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Body versus SARS-CoV-2 Virus

Spotlights on Virus Pathogenesis Human Immunity Interactivity

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Abstract

A novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2) causes COVID-19; a newly emerged global pandemic disease and found to be more infective and more pathogenic than former human respiratory corona viruses due to its higher specific receptor binding affinity. Exposed COVID-19 data clearly recognize that the human immune response to SARS-CoV-2 is the prime factor affecting the course of disease. This article places emphasis on virus pathogenesis, host cell interaction, immunological response for COVID-19 trying to light on the obscured areas of this novel human health menace.

Keywords: COVID-19, COVID-19 immunity, COVID-19 interleukin storm, COVID-19 pathogenesis, SARS-CoV2.

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Introduction

COVID-19 is a WHO term which called on a worldwide spread, highly human to human transmitted disease, in certain risky conditions may lead to death. As of 11th December 2022, over 645 million confirmed cases and over 6.6 million deaths have been reported globally. The etiology of the disease is a novel beta corona virus; "severe acute respiratory syndrome coronavirus 2" (SARS-CoV2) which belonged to coronary virus [1, 2].

Finding out how the virus invades and interacts with human cells then tracking its pathogenesis is greatly helping in efficient fight against covid-19. Current clinical data suggest that severe COVID-19 is due to an over reactive immune response resulting in a cytokine storm and development of acute respiratory distress syndrome (ARDS) [3, 4].

Innate immunity supplies a prime line of defense versus invading pathogens comprising viruses in which the inducement of type I interferon (IFN-I) cytokines plays a substantial role in hindering virus replication and dissemination [5].

This review gives attention about the virus pathogenesis, host cell interaction, immune response,and why the COVID-19 becomes life-threating in certain cases.

I. Pathogenesis

The pathogenesis of COVID-19 is greatly obscured; however, it may mimic SARS to some extent. The viral infection targets human airway epithelial cells as well as alveolar

ones. Similar to what was noticed in response to SARS-CoV, immune-mediated hurt may play a substantial role in the pathogenesis of COVID-19, particularly among those who are critically ill due to severe disease. Viral infection of pneumocytes induces local inflammatory responses and the primary results suggest a critical role for T cells in modulating the COVID-19-related lung inflammatory response figure(1) [6].

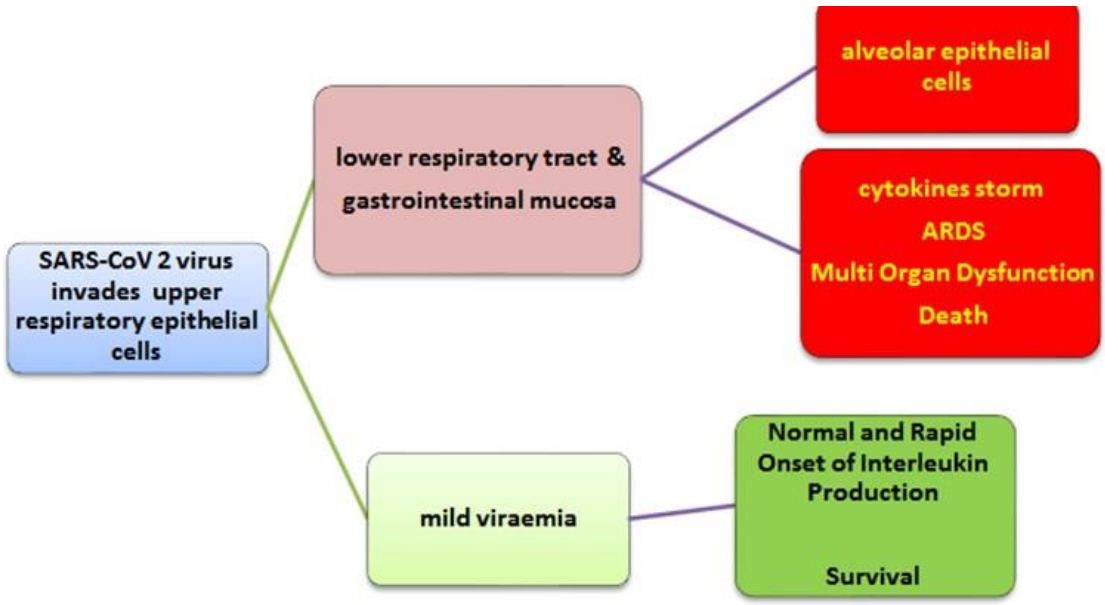

Fig. (1): summarized SARS-CoV 2 virus pathogenesis showing good (green) or bad (red) consequences.

An autopsy report of a 50-year old male Chinese patient died due to acute respiratory distress syndrome (ARDS) as the most critical form of COVID-19 was detailed. The report demonstrated many features that included desquamation of pneumocytes, hyaline membrane formation, interstitial inflammation and infiltration of large numbers of lymphocytes, in addition to atypical enlarged pneumocytes, were detected in the intra-alveolar spaces [3]. Another complete autopsy study, conducted on 12 (9 males and 3 females) died patients of (range, 52 to 87 years) in Germany; the postmortem computed tomography and histopathologic analyses were performed. Autopsy examination disclosed deep venous thrombosis in 7 of 12 patients (58%); pulmonary embolism was the direct cause of death in 4 patients. Postmortem computed tomography exposed reticular infiltration of the lungs with severe bilateral, dense consolidation, whereas histo-morphologically diffuse alveolar damage was observed in 8 patients. The high incidence of thromboembolic events suggests asubstantial role of COVID-19–induced coagulopathy [7].

II. SARS-CoV2 vs. human cell Interaction

The Spike glycoprotein (S protein) is one of the structural proteins which present on the surface of coronaviruses. SARS-CoV2 –S protein consists of S1 subunit, boundary of

cleavage and S2 subunit (fusion site). The S1 contain what is called receptor binding domain RBD, which binds to a specific receptor 'Angiotensin-converting enzyme 2' (ACE2) receptor on host cell; this binding is considered the first step in the initiation of the virus infection. The ACE2 receptor is the same target receptor of SARS-CoV while MERS-CoV targets another host receptor; dipeptidyl peptidase-4 (DPP4) figure (2), [8].

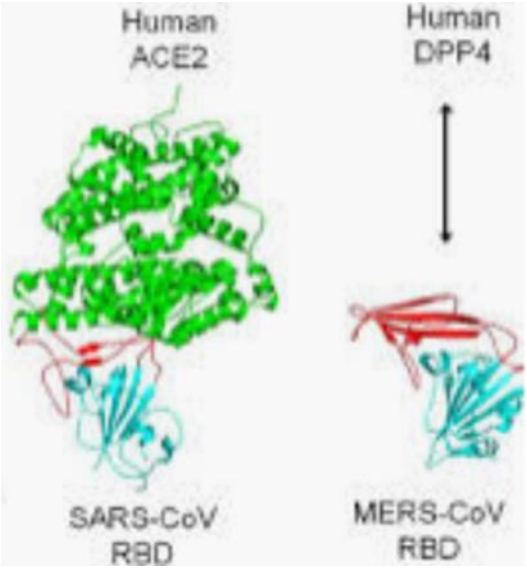

Fig. (2): the human receptors bonded to SARS-CoV2 virus vs MERS.

How does RBD contact with ACE2?

RBD in S1 subunit contains a core of short β5, β6 strands, α4, α5 helices and loops contain pair of cysteine (Cys480-Cys488) besides other three pairs of cysteine residues which help to stabilize the β sheet structure. On the other side, ACE2 contain N-terminal peptidase domain that has two lobes. As a result, RBM contacts with bottom side of ACE2 small lobe that is form interface between RBM and ACE2, while the concave outer surface in the RBM harbor the N-terminal helix of the ACE2 that results in a large buried surface figure(3), [9].

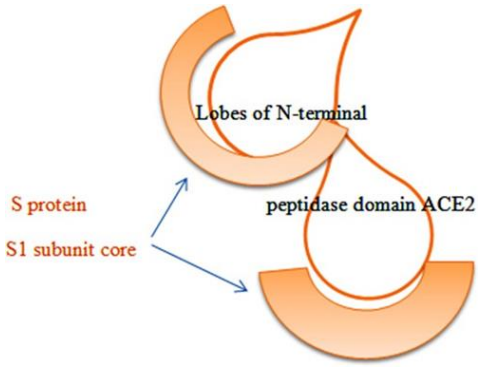

Fig. (3): the binding between S protein domain and ACE2

Nearly, SARS-CoV-2 RBDs interact with the ACE2 in a similar manner as SARS-CoV, with few exceptions; A number of 14 amino acids in SARS-CoV2 RBD share in the interface reaction with ACE2 receptor while the number is16 amino acids in case of SARS-CoV RBD. There are eight amino acids identical between SARS- CoV2 and SARS-CoV that result in similar biochemical property. Another difference; rather than RBD, SARS-CoV-2 has a unique ACE2-interacting residue (Lys417) which forms salt-bridge interactions with (Asp30) of ACE2. This site is replaced by a Valine in the SARS-CoV RBD that fails to take part in ACE2 binding. Furthermore, the same interacting residue; (Lys417) induces a positive charged patch on the SARS-CoV-2 RBD surface, which is not present in SARS-CoV RBD [10].

The differentiation in glycosylation sites between SARS-CoV-2 and SARS- CoV may also affect the interaction of RBD with ACE2; share in the high affinity binding and lower number of viruses required to infect a cell [9, 11].

After binding, the virus needs to cleave of S protein and the S2 domain fuses with host cell membrane, thus the virus can enter the host cell. Accordingly, the unique furin like enzyme in SARS-CoV2 cleaves S protein at site1besides the other cellular host proteases including cathepsins and (TMPRSS) which cleave S protein at site 2 into S1 subunit and S2 subunit [12, 13]. The other related coronaviruses as SARS-CoV lack the furin like enzyme, so that the SARS-CoV2 may have more efficient spreading among human compared to other beta coronavirus [8].

After cleavage of spike protein, the heptad repeats 1 (HR1) and 2 (HR2) domains of S2 subunit interact with each other forming a hydrophobic six-helix bundle (6- HB) fusion core that lead to fusion between viral and cellular membranes and infection starts. This interaction occurs via the three HR1domains form a parallel trimeric coiled center that interacts with three HR2 domains as an antiparallel manner. The SARS-CoV2, 6- HB is more stabilizer than other coronaviruses 6-HB due to many differences in salt bridges and chemical bonds; resulting in enhancement and rising of virus infectivity [11].

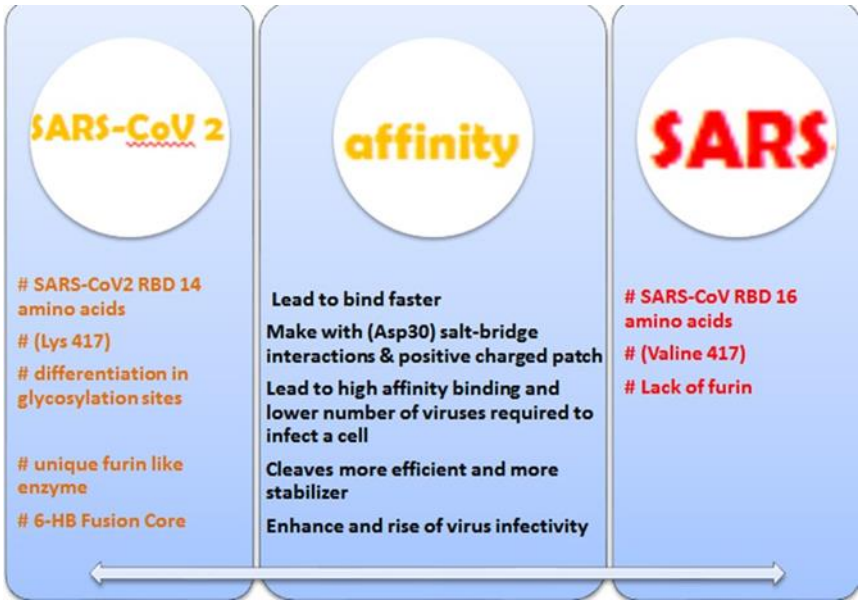

Fig. (4): causes of high affinity of SARS-CoV2

III. Internal Immune response to SARS-CoV-2 and other coronaviruses

Currently, there is a considerable knowledge about host immunity against SARS-CoV2; It is known that the innate immune cells recognize the virus via what is called pathogen associated molecular patterns (PAMPs). In case of coronaviruses "which has RNA as genetic material", PAMPs recognize them mainly by binding unique molecular determinant, in addition to, sensing of unfitted cellular sites of biomolecules. The recognition is conducted via many approaches; the endosomal RNA receptors, the cytosolic RNA sensor, Retinoid-inducible gene (RIG-I) and melanoma differentiation associated gene 5 (MDA5) [14, 15].

Briefly, the endosomal membrane receptors comprise Toll-like receptor3 (TLR3) and Toll-like receptor 7 (TLR7) which can recognize the single stranded RNA (ssRNA) of coronaviruses. RIG-1 detects RNA molecules with triphosphate groups at 5′ ends with or without a methyl cap which stimulates the antiviral responses. Finally, MDA5 detects viral double strand RNA in cytoplasm during replication of RNA virus [16, 17]. What else?

This recognition triggers activation of signal transduction cascades that include transcription of nuclear factor-κ Band activation of interferon regulatory factor 3(IRF3), then ended with production of (IFN) type 1 and other pro-inflammatory cytokines. Production of interferon 'especially IFN type 1' is the major innate immune response against viral infection as exerting trials to control viral replication in early stage. Furthermore, the interferon initiates the response of pneumocyte type II which is considered the main target of SARS CoV-2 and has essential roles not only in innate immune response but also the adaptive immune one; it provides barrier effect, pathogen sensing and inducing production of anti-viral cytokines [18].

Regarding the known concepts of adaptive immune response against viral infection; when the myeloid lineage cells are activated through PRR or other stimuli, they can successfully present viral peptides on MHC/HLA and start expressing co-stimulatory molecules that aid prime T cells of the adaptive immune system. Both $CD8^+$ T lymphocytes, which recognize peptides, bound to HLA-I, and $CD4^+$ T lymphocytes, which recognize peptide: HLA-II, are essential for viral clearance in mouse models of SARS-CoV-1 infection [19].

Mainly the cellular adaptive immunity is the response of choice; as primed $CD8^+$ T cells are competent to kill virally infected cells; on the other side the $CD4^+$ T cells secrete factors not only to help B cells for initiation of antibody responses but also to enhance $CD8^+$ T cell function. Contemporary, B cells also become activated by nigh viral antigens through their antibody receptors. This immune response drove to controlling the viral replication, limiting the spread of virus, and cleaning the infected cells [20]. In typical antibody responses, generate germinal centers and antibody affinity maturation. Both activated B and T cells donate immunological memory; memory is composed of cells that respond more

rapidly than do their naïve precursors to subsequent infections and of long-lived [21] figure (5).

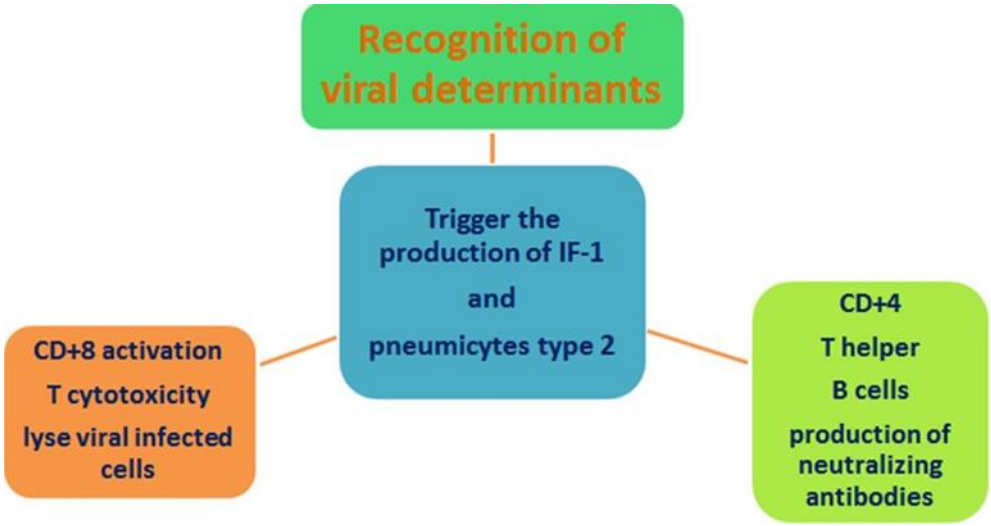

Fig. (5): the host immune response against SARS CoV-2

As the humoral immunological response's knowledge against SARS-2 is not well established, the guide of the response against SARS-1 could be followed. The most efficient neutralizing antibodies are those target the receptor-binding domain of the S protein, thereby competitively prohibiting viral entry into host cells, subsequently it was the base of SARS-1 vaccine principle. By analogy, the same way has been tracked but with attention to that the affinity of SARS-2 S protein for its receptor is approximately over 20 times tighter binding than that observed by SARS-1 S protein [22-24]. Another barrier is contributed to that other neutralizing antibodies cross-react between SARS-2 and SARS-1 and appears to bind the S protein core rather than the receptor-binding domain [25-27]

Interestingly, patients infected with COVID-19 has high levels of IL-1B, IFNγ, inducible protein-10 (IP10), and monocyte chemo-attractant protein-1 (MCP1), supposedly leading to turning T-helper-1 (Th1) cell responses on [28]. In patients with progressed COVID-19, there are lower levels of helper, cytotoxic suppressor and regulatory T cells than non- severe patients. Regulatory T cells are responsible for the conservation of the immune equilibrium via suppressing the activation, proliferation of most lymphocytes to avoid extra immune response bad consequence. Furthermore, the percentage of naïve helper T cells is highly increasing, in contrast to remarkable decreasing in memory helper T cells in severe COVID-19. It is obvious that the homeostasis between the naïve T cells and memory T cells is essential for mediating the efficient immune response [29].

These changes alteration in level of the subgroup of lymphocytes lead to an immune dysregulation with the induction of thumping cytokine and chemokine response, all of which might result in cytokine storm and further tissue damage and multi-organ dysfunction [19].

Coronaviruses can escape from innate immune system via hindering the production of type 1 INF through ORF3b, ORF6 and nucleocapsid proteins (N proteins). Encoding of an enzyme that adds a 2' O- methyl group to viral RNA, so that it not detected by MDA-5, ORF6 inhibits host antiviral responses through creation of double membrane vesicles in site of replication, thus help the virus to evade the recognition by cytosolic pattern recognition receptors (PRRs). Moreover, viral N proteins activate RIG1 that lead to prevent production of interferon type 1 which increases severity of the disease [30-32].

Summarily, the release of (IFN) type 1 in the early stage of infection can promote the protection, but the delay in interferon production causes uncontrolled and exaggerated disease situation [16].

The bad consequence; disease severity and death depend on increasing in neutrophil with decreasing in lymphocytes, which is an indicator for immune system impairment. This impairment is confirmed by the evidence which ICU patients have higher plasma levels of many cytokines; IL2, IL7, IL10, IP-10, MCP-1, MIP-1A, GCSF and TNFα than the non-ICU patient [33].

The worst consequence is the stimulation of what is known as uncontrolled cytokine storm (CS) which is termed as macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH). As lymphocytes and certain subsets of T cells are able to balance immune response but in COVID-19 the decreasing in lymphocytes leads to the out of controlling in cytokine production, and disease severity [28].

Notably, the high inflammatory picture is usually observed in the progression and severity of conditions associated with SARS-CoV and MERS-CoV infection [15]. However, that picture is not observed in SARS-CoV-2 as the virus initiates the increasing of T-helper-2 (Th2) cytokines (IL4 and IL10) that suppress inflammation [28].

Regrettably, the main death reason of COVID-19 is the induction of acute respiratory distress syndrome (ARDS) that is caused by previous mentioned immune- pathological cytokine storm. A large amount production of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc...) as well as chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10.This storm violently attacks the body starting viral sepsis, inflammation then complications occur; pneumonia , ARDS , respiratory failure , shock, organ failure particularly kidney and finally death [33].

Interestingly, the children and young people are not showed severe disease about SARS-COV-2, this is contributed to their strong immunity which able to curb SARS-CoV-2 virus. In contrast, the older people with or without chronic disease have remarkable weak immunity, because immune system suffers abundant age-related changes that affect not only many cellular and molecular elements of both the innate [34] and adaptive [35, 36], but also the coordination between them, these changes are collectively termed 'immune senescence' [37].

Age-related changes start early in life by the end of puberty; there is a drop-in production of new T cells to 10% due to thymus atrophy [38]. Another drop-in production of both naïve T cells to 1% [39], and naïve B cells occurs between 40 and 50 years of age [38]. Moreover, the lymph nodes 'the major site of Naïve T and B cells maintenance' undergo dramatic age-related changes in the final third of life [40].

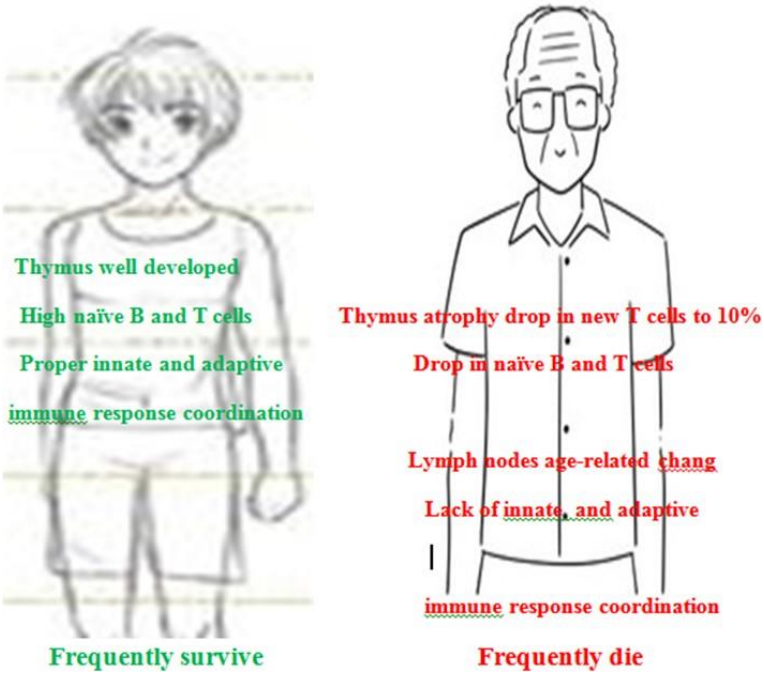

Fig. (6): the age related immune declining picture.

Consequently, the naive T cells are not maintained or unable to coordinate with innate immune cells to meet immune responses to emerging infection strikes [41].

All previous alterations lead to inefficient activation of innate immune cells as well as reduced proliferation and differentiation of both T and B cells, as a repercussion, the immune responses to a new emerging infection is diminished [42].

Certainly, these issues; lack of innate and adaptive immune response coordination occurs in older adults facing a COVID-19 infection and result in increased virus virulence and mortality in older populations. The sum of these changes leaves older adults particularly vulnerable to new, emerging infectious diseases—exactly as seen with SARS-1, MERS, the West Nile virus (WNV), chikungunya virus (CHIKV) [REFS], andnow SARS-2 [14].

CONCLUSIONS

SARS-CoV2 has more affinity to its specific target receptors than SARS-CoV about 10- to 20-fold and maybecause in high human to human transmission in SARS-CoV2. It is believed that the delay in interleukin production, consequently cytokine storm and activated immune cell migration to the lungs are implemented in the bad prognosis of the disease; severe lung damage and initiation of acute respiratory distress syndrome. The bad progress of COVID-19 in elder patients is contributed to the depleting changes in immune system leading to severity of the disease.

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