Inflammasome Activation and Molecular Mechanisms Involved in COVID-19 Severity: A Systematic Review

ABSTRACT

Introduction: In recent decades, three significant coronaviruses have posed threats to public health: Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and in December 2019, a novel SARS-CoV-2 type coronavirus was reported in patients with viral pneumonia in Wuhan province. It was later named COVID-19 in March 2020 when the World Health Organization (WHO) declared the outbreak a pandemic. SARS-CoV-2 infections primarily manifest as respiratory illnesses leading to Acute Respiratory Distress Syndrome (ARDS). There is hyperactivation of the inflammatory response that results in increased production of inflammatory cytokines, such as interleukin IL-1β, and its downstream molecule IL-6, which serves as an aggravating factor of this disease. The inflammasome is a multiprotein complex involved in caspase-1 activation that leads to IL-1β activation in various diseases and infections, such as SARS-CoV-2 infection, and in different tissues.

Methodology: A systematic review was conducted to investigate the mechanism of inflammasome activation by SARS-CoV-2 infection, the role of the inflammasome in ARDS, and other potential mechanisms of inflammasome involvement in the severity of pathogenesis in patients with COVID-19. We conducted searches in the following databases: PubMed, LitCovid, MedRxiv, and ScienceDirec, in addition to manually searching for key materials.

Results: A total of 101 references were included. Regarding general characteristics, 57.7% were directly related to COVID-19 and SARS-CoV-2; 7.7% addressed aspects of the pandemic, including discussions about social aspects, and 34.6% covered general theoretical aspects related to the subjects included in this review.

Conclusion: This review highlights the inflammasome in interfering with different aspects associated with SARS-CoV-2. The simultaneous activation of inflammasomes and the inhibition of negative regulatory mechanisms that suppress them can lead to severe uncontrolled inflammation.

Keywords: Coronavirus, Severe Acute Respiratory Syndrome, SARS-CoV-2, COVID-19, Inflammasome, Cytokine Storm

1. INTRODUCTION

"At the end of December 2019, in the province of Wuhan, China, the world was confronted with a new coronavirus known as Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) in patients with viral pneumonia" [1]. "The disease caused by this pathogen was named Coronavirus Disease 2019 (COVID-19), with a rapid spread, and in March 2020, the World Health Organization (WHO) declared the outbreak a pandemic" [2].

"SARS-CoV-2 is highly transmissible among humans, spreading mainly through direct contact with secretions such as saliva or infected respiratory droplets. Typically, Coronaviruses (CoVs) cause only common colds, resulting in mild respiratory symptoms and occasional gastrointestinal involvement. However, SARS-CoV-2 infection presents with a range of symptoms. While some infected individuals remain asymptomatic, others exhibit signs ranging from flu-like symptoms to a potential progression to severe acute respiratory syndrome (ARDS)" [3].

“Although the molecular mechanisms that determine the severity of the disease remain unclear, the clinical association of mediators such as IL-6, lactate dehydrogenase (LDH) and the cytokine storm with severe cases suggests that excessive inflammation plays a decisive role in the clinical outcome” [4,5]. “The induction of inflammatory processes in the host cell often requires the involvement of inflammasomes, which are protein structures that aggregate in the cytosol in response to various stimuli. The NLRP3 inflammasome, possibly the most studied, consists of the NLRP3 receptor, the ASC adapter molecule and caspase-1. Caspase-1 is activated through proteolytic cleavage and promotes the activation of several substrates, including the inflammatory cytokines IL-1β and IL-18, as well as Gasdermin-D, a pore-forming protein that triggers an inflammatory form of cell death known as pyroptosi” [6].

“The activation of NLRP3 in response to microbial infections, cellular damage, or aggregates in the host cell cytoplasm promotes ASC polymerization, resulting in the formation of a microscopic structure known as a puncta (or spot), which serves as a hallmark of active inflammasomes in cells” [7]. “The presence of cell death and inflammatory products such as IL-1β, IL-18, and LDH in the serum of patients suggests the involvement of the inflammasome” [4,5,8-10], “the definitive demonstration of the participatioçn of this protein platform is still necessary, as these products can be produced by alternative pathways” [11,12,13]. Meanwhile, our understanding of the involvement of inflammasomes in the pathogenesis of COVID-19 remains limited.

The impacts on public health, as well as the economic consequences stemming from the pandemic, have presented significant challenges to humanity [14]. Among these challenges is the imperative need to comprehend the mechanisms contributing to the severity of the disease. Consequently, the inflammatory characteristics identified in COVID-19 prompt the investigation of inflammasome activation by SARS-CoV-2, along with its role in the development and/or exacerbation of the disease.

2. METHODOLOGY

This review followed the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model. To conduct the literature review, we searched the PubMed, LitCovid, MedRxiv, and ScienceDirect databases using the following search terms: Coronavirus, Severe Acute Respiratory Syndrome Coronavirus, SARS-CoV-2, SARS-CoV, MERS-CoV, COVID-19, Inflammasome, and Cytokine Storm. We included studies published from 2019, and only terms in English were utilized. Furthermore, we conducted a manual search by examining the references of selected articles to identify any additional relevant articles. Manual searches were performed within the bibliographic references of the located articles.

Priority was given to studies that included planned in vivo (human or animal) and in vitro (cell culture) clinical trials, systematic reviews of molecular mechanisms, and clinical practice guidelines. These studies had clearly described objectives related to the prevalence of development and/or associated factors, along with well-defined methodologies.

After consulting the databases and applying the search strategies, duplicated studies found in multiple databases were excluded. All the resulting abstracts were read. In cases where reading the abstract was insufficient to determine whether the article should be included, considering the defined inclusion criteria, the full article was read to determine its eligibility. When the abstract provided enough information, the articles were selected, and their full versions were obtained after analysis and inclusion in the study.

To extract the data from the articles, the Obsidian® program was used as a smart note-taking tool. It was employed to establish a network of links that included complementary information between articles, inspired by the Zettelkasten annotation method [15]. The data extracted included the following information: authors, year of publication, place of publication, type of study, sample size, method of assessing scope (applicability to local conditions), and type of statistical analysis.

The analysis of the identified studies was conducted in two phases, with a descriptive approach. The first phase encompassed the following aspects: year of publication, authorship, study location, type of study, study design, and method of result evaluation. In the second stage, we analyzed the overall findings and factors associated with them.

All works found were detailed for eligibility according to the following criteria: (i) concise approach to the impact of inflammasome complex activation on the severity of COVID-19, (ii) the work carried out with humans and (iii) studies carried out with adults. The following publications were archives of this review: letters, case reports, reviews and meta-analyses, congress abstracts, studies related to other types of pathology and method validation studies.

3. RESULTS

Initially, 134 articles published between 2019 and 2022 were selected, out of which 48 were excluded after analyzing their titles and abstracts, and 8 were found to be duplicates, leaving a total of 81 eligible articles. In the end, 25 additional studies were included in this narrative review through a manual search to enrich the methodological and theoretical aspects of the subject, bringing the total to 106 articles. Figure 1 provides a summary of the article selection process.

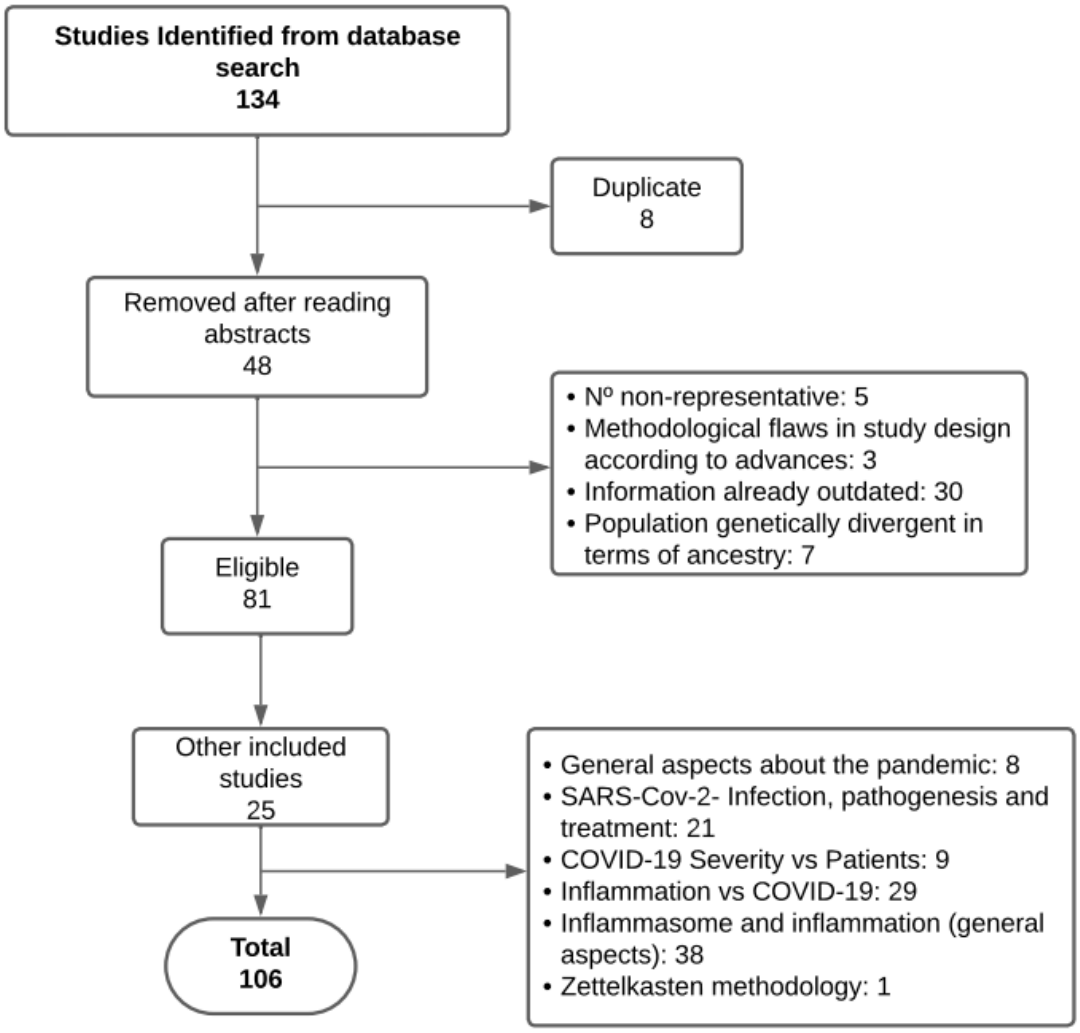

Figure 1. Flowchart for identification and selection of articles for systematic review following the PRISMA guideline on the relationship between the severity of Covid-19 and inflamasomes.

To enhance the understanding and analysis yield of the subjects (Figure 1), certain classifications were defined. "General aspects about the pandemic" encompassed the global impacts caused by the pandemic over the two years it has been ongoing. "SARS-CoV-2 - Infection, Pathogenesis, and Treatment" focused primarily on viral entry, molecular mechanisms, and genetic aspects related to the virus. This category also included in vivo clinical trials concerning potential treatments. "COVID-19 Severity vs. Patients" and "Inflammation vs. COVID-19" contained articles addressing genetic aspects, associated pathologies, and molecular events associated with the disease. These articles were organized into groups that covered patients affected by the disease, animal models infected by SARS-CoV or MERS-CoV, and similarly infected cell cultures. The categories "Inflammasome and Inflammation" and "Zettelkasten Methodology" provided additional information derived from the previously mentioned classifications.

Thus, regarding the general characteristics, 57.7% of the articles were directly related to COVID-19 and SARS-CoV-2. 7.7% dealt with aspects of the pandemic on a global scale, involving discussions about social aspects. The remaining 34.6% brought general theoretical aspects about the subjects included in this review.

4. DISCUSSION

The COVID-19 pandemic has underscored one of the greatest health challenges of the century. In times of crisis, each nation typically leverages its best resources to confront difficulties, and this process reveals both strengths and weaknesses. Asian countries, for instance, responded to the pandemic by allocating significant economic and technological resources to mitigate its impact. In Europe, despite its relative uniformity in social and economic matters, there were challenges in controlling the transmission and mortality rates associated with the disease [16]. In contrast, the African continent, known for its social and health challenges, experienced lower incidences and fatalities from COVID-19 when compared to other regions. This phenomenon may be attributed to significant differences in age demographics between European and African populations, low population density [17], environmental factors such as ambient temperature, potential underreporting of cases, and the possibility of resistance among the continent's inhabitants [18]. Turning to the Americas, the United States, as the world's largest economy, found itself at the epicenter of the disease for a period. In Latin America, the first recorded case of COVID-19 was in a Brazilian individual on February 26, 2020, who had recently traveled to European countries [19]. Brazil gained global attention due to its high incidence and mortality rates [20].

“Coronaviruses (CoV) belong to the Coronaviridae family within the order Nidovirales. They are enveloped viruses with a positive RNA genome and are divided into four genera (α, β, γ, and δ), with SARS-CoV-2 belonging to the β genus. CoVs consist of at least four structural proteins: membrane protein (M), envelope protein (E), nucleocapsid protein (N), and Spike protein (S). The Spike protein (S) is responsible for the virus's entry into the human host” [21].

The point of viral access to human cells is a crucial factor for host immune surveillance and therapeutic strategies. It also plays a pivotal role in infectivity and disease pathogenesis [22]. “For the virus to effectively enter the host's intracellular environment, several steps are involved, including receptor binding, proteolytic cleavage, and membrane fusion. These processes engage distinct domains within the viral S protein. It has been established that SARS-CoV-2 can utilize angiotensin-converting enzyme 2 (ACE2) as a receptor for cell entry. ACE2 receptors are found in the heart, kidneys, blood vessels, and respiratory tract epithelial cells” [23]. “However, beyond the receptor, host entry activation proteases are also required. These include TMPRSS2 and cathepsins, which are part of the lysosomal proteases [22]. Factors such as the expression and tissue distribution of entry receptors influence pathogenicity and viral tropism. Throughout the intracellular replication cycle, CoVs use the host's cellular machinery to replicate their genetic material and proteins to form new viral particles, which will later be secreted from the infected cell by exocytosis and which will be available to infect new cells” [24].

“SARS-CoV-2 is highly transmissible among humans, primarily spreading from person to person through direct contact with secretions such as saliva or infected respiratory droplets, as well as indirect transmission can occur through contact with contaminated surfaces or objects. The average incubation period is estimated to be 5.1 days (95% CI, 4.5–5.8), with 97.5% of infected individuals showing symptoms within 11.5 days (95% CI, 8.2–15.6) after exposure to the pathogen. As a result, control and prevention measures have been implemented throughout the pandemic, including the use of masks, regular hand hygiene, contact tracing, and social distancing” [2].

The most common symptoms include fever, cough, dyspnea, muscle pain, loss of taste, and gastrointestinal manifestations such as diarrhea, nausea, and vomiting. In severe cases, individuals may experience respiratory failure, pneumonia, septic shock, kidney failure, myocardial injury, coagulation disorders, and even death [25]. Like other diseases, there are still specific risk groups, which encompass the elderly, individuals with chronic conditions such as hypertension and diabetes, obese individuals, pregnant women, among others [26].

Severe pneumonia is present in about 10 to 15% of cases, and may progress to hypoxia and ARDS, which requires intensive care and has a high mortality rate. Still, a series of other disorders can be present in severe cases, such as multiple failure, acute kidney injury and disseminated intravascular coagulation [27,28,29,30,31,32,33,34,35]. As of now, emerging data indicate that dexamethasone therapy [36], reduces 28-day mortality in patients requiring supplemental oxygen compared with usual care [37], ongoing studies are testing the effectiveness of antiviral therapies, immune modulators [38] and anticoagulants in preventing disease progression and complications [39,40], while monoclonal antibodies may provide additional preventive strategies [41]. However, such approved treatments for COVID-19 provide supportive care as their primary action, but they do not have a direct impact on reducing mortality [42,43,44].

Although several vaccines against SARS-CoV-2 are already being applied internationally, there will still be a high number of infections, as there is a large mass of unvaccinated people in regions with inadequate acceptance of vaccination. Furthermore, the emergence of immunoevasive variants stood out as a problem in the challenge of ending the pandemic, bringing with it the improbability of achieving herd immunity and highlighting the continuing need for additional treatments that mitigate the progression of the disease [45, 46,47,48,49,50].

Among the mechanisms that trigger complications, several researchers concur that an inadequate hyper-inflammatory response with excessive release of inflammatory cytokines plays a key role in most severe cases of COVID-19 [51]. “Consistently, comorbidities such as obesity, diabetes, heart disease, hypertension, and aging, which are risk factors for clinical severity, are associated with elevated basal inflammation” [52].

“It has been proposed since the onset of the pandemic that these comorbidities and the resulting hyper-inflammatory response may be etiologically connected through hyperactive inflammasome signaling. In this context, one can elucidate the association of these comorbidities with cases of severe COVID-19, as well as for the progression of COVID-19 with a robust acute inflammatory response” [53-58].

Inflammasomes are cytosolic complexes that form in response to “Pathogen-Associated Molecular Patterns” (PAMPs) or Damage (DAMPs), trough the interactions between cytoplasmic receptors of innate immunity, such as proteins containing the NACHT, LRR and PYD domains, NLRP1, NLRP3, pyrin, or Absent in Melanoma-2 protein (AIM-2), along with the ASC adapter protein, and the inflammatory caspase, caspase-1. Thus, when the receptor is stimulated, it recruits ASC and caspase-1, and activates the processing and release of pro-inflammatory cytokines IL-1ß and IL-18 [59,60] (Figure 2).

Due to its high inflammatory potential, the activation of the inflammasome complex is controlled by several mechanisms, including the control of gene transcription (NF-kB, IRFs, microRNAs), the half-life of its components (ubiquitination, nitrosylation), and through inhibition mediated by cytosolic proteins (CARD8, proteins containing PYD/POPs domain, or proteins containing CARD/COPs domain) [61]. Most components of the inflammasome (NLRP3, AIM2, CASP1, IL-1B) are transcribed via NF-kB following activation of PAMPs, pattern recognition receptors (PRRs) or damage-associated receptors DAMPS, or cytokine receptors (TNFR, IL-1R) [61]. Both PAMPs and DAMPs can activate the inflammasome through different receptors, some extremely specific, such as NLRC4 and AIM2 that recognize bacterial flagellin and cytosolic DNA respectively; or pyrine which binds to host proteins modified by bacterial toxins; and others with broader activation mechanisms such as NLRP3, which can be activated by high extracellular concentrations of ATP (sign of cell death in tissue), production of oxygen radicals or lysosomal disruption [62].

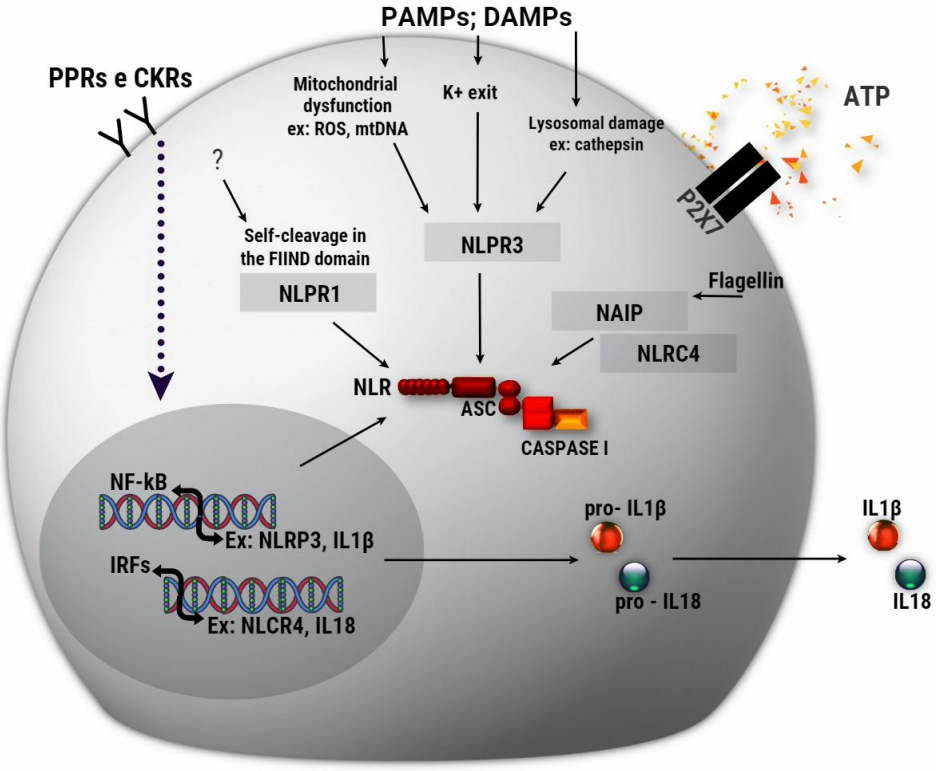

Figure 2: The inflammasome overview. The figure schematically shows four main inflammasome receptors (NLRP1, NLRP3, NAIP and NLRC4), their respective inducers, the adapter molecule ASC, and the effector molecule caspase-1, which cleaves the inactive forms of IL-1ß

and IL- 18 (pro-IL-1ß and pro-IL-18) in their respective biologically active and released forms. The NLRP1 inducer has not yet been identified in human cells, but activation of this receptor occurs after self-cleavage in the FIIND domain itself. NLRP3 is activated by changes in the cytosol. In general, binding of Lipopolysaccharides to a Toll-like receptor (TLR) activates NFkB or the transcription factors induced by interferons (IRFs), which then initiates the transcription of genes encoding for components of the inflammasome and inflammatory cytokines. Assembly of the differents NLRP inflammasome can be induced by different danger signals, including pore-forming toxins, exogenous ATP, K+ exit from the cells, lysosomal damage, reactive oxygen species and oxidized mitochondrial DNA produced as consequence of mitochondrial dysfunction. PAMPs, pathogen-associated molecular patterns; DAMPs, danger-associated molecular patterns, P2X7, Purinergic 2X7 receptor; etc. NLR, NOD-like receptor; ASC, apoptosis-associated speck-like protein containing a CARD forming the complex.

The inflammasome is not only confined in leukocytes, but is also find in non-strictly immune cells and tissues. Depending on the cell type, the expression of the components can be constitutive or induced. In tissues or cells where expression is constitutive (leukocytes), the inflammasome can be rapidly activated upon damage, whereas in cells (resident macrophages, dendritic cells, endothelial cells) where transcription of the components or cytokines (biologically inactive pro-forms of IL-1ß and IL-18) must be induced, the activation of the complex requires a longer time [60,63].

Following the activation of the complex and the release of cytokines, feedback mechanisms come into play to deactivate the inflammasome, controlling the inflammatory process and restoring tissue homeostasis. Dysfunction of the inflammasome can result in chronic inflammation and serve as either a primary cause or a contributing factor in various conditions, including monogenic diseases (inherited autoinflammatory diseases) or multifactorial ones (such as autoimmune diseases, cancer, obesity, cardiocirculatory disorders, and neurodegenerative pathologies). Dysregulation of the complex and the production of IL-1ß and/or IL-18 can be attributed to both genetic factors (mutations, polymorphisms) and chronic infections [60,65,66].

"Polymorphisms that result in increased activation of this complex (GoF variants) generally affect the near/inactive state or increase the expression level of target genes. For example, NLRP1 SNPs rs12150220 (c.464 T>A, p.(Leu155His)), located in a linker region between the PYD and NACHT domains, and rs11651270 (c.3550 A>G, p.(Met1184Val)), located close to the self-cleavage site in FIIND, it increases the processing of IL-1ß in peripheral blood mononuclear cells, especially when present in a combined haplotype" [67]. It is also important to remember that in addition to the fundamental role in the processing and release of IL-1ß and IL-18, they are involved in pyroptosis and also in caspase-independent functions, such as the role of transcriptional cofactor for a Th2 polarization proposed for NLRP3 [68] or the inhibitory role for NF-kB of NLRP6, NLRP7 [69]. All these considerations were summarized graphically in figure 3.

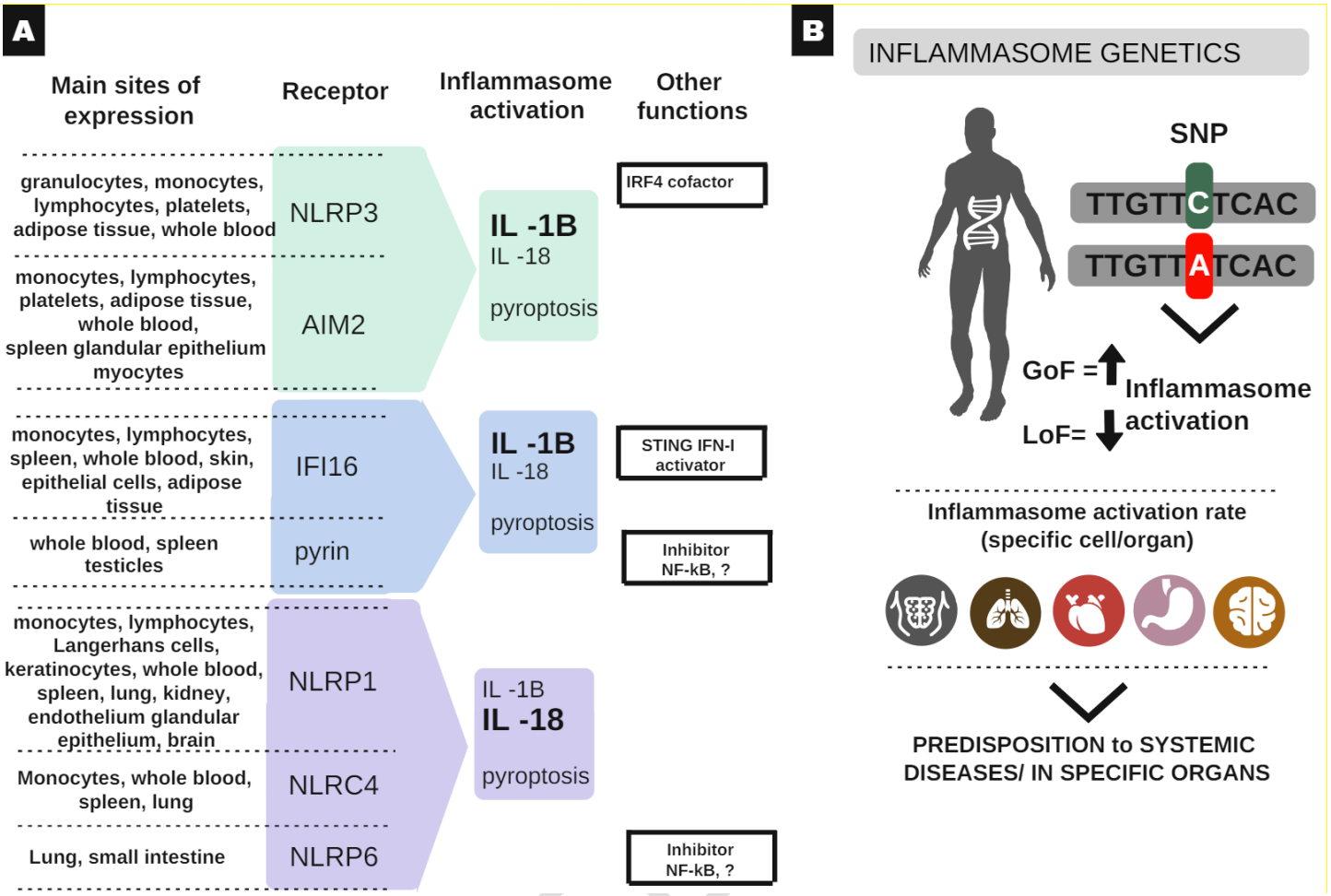

Figure 3. Inflammasome genetics. A) Major expression sites for inflammasome receptors are reported along with preferential processing of cytokines (larger, bold characters). Alternative function of inflammasome receptors is eventually indicated. Expression data were obtained from public databases (https://www.GTEX.org) and/or (https://www.proteinatlas.org). Of these, those containing the symbol "?" These are ongoing studies with a speculative nature to date. B) Schematic representation of the effect of genetic variants of the inflammasome on its constitutive activation rate, and the consequent role in disease predisposition, taking into account the fact that the genes of this complex often have specific expression in different cells/tissues. Gof: Gain of function variations, Lof: Loss of function variations.

The initial studies suggesting inflammasome activation in COVID-19 highlighted the serum concentration of LDH as a single predictor, distinct from various other serum factors, for severe disease. This correlation held true regardless of physiological criteria, the Assessment of Chronic Health II (APACHE II), mortality prediction scores, organ failure assessment scores, or even pneumonia-related severity indices [8]. Subsequently, this correlation was validated in other patient cohorts [20,48,49].

Commonly, LDH rises in situations involving tissue damage sustained by the generalized cell death observed among monocytes, alveolar epithelial cells and endothelial cells of the lungs and kidneys, thus being used as a general indicator of this type of injury [70, 71]. All these cell types are competent to activate inflammasomes and undergo pyroptosis [72,73,74].

"The extensive characterization of serum cytokines in COVID-19 has highlighted an overabundance of chemokines such as CXC chemokine ligand 8 (CXCL8; also known as IL-8) and pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF) throughout the course of the disease" [5,51,75]. Such a pro-inflammatory response brings with it some possible serum markers of inflammation associated with a poor prognosis, such as liver factors induced by IL-6, C-reactive protein and ferritin, in addition to the elevation associated with the concentration of the D-dimer coagulation product [4,76]. These cytokines related to severe inflammation, in turn, can be strongly induced by acute phase IL-1β, which already has previously described action in the production of IL-6 [77]. However, their appearance is not necessarily linked to inflammasome activation, and may be induced through other inflammatory pathways, including those stimulated by NF -κB. Thus, the hypothesis is supported by the fact that IL-1β acts as a pro-inflammatory cytokine, with its action

observed in vitro, where the exogenous antagonist of the IL-1 receptor (IL-1R) completely abolishes the secretion of IL-6 and TNF in primary monocytes infected with SARS-CoV-2 [78]. In addition to IL-1β activity, to reinforce the theory of inflammasome activation in severe cases of COVID-19, IL-18, whose secretion processing depends on inflammasome activation, was associated with disease severity, emerging as a biomarker predictive of death [5,79,80].

Inflammasome activation can be significantly amplified through positive feedback loops, resulting in runaway overactivation and a cytokine storm. The binding of IL-1β to IL-1R triggers an NF-κB response, which increases the transcription of pro-IL-1β. This process can occur in myeloid cells recruited to the lung [57]. Consequently, pro-inflammatory cytokines, whose levels are elevated in COVID-19, may also contribute to positive feedforward loops that exacerbate lung injury. For instance, IL-1β-mediated activation of endothelial cells can down-regulate the transcription of vascular endothelial cadherin (VE-cadherin), leading to the loss of adherent junctions critical for maintaining barrier integrity [81]. Simultaneously, IL-1β-induced IL-6 secretion can increase the production of vascular endothelial growth factor, which, in turn, weakens lung endothelium through the internalization of VE-cadherin [82]. These events can promote the accumulation of interstitial and alveolar fluid, compromising gas exchange [34,83]. Alveolar fluid accumulation can disrupt pulmonary surfactant, resulting in increased alveolar surface tension and collapse [34,79,84]. Consequently, the feedback-amplified immune cell recruitment and cascade feedforward tissue damage may synergistically worsen lung injury in response to early IL-1-directed proinflammatory cytokine release.

The NLRP3 inflammasome is known to be activated by highly pathogenic coronaviruses, such as SARS-CoV, SARS-CoV-2, MERS-CoV, and mouse hepatitis virus [62,85]. This inflammasome is expressed not only in immune cells of myeloid and lymphoid origin but also in alveolar epithelial and pulmonary endothelial cells, where its overactivation can contribute to lung injury [86,87,88]. One mechanism of NLRP3 inflammasome activation involves K+ efflux or Ca2+ influx induced by viral ion-conducting transmembrane proteins, also known as 'viroporins' (such as ORF3a and envelope protein E). ORF3a activates NLRP3 when overexpressed in monocytic cells or macrophages and has been associated with viral pathogenesis [4,89]. The SARS-CoV E protein incorporates into the membranes of the intermediate compartment of the Golgi endoplasmic reticulum (ERGIC) and induces the influx of cytosolic Ca2+ to activate NLRP3 in reconstituted Vero-type epithelial cells [93,91]. Another mechanism of NLRP3 inflammasome activation involves direct interactions with viral proteins. ORF3a can interact with the ASC inflammasome adapter, leading to its polyubiquitination and aggregation [4,92]. The SARS-CoV protein ORF8b, which is generated de novo due to a 29-nucleotide deletion in the ORF8 mutation hotspot during the SARS-CoV outbreak [93], can also directly activate the NLRP3 inflammasome by binding to the leucine-rich repeat region of NLRP3, promoting oligomerization and forming insoluble aggregates that co-localize with NLRP3 and ASC [94]. Importantly, an in vivo study using mouse-adapted recombinant SARS-CoVs showed that single amino acid mutations of the E protein that suppressed ionic conductivity reduced the pro-inflammatory activity of the virus, resulting in disease recovery and mouse survival [93,95].

In addition to direct activation of the inflammasome mediated by SARS-CoV-2 infection, indirect activation in COVID-19 can also be observed through several mechanisms. These mechanisms include the inhibition of host translation by SARS-CoV-2, which suppresses an early type I interferon response, allowing uncontrolled viral replication [96,98]. When infected lung cells undergo lysis, they can release alarmins that activate inflammatory macrophages and promote their recruitment to the lung [48]. This recruitment can induce IL-1β secretion by receptor macrophages, likely through NLRP3, but also potentially through other inflammasome sensors like AIM2 and NLRC4 [97]. Interestingly, one study pointed out that loci of quantitative traits (QTL) associated with increased expression of NLRC4 and NLRP3 were correlated with severe COVID-19, suggesting the possible involvement of multiple inflammasome sensors in the disease [98].

In the context of viral infections, including SARS-CoV and H1N1 influenza, the SARS-CoV-2 virus has exhibited a propensity to induce an inflammation-driven coagulopathy (Figure 4.). This phenomenon, prominently associated with an elevated incidence of venous and arterial thrombotic events and increased mortality rates in COVID-19 patients, is characterized by heightened plasma clotting markers, such as D-dimer, factor VIII, and von Willebrand factor, as well as abnormalities in prothrombin time [99]. While proinflammatory cytokines are recognized contributors to this condition, an intricate factor comes into play—the activation of Gasdermin D (GSDMD) by inflammasomes within monocytes and neutrophils. This activation triggers coagulation through diverse mechanistic pathways independently of cytokine signaling. Additionally, inflammasome-induced coagulopathy may involve phosphatidylserine-mediated tissue factor activation, further exacerbating clot formation. Dysregulated GSDMD activation plays a crucial role in the formation of neutrophil extracellular traps (NETs), complex fibrous structures composed of DNA and antimicrobial proteins. During viral infections like COVID-19, NETs contribute to coagulopathy by promoting platelet recruitment, microthrombi formation, and aggravating lung damage. This intricate interplay highlights the multifaceted nature of coagulopathy in severe COVID-19 cases, with GSDMD activation emerging as a pivotal mechanistic factor contributing to both coagulation and inflammation [100].

Furthermore, there is an intriguing proposition that inflammasome activation may be the central driver of both severe inflammation and coagulation in COVID-19. This suggests the potential therapeutic utility of targeting this pathway. Host mechanisms that trigger inflammasomes in COVID-19 may involve innate or adaptive lymphocytes, particularly cytotoxic T lymphocytes and natural killer cells, which can induce pyroptosis in infected cells. This process releases Granzyme A or Granzyme B, cleaving gasdermin B (GSDMB) or gasdermin E (GSDME) and resulting in pore formation. Given the substantial expression of GSDMB in the airway epithelium, cytotoxic lymphocyte-mediated killing of infected cells may contribute to the release of cytokines and damage-associated molecular patterns (DAMPs) during pulmonary infection [96] causing a cumulative cyclical process.

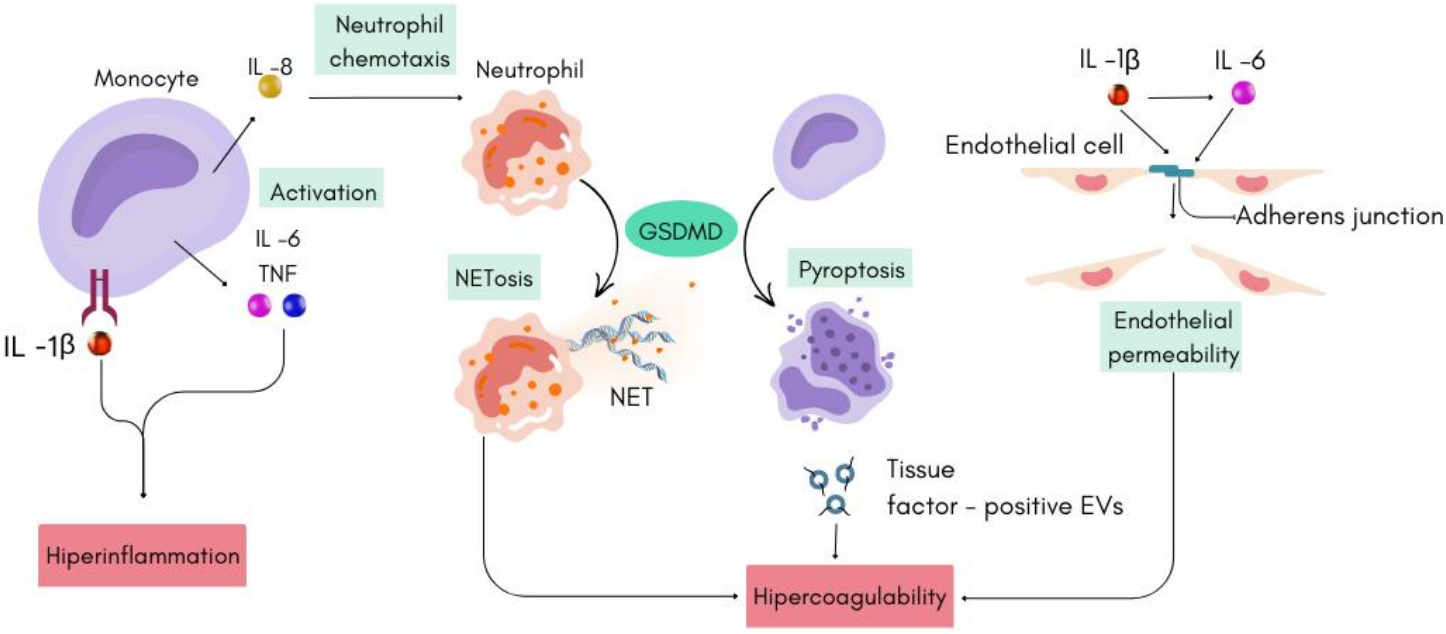

Figure 4: Mechanisms underlying inflammasome-driven COVID-19. The release of IL-1β triggered by inflammasome signaling stimulates monocytes, leading to the secretion of IL-6, tumor necrosis factor (TNF), and IL-8. These cytokines induce inflammation through various pathways, including the recruitment of neutrophils to the lung. Activation of Gasdermin D (GSDMD) in neutrophils results in the formation of neutrophil extracellular traps (NETs), which can attract platelets and enhance hypercoagulability. IL-1β and IL-6 may also reduce the expression of adherens junctions in endothelial cells, increasing their permeability and potentially contributing to coagulation in the pulmonary vasculature. Moreover, tissue factor-positive extracellular vesicles (EVs) released by pyroptotic monocytes can directly trigger the clotting cascade and promote coagulation in COVID-19.

Another hypothesis of indirect activation of the inflammasome arises from its connection with other systems, such as the complement system. When the complement product is cleaved by the pathogen, C5a, it becomes highly abundant in bronchoalveolar lavage fluids of patients with severe COVID-19 [98]. This complement product may facilitate IL-1β release, as observed in MERS-CoV-infected mice, and it may also trigger NLRP3 activation via a reactive oxygen species (ROS)-dependent mechanism in CD4+ T cells [101,102].

Another ROS-dependent mechanism, perhaps more pathologically relevant, involves the oxidation of the phospholipid-rich surfactant typically secreted by the alveolar epithelium. This process generates an enormous amount of oxidized phospholipids, which act as potent inducers of ARDS in mouse and non-canonical inflammasome models of infection (involving human caspase 4/5 or mouse caspase11 in dendritic cells and macrophages) [103,104].

Together, these phenomena indicate a complex response to DAMPs, and inflammasome sensors such as NLRP3 may serve as key pleiotropic drivers of COVID-19 pathogenesis. Compelling evidence supporting this idea also comes from bats, which coexist asymptomatically with highly pathogenic human coronaviruses. Peripheral blood mononuclear cells from bats express a hypomorphic isoform of NLRP3 and therefore do not release IL-1β after MERS-CoV infection. This suggests that NLRP3 suppression may be a potent strategy to reduce the pathogenicity of the coronavirus [87,105,106].

5. CONCLUSION

Recent data support the involvement of the inflammasome in severe COVID-19, either through direct infection-mediated activation or indirect DAMP-mediated activation. A protective role for inflammasome signaling and IL-1β release has been demonstrated against multiple pathogens, particularly in the acute phase of infection. However, its prolonged and delayed activation may underlie immunopathology, including excessive cytokine release, lung endothelial damage accompanied by immune cell infiltration, and systemic hypercoagulability. This review highlights the inflammasome's interference in various aspects associated with SARS-CoV-2. However, it is crucial to pay attention to this information since inflammasome signaling is necessary to combat viral infection, while simultaneously, "abnormal" activation of this complex may be responsible for the hyperactivated inflammatory response that leads to major complications or even death.

Variability in the course of the disease may be related to the extent or spread of inflammasome-activating stimuli, the site of inflammation, or the type of inflamed cell. Indeed, classic experiments in mice show that overexpression of IL-1β specifically in the lungs is sufficient to recapitulate many of the ARDS phenotypes. Differences in the pathology induced by this system can also be explained by negative regulatory mechanisms that limit feedback amplification downstream of chronic signaling in this system. Simultaneous activation of inflammasomes and inhibition of negative regulatory mechanisms that suppress them can lead to severe uncontrolled inflammation.

It is important to note that the feedback mechanisms that suppress and terminate inflammasome activation are still poorly understood. Given the number of people affected by COVID-19 worldwide, a better understanding of its associated systemic effects during and after the resolution of the infection is of paramount importance. Additionally, considering the possibility that SARS-CoV-2 infections may become a seasonal occurrence similar to influenza virus infections, it remains essential to identify and elucidate the mechanisms involved. This pursuit aims to develop new therapies that can be used for the treatment of COVID-19 and its associated systemic manifestations.

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