

The enigma of memory T cells in viral infections (including SARS-CoV-2)

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ABSTRACT

Viral infections and vaccinations produce immune responses mostly through B cells (plasmocytes/antibodies) and effector T cells (helper and cytotoxic). After removing the antigen, 90-95% of the effector cells disappear, but the remaining ones turn into T cells with long memory. The maintenance of cellular memory, the mode of information storage and the lifespan of T cells are insufficiently known. After measles, resident T cells in the plasma will offer protection only against the measles virus, generating a long period of immunodepression (immune amnesia). After the flu, memory T cells generate immune protection for 1-2 years for secretory IgA and longer for serum IgG. In SARS-CoV-2 infection, memory T cells (B and T) respond quickly to reinfection for 8-10 months. In conditions of intense stimulation in SARS-CoV-2, SARS-CoV, MARS infection, marked leukopenia occurs with lymphopenia generating immunodepression and high mortality, disorders similar to septic shock. An important role in these disorders is played by the host's genetic structure and epigenome.

Keywords: immune memory, measles, flu, SARS-CoV-2, cell exhaustion

Immune memory represents the ability of the immune system to recognize an antigen previously encountered and to generate a specific response in a short time interval. The immune system has 2 main lines of defense: innate and adaptive immunity. During viral infections, both types of response are involved with well-defined particularities

Innate immunity is largely based on inflammatory responses triggered in the first instance by macrophages, polynuclear leukocytes and mast cells, cells that destroy infectious agents in an inflammatory process. Some of these cells have the ability to block viral replication or to destroy cells infected with viruses, processes in which type I IFN and NK cells play an important role [1].

Adaptive immunity. In general terms, B cells produce antibodies (AC) and T cells provide help to other immune cells and directly eliminate infected cells. The control of the viral infection involves the populations of

CD4+ (helper) and CD8+ (cytotoxic) cells by stimulating the production of antibodies and by apoptotic destruction of cells populated by viruses. CD4+ cells activate B cells that produce antibodies that act by blocking viral receptors, by blocking fixation on the host cell and by opsonizing viral particles. Clearance of the initial infection provides a basis for protection against subsequent infections through T and B cells, specific CD4+ and CD8+ virus populations and neutralizing antibodies.

Immune defense against viral infections is based on 2 coordinates: elimination of active infection and protection against subsequent infections. A series of clinical, epidemiological and immunological data show that sometimes the "textbook" scenario does not correspond to reality.

Measles – memory T-cell amnesia. Measles is a contagious disease produced by a single-stranded RNA lymphotropic virus. The widespread introduction of vaccination (note the active anti-vaccination currents)

TABLE 1. Features of the innate and adaptive immune system Adapted from Abbas et al [1], Engleberg et al [2], Janeway and Medzhitov [3]

Structures	Innate immune system	Adaptive immune system
	Phagocytic cells (neutrophils, macrophages), dendritic cells (DC), mast cells, natural killer cells (NK), innate lymphoid cells (iLCs) Complement system	B lymphocytes, T lymphocytes, Ly T helper, Cytotoxic Ly, regulatory Ly T
Receptors	Fixed in the genome It does not require rearrangements	Coded in gene segments. Rearrangements are required
Distribution	Non clonal. All cells are of the same class	Clonal. All cells are of distinct classes
Identification	Global molecular structures (LPS, glycans...)	Molecular structure details (proteins, peptides, carbohydrates)
Self-nonsel self discrimination	Perfect, selected by evolution	Imperfect: selected in individual somatic cells
Action time	Immediate activation of effectors	Delayed activation of effectors
Response	Co-stimulatory molecules: cytokines, chemokines	Effector cytokines (IL-4, IFN-γ)

TABLE 2. Differentiation and activity of CD4+ cells

<p>CD4+ helper cells ensure the maturation of B cells into plasma cells, activate cytotoxic T cells and macrophages. Through the cytokines produced, they are differentiated into:</p> <ul style="list-style-type: none"> • Th1 (IFN-γ, IL-2): inflammatory response, active on intracellular viruses and bacteria • Th2 (IL-4, IL-5, IL-13), active on extracellular pathogens (intestinal parasites) • Th17 (IL-17, IL-22), protector of mucous membranes • Tfh (T helper follicular) favors the generation of antibodies with high affinity for viruses Nissel J Seminars in Immunology, https://doi.org/10.1016/J.smim.2021.101505

TABLE 3. Structure of CD8+ lymphocyte subsets

<p>CD8+ cells are made up of 3 subsets of lymphocytes: naïve, effector and memory</p> <ul style="list-style-type: none"> • Naïve T cells are lymphocytes that have not yet encountered the viral agent • Effector T cells develop from naïve T cells after being exposed to antigenic contact • A part of the effector T cells transforms into memory T cells. These are antigen-specific T lymphocytes that persist for a long time in the tissues after the elimination of the infection and proliferate like the effector T upon re-exposure. Youngblood et al Nature, 2017, 552, 404-409

which is safe, effective and accessible has led to the saving of millions of lives [4]. Measles virus (MV) initially infects the macrophage cells in the pulmonary alveoli through its tropism towards their membrane glycoproteins. Entering the cell, MV releases its own genome and induces viral multiplication. Infected macrophages and dendritic cells (DC), carrying the virus, transfer the virions to memory T and B immune cells and naïve B cells of the immune system where the virus undergoes intense replication. In the following period, there is a firm stimulation of immunity against MV through the rapid expansion of specific B and T lymphocytes with the appearance of CD4+ cells producing IFN-γ and cyto-

toxic CD8+ cells [8], After the peak of viremia, the elimination of infected lymphocytes takes place, highlighted laboratory through transient lymphopenia [5], but important, followed by marked immunodepression against various other pathogens [8]. **It was found that the changes are determined by the appearance of cell clones with long-term memory only against the measles antigen** [4,5,6] because the virus destroys the long-lived plasma cells stored in the bone marrow, holders of the immune memory pool [10,11]. The immunological imbalance during an extended period of immunodepression also called “**immune amnesia**” lasts 2-3 years or more after the measles episode [7,8,9]. Using BCR receptor sequencing of peripheral blood lymphocytes before and after MV infection, Petrova et al [7] identified 2 immunological consequences underlying immunodepression:

- Incomplete reconstitution of the naïve B cell pool generating immunological immunity
- Compromising the immune memory against previously encountered pathogens by reducing the proliferation of innate immunity cells, with a drastic effect on the risk of infection

Mina et al [10] examined infant mortality rates in the US, UK and Denmark in the pre-vaccine decades and after the introduction of the RV vaccine. In the pre-vaccination epidemic episodes, almost half of the children’s deaths from infections were preceded by the measles infection. The MV vaccination induces an unexpected protection against other infections and the decrease in the mortality of children in the first years of life. Mina [11] considers that the reduction of measles-related infections was the main factor for the global decrease in mortality from infectious diseases in the periods after the introduction of vaccination. The introduction of MV vaccination in rural areas of Bangladesh in 1982 led to a 36% decrease in the global mortality rate and a 57% decrease in mortality directly attributable to measles [12].

Changes in the population of memory T cells during influenza infection. Influenza infects 5-15% of the world's population every year. The flu virus constantly evolves through rapid and unpredictable mutations, producing new viral strains that bypass the humoral immunity generated by flu vaccines [13].

The influenza A virus contains a genome formed by RNA surrounded by nucleoproteins (ribonucleoprotein complex) contained in the capsid. The viral envelope contains 2 proteins: hemagglutinin and neuraminidase, with a role in the attachment and respectively the penetration and subsequent diffusion of the particles formed in the infected cells. The structure of influenza B and C viruses is largely similar to that of type A

Post-vaccination immunity induces neutralizing antibodies against viral surface glycoproteins. Both hemagglutinin and neuraminidase often undergo mutations. Seasonal viruses have the ability to evade the immune system through the gradual acquisition of mutations of exposed hemagglutinin epitopes [14]. In this "war" current vaccines lose their effectiveness. For this reason, the vaccines also "adapt" by changing the composition frequently depending on the antigenic stimuli. Vaccination induces the formation of influenza A virus-specific T-cell reservoirs along the respiratory tract and consequently long-term immunity against circulating seasonal influenza strains [13].

Immunological imprinting The immune system is imprinted by antibodies (AB) produced in response to previous infections/vaccinations in life. Each vaccination produces new ABs specific to the new strain, but they degrade over time, returning to the repertoire existing before vaccination. However, over 70% of AB identified in the blood of donors remain unchanged for more than 5 years; 2/3 of them attack the invariable part of the virus. Lee J, Paparoditis P, Horton A et al. Persistent Antibody Clonotypes Dominate the Serum Response to Influenza over Multiple Years and Repeated Vaccination. *Cell Host Microbe*, 2019;25,3:367

Natural infection, in contrast, offers better protection against homologous and heterologous strains of the influenza virus through memory T cells from the pulmonary [13] and nasal [14] epithelium. They recognize the more stable internal viral components and can provide cross-protection against a wide range of virus variants [15]. Both primary infection and vaccination produce immediate and long-term immune responses through the differentiation of naïve T cells into effector B cells (plasmocytes/antibodies) and through effector T cells (CD4 helper and cytotoxic CD8) [14,16]. Memory T cells that remain resident in the lung provide strong protection against subsequent influenza A virus infections [13]. The longevity of antibodies varies between

1-2 years for secretory IgA and decays for serum IgG [17].

The role of memory T cells in SARS-CoV-2 infection. Immune memory is an attribute of both the B and T cell lines. Memory B cells show clonal expansion, the ability to differentiate and divide rapidly, the ability to produce specific antibodies (predominantly IgG) in response to the antigenic stimulus [18]. Memory T cells, differentiated as CD4 helper and cytotoxic CD8, react to the molecules expressed by SARS-CoV-2 and presented by dendritic cells (DC) by activating the Th1 line (IFN- γ , IL-2 and TNF- α) [19]. CD8 T cells recognize viral peptides on the surface of infected cells and trigger their apoptosis (programmed cell death). They are located in the blood, lymphoid organs and tissues. A number of responses are characteristic of memory T cells:

- Formation of a pool of cells reactive to the pathogen through specific receptors
- Fast and strong response to infection
- Pre-programming to generate an adapted set of effector cells
- The presence of memory T cells in the barrier tissues for rapid detection and control of infection [18].

Resident T cells with memory (T_{rm}) settle in the lung, skin, being stable and not included in circulatory exchanges [20]; for this reason, they cannot be evaluated in blood samples collected in the laboratory. Natural infection and vaccination against SARS-CoV-2 produce specific neutralizing antibodies considered a success of immunization, but the level and duration of their protection remain in debate. Cellular immunity provides a different response, based as it has been shown, on memory T cells.

Memory storage in the T cell. The way of storing and maintaining information in cells against the infectious agent was elucidated relatively recently through epigenetic mechanisms [21,22,23]. Once naïve CD8 cells encounter an antigen, they go into a rapid proliferation phase and differentiate into effector T cells, being able to generate IFN- γ , TNF- α and other cytokines. After the antigen has been eliminated, 90-95% of the effector cells disappear, but those that survive are transformed into T cells with long memory [23] located mainly in the tissues/organs where the primary infection is located. The subsets of cells that give rise to memory cells acquire DNA programs that maintain the effector genes in a demethylated position, being associated with histone modifications that create the open configuration of chromatin [22]. These changes are maintained for a long period of time during subsequent cell proliferation, the inhibition of the programmed cell death program (programmed cell death protein-1 [PD-1]) also having a role [23]. The open profile of effector genes is maintained in the memory of isolated CD8+ T

cells even decades after vaccination, indicating that they retain the epigenetic imprint of their effector history and remain ready to respond rapidly to pathogen re-exposure as shown by yellow fever vaccination studies by Akondy et al [41]. Memory T cells were highlighted in healthy individuals exposed to SARS-CoV-2 infection suggesting their passage through an asymptomatic infection, 93% of them having a specific cellular response [24]. Asymptomatic infections could be quite widespread, especially since antibody testing underestimates the real prevalence of infection.

Cell exhaustion and lymphopenia. Under conditions of intense or sustained stimulation, memory T cells become non-functional, lose their ability to proliferate and produce cytokines, a process called cell exhaustion [23]. The decrease in the number of lymphocytes, lymphopenia, mostly transient, frequently reported in some viruses (measles, flu, infections from the SARS group, MERS) affects the populations of CD4+ T, CD8+ T, B cells and other immune cells [24]. Although the mechanisms responsible for the installation of lymphopenia are not well known, the damage to CD8 T cells is more severe and parallel to the severity of the evolution. Based on data from the literature, several hypotheses regarding the causes of severe lymphopenia in SARS-CoV-2 infection have been outlined [18,24,25,26,31]:

- The storm of cytokines would be the key factor, especially through TNF- α , IL-6 and Fas-FasL (receptor on the surface of apoptosis-inducing cells) directly influencing the cellular self-destruction process.
- The SARS-CoV-2 virus directly infects T cells. The hypothesis does not have wide support because the viral genes are not expressed in the leukocytes of patients with COVID-19, that is, the lymphocytes are not infected and the cytopathic effects are not at the origin of the lymphopenia.
- SARS-CoV-2 infection interferes with the expansion of T cells. In severe forms of infection, some genes involved in the activation and functions of T cells are inhibited, their expression returning to normal after the patients recover.
- The systemic inflammatory profile in severe forms of the disease and the hypersecretion of pulmonary chemokines induce the migration of lymphocytes to this organ and their depletion in the general circulation. The autopsy of some deceased COVID-19 patients showed in the bronchoalveolar lavage abundant infiltrates with T cells in the lungs.

Data from the period 2003-2004 show that in SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East Respiratory Syndrome), both caused by coronavirus infections, there are severe changes in the

number of leukocytes and lymphocytes. In the acute phase of SARS-CoV infection, Channanappanavar et al [32] mention marked leukopenia with lymphopenia (~80% of patients) with a marked decrease in CD4 cells (~90-100%) and CD8 (~80-90%). The decrease in the number of T cells was strongly correlated with the severity of the acute phase of the infection [33,34]. **Lymphopenia** is an evolutionary feature in severe bacterial sepsis and in infectious shock, immunosuppression being the result of immune cell reprogramming through the depletion of dendritic cells (DC), T and B cells through apoptosis [27,28] resulting in prolonged serious evolution and increase in late mortality [29]. It is possible that in the severe forms of SARS-CoV-2 infection and in lymphopenia septic shock, there are similar pathogenic changes.

Longevity of memory T cells in the context of the life span of other types of cells Table 4, Table 5. Memory CD8+ T cells were detected 6 months or more from the onset of symptoms to 50-70% of SARS-CoV-2 convalescents [30]. Some CD8+ T cells that act against seasonal coronaviruses can persist long-term as memory cells and act through cross-reactivity against SARS-CoV-2 infection [31]. However, maintaining a response of memory T cells does not seem strong enough to prevent further illnesses, as medical practice shows us.

TABLE 4. Longevity of some human cells (synthesis)

Cell type	Lifespan
Neurons	Lifetime
Crystalline	Lifetime
Ova	50 years
Cardiac myocytes	Lifetime
Intestinal cells (exclusively absorptive)	15.9 years
Skeletal muscles	Lifetime
Fat cells	8 years
Hematopoietic stem cells	5 years
Hepatocytes	10-16 months
Immune memory T cells	Depending on the type of infection SARS 11 years SARS CoV-19 6-9 months

The substrate of the host-viral infectious agent relationship. The genetic predisposition to severe infections is manifested both in the antigen recognition phase and in the body's response phase [45]. Some genetic variants have been identified as severity or resistance factors in different viral infections.

During the SARS-CoV-2 pandemic, a wide individual variability of the evolution was evident, the aggravating factors being the male gender, advanced age, smoking, comorbidities. Previously healthy patients, without notable pathology, sometimes developed severe forms of the disease and lasting complications. The suspected

TABLE 5. Duration of immunity in different viral infections

Affection	Infectious agent	Virus type	Humoral immunity (the B)	Cell immunity (T cell)	Bibliography
Smallpox	Smallpox virus	DNA	Tested up to 75-80 years with neutralizing ACs	20-30 years decreases slowly over time	35 36 37
Yellow fever	Yellow fever virus	RNA	AC neutralizers, duration?	25 years through CeIT apparently unchanged	38 39 44
Measles	The measles virus	RNA	10 years ago after 2 vaccination doses	Central role in maintaining immunity	40
Flu	Influenza virus	RNA	Effective ~6 months. AC persistent over 5 years	?	14 17 41
COVID-19 infection	SARS-CoV-2 coronavirus	RNA	AC neutralizers 5-8 months (6-7 months)	The CD4+ and CD8+ over 10 months after infection	42 43

TABLE 6. Genetic factors that influence the evolution of some viruses According to Oladejo et al [46]

Viral infection/pathology	Genetic variants	The type of answer
Influenza virus (severe pneumonia)	IRF7, IRF9, TLR3, IFITM3, SFPA/B	Susceptibility
Rhinovirus (severe pneumonia)	IFN1	Susceptibility
Immune deficiency virus	CCR5, HLAB57	Resistance
Herpes simplex virus (encephalitis)	TLR3, TRIF, TRAF3, IRF3, TBK1,	Susceptibility
Norovirus and rotavirus	FUT2	Resistance
Respiratory syncytial virus (bronchiolitis)	IL4, IL4RA, IL 8, IL10, IL13, SFPA/D	Susceptibility

genetic factors involved the ABO blood group, viral receptor genes, inborn errors of IFN type 1, antibodies to interferon [47]. On the other hand, it was found that the presence of a rare variant of the gene that codes for ACE 2 (angiotensin converting enzyme 2) is protective by reducing the expression of the enzyme by 37% [47,48]. In this complicated puzzle must be included

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the ability of COVID-19 to antagonize the regulation of the host's epigenome through histone modifications, DNA methylation and chromatin remodeling for viral protein coding [49]. At this moment, it is not clear to what extent the response to viral infections changes the host's phenotype over time or if epigenetic regulation is a source of phenotype variations [49].

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