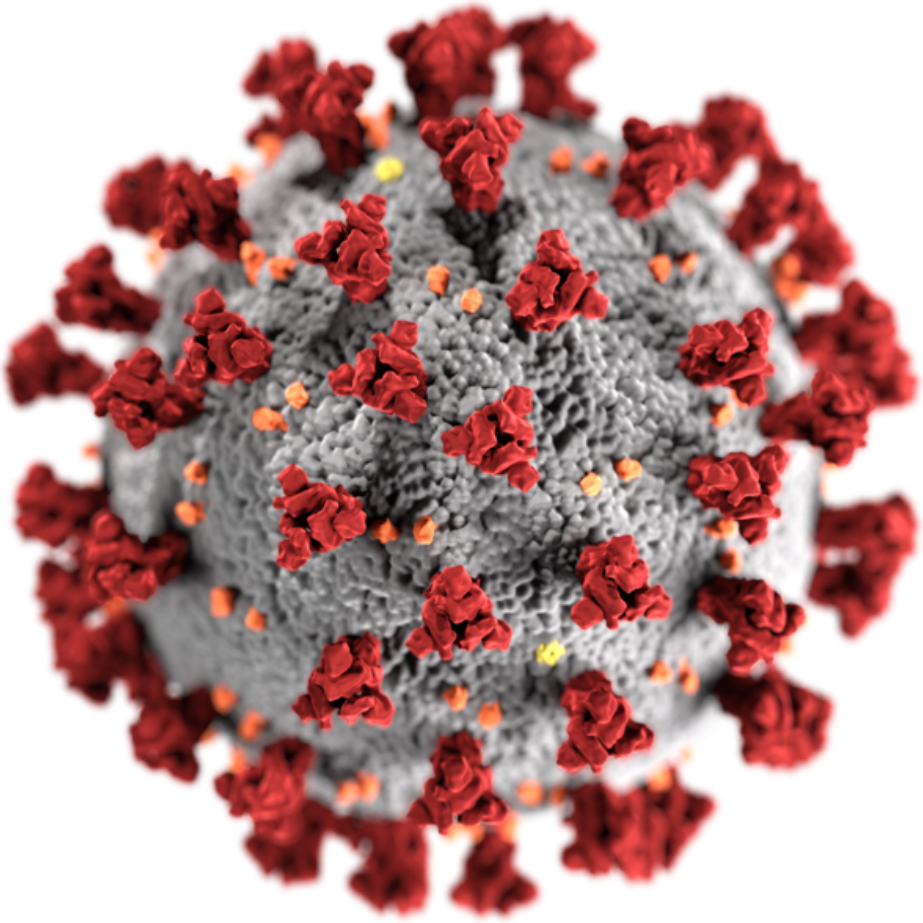
Chapter 40 Basic Principles of Animal Form and Function

Subject : Effect of COVID - 19 on the different biological level of the organism



By Delamare Irina

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Intro

In December 2019, a new pathology started spreading through the Chinese population, causing COVID-19 disease! The responsible, a virus named Severe Acute Respiratory Syndrome-Related Coronavirus 2, commonly called Coronavirus or SARS CoV-2 [1, 2]. With his exponential growth, he reached in a few months the entire world population and was soon declared, in March 2020, a global pandemic. Coronavirus is the name of viruses belonging to a family possessing crown-like protein spikes on their surfaces [3]. SARS CoV-2 is a virus composed of a single-stranded RNA as his genetic material, a lipid envelope, and some surface glycoproteins called spikes [2]. It is important to note that some of these spikes bind to ACE2 enzyme receptors of the host cell [4].

Coronavirus can be transmitted by contact with a sick person, via coughing for example. It seems to also spread via surfaces, but it is unclear how long it can survive on them. What happened after the virus entered your organism? What effects COVID-19 have on the different biological scales of our organism?

Thought process

I had a hard time finding papers about COVID-19 symptoms and operating methods. The majority of papers I found via Google Scholar were about pandemic growth and the prediction of its evolution, or about the impact of the disease on patients with preexisting health conditions. I decided to change my way of looking for pieces of information.

I realized that my list proposal of videos on Youtube displayed a lot of content about COVID-19 and SARS CoV-2. I decided to look into it and realized that many videos gave me good, and supported by sources, information about COVID-19 symptoms and SARS CoV-2 transmission. By looking a bit deeper into scientific focus videos I learn a lot about coronavirus pathophysiology and evolution in the body. Most of these videos cited papers. From there I was able to find research articles on symptoms and operating methods of the virus.

I discovered many public associations that goals are to centralize information about COVID-19 disease and coronavirus, going from the WHO (World Health Organisation) who popularize information for the general public (Ok its a bit more than a public association !) to the NCIC (Novel Coronavirus Information Center) who targets scientists by displaying all-new research papers published about coronavirus.

I also discovered that the “Coronavirus disease 2019” [1bis] Wikipedia page was often updated to match the research published every day, which was very helpful to not miss any information.

1- Macroscopic level/The organism ⇒ the symptoms

Symptoms of COVID-19 are closed to flu symptoms caused by the influenza virus. However, COVID-19 is way more dangerous with a death rate of 5.5% worldwide against 0.2% for the flu. Countries with a poor healthcare system have a higher death rate. The virus incubation period is from 2 to 14 days. [5]

Most patients are symptomatic or presymptomatic (they have the virus but do not express symptoms yet). So they are contagious without being aware of it. 90 % of infected adult patients have a fever (44% for children), 58 to 72% have a dry cough (22% for children), 46% have trouble breathing, 29 to 43% of patients have tiredness and muscle aches, and 66% of patients have lost their sense of smell. Other rarer symptoms are sore throat (11% of patients), headache (8%), diarrhea (6%) and other digestive symptoms. [6, 7, 8, 9, 12, 13]

Other people are asymptomatic, meaning they are infected but will not express any symptoms. It is the case for many children and young people.

Most cases of COVID-19 patients will recover with no difficulty. However, in some severe cases, the disease will lead patients to the hospital. Older people and persons enduring preexisting conditions like diabetes, heart disease, chronic kidney or lung disease, are more at risk [8, 10].

Syndromes can evolve for some patients into pneumonia, and even into acute respiratory distress syndrome (ARDS) for 15 to 33% of pneumonia cases [7]. Pneumonia is a lung inflammation caused by bacterial or viral infection where the alveoli (the air sac) fill up with fluid. It leads to shortness of breath that, without any medical care, can be fatal. Acute respiratory distress syndrome is a respiratory failure caused by lungs' inflammation that affects its ability to exchange oxygen and carbon dioxide. Symptoms include shortness of breath, rapid breathing, and bluish skin coloration.

2 - Impact on Systems

5% of COVID-19 ill patients are in critical states. They can be affected with respiratory failure from acute respiratory distress syndrome involving the respiratory system. COVID-19 may also damage systems such as the blood and the immune system, or cause multi-organ injuries [11]. Patients in critical states eventually die of multiple organ failure, shock, acute respiratory distress syndrome, heart failure, arrhythmias, and renal failure.

The immune response to coronavirus involves multiple systems like the immune system, the nervous system, the cardiopulmonary system.

The inflammation occurring in the lungs stimulates nerve ending responsible for the cough reflex. Decreasing oxygen levels in the blood called hypoxemia will stimulate chemoreceptors in the brain which will trigger the cardiopulmonary response for the lungs to breathe more to increase the oxygen level in the blood, and for the heart to pump faster to deliver quicker oxygen to your body. [5]

The immune system response :

Injured cells emit cytokines and have a change in their adhesion molecules (proteins located on the cell surface involved in binding with other cells or with the extracellular matrix).

Alveolar macrophages detect injured cells by their adhesion molecules and start secreting cytokines such as TNF alpha, interleukin 1, 6 and 8, and other chemokines. [5]

See the table (figure 1) below!

The monocytes recruited by the pro-inflammatory cytokines have high interleukin 6 expressions that accelerate the inflammation [14].

The increase in vascular permeability causes pulmonary edema, defined as fluid accumulation in the tissue and air spaces of the lungs. It will result in a low oxygen level in the blood, hypoxemia. [15]

Neutrophiles start releasing enzymes that destroy infected cells as well as healthy ones when arriving at the infected spot. This leads to an increase in damaged tissue and a decrease in surfactant production. This results in hypoxemia.

The injured lung tissue, the accumulation of fluid into alveoli, and hypoxemia cause Acute Respiratory Distress Syndromes (ARDS). It is the first cause of mortality from COVID 19.

In most cases the immune system succeeds in killing all the infected cells and in destroying all the viruses left, allowing the patient to recover from the disease. However, some patients who recovered from COVID-19 show a drop of 20% to 30% in lung capacity, and lung scans suggested organ damage

[16].

Figure 1 : Table of secreted cytokines and their effects :

Name	**Type**	**Effects**	**Targeted Immune Cells = Recruitments**
TNF - ***α***	pro-inflammatory cytokines	Increase in : - **vascular permeability** - expression of adhesion molecules - Responsible for fever	- Neutrophils - Monocytes
Interleukin 1B			
Interleukin 6	Chemokine (⇒ Small cytokines)	- Stimulate acute phase reactions in the liver - Responsible for fever	- Neutrophils - Leukocytes
Interleukin 8	Chemokine (⇒ Small cytokines)	- induces **chemotaxis** in target cells causing them to migrate toward the site of infection - stimulates **phagocytosis**	- Neutrophils - Granulocytes
Other chemokines	Small cytokines	- Induce **chemotaxis**	- Monocytes - Neutrophils - Granulocytes - Macrophages

After phagocytosis, macrophages present on their outer layer the spike protein of coronavirus they destroyed. They become antigen-presenting cells.

Specific T-lymphocytes recognize the spike protein and start the adaptive immune response (figure 2). The immature T-cells transform into activated $CD4^+$ T cells and $CD8^+$ T cells [13].

Activated $CD4^+$ T cells are helper cells that secrete cytokine to attract macrophages, neutrophils, and other lymphocytes to the infected spot.

Activated $CD8^+$ T cells are cytotoxic cells that kill infected cells.

B cells are activated to secrete antibodies like immunoglobulin M (IgM) and immunoglobulin G (IgG) [17]. These antibodies travel through the bloodstream and bind to SARS CoV-2 inactivating it, which prevents it from binding to host cells. B cells are also antigen-presenting lymphocytes.

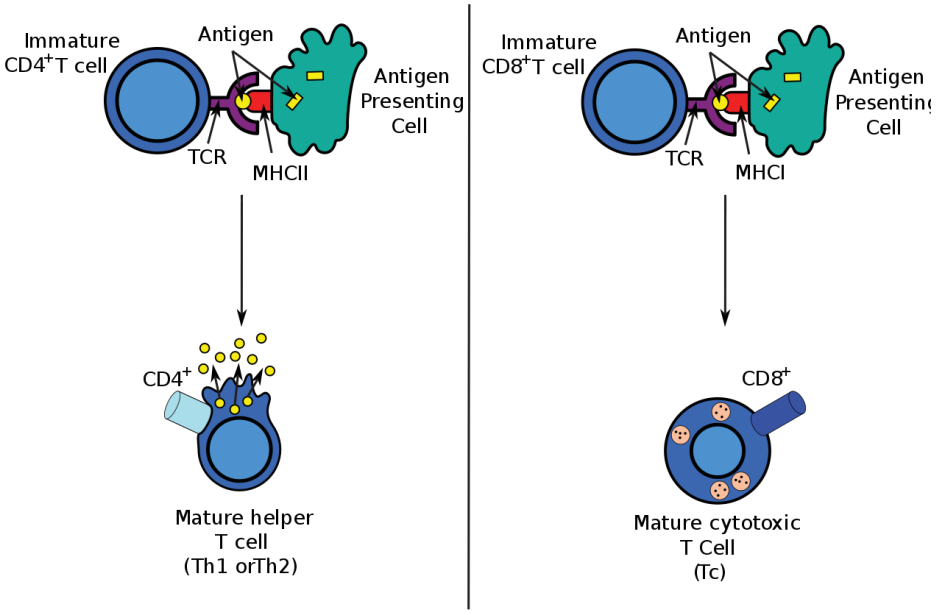

Figure 2 : Antigen-presenting cells stimulate the activation of helper and cytotoxic T cells

https://en.wikipedia.org/wiki/Adaptive_immune_system#/media/File:Antigen_presentation.svg

A study has demonstrated that excessive non-effective host immune responses by pathogenic T cells and inflammatory monocytes may be associated with severe lung pathology by breaking into the pulmonary circulation [14].

3 - Impact on Organs

The virus targets the throat, the lungs, the intestine, or the spleen. But the lungs are from far the most affected organ. This is easily explained by the abundant presence of the enzyme receptor ACE2 in type II alveolar cells of the lungs, which permit the coronavirus to access the host cell.

The number of infected cells grows exponentially which allows billions of viruses to swarm the lungs and to infect millions of body cells in 10 days [2].

Alveoli are a hollow cup-shaped cavity in the lungs where gas exchange takes place: oxygen enters, carbon dioxide leaves. Alveolar cells coat the lung tissue and are targeted by the virus, which stops them from producing surfactant. The surfactant lowers the surface tension of alveoli and keeps them open to allow gas exchanges. So with a lower alveolar cell density in the lungs (due to infected cells), less surfactant is produced, which leads to a bad oxygen/carbon dioxide exchange. Therefore there is less oxygen in the blood, it is also called hypoxemia. [5, 18]

ACE2 is also expressed in gastrointestinal organs as the glandular cells of the gastric, duodenal and rectal epithelium [19] as well as endothelial cells and enterocytes of the small intestine [20]. So the virus affects gastrointestinal organs too. We also notice liver derangement.

Many critically ill patients have evidence of underlying illnesses such as cardiovascular disease, liver disease, kidney disease, or malignant tumors [11]. In some cases, the heart can leak troponin which is a marker of a cardiac injury.

4 - Impact on tissues

SARS CoV-2 gets in contact with cells having ACE2 receptors on their surface. The density of ACE2 in each tissue correlates with the infection severity in that tissue [21].
ACE2 receptors are present in the oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain at different densities [20]. So many tissues and organs can be affected.

5 - Impact on cells

SARS CoV-2 uses its spikes protein to enter living cells to reproduce and make more copies of itself [2]. Coronavirus connects to a specific receptor (ACE2 Receptor [4, 22, 23]) on the epithelial cell membrane via the surface protein. It then enters via either endocytosis (invagination of the virus by the formation of a vacuole) or direct fusion (fusion of the viral envelope with the host membrane) [5]. The genome enters the cell's cytoplasm after uncoating (removal of the viral capsid to release the viral genomic nucleic acid).

The genome of this virus is a positive single strand of RNA, so it doesn't need to inject his genetic material into the host cell nucleus to reproduce. It can directly produce the new viral protein and RNA in the cytoplasm by attaching to the host cell's ribosome. The ribosome then translates the viral RNA to make proteins, which will foil into RNA polymerase. The RNA polymerase goal is to produce more positive strands of RNA. To do so it will read the positive strand of RNA and make a complementary negative RNA strand. The negative RNA strand will be used by the RNA polymerase to make another positive RNA strand. This process is repeated many times to produce many positive RNA strands copies of the virus [5].

These RNA strands will be read by ribosomes in the endoplasmic reticulum of the host cell and make the structural component of the virus. The new-made virus proteins are transferred from the endoplasmic reticulum to the Golgi apparatus where it will be packaged up with the positive RNA strand to form a new virus. Then they are carried to the cell membrane where the vesicle will fuse with the cell outer layer. The new virus just detached itself from the cell, his membrane is made from the cell membrane [3]. This is called exocytosis [5].

During the reproduction phase of the virus, the pathogen deals damage to the host cell and initiates the inflammatory response. Injured alveoli cells release interferons (a group of signaling glycoproteins of cytokine family made and released by host cells in response to the presence of several viruses) and cytokines (small proteins important in cell signaling). Interferons are paracrine factors, which means that they allow cell-to-cell communication via paracrine signaling. A cell produces interferons as a signal to induce changes in nearby cells, altering their behavior to increase their antiviral response.

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First picture’s link, free to use, picture of SARS CoV-2 virus :
https://commons.wikimedia.org/wiki/File:SARS-CoV-2_without_background.png