EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 11
316-326
Year: 2020

ROLE OF LYMPHATIC SYSTEM IN COVID-19 PATIENT: AN OBSERVATION STUDY

Mugdha Nandedkar*[1], Priya Parghane[2], Shital Narnor[3], Yogita Ware[4], Bhagyashri Randhawan[5] and Rajesh Oswal[6]

[1]Assistant Professor, Department of Pharmaceutical Chemistry, G S Moze College of Pharmacy, Wagholi, Pune, India.
[2,3,4,5]U.G Students, G S Moze College of Pharmacy, Wagholi, Pune, India.
[6]Principal, G S Moze College of Pharmacy, Wagholi, Pune, India.

***Corresponding Author: Mugdha Nandedkar**
Assistant Professor, Department of Pharmaceutical Chemistry, G S Moze College of Pharmacy, Wagholi, Pune, India.

Article Received on 21/09/2020 **Article Revised on 12/10/2020** **Article Accepted on 02/11/2020**

ABSTRACT
As the world is witnessing the epidemic of COVID-19, a disease caused by a novel coronavirus, SARS-CoV-2, emerging genetics and clinical evidences suggest a similar path to those of SARS and MERS. A cascade of viral particles enters the body through the nose, eyes or mouth. Breathing carries some of these particles to the lower respiratory tract where the spike proteins of the coronavirus, acting like a key, lock into epithelial cells that line the respiratory tract as well as those in the air sacs in the lungs. SARS-CoV-2 is able to stay undetected longer than many flu or coronaviruses and its spike proteins are able to gain entry by unlocking the ACE2 protein on the lung cells. Once in, they hijack the cell's machinery, replicate and multiply and infect adjoining cells. Like the defining ACE2 proteins on the epithelial cells, viruses too have a tell-tale signature on their surface called antigens and spotting these is what kicks the immune system into action by producing antibodies. Researchers reveal that a broad range of immune cells react to COVID-19 and aid recovery, findings which could inform the development of a potential vaccine. The blood and lymphatic systems are the two major circulatory systems in our body. Although the blood system has been studied extensively, the lymphatic system has received much less scientific and medical attention because of its elusive morphology and mysterious pathophysiology. However, a series of landmark discoveries made in the past decade has begun to change the previous misconception of the lymphatic system to be secondary to the more essential blood vascular system. In this article, we review the current understanding of the development and pathology of the lymphatic system. We hope to convince readers that the lymphatic system is no less essential than the blood circulatory system for human health and well-being.

KEYWORDS: Lymphatic System, Lymph, Lymphatic vessels, Covid-19, SARSCoV-2.

INTRODUCTION
The human body has two major circulatory systems: the blood and lymphatic systems. Although both systems were initially described by Hippocrates and share so many functional, structural, and anatomical similarities, the two vascular systems have had very different fates in science and medicine: Although the blood vascular system has been intensively and extensively studied for a long time, the lymphatic system, in contrast, has been considered less important, invisible, secondary to the blood vascular system, and thus largely neglected by scientists and clinicians until recent years. However, a series of landmark discoveries in past decades has unravelled much of the mystery of the lymphatic system and yielded a burst of new knowledge in the field of vascular biology and medicine. Modern molecular, cellular, and genetic approaches as well as the state-of the-art imaging technologies have allowed true appreciation of the value of the lymphatic system as the other vascular system, no longer secondary to the blood vascular system. In this review, we discuss the current understanding of the development and function of the lymphatic system and human diseases related to the lymphatic system.

The world experienced the outbreaks of coronavirus infection that threaten global pandemic in 2002-2003 by Severe Acute Respiratory Syndrome (SARS) and in 2011 by Middle East Respiratory Syndrome (MERS). In both cases, the causative agents (SARS-CoV and MERS-CoV, respectively) were newly identified coronavirus in the genus Beta coronavirus with zoonotic origin. At the end of 2019, outbreak of another coronavirus that causes respiratory-related illness was reported in Wuhan, Hubei, China, a disease now officially called "the Corona Virus Disease 2019; COVID-19". The coronavirus that is the causative agent of this respiratory disease was identified and its genome is fully sequenced. More than 100 years since the outbreak of the 1918 influenza pandemic, we now seem to face another pandemic. The outbreak of the new coronavirus (SARS-CoV-2) infection is spreading to every continent, forcing us to live with this virus for perhaps a long time. Scientists and clinicians have learned much of coronavirus disease 2019, COVID-19, and its pathogenesis not all people exposed to SARS-CoV-2 are infected and not all infected patients develop severe respiratory illness. Accordingly, SARS-CoV-2 infection can be roughly divided into three stages: stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load. From the point of view of prevention, individuals at stage I, the stealth carriers, are the least manageable because, at least on some occasions, they spread the virus unknowingly indeed, the first asymptomatic transmission has been reported in Germany. The role of asymptomatic SARS-CoV-2 infected individuals in disseminating the infection remains to be defined.

Anatomy and Physiology

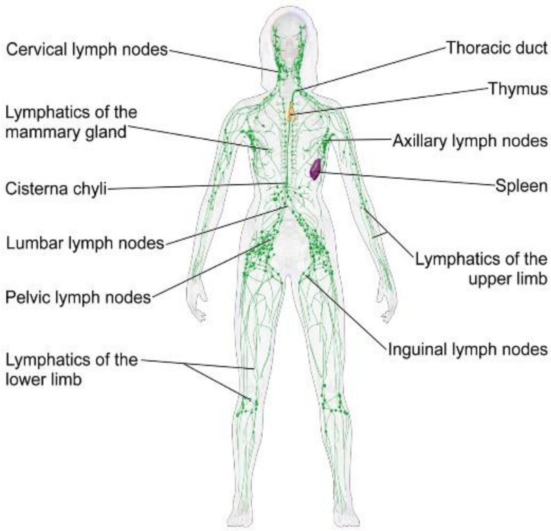
The lymphatic system as a functional whole includes several organs whose association as a system is not readily apparent. Lymphoid organs include the spleen, thymus and tonsils; in addition, a vital component is the bone marrow where white cells are manufactured. This review will concentrate on the lymphatic vascular system, which comprises a network of vessels extending to every part of the body except the brain and spinal cord. An alternative clearance system has been hypothesized for these tissues, since lymphatic vessels have been found only in the dura mater. Functionally, the lymphatic vascular system runs in parallel to the blood venous system, in that both return fluids centrally Lymphatic vessels carry lymph, which is largely water gathered from interstitial tissue spaces. Fluid appears in the interstitial spaces because blood capillary walls are somewhat leaky, admitting part of the aqueous component of blood, along with some proteins. The leak passages are glycocalyx-covered intercellular clefts, acting overall as a semi-permeable membrane.

The lymphatic vascular system scavenges this water and protein, ultimately returning it to the venous circulation via junctions with the subclavian veins at shoulder level. The maintenance of the interstitial milieu is one of its vital functions; if fluid is not returned to the blood system at the same rate as it leaves, the painful and debilitating condition of œdema can develop. Also scavenged are particles, viruses and bacteria. All lymph passes through at least one lymph node, where this potentially harmful foreign matter is mechanically sieved and neutralized by dendritic cells, macrophages and the T and B cells of the body's immune system. There are some 500−600 lymph nodes in the human body. There are also specialized blood vessels inside nodes, across which fluid, proteins, and cells may translate in either direction. Under normal conditions, some of the incoming (afferent) lymph fluid is taken up into blood, but very concentrated afferent lymph can also be diluted (Adair & Guyton 1983, Adair & Guyton 1985). Absorption of (mainly) water in this way results in post-nodal lymph usually having higher protein concentration. It is estimated (Renkin 1986) that capillaries lose to the interstitium some 8 L/day of fluid which becomes afferent lymph; after reabsorption at nodes (usually several nodes along a typical lymphatic vessel pathway), the total post-nodal (efferent) flowrate is about 4 L/day.

While there are wide variations in lymphatic vascular anatomy between organs two principal vessel types are distinguished. Initial lymphatics are the vessels which receive interstitial fluid; starting from blind stumps of some 50 μm in diameter they form a converging manifold conveying lymph to the collecting lymphatics. Initial lymphatics have occasional internal one-way valves and thin non-muscular walls. They lead to the collecting lymphatics, which are subdivided into short segments called lymphangions by regularly spaced one-way valves, and have muscular walls capable of mounting more or less periodic contractions. The contraction of lymphangions, combined with the valve action, transports lymph by a mechanism (intrinsic pumping) analogous to that occurring in the chambers of the heart. A second transport mechanism (extrinsic pumping) results from intermittent squeezing by the relative motion of or pressure change in surrounding tissues, through skeletal muscle use, breathing cardiac-induced blood vessel pulsation, intestinal peristalsis, external body compression, etc.

Structure and Function of The Lymphatic System

The lymphatic system is a linear network of lymphatic vessels and secondary lymphoid organs. Macroscopically, the blood vascular system is literally a circular system in which the fluid (blood) leaves the heart; runs through the arteries, arterioles, capillary plexus, venules, and veins; and returns to the heart. In contrast, the lymphatic system is a blunt-ended linear system, in which tissue fluids, cells, and large extracellular molecules, collectively called lymph, are drained into the initial lymphatic capillary vessels that begin at the interstitial spaces of tissues and organs; are transported to thicker collecting lymphatics, which are embedded with multiple lymph nodes; and are eventually returned to the blood circulation through the thoracic or lymphatic ducts that join to the subclavian veins. Microscopically, whereas blood capillaries are lined by the innermost blood vascular endothelial cells (BECs), which are covered by the basement membranes and then surrounded by smooth muscle-like pericytes, lymphatic capillaries are lined with a single layer of partly overlapping lymphatic endothelial cells (LECs) without being surrounded by the basement membrane or pericytes Whereas cross sections of blood capillaries are round and homogeneously shaped owing to hemodynamic pressure, lymphatic capillaries are irregularly shaped and usually stay collapsed Lymphatic vessels can be found in all of the vascularised organs and tissues except retina, bone, and brain.



FUNCTIONS OF THE LYMPHATIC SYSTEM

Lymphatic system actually has many functions. Its key functions include:

Maintains fluid levels in your body: As just described, the lymphatic system collects excess fluid that drains from cells and tissue throughout the body and returns it to the bloodstream, which is then recirculated through the body.

Absorbs fats from the digestive tract: Lymph includes fluids from the intestines that contain fats and proteins and transports it back to the bloodstream.

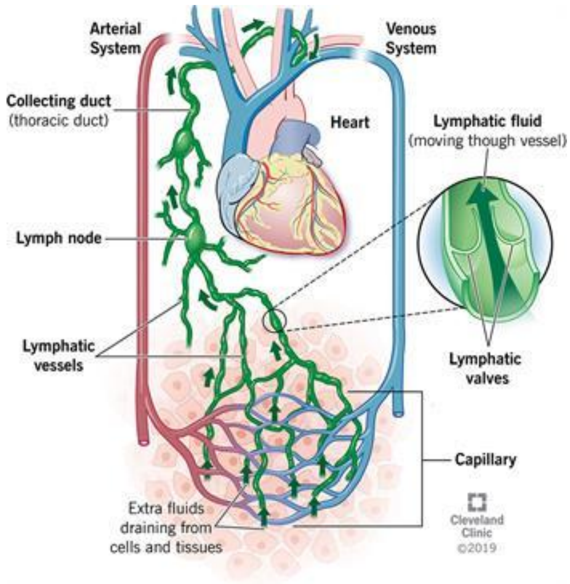
Protects your body against foreign invaders: The lymphatic system is part of the immune system. It produces and releases lymphocytes (white blood cells) and other immune cells that monitor and then destroy the foreign invaders — such as bacteria, viruses, parasites and fungi — that enter the body.

Transports and removes waste products and abnormal cells from the lymph.

What are the parts of the lymphatic system?

The lymphatic system consists of many parts. These include:

- Lymph: Lymph, also called lymphatic fluid, is a collection of the extra fluid that drains from cells and tissues (that is not reabsorbed into the capillaries) plus other substances. The other substances include proteins, minerals, fats, nutrients, damaged cells, cancer cells and foreign invaders (bacteria, viruses, etc). Lymph also transports infection-fighting white blood cells (lymphocytes).
- Lymph nodes: Lymph nodes are bean-shaped glands that monitor and cleanse the lymph as it filters through them. The nodes filter out the damaged cells and cancer cells. These lymph nodes also produce and store lymphocytes and other immune system cells that attack and destroy bacteria and other harmful substances in the fluid. You have about 600 lymph nodes scattered throughout your body. Some exist as a single node; others are closely connected groups called chains. A few of the more familiar locations of lymph nodes are in your armpit, groin and neck. Lymph nodes are connected to others by the lymphatic vessels.
- Lymphatic vessels: Lymphatic vessels are the network of capillaries (micro vessels) and large network of tubes located throughout the body that transport lymph away from tissues. Lymphatic vessels collect and filter lymph (at the nodes) as it continues to move toward larger vessels called collecting ducts. These vessels operate very much like your veins do: they work under very low pressure, have a series of valves in them to keep the fluid moving in one direction.
- Collecting ducts: Lymphatic vessels empty the lymph into the right lymphatic duct and left lymphatic duct (also called the thoracic duct). These ducts connect to the subclavian vein, which returns lymph to your bloodstream. The subclavian vein runs below your collarbone. Returning lymph to the bloodstream helps to maintain normal blood volume and pressure. It also prevents the excess build-up of fluid around the tissues (called edema).



The lymphatic system collects excess fluid that drains from cells and tissue throughout the body and returns it to the bloodstream, which is then recirculated through the body.

- **Spleen:** This largest lymphatic organ is located on your left side under your ribs and above your stomach. The spleen filters and stores blood and produces white blood cells that fight infection or disease.
- **Thymus**: This organ is located in the upper chest beneath the breast bone. It matures a specific type of white blood cell that fights off foreign organisms.
- **Tonsils and adenoid:** These lymphoid organs trap pathogens from the food you eat and air you breathe.

They are your body's first line of defence against foreign invaders.

- **Bone marrow:** This is the soft, spongy tissue in the centre of certain bones, such as the hip bone and breastbone. White blood cells, red blood cells, and platelets are made in the bone marrow.
- **Peyer's patches:** These are small masses of lymphatic tissue in the mucous membrane that lines your small intestine. These lymphoid cells monitor and destroy bacteria in the intestines.
- **Appendix:** Your appendix contains lymphoid tissue that can destroy bacteria before it breaches the intestine wall during absorption. Scientists also believe the appendix plays a role in housing "good bacteria" and repopulating our gut with good bacteria after an infection has cleared.

How the Lymphatic System Works

The lymphatic system as the body's drainage system, working around-the-clock to clean up and properly dispose of waste left behind by other body systems. A healthy lymphatic system also contributes to many other major bodily functions, including:

Drains fluid back into the bloodstream

One of the lymphatic system's primary jobs is to collect excess fluid (particularly lymph fluid) surrounding the body's tissues and organs and return it to the bloodstream. If the lymphatic system didn't drain excess fluid from the tissues, the lymph fluid would build up in the body and cause swelling.

Filters lymph

As lymph passes through the lymph nodes, the white blood cells attack any bacteria or viruses found in the lymph. If cancer cells break away from a tumour, they can attach to the nearby lymph nodes. This is the reason doctors will check the lymph nodes first when determining how far cancer has spread.

Filters the blood

The spleen filters blood, removing old red blood cells and replacing them with new red blood cells that are made in the bone marrow.

Removes impurities from the body

The lymphatic system also helps to remove toxins and other impurities from the body, such as carbon dioxide, sodium and other by-products of cellular feeding on oxygen, minerals and nutrients. The system helps to remove these impurities and dispose of them through perspiration, bowel movements, urine and your breath.

Fights infection

The lymphatic system helps defend the body against illness-causing germs, bacteria, viruses and fungi. The system builds immunity by making special white blood cells (called lymphocytes) that produce antibodies which are responsible for immune responses that defend the body against disease.

Mechanism of Lymphatic System In Human Body Against Covid-19

About 15% of COVID-19 patients develop pneumonia; about 5% of them go on to have multiple organ failure. During such critical conditions, the immune response is critically impaired.

In the immune system, white blood cells patrol the body – through the blood – looking for the virus. Of the different types of white blood cells, lymphocytes are particularly important because they recognise viruses and secrete antibodies against them. In people with a severe form of COVID-19, the number of lymphocytes is sharply reduced.

Lymphocytes include T-cells, B-cells and natural killer (NK) cells. T-cells develop from the thymus gland. B-cells and NK cells originate from the bone marrow. T-cells are of two types: helper T-cells and cytotoxic T-cells. Helper T-cells activate various other immune cells and release signalling molecules called cytokines. Cytotoxic T-cells go for the virus, release toxic granules into them and kill them.

B-cells perform a diverse range of functions, notably secreting antibodies. NK cells kill those cells that have already been infected by the virus. This prevents the virus from spreading further. A decrease in the number of T, B, and natural killer cells leads to a marked deterioration in the immune response of the affected individual.

A common feature among COVID-19 patients is a dropping T-cell population. Those T-cells that still remain have compromised function. B- and NK cells' populations also decline in people with severe COVID-19.

When any infection takes hold, the body responds by secreting antibodies that circulate in the blood for some time. They bind to the viruses, neutralise them and expel them from the body. This binding is akin to a key 'binding' to a lock. Specifically, the antibody recognises a particular part of the virus, called the epitope, and forms a bond with it using a part called the paratope.

Any microorganism is capable of evolving into new strains, or genetic variants, in the natural course of evolution – viruses more so.

Say antibodies are secreted against one strain. Their paratopes could develop a structural change that allows them to bind to the epitopes corresponding to this strain. However, the binding itself doesn't destroy the viruses.

In some cases, as with the dengue virus, the virus-antibody complex keeps circulating in the bloodstream and gets attached to nearby cells. As a result, the antibody itself ends up enhancing the virus's uptake into the cells, and allows the viral population in the body to grow faster. This process is called antibody-dependent enhancement (ADE).

Cytokine Storm and Lung Damage
A phenomenon called cytokine storm leads to mortality in terminally ill COVID-19 patients. Cytokines are small proteins synthesised by several types of cells. However, they are predominantly produced by the helper T-cells and macrophages. Cytokines warn the cells of an invading virus, and stimulate them to move towards the sites of infection and inflammation to fight the virus. If white blood cells are police, the cytokines could well be their bullets.

Cytokines accelerate inflammation in the body to prevent the virus from circulating further. Controlled inflammation is essential to expel the virus – but sometimes unrestrained cytokine synthesis leads to a rampaging inflammatory response called a cytokine storm. In a COVID-19 patient, a cytokine storm elevates the patient's status to a critical condition known as acute respiratory distress syndrome, which is often fatal.

Understanding the body's response to the SARS-CoV-2 virus is important to comprehend the underlying mechanisms of vaccines and antiviral drugs. Coronaviruses have not popped up all of a sudden. We have been living with various human and animal coronaviruses for decades. Nevertheless, this novel coronavirus is wreaking havoc owing to its rapid rate of transmission. Further investigation will unravel the complete behavioural patterns of this virus, allowing researchers to develop a potential vaccine soon.

The cytokine release syndrome (CRS) seems to affect patients with severe conditions. Since lymphocytopenia is often seen in severe COVID-19 patients, the CRS caused by SARS-CoV-2 virus has to be mediated by leukocytes other than T cells, as in patients receiving CAR-T therapy; a high WBC-count is common, suggesting it, in association with lymphocytopenia, as a differential diagnostic criterion for COVID-19. In any case, blocking IL-6 may be effective. Blocking IL-1 and TNF may also benefit patients. Although various clinical sites in China have announced the use of mesenchymal stromal/stem cells (MSCs) in severe cases with COVID-19 infection, solid results have yet to be seen. One caveat is that MSCs need to be activated by IFN γ to exert their anti-inflammatory effects, which may be absent in severely affected patients as T cells are not well activated by SARS-CoV-2 infection. To enhance effectiveness, one could consider employing the "licensing-approach":pre-treat MSCs with IFN γ with/without TNF or IL-1.

Causes of Corona virus infection
When an infected person expels virus-laden droplets and someone else inhales them, the novel coronavirus, called SARS-CoV-2, enters the nose and throat. It finds a welcome home in the lining of the nose, according to a preprint from scientists at the Welcome Sanger Institute and elsewhere. They found that cells there are rich in a cell-surface receptor called angiotensin-converting enzyme 2 (ACE2). Throughout the body, the presence of ACE2, which normally helps regulate blood pressure, marks tissues vulnerable to infection, because the virus requires that receptor to enter a cell. Once inside, the virus hijacks the cell's machinery, making myriad copies of itself and invading new cells.

As the virus multiplies, an infected person may shed copious amounts of it, especially during the first week or so. Symptoms may be absent at this point. Or the virus' new victim may develop a fever, dry cough, sore throat, loss of smell and taste, or head and body aches.

If the immune system doesn't beat back SARS-CoV-2 during this initial phase, the virus then marches down the windpipe to attack the lungs, where it can turn deadly. The thinner, distant branches of the lung's respiratory tree end in tiny air sacs called alveoli, each lined by a single layer of cells that are also rich in ACE2 receptors.

Normally, oxygen crosses the alveoli into the capillaries, tiny blood vessels that lie beside the air sacs; the oxygen is then carried to the rest of the body. But as the immune system wars with the invader, the battle itself disrupts this healthy oxygen transfer. Front-line white blood cells release inflammatory molecules called chemokines, which in turn summon more immune cells that target and kill virus-infected cells, leaving a stew of fluid and dead cells—pus—behind. This is the underlying pathology of pneumonia, with its corresponding symptoms: coughing; fever; and rapid, shallow respiration (see graphic). Some COVID-19 patients recover, sometimes with no more support than oxygen breathed in through nasal prongs.

But others deteriorate, often quite suddenly, developing a condition called acute respiratory distress syndrome (ARDS). Oxygen levels in their blood plummet and they struggle ever harder to breathe. On x-rays and computed tomography scans, their lungs are riddled with white opacities where black space—air—should be. Commonly, these patients end up on ventilators. Many dies. Autopsies show their alveoli became stuffed with fluid, white blood cells, mucus, and the detritus of destroyed lung cells.

Putative Signaling Pathways Triggered By Sars-Cov-2
It is well-established that, upon binding of the viral spike protein to the host cells by the entry receptor ACE2, the viral RNAs, as pathogen-associated molecular patterns (PAMPs), are detected by the pattern recognition receptors, which include the family of Tolllike receptors (TLRs). In particular, for RNA virus such as CoVs, viral genomic RNA or the intermediates during viral replication, including dsRNA, are recognized by either the endosomal RNA receptors, TLR3 and TLR7/8, and the cytosolic RNA sensor, retinoic acid-inducible gene

(RIG-I)/MDA5.38 Consistently, such TLRs have been found to activate different signalling pathways in human CD14+ monocytes, correlating with differential type I IFN and cytokine secretion involved in CD4+ T cells polarization.38 As a result of virus recognition, downstream transduction pathways, crucial for proper antiviral response, such as IRF3 (IFN regulatory factor-3), nuclear factor κB (NF-κB), JAK (Janus kinase)/STAT (signal transducer and activator of transcription) signalling pathways, are activated.39 The identification of the most relevant intracellular signalling pathways involved in the modulation of host immune systems may give important hints on how to overcome the infectious disease driven by SARS-CoV-2. In particular, taking into account the structural similarities of SARS-CoV-2 as well as the analogies in the infection mechanisms with pathogenic SARS-CoV, it is tempting to speculate that the viral infection may induce the activation of shared intracellular pathways, in particular of those mainly involved in the innate immune response. However, to date, it has to be demonstrated whether such sequence similarities between SARS-CoV and SARS-CoV-2 can be directly translated into similar biological outcomes. Taking into account such limitation, the identification of signalling pathways altered during viral infections may help to unravel the most relevant molecular cascades implicated in biological processes mediating viral infections and to unveil key molecular players that may be targeted. The advantage of targeting intracellular molecules rather than viral proteins is that their effect is not likely to be negated by mutations in the virus genome. In fact, antiviral drugs inhibiting virus replication may select for mutational escape, thus rendering the therapy ineffective. Thus, the modulation of the host immune response shows the potential advantage of exerting less-selective pressure on viral populations.40 Repurposing of existing drugs targeting specific signal transducers will be discussed as potential treatment options for the management of COVID-19.

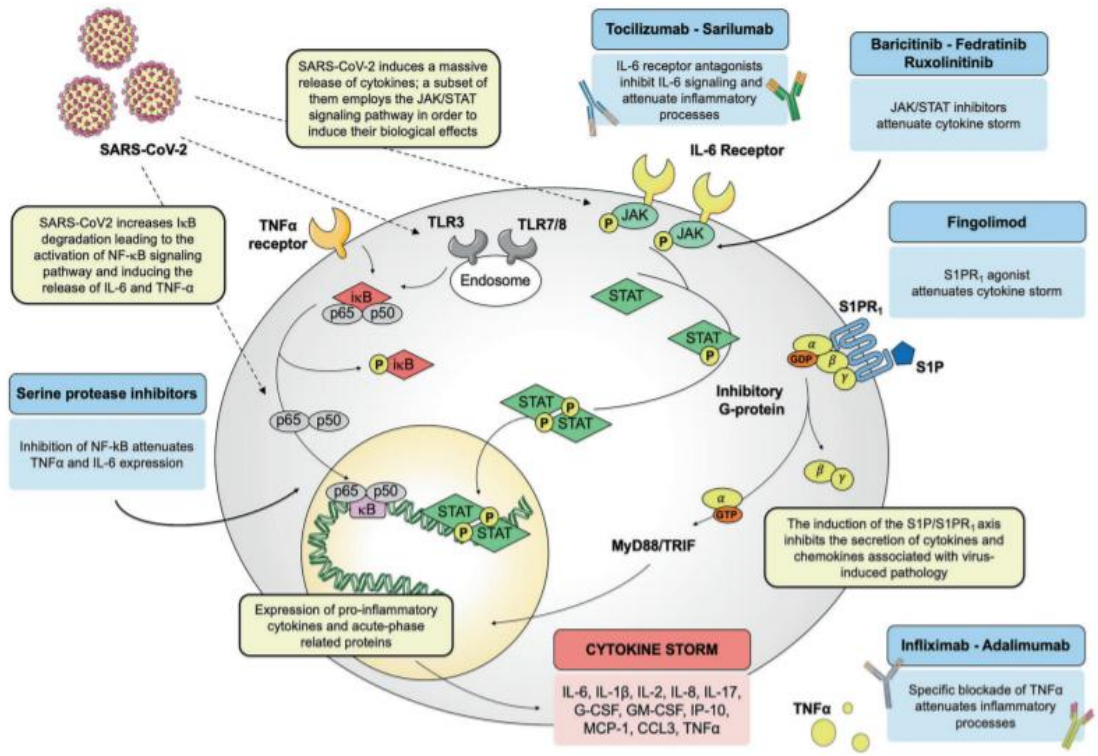


Fig. Schematic representation of SARS-CoV-2-driven signalling pathways and potential drug targets.

Pathogenesis and immune response

Like most other members of the coronavirus family, Beta coronavirus exhibit high species specificity, but subtle genetic changes can significantly alter their tissue tropism, host range, and pathogenicity. A striking example of the adaptability of these viruses is the emergence of deadly zoonotic diseases in human history caused by SARS-CoV and MERS-CoV. In both viruses, bats served as the natural reservoir and humans were the terminal host, with the palm civet and dromedary camel the intermediary host for SARS-CoV and MERS-CoV, respectively. Intermediate hosts clearly play a critical role in cross species transmission as they can facilitate increased contact between a virus and a new host and enable further adaptation necessary for an effective replication in the new host. Because of the pandemic potential of SARSCoV-2, careful surveillance is immensely important to monitor its future host adaptation, viral evolution, infectivity, transmissibility, and pathogenicity.

However, receptor recognition is not the only determinant of species specificity. Immediately after binding to their receptive receptor, SARS-CoV-2 enters host cells where they encounter the innate immune response. In order to productively infect the new host, SARS-CoV-2 must be able to inhibit or evade host innate immune signalling. However, it is largely unknown how SARSCoV-2 manages to evade immune response and drive pathogenesis. Given that COVID-19 and SARS have similar clinical features, SARS-CoV-2 may have a similar pathogenesis mechanism as SARSCoV. In response to SARS-CoV infections, the type I interferon (IFN) system induces the expression of IFN-stimulated genes (ISGs) to inhibit viral replication. To overcome this antiviral activity, SARSCoV encodes at least 8 viral antagonists that modulate induction of IFN and cytokines and evade ISG effector function. The host immune system response to viral infection by mediating inflammation and cellular antiviral activity is critical to inhibit viral replication and dissemination. However, excessive immune responses together with lytic effects of the virus on host cells will result in pathogenesis. Studies have shown patients suffering from severe pneumonia, with fever and dry cough as common symptoms at onset of illness. Some patients progressed rapidly with Acute Respiratory Stress Syndrome (ARDS) and septic shock, which was eventually followed by multiple organ failure and about 10% of patients have died. ARDS progression and extensive lung damage in COVID-19 are further indications that ACE2 might be a route of entry for the SARS-CoV-2 as ACE2 is known abundantly present on ciliated cells of the airway epithelium and alveolar type II (cells (pulmonary cells that synthesize pulmonary surfactant) in humans.

INNATE IMMUNE RESPONSES TO SARS-CoV-2 INFECTION

Gaining insight from strategies used by sars-cov and mers-cov

Currently, only limited information is available on the host innate immune status of SARS-CoV-2 infected patients. In one report where 99 cases in Wuhan were investigated, increased total neutrophils (38%), reduced total lymphocytes (35%), increased serum IL-6 (52%) and increased c-reactive protein (84%) were observed. Effective innate immune response against viral infection relies heavily on the interferon (IFN) type I responses and its downstream cascade that culminates in controlling viral replication and induction of effective adaptive immune response. While SARS-CoV and SARS-CoV-2 seem to share the entry receptor of ACE2, MERS-CoV uses dipeptidyl peptidase (DPP)-4 as a specific receptor. The putative receptor of SARS-CoV-2, ACE2, is mainly expressed in a small subset of cells in the lung called type 2 alveolar cells. It has been reported that SARS-Co-V directly infects macrophages and T cells, a key feature in SARS-CoV-mediated pathogenesis. Whether SARS-CoV-2 infects any immune cells are still unknown. Only minimal percentages of monocytes/ macrophages in the lung expressed ACE2.26. If ACE2 is minimally expressed in the potential target immune cells, it is possible that other receptors may exist, or other cellular entry mode is utilized such as antibody-dependent enhancement.

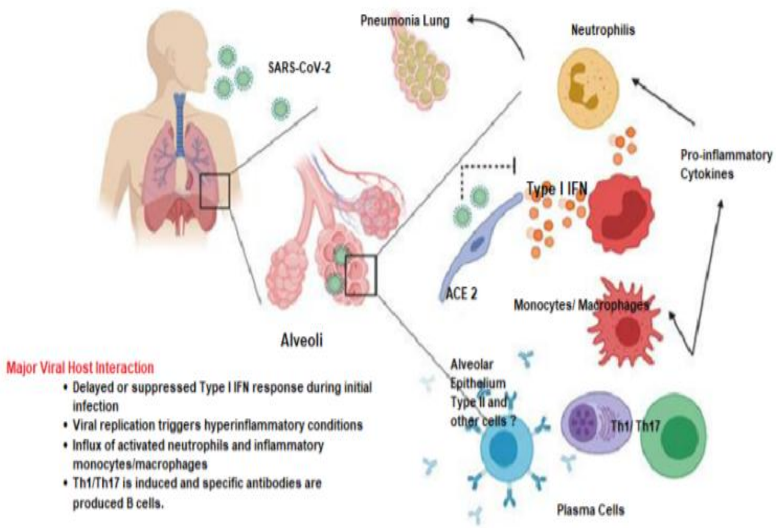


Figure: Proposed host immune responses during SARS-CoV-2 infection

Thymus Gland Responsible For Providing Immunity

To boost the self-protective mechanism of the body, we need to be more vigilant and informed about how this defence mechanism of our body works. First, lets discuss about the most important thymus gland of our body which is responsible for providing immunity, but this gland appears to be undervalued, rarely mentioned.

Thymus is a tiny pyramid shaped gland situated behind the sternum(chest bone), active until puberty. When ageing continues it typically atrophies and replaced by fat, but its function remains lifelong. This gland is central to the development and maturation of the lymphocytes or T-cells, a specific form of white blood cells which provides immunity to fight against foreign bodies (bacteria, viruses, etc.). certain types of precursor cells originate in the bone marrow of bones from the stem cells which travel through the blood stream to the thymus gland where they develop and are conditioned to fulfil their unique defensive functions.

Thymus secrets the thymosin hormone, which stimulates the T cell development and production. These produced cells go through specific training and selection process, some of them that is 1-2% get selected, matured and released in the lymphatic system to perform their function of defence against foreign bodies. Rest of them die inside the thymus. Further, these released cells in the lymphatic system categorised as T-cells (Thymus cells) and B-cells (Bone Marrow cells). T-cells mainly fight against foreign pathogens and further categorised into Natural Killer T-cells, Helper T-cells and regular T-cells.

Natural killer T-cells release certain chemicals such as cytokines which helps to fight and kill viruses or other foreign bodies. Helper T-cells as the name indicates help natural killer T-cells to kill the pathogens by identifying them as harmful. And regulatory T-cells basically plays the role ofhomeostasis, so that T-cells kills only harmful foreign pathogens and leaves body's own cells. Coming on to the B-cells whose central role is to produce antibodies. The job of antibodies is to identify the harmful pathogens and tag them so that natural killer can kill them.

Analysis of possible reasons for lymphopenia in COVID-19 patients

Lymphocytes play a decisive role in maintaining immune homeostasis and inflammatory response throughout the body. Understanding the mechanism of reduced blood lymphocyte levels is expected to provide an effective strategy for the treatment of COVID-19. We speculated four potential mechanisms leading to lymphocyte deficiency. (1) The virus might directly infect lymphocytes, resulting in lymphocyte death. Lymphocytes express the coronavirus receptor ACE2 and may be a direct target of viruses. (2) The virus might directly destroy lymphatic organs. Acute lymphocyte decline might be related to lymphocytic dysfunction, and the direct damage of novel coronavirus virus to organs such as thymus and spleen cannot be ruled out. This hypothesis needs to be confirmed by pathological dissection in the future. (3) Inflammatory cytokines continued to be disordered, perhaps leading to lymphocyte apoptosis. Basic researches confirmed that tumour necrosis factor (TNF)α, interleukin (IL)-6, and other pro-inflammatory cytokines could induce lymphocyte deficiency. (4) Inhibition of lymphocytes by metabolic molecules produced by metabolic disorders, such as hyperlactic acidemia. The severe type of COVID-19 patients had elevated blood lactic acid levels, which might suppress the proliferation of lymphocytes. Multiple mechanisms mentioned above or beyond might work together to cause lymphopenia, and further research is needed.

How does the system respond to a coronavirus attack?

A cascade of viral particles enters the body through the nose, eyes or mouth. Breathing carries some of these particles to the lower respiratory tract where the spike proteins of the coronavirus, acting like a key, lock into epithelial cells that line the respiratory tract as well as those in the air sacs in the lungs. SARS-CoV-2 is able to stay undetected longer than many flu or coronaviruses and its spike proteins are able to gain entry by unlocking the ACE2 protein on the lung cells. Once in, they hijack the cell’s machinery, replicate and multiply and infect adjoining cells. Like the defining ACE2 proteins on the epithelial cells, viruses too have a tell-tale signature on their surface called antigens and spotting these is what kicks the immune system into action by producing antibodies.

The signals they generate trigger another class of chemicals — cytokines and chemokines — and they alert the immune system to send an array of different kinds of cells that specialise in destroying viral particles. However, these cytokines and chemokines trigger inflammation in the cells. In the nose and upper regions of the respiratory system, this inflammation produces mucus and a runny nose to trap viral particles and prevent their ingress. This also triggers sneezes to expel them. When the sinuses are inflamed, we get a headache and the general stuffiness that we associate with a cold. When a gland called the hypothalamus is inflamed, it results in a fever.

However, in the case of SARS-CoV-2, the virus seems better at penetrating deeper. The inflammation triggers a fluid build-up in the lungs. The fluids also contain the residue of a host of specialised cells — including T cells — that carpet bomb and damage many of the body’s own cells as well as the viral particles. It is in expelling this fluid that a dry cough, characteristic of the coronavirus infection, begins. As more air sacs are infected, the lungs find it harder to perform their core job of extracting oxygen from the air, and eventually, this aggravates breathlessness.

HOW TO MINIMIE THE RISK OF INFECTION?

- **Improve your diet**

The food you eat plays a key aspect in determining your overall health and immunity. Eat low carb diets, as this will help control high blood sugar and pressure. A low carb diet will help slow down diabetes and focus on a protein-rich diet to keep you in good shape. And regularly consume vegetables and fruits rich in Beta carotene, Ascorbic acid & other essential vitamins. Certain foods like mushrooms, tomato, bell pepper and green vegetables like broccoli, spinach are also good options to build resilience in the body against infections. You can also eat supplements rich in omega 3 & 6 fatty acids for your daily dose, if stepping out to buy groceries is not an option during social distancing. Some natural immunity supplements include ginger, gooseberries (amla) and turmeric. Some of these superfoods are common ingredients in Indian dishes and snacks. There are several herbs that help in boosting immunity like garlic, Basel leaves and Black cumin. Certain seeds and nuts like sunflower seeds, Flax seed, pumpkin seeds and melon seeds are excellent sources of protein and vitamin E.

- **Don't compromise on sleep**

Good snooze time for 7-8 hours is the best way to help your body build immunity; lesser sleep will leave you tired and impair your brain activity. The lack of sleep will prevent the body from resting and this will impair other bodily functions that will have a direct impact on your immunity. Lack of sleep adversely affects the action of the flu vaccine.

- **Stay hydrated**

Drink up to 8-10 glasses of water every day, to stay hydrated. Hydration will help flush out the toxins from the body and lower the chances of flu. Other alternatives include juices made of citrus fruits and coconut water, to beat the heat.

- **Don't skip on exercise**

A good diet should be followed by an exercise routine. Remember to exercise regularly; even light exercise will go a long way in releasing the toxins from your body. It is recommended to exercise for 30 to 45 minutes, depending on your stamina. If you have not started exercising yet, then it is a good time to start. There are several YouTube channels and apps to help you exercise at home. Regular exercise improves metabolism, which has a direct correlation with body immunity.

- **Destress yourself**

These are testing times, and a prolonged period of staying indoors has its implications on your mental wellbeing. The growing anxiety around the pandemic is another concern that is affecting millions across the globe. While the uncertainty might be overwhelming, there are few steps we can follow regularly to help relieve our stress, stress is known to have an adverse effect on immunity.

How we can strengthen the defence system of the body?

According to various studies, acidic medium is the favourable environment for the survival of pathogens. So, if the body medium is acidic, that means body is more susceptible for infections. Here, I propose a novel therapeutic approach to boost the immunity by transforming the body's environment from acidic to alkaline.

Alkaline environment is not the feasible one for viruses to thrive, so it will curb down the infection rate and its severity. We are now aware of the vicious virus, Covid-19 (Corona virus). It affects those that have compromised immune systems and if not prepared, may potentially devastate the body. Unfortunately, immune-compromised individuals are often more vulnerable. That's why it is important to learn how to integrate and regulate immune system. Drinking nutrient-rich water is one of the important techniques of all as seventy percent of the body constituent is water. So, alkaline water has potential to strengthen the immune system significantly.

Role of Lymphatic System

The lymphatic system is a network of tissues and organs that help rid the body of toxins, waste and other unwanted material. The system is made up of lymphatic vessels, which are similar to the veins and capillaries of the circulatory system. The vessels are connected to lymph nodes, where the lymph is filtered.

Lymphatic vessels have three primary roles in normal human biology. One of the three is to facilitate the host's immune defenses. Lymphatic vessels function as channels through which antigens and immune cells are transported to their draining lymph nodes for immune protection. When infectious microorganisms invade, lymphatic vessels transport the pathogens or the antigen to the lymph nodes. This initiates adaptive immunity that leads to the production of cells and antibodies that will clear the pathogen and generate memory against it. There are hundreds of lymph nodes in the human body, deep inside the body, such as around the lungs and heart, or closer to the surface, such as under the arm or groin.

Supporting your lymphatic system is important to your overall health especially during the current COVID-19 threat. Ignoring the health of your lymphatic system means your immunity is going to suffer and this could but you at risk.

- The lymphatic system comprises a network of vessels lined by endothelial cells.
- Lymphatic vessels drain nearly all tissues and organs in the body and interconnect lymph nodes.
- Lymphatics are essential for returning proteins, fluids and cells to blood, absorbing fat from the gut and are involved in the homeostasis of interstitial macromolecules.
- The lymphatic system is a key regulator of extracellular fluid volume and is involved in preventing oedema.
- The lymphatics play a central role in integrating the immune system.

Keep Your Lymphatic System Healthy:

- Maintaining a healthy lymphatic system is important to prevent illness and keep other important body systems functioning. Encourage proper function of your lymphatic system by incorporating these healthy lifestyle tips:
- Drink plenty of water.
- Eat a healthy diet rich in alkaline foods and vegetables that provide a full range of vitamins, minerals and nutrients.
- Include healthy fats in your diet.

- Exercise daily, including both aerobic and anaerobic physical activity.
- Avoid pollutants, toxic substances and unhealthy environments.
- Learn to manage stress through techniques such as yoga, meditation and exercise to promote wellness.
- Your lymphatic system is constantly working to keep your body balanced. Maintaining its health is important not only for its own role but the role it plays in many other body systems.

10 Ways To Cleanse Lymphatic System

The lymphatic system doesn't have its own active pumping system and it needs the body's movement, breathing, intestinal activity, and muscle action to create flow and push the toxins out of the body. Below are 10 ways to help create flow in your lymphatic system and remove toxins from your body.

1. Exercise

Regular exercise is key for a healthy lymphatic system. Start with less vigorous training sessions, and try to slowly incorporate more intense exercises to your routine. The most stimulating exercise for the lymphatic system is rebounding on a small trampoline.

2. Alternative Treatments

A lymphatic drainage with Lymph-Biologics is one of the easiest ways to detoxify the lymphatic system. This 3-part light wave with oscillating frequency can stimulate circulation in the lymph, and drain fat, fluids, and toxins away from your cells for proper elimination. Acupuncture is another effective treatment that will help you stimulate lymph flow and help remove toxins from the body.

3. Hot and Cold Showers

The hot water helps dilate the blood vessels, while the cold water shrivels them. This creates a "pump" action that forces out the toxic fluids that have remained in the body. This therapy is not recommended for pregnant women or for those who suffer from cardiovascular disease.

4. Use Dry Brushing

Brush your dry skin in a circular motion for 10 minutes by using a natural bristle brush, and then take a shower. You can combine dry brushing with hot and cold showers for better effects.

5. Drink Clean Water

It is advisable to drink up to half your bodyweight in ounces of water per day to further cleanse your system of toxins. (For example, if you are 160 lbs. = 80 ounces of water). You should also drink a few glasses of lemon water as well.

6. Avoid Wearing Tight Clothes

By wearing excessively tight clothing, you are reducing circulation in the lymphatic system. Tight clothing can cause blockages in the lymphatic system, which can lead to an accumulation of toxins.

7. Breathe Deeply

Our bodies have 3 times more lymph fluid than blood, but there is no organ to pump it. The pumping action of deep breathing will help the lymphatic system transport the toxins into the blood before they are detoxified by the liver.

8. Eat Foods That Promote Lymph Flow

Eating raw and nutrient rich foods promotes a healthy lymphatic system. Some of the best cleansing foods for the lymphatic system are:

- Leafy green vegetables
- Low sugar fruits
- Ground flaxseed
- Chia seeds
- Avocados
- Garlic
- Brazil nuts
- Almonds
- Walnuts
- Cranberries

9. **Avoid Foods That Cause Blockages to The Lymphatic System**

Improve your lymphatic health by avoiding the following foods:

- Processed foods
- Conventionally raised meat
- Artificial sweeteners
- Conventional dairy
- Sugar
- Soy
- Table salt

10. Drink Herbal Tea That Stimulates Lymph Flow:

There are many herbs that can be very helpful for the lymphatic system. Use the following herbs to prepare teas that promote lymph health:

- Echinacea
- Astragalus
- Wild indigo root
- Goldenseal
- Cilantro
- Poke root
- Parsley

Clinical manifestations

Clinical manifestations of 2019-nCoV infection have similarities with SARS-CoV where the most common symptoms include fever, dry cough, dyspnoea, chest pain, fatigue and myalgia. Less common symptoms include headache, dizziness, abdominal pain, diarrhoea, nausea, and vomiting. Based on the report of the first 425 confirmed cases in Wuhan, the common symptoms include fever, dry cough, myalgia and fatigue with less common are sputum production, headache, haemoptysis, abdominal pain, and diarrhoea. Approximately 75% patients had bilateral pneumonia. Different from SARS-CoV and MERS-CoV infections, however, is that very few COVID-19 patients show prominent upper respiratory tract signs and symptoms such as rhinorrhoea, sneezing, or sore throat, suggesting that the virus might have greater preference for infecting the lower respiratory tract. Pregnant and non-pregnant women have similar characteristics. Severe complications such as hypoxaemia, acute ARDS, arrythmia, shock, acute cardiac injury, and acute kidney injury have been reported among COVID-19 patients. A study among 99 patients found that approximately 17% patients developed ARDS and, among them, 11%diedofmultiple organ failure. The median duration from first symptoms to ARDS was 8 days.

CONCLUSION

The current COVID-19 pandemic is clearly an international public health problem. There have been rapid advances in what we know about the pathogen, how it infects cells and causes disease, and clinical characteristics of disease. Due to rapid transmission, countries around the world should increase attention into disease surveillance systems and scale up country readiness and response operations including establishing rapid response teams and improving the capacity of the national laboratory system.

This review on boosting the lymphatic system is a potential resource for the treatment of patients with COVID-19. The process and mechanism of the lymphatic system can be a good source of knowledge for immune system development. The lymphatic system was considered a secondary vascular system that supports the blood vascular system. However, a series of landmark discoveries in lymphatic research has significantly advanced our understanding of not only the organogenesis, function, and anatomic structure of the system, but also the cellular and molecular biology of LECs. In particular, substantial attention has been given to the elucidation of the molecular control of physiological and pathological lymph angiogenesis, revaluating its essential roles in human health and wellbeing. This paradigm shifts simultaneously forced us to take a brand-new look at the lymphatic system as the other, not the secondary, vascular system. Considering the vital functions that the lymphatic system engages in and how little knowledge we have regarding the system, lymphatic research is truly a gold mine that invites ambitious young scientists and clinicians.

REFERENCES

1. https://my.clevelandclinic.org/health/articles/21199-lymphatic-system
2. https://www.nature.com/articles/s41392-020-0148-4
3. https://novelcoronavirus.onlinelibrary.wiley.com/doi/abs/10.1002/9780470015902.a0000523.pub2
4. https://science.thewire.in/the-sciences/the-human-bodys-immune-response-to-the-novel-coronavirus/
5. https://www.unitypoint.org/desmoines/article.aspx?id=3c97b5ba-0fe3-4616-aee1-6033a81d1c57
6. https://healthvision.in/covid-19-thymus-gland-and-alkaline-water/
7. https://synergyhealthassociates.com/blog/cleanse-clogged-lymphatic-system/
8. https://klosetraining.com/hn-article/
9. https://www.longdom.org/open-access/immune-response-towards-covid19-a-review-on-host-body-53795.html
10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189839/
11. https://jintensivecare.biomedcentral.com/articles/10.1186/s40560-020-00453-4
12. https://www.thehindu.com/sci-tech/health/coronavirus-how-does-the-immune-system-respond-to-a-coronavirus-attack/article31319716.ece
13. https://www.footache.com/post/use-your-lymphatic-system-to-aid-in-your-immunity
14. https://www.sciencemag.org/news/2020/08/coronavirus-may-shut-down-immune-system-s-vital-classrooms
15. https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes
16. https://onlinelearning.hms.harvard.edu/hmx/immunity/
17. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30310-8/fulltext
18. https://www.nature.com/articles/s41392-020-0191-1
19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3312397/
20. https://www.researchgate.net/publication/342588912_3COVID-19_Hypnosis_for_your_lymphatic_system
21. https://www.sciencedirect.com/science/article/pii/S1876034120304329