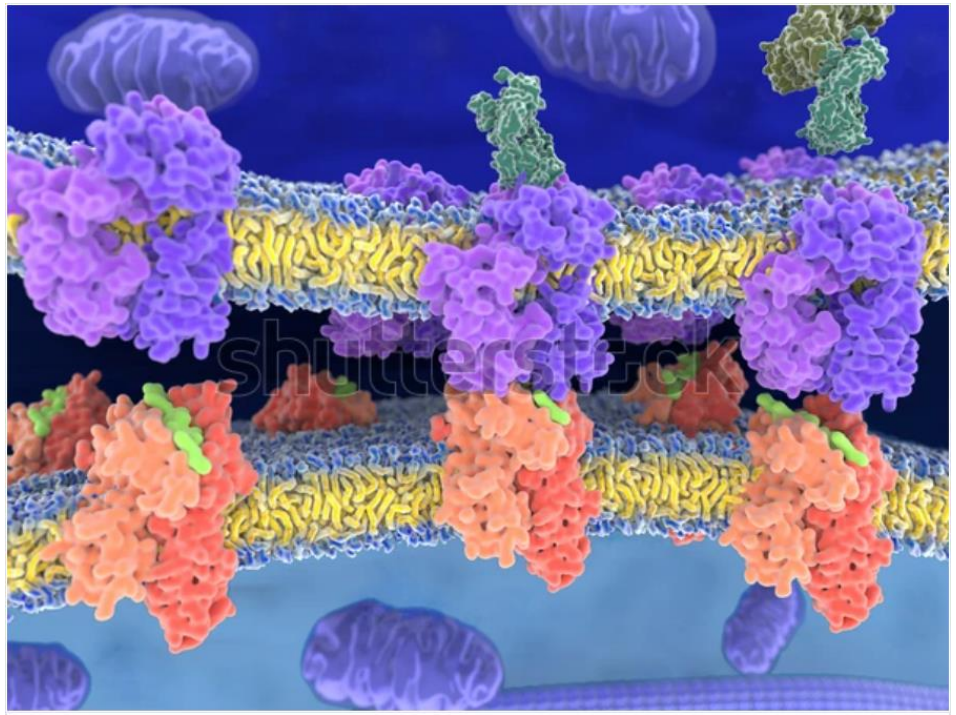
That is why it must switched-off when other taks (reproduction, hunting and collection start)

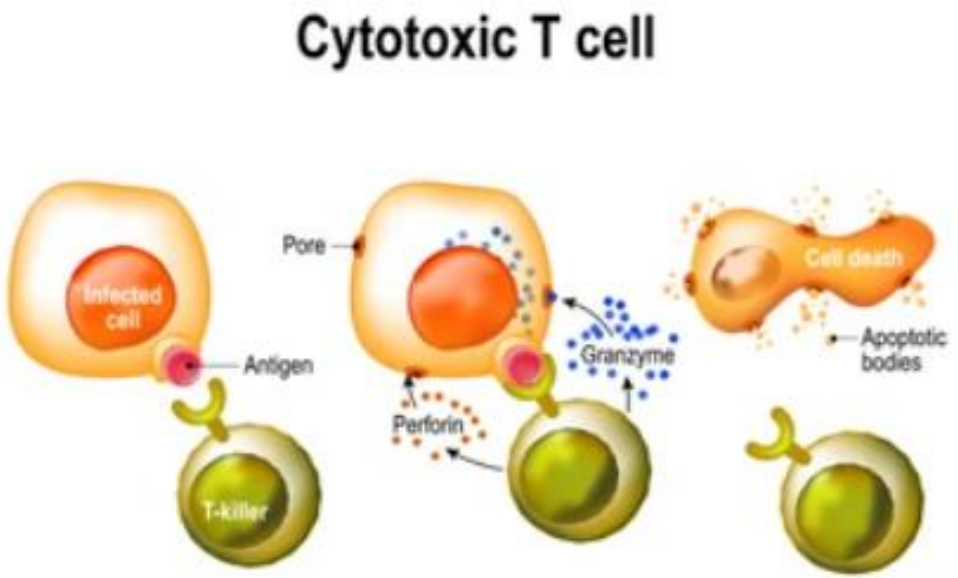
Antigen processing for peptide presentation to CTL



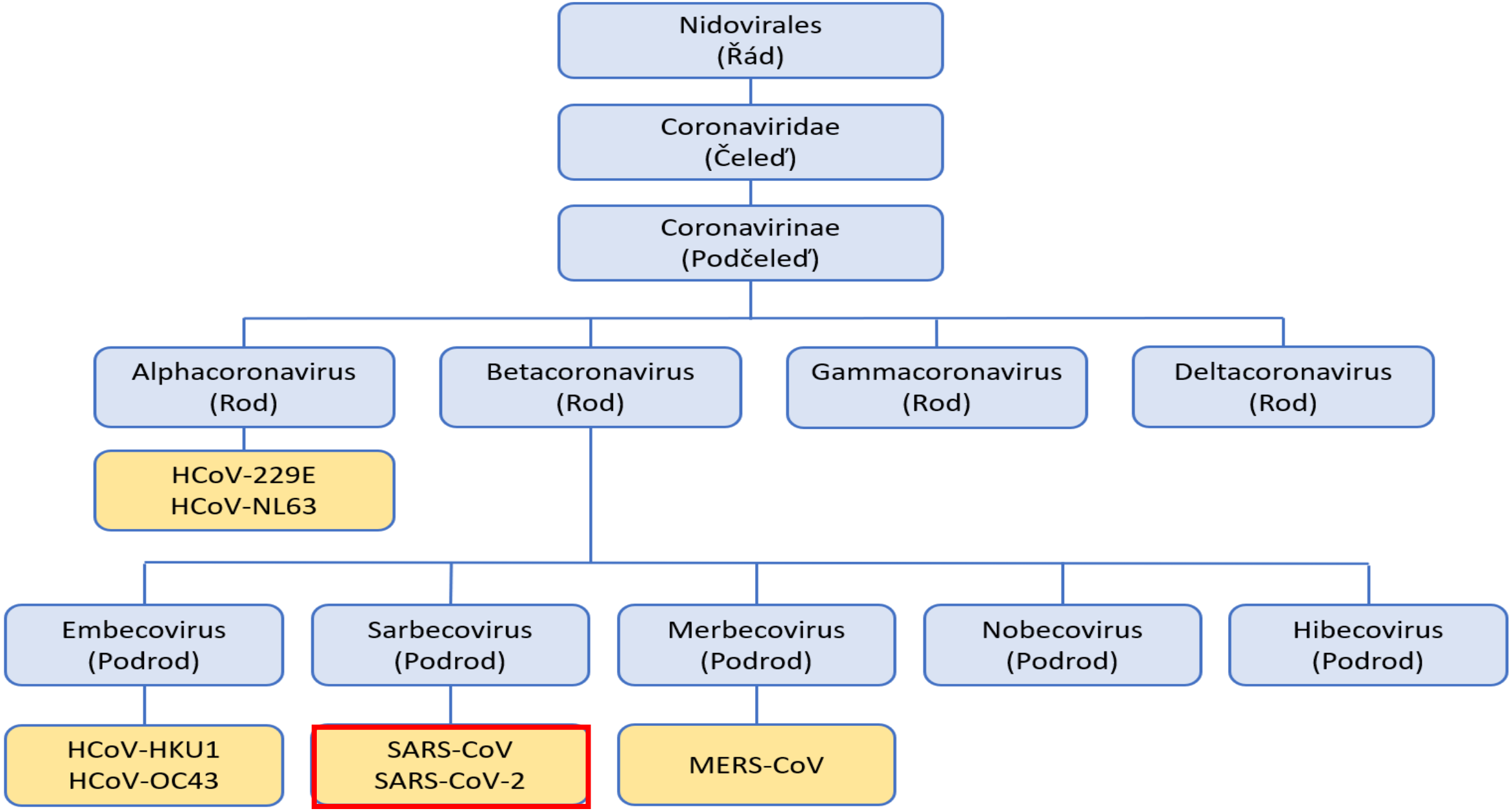
CD8+ T-cell mediated “Seek and Kill”







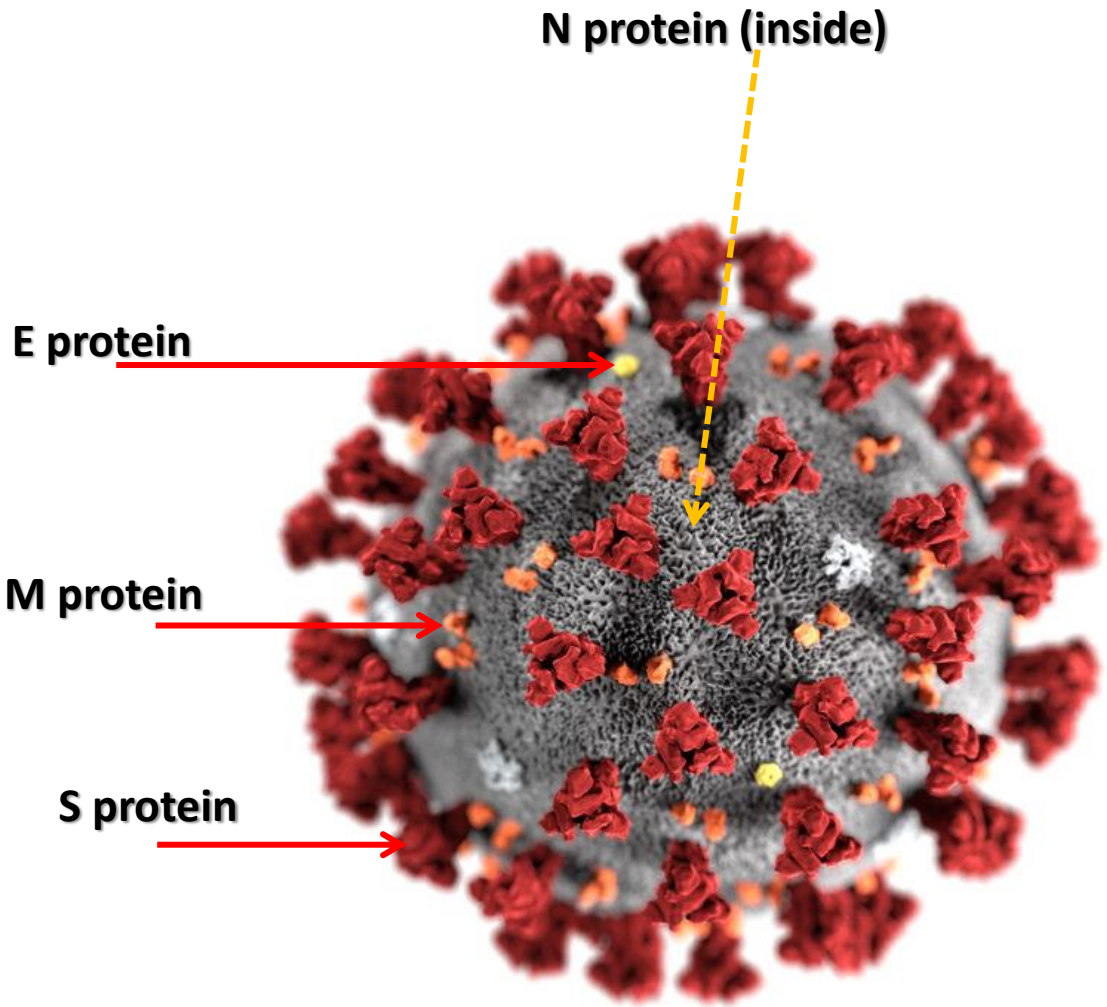
Coronaviruses - Taxonomy



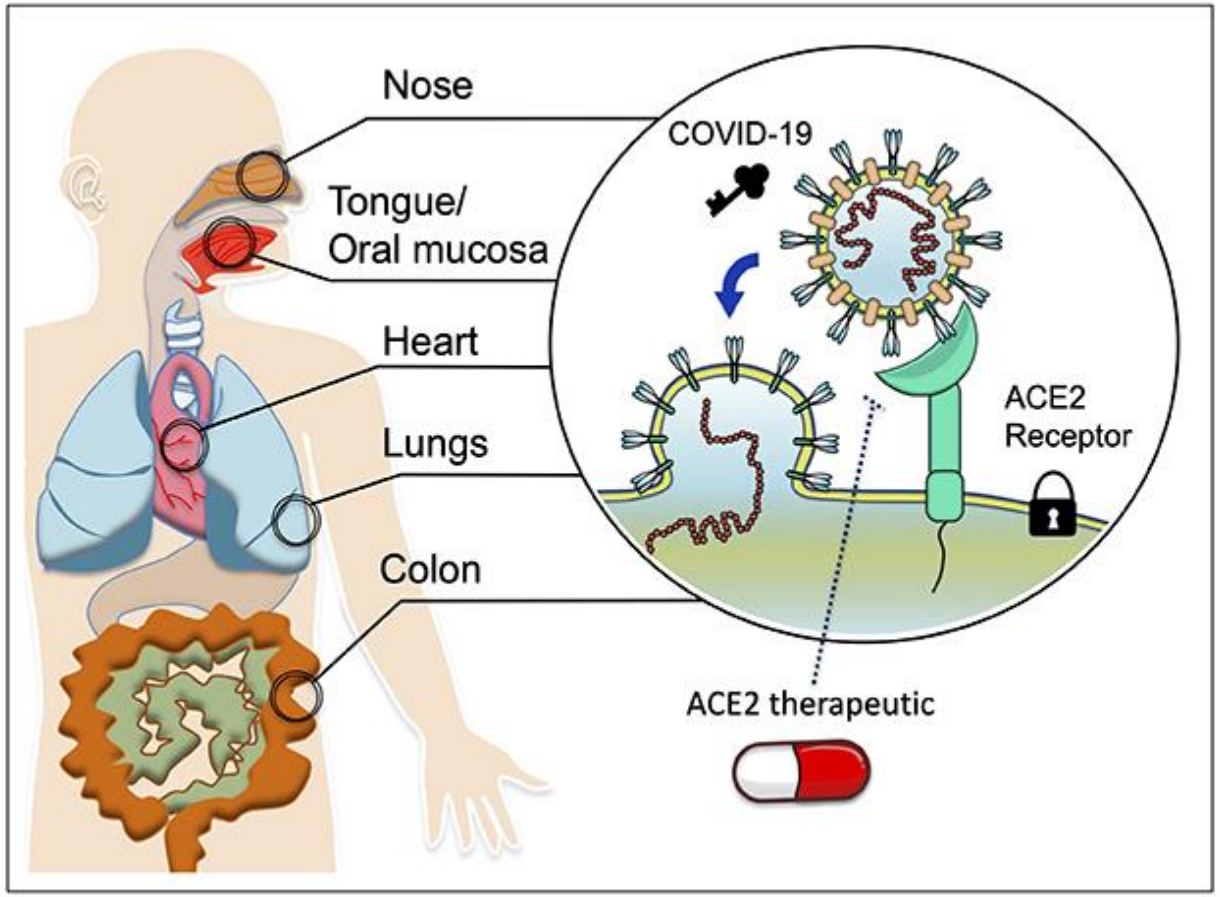
Why is infection much better than vaccination in terms of durability and flexibility of protection?

SARS Cov-2 positive stranded RNA encodes for 28 (or 29) proteins, 4 of them structural. CTL immunity is thus mounted against all of such procucts and a couple of mutations cannot compromise it.

mRNA vaccines are, in opposite, designed to mount anti S-protein antibodies that are easily knocked-out by S-protein mutation.



Why do mRNA vaccines mount short-living immunity that cannot prevent infection and virus transmission?



Surface (mucosal) and **systemic** (withing the body) **immunity are largely separated.**

SARS Cov-2 is a respiratory, “common cold” or “running nose” virus, a traveler with “infect, multiply and go-away” strategy of existence. Intra-muscular injection builds systemic immunity with little effect on the surface.

It appears that mRNA technology cannot induce antigen deposits at the proper loci – spleen and lymph nodes. That is why antibody titers drop rapidly.

Clin Immunol. 2006 Aug;120(2):171-8. doi: 10.1016/j.clim.2006.05.002. Epub 2006 Jun 16.

Long-lived effector/central memory T-cell responses to severe acute respiratory syndrome coronavirus (SARS-CoV) S antigen in recovered SARS patients

2006

Li-Tao Yang [1], Hui Peng, Zhao-Ling Zhu, Gang Li, Zi-Tong Huang, Zhi-Xin Zhao, Richard A Koup, Robert T Bailer, Chang-You Wu

More than 1 year after infection

Circulating

CD4+ central memory

CD8+ effector memory (memory CTL)

The role of cell-mediated immunity in human SARS-CoV infection is still not well understood. In this study, we found that memory T-cell responses against the spike (S) protein were persistent for more than 1 year after SARS-CoV infection by detecting the production of IFN-gamma using ELISA and ELISpot assays. Flow cytometric analysis showed that both CD4(+) and CD8(+) T cells were involved in cellular responses against SARS-CoV infection. Interestingly, most of SARS-CoV S-specific memory CD4(+) T cells were central memory cells expressing CD45RO(+) CCR7(+) CD62L(-). However, the majority of memory CD8(+) T cells revealed effector memory phenotype expressing CD45RO(-) CCR7(-) CD62L(-). Thus, our study provides the evidence that SARS-CoV infection in humans can induce cellular immune response that is persistent for a long period of time. These data may have an important implication in the possibility of designing effective vaccine against SARS-CoV infection, specifically in defining T-cell populations that are implicated in protective immunity.

15 years later we have discovered a wheel

nature

Article | Open Access | Published: 07 December 2021

Signature of long-lived memory CD8$^+$ T cells in acute SARS-CoV-2 infection

Sarah Adamo, Jan Michler, Yves Zurbuchen, Carlo Cervia, Patrick Taeschler, Miro E. Raeber, Simona Baghai Sain, Jakob Nilsson, Andreas E. Moor & Onur Boyman

2021

More than 1 year after infection

Circulating

CD4+ central memory

CD8+ effector memory (memory CTL)

Immunological memory is a hallmark of adaptive immunity and facilitates an accelerated and enhanced immune response upon re-infection with the same pathogen[1,2]. Since the outbreak of the ongoing COVID-19 pandemic, a key question has focused on which SARS-CoV-2-specific T cells stimulated during acute infection give rise to long-lived memory T cells[3]. Here, using spectral flow cytometry combined with cellular indexing of transcriptomes and T cell receptor sequencing, we longitudinally characterized individual SARS-CoV-2-specific CD8$^+$ T cells of patients with COVID-19 from acute infection to 1 year into recovery and found a distinct signature identifying long-lived memory CD8$^+$ T cells. SARS-CoV-2-specific memory CD8$^+$ T cells persisting 1 year after acute infection express CD45RA, IL-7 receptor-α and T cell factor 1, but they maintain low expression of CCR7, thus resembling CD45RA$^+$ effector memory T cells. Tracking individual clones of SARS-CoV-2-specific CD8$^+$ T cells, we reveal that an interferon signature marks clones that give rise to long-lived cells, whereas prolonged proliferation and mechanistic target of rapamycin signalling are associated with clonal disappearance from the blood. Collectively, we describe a transcriptional signature that marks long-lived, circulating human memory CD8$^+$ T cells following an acute viral infection.