COVID-19 : history, pathogenesis and host immune response.

COVID-19 : histoire, pathogénèse et réponse immunitaire de l'hôte.

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ABSTRACT

By the end of 2019, a pneumonia of unknown etiology occurred in Wuhan, China. Local hospitals started receiving patients presenting symptoms like dry cough, fatigue, and breathing difficulties, most of these patients were linked to the Huanan seafood market, Wuhan, China. The pandemic was afterward confirmed to be associated to a novel coronavirus. The virus spread quickly from Wuhan to other provinces of China, then from China to the rest of the world causing thereby one of the most brutal pandemics in world's history. SARS-CoV-2 has a long incubation period ranging from 3 to 7 days and can go up to 14 days in some cases which makes the infection difficult to be detected early and subsequently the disease spread harder to be controlled. SARS-CoV-2 is a single stranded RNA virus with 4 main structural proteins, the spike (S) glycoprotein, the small envelope (E) glycoprotein, the membrane (M) glycoprotein as well as the nucleocapsid (N) protein. Current knowledge about the virus shows that it uses its spike protein to invade host cells, mainly the alveolar epithelial cells. The lung is the most targeted organ among many other organs like heart, small intestine and kidneys that are vulnerable to SARS-CoV-2 infection. The COVID-19 is known to be mild in most cases, but in some cases, it can be severe or even fatal. In the severe cases, acute respiratory distress syndrome was reported, and the capability of SARS-CoV-2 to infect many organs can lead to multiorgan failure and death. SARS-CoV-2 invasion induces several immune responses that could be efficient for infection clearance in mild cases, while in severe cases, the immune response dysfunctions can even contribute to the disease aggravation. Neither the pathogenic mechanism by which SARS-CoV-2 infects host cells, nor the host immune response to its infection have been fully understood, hence further studies are needed to give further evidences about these two phenomena.

Keywords : COVID-19, SARS-CoV-2, Coronavirus, Structural proteins, Immune response.

INTRODUCTION

Coronaviruses are a non-segmented single stranded RNA viruses (ssRNA), they have the largest genomic size comparing to all other RNA viruses with 27 to 34 kb of length (1).

The world has already witnessed two major health threats due to coronaviruses, the first was the severe acute respiratory syndrome (SARS) which occurred in 2002 in China, whose causative agent was the SARS-CoV; 10 years afterward, another epidemic occurred in Saudi Arabia, it was called the middle east respiratory

RÉSUMÉ

À la fin de 2019, une pneumonie d'étiologie inconnue est apparue à Wuhan, en Chine. Les hôpitaux locaux ont commencé à recevoir des patients présentant des symptômes tels qu'une toux sèche, asthénie et difficultés respiratoires, la plupart de ces patients ont fréquenté le marché des fruits de mer de Huanan, à Wuhan, en Chine. Il a ensuite été confirmé que la pandémie était associée à un nouveau coronavirus. Le virus s'est rapidement propagé de Wuhan à d'autres provinces de la Chine, puis de la Chine au reste du monde, provoquant ainsi l'une des pandémies les plus brutales de l'histoire du monde. Le SRAS-CoV-2 a une longue période d'incubation allant de 3 à 7 jours et qui peut s'étendre jusqu'à 14 jours dans certains cas, ce qui rend l'infection par ce dernier difficile à détecter précocement et subséquemment, la propagation de la maladie plus difficile à contrôler. Le SRAS-CoV-2 est un virus à ARN simple brin comportant 4 protéines structurales principales : la glycoprotéine de pointe (S), la glycoprotéine d'enveloppe (E), la glycoprotéine de membrane (M) ainsi que la protéine de nucléocapside (N). Les connaissances actuelles sur le virus montrent qu'il utilise sa protéine de pointe pour envahir les cellules hôtes, principalement les cellules épithéliales alvéolaires. Le poumon est l'organe le plus ciblé parmi de nombreux autres organes comme le cœur, l'intestin grêle et les reins qui sont vulnérables à l'infection par le SRAS-CoV-2. La COVID-19 est connue pour être bénigne dans la plupart des cas, mais dans certains cas, elle peut être grave, voire mortelle. Dans les cas graves, un syndrome de détresse respiratoire aiguë a été signalé et la capacité du SRAS-CoV-2 à infecter de nombreux organes peut entraîner une défaillance multi-organique et la mort. L'invasion du SRAS-CoV-2 induit plusieurs réponses immunitaires qui pourraient être efficaces pour l'élimination de l'infection dans les cas bénins, tandis que dans les cas graves, les dysfonctionnements de la réponse immunitaire peuvent même contribuer à l'aggravation de la maladie. Ni le mécanisme pathogène par lequel le SRAS-CoV-2 infecte les cellules hôtes, ni la réponse immunitaire de l'hôte à son infection n'ont été pleinement compris, par conséquent des études supplémentaires sont nécessaires pour donner des évidences ampliatives sur ces deux phénomènes.

Mots clés : COVID-19, SRAS-CoV-2, Coronavirus, Protéines structurales, Réponse immunitaire.

syndrome (MERS) and It was due to MERS-CoV (2, 3).

By the end of 2019, a novel pandemic emerged in Wuhan, China. Cough, fatigue, and shortness of breath were its major symptoms, The pandemic causative agent has quickly been identified to be a novel coronavirus, that was later named 2019-nCoV by the World Health Organization (WHO), and then SARS-CoV-2 by the International Committee on Taxonomy of Viruses (4, 5).

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The virus has quickly spread from China to the rest of the world and by the time of writing 213 Countries and Territories around the world are recording 16,226,400 confirmed cases of COVID-19 including 648,865 deaths (6).

The exact mechanism by which SARS-CoV-2 infects human cells and the host immune responses remains poorly understood, and no efficient treatment has been developed yet (7).

In this paper, we briefly introduce the SARS-CoV-2, summarize the history of coronaviruses due health threats, and discuss the mechanism by which the virus infects human cells as well as the most important events of the host immune response.

HISTORY

Coronaviruses belong to the family Coronaviridae, suborder Cornidovirineae and order Nidovirales, and comprise a total of 39 species under the large realm of riboviria (8). They are enveloped, positive-sense RNA viruses, characterized by cub-like spikes that project from their surface, which gives them a crown resembling appearance under the electron microscope, from which the name coronavirus was coined (9).

In the past 20 years, the world has experienced two events where severe disease has resulted from crossing over of animal β -coronaviruses from animals to humans. In november 2002, a new β -coronavirus causing severe acute respiratory syndrome (SARS) appeared in southern China. After being brought to Hong Kong in February 2003, the SARS-CoV virus spread rapidly all over the world and caused 916 deaths from 8422 total cases (fatality rate of 11%) before being contained in June 2003 (10).

In 2012, Saudi Arabia witnessed the emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV), a virus who originated from bats, but was found to crossover to humans via dromedary camels who were and are to this day an intermediate reservoir host. MERS-CoV caused >2,400 cases globally including >850 deaths (mortality rate $\approx$ 35%) (11).

In December 2019, an unknown acute respiratory tract infection spread first in Wuhan province, China. Local hospitals started receiving people suffering from pneumonia with unfamiliar etiology. The Huanan seafood and wild animals market in the city of Wuhan was the main place where the new infection emerged (12). On January 7 2020, the causative agent was identified to be a new coronavirus (13) that was later named 2019-nCoV by the World Health Organization, then renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses (4).

The virus quickly spread from Wuhan to all provinces of china, and from china to the rest of the world especially with the elevated travel rates of chinese people during the winter vacation and the chinese New Year holiday (14). China has recorded 83,830 confirmed cases from which 4,634 deaths and 78,908 recovered cases up to 26 July 2020 (15).

Afterward, the virus metastasized to the rest of the world, to the point that by the time of writing, countries like Italy (Figure 1a), United states (Figure 1b), Spain (Figure 1c) and Algeria (Figure 1d) recorded 245,864; 4,315,709; 319,501 and 26,764 total confirmed cases including 35,102; 149,398; 28,432 and 1,146 deaths (fatality rates 14.27%, 3.46%, 8.89%, 4.28%) respectively (16-20).

Figure 1. Total confirmed cases, deaths and recovered cases in Italy (a), United States (b), Spain (c) and Algeria (d) up to 26 July 2020.

In total, 16,226,921 cases are being recorded worldwide including 648,873 deaths (fatality rate 6.53%) and 9,928,755 recovered cases up to date (Figure 2) (21).

Figure 2. Total Confirmed cases, deaths and recovered cases worldwide up to 26 July 2020.

COVID-19 pathogenesis (Structure and life cycle of SARS-CoV-2)

SARS-CoV-2 is part of the β -coronavirus group, who belongs with 3 other genera to the subfamily Coronavirinae, the latter one is a member of the family Coronaviridae, which affiliates to the order Nidovirales (Figure 3). SARS-CoV-2 has a positive sense single stranded RNA genome, 29,9kb in length (22, 23).

SARS-CoV-2 is mainly formed by four structural proteins (spike (S) glycoprotein, small envelope (E) glycoprotein, nucleocapsid (N) protein and the membrane (M) glycoprotein) (Table 1), together with other accessory proteins. These proteins are encoded by the one third of the genome near the 3' terminus of the virus RNA, while the remaining two thirds (ORF1a and ORF1b) encode for sixteen non structural proteins (NSPs) (24, 25).

SARS-CoV-2 virion binds to human host cells via their ACE2 (Angiotensin Converting Enzyme 2) receptors, these receptors are expressed on many organs such as lungs, heart, small intestine and kidneys (27, 28). The S glycoprotein contains 2 subunits, subunit 1 (S1) and subunit 2 (S2), the S1 has a Receptor Binding Domain (RBD) which allows cellular tropism and attachment to target cells, RBD has 6 important aminoacids conferring its high binding affinity to the ACE2 receptor, these aminoacids are L455, F486, Q493, S494, N501 and Y505 (29). Once the virion is attached to the host cell, the endocytosis process begins.

Figure 3. Classification scheme of SARS-CoV-2 (23).

Table 1. Different functions of SARS-CoV-2 structural proteins (25, 26).

Structural Proteins (SP)	Function
Spike (S) Glycoprotein	Sub-unit 1 (S1)
	<ul style="list-style-type: none"> - Attachment to human cells, - Determination of target host cells for the virus, - Assuring tissue tropism.
	Sub-unit 2 (S2)
	<ul style="list-style-type: none"> - Virus-cell membrane fusion by HR1 (Heptad Repeats 1) and HR2 (Heptad Repeats 2), - Virus-cell entry facilitation.
Small Envelope (E) Glycoprotein	<ul style="list-style-type: none"> - Plays a role In the viral morphogenesis, assembly and maturation.
Nucleocapsid (N) Protein	<ul style="list-style-type: none"> - Ensuring viral-rna encapsidation, - Implicated in viral replication cycle.
Membrane (M) Glycoprotein	<ul style="list-style-type: none"> - Impart curved circular shape to the virus, - Binding to nucleocapsids to stabilize them, - Stabilizing N protein-RNA complex promoting therefore viral assembly completion.

A recent study speculated an implication of a priming protease (TMPRSS2) that clears the ACE2 receptor leading thereby to the activation of the spike protein (30). Host cell's proteases such as "furin" cleaves the S protein at the S1/S2 junction on its polybasic cleavage site (RRAR) resulting in an S1 detachment and S2's fusion peptide exposure, the fusion peptide embeds into the cell membrane (29, 31, 32), then HR1 and HR2 groups together after S2 protein folds on itself, allowing membrane fusion and viral material release into the target cell cytoplasm (26, 32).

After the viral RNA genome is released in the cytoplasm, two large overlapping polyproteins (pp1a and pp1ab) are directly translated from the ORF1a and ORF1b using host cell's ribosomes, two protease enzymes (Mpro) and a papain like protease process these two polyproteins into sixteen mature

non-structural proteins (nsps) via a proteolytic cleavage between pp1a and pp1ab (33, 34), subsequently, a replication transcription complex (RTC) is formed by a set of these non structural proteins in double membrane vesicles, this complex, transcribes a negative sense templates of the viral RNA and subgenomic RNAs for the transcription of positive sense versions by the RNA-dependent RNA polymerase (RdRp) (25, 35, 36), then structural proteins and other accessory proteins are translated from the subgenomic RNAs employing Endoplasmic Reticulum and Golgi, the M, S and E proteins move to the reticulum-golgi intermediate compartment (ERGIC) and the nucleocapsid is formed after the newly viral genome joins the N proteins then move to the ERGIC, the nucleocapsids and the other structural proteins group together into small virion-containing vesicles and move to the cell membrane to be exocytosed (**Figure 4**) (37).

Figure 4. SARS CoV-2 entry and life cycle.

Host immune response

SARS-CoV-2 uses its Spike protein's RBD for binding to the angiotensin-converting enzyme 2 that it uses as an entry receptor to infect the host cell, mainly the epithelial cells of the lower human airway, the incubation period of the virus was reported to be between 3 to 7 days (38, 39). Cough, breathing shortness, loss of taste or smell, fever, muscle pain and chills are the most common symptoms of the infection (40). Acute respiratory distress syndrome (ARDS) and cytokine storm are the abundant causes of fatality in 70% and 28% of fatal COVID-19 cases, respectively (41).

The virus entry into the host cell activates innate immune sensing, when its pathogen-associated molecular patterns (PAMPs), including single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA), get recognized by the endosomal RNA receptors mainly the pattern recognition receptors (PRRs) such as TLR7 and TLR8 and also via the recognition of damage-associated molecular patterns (DAMPs) such as host DNA and ASC oligomers released after host cell's pyroptosis (41, 42). The DAMPs recognition is carried out by the extracellular toll like receptors of neighboring epithelial cells and alveolar macrophages (41, 43). This recognition induces a cascade of signaling pathways, and transcription factors (TFs) activation, two major gene-expression programs can be

activated, the NF- κ B and the interferon regulatory factor (IRF) family leading to the transcription of target genes implicated in pro-inflammatory and antiviral responses (44-46).

The activation of the NF- κ B pathway leads to the transcription of the pro-inflammatory cytokines mainly TNF- α , IL-1, IL-6 and IL-8 and chemokines such as CCL2, CCL3, CXCL8 and CXCL10. While, interferon regulatory factors, essentially IRF3 and IRF7, lead to the type I interferon (IFN- α and IFN- β) production (46, 47).

These cytokines and chemokines attract immune cells notably monocytes and T lymphocytes to the infected sites, which leads to the activation of adaptive immune responses via the release of more pro-inflammatory cytokines such as IL-2, IFN- γ , MCP-1, GM-CSF indicators of Th1 helper response, which activates CD8⁺ T cells to cytotoxic T lymphocytes (CTLs). CTLs recognizes and eliminates infected cells (48, 49). Moreover, SARS-CoV-2 infection induces neutralizing antibodies production against N and S structural proteins, detected after 2 to 3 weeks of the infection. Normally at this level, viruses are inactivated by neutralization and cleared up by alveolar macrophages (35, 41, 50). In most cases, mainly asymptomatic people, the immune response is sufficient for the infection clearance and health state recovery. And provide a preventive effect due to the T and B memory cells, Ready to inactivate and eliminate the virus via antibodies

neutralization and Cytotoxic T lymphocyte in case of second infection by SARS-CoV-2 (51).

Although patients with severe SARS-CoV-2 infection, show a lymphopenia (depletion in T lymphocytes), neutrophilia, an increased systemic level of a subsets of cytokines and chemokines mainly (TNF α , IL-1RA, IL-6, IL-8, IL-10, CCL2, CCL3, CXCL10) leading thereby to a cytokine storm, and delayed type I interferon response, the abnormal immune response observed in these patients causes hyper-inflammation and antiviral immune repression (47, 52, 53).

The main factors leading to these immune response changes in SARS-COV-2 patients still unclear. Recent studies suggested that a decrease of lymphocytes number in blood mainly CD8⁺ T cells observed in patients with SARS-CoV-2 may be explained by four potential causes : i), lymphocytes redistribution in the body by their migration to the infected sites. ii), the inhibitory effect of increased IL-6 level on T cells. iii), the use of steroid treatments to appease inflammation. iv), induction of T cell apoptosis through death receptor (FasR) expression on their surface (47, 54).

A recent in-vitro study showed a possible infection of T-cell by SARS-CoV-2, T-cells were more sensitive to SARS-CoV-2 than SARS-CoV. They reported that the virus entry to the cell was mediated by the spike protein in a receptor-dependent membrane fusion manner, even in the absence of ACE2 receptor expression, using possibly another alternative entry

Figure 5. Severity Factors of COVID-19 are associated with immune system dysregulation.

The disease severity is mainly associated with immune response dysfunctions, the SARS-CoV-2 uses its spike protein to bind the ACE2 receptor of the alveolar epithelial cells, the virus entry into the host cell and RNA genome release lead to its replication and multiplication to many virions, inducing host cell's pyroptosis and DAMPs, type I interferon, pro-inflammatory cytokines and chemokines release which attracts immune cells to the infected site, although, the type I interferon signaling pathway (Type I IFN-IFNR/JAK-STAT/ISG) is delayed. In resident macrophages, PAMPs and DAMPs are recognized by the TLR receptors, activating the NF- κ B pathway through the recruitment of many adaptor proteins such as IRAK4//TRAF6 for TLR7, the NF- κ B translocation to the nucleus induces inflammatory genes transcription, ORF3a accessory protein forms a complex with the TRAF3 adaptor protein and also activates NF- κ B pathway, the same complex can also activate the NLRP3 inflammasome by ASC ubiquitination. meanwhile, resident macrophages and monocytes release inflammatory cytokines IL-6, TNF- α which attracts immune cells (dendritic cells, monocytes, neutrophils „etc.) from blood to the injury site and induce adaptive immune response by TCD4⁺, TCD8⁺ and B lymphocyte activation. moreover, NLRP3 inflammasome activation activates caspase-1 leading to the production of mature IL-1 β and IL-18, an abnormal inflammatory cytokine release mainly (IL-6, IL-8, IL-10, TNF- α , Type I IFN, IL-1 β , IL-18) triggers contributing thereby to the cytokine storm which leads to an hyper-inflammation. The overproduction of IL-6 and TNF-alpha induces a t cell immunoparalysis. SARS CoV-2 infects T lymphocytes (Th1, Tc1) via their CD147 receptors (a new identified virus entry route) inducing FASR expression leading to their elimination by AICD in the peripheral lymphoid organs; lymph node and spleen, which causes lymphopenia, although, the viral replication inside the T cells have not been evidenced.

route mediated by CD147 receptor. But the virus replication process inside the cell is aborted, however the virus entry into the T cell induces FasR expression which lead probably to their apoptosis, which may explain the massive apoptotic death of T cells observed in lymph nodes and spleen of postmortem patients (47, 55-57).

Also, at the infected sites, an abundant infiltration of mononuclear phagocytes (mainly CD14+, CD16+) associated with an hyperinflammation was reported (58). This might be due to a possible activation of NLRP3 inflammasome by ORF3a accessory protein which forms a complex with TRAF3 protein and promotes ASC ubiquitination, leading to caspase-1 activation which cleaves pro-IL-1B and pro-IL-18 to mature IL-1B, IL-18 inducing inflammatory cytokine release (**Figure 5**) (47, 59, 60).

Up to date, the molecular mechanism by which SARS-CoV-2 induces immune response is not well understood. Therefore, these suggestions remain hypothetical and need to be supported with experimental studies to clarify the exact mechanism involved in the immune response against SARS-CoV-2.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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