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Is Toll-like receptor 4 involved in the severity of COVID-19 pathology in patients with cardiometabolic comorbidities?

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A B S T R A C T

The severe form of COVID-19 is marked by an abnormal and exacerbated immunological host response favoring to a poor outcome in a significant number of patients, especially those with obesity, diabetes, hypertension, and atherosclerosis. The chronic inflammatory process found in these cardiometabolic comorbidities is marked by the overexpression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumoral necrosis factor-alpha (TNF-α), which are products of the Toll-Like receptors 4 (TLR4) pathway. The SARS-CoV-2 initially infects cells in the upper respiratory tract and, in some patients, spread very quickly, needing respiratory support and systemically, causing collateral damage in tissues. We hypothesize that this happens because the SARS-CoV-2 spike protein interacts strongly with TLR4, causing an intensely exacerbated immune response in the host’s lungs, culminating with the cytokine storm, accumulating secretions and hindering blood oxygenation, along with the immune system attacks the body, leading to multiple organ failure.

1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus targets the airway, alveolar and vascular endothelium as well as macrophages in the lung, binding to the angiotensin-converting enzyme 2 (ACE2) expressed in those cells [1–4]. The severe form of COVID-19 (COroneVirusDisease 2019) pathophysiology, however, is marked not only by the viral infection but also by the aggressive inflammatory response from the host able to cause severe systemic damage [5].

Comorbidities such as hypertension, diabetes, obesity, and atherosclerosis are related to the severe form of the disease, being more prevalent among hospitalized individuals with a higher average-case lethality [6–12]. The disease severity is characterized by the over-activation of the immune system causing a cytokine storm responsible for cytokine release syndrome (CRS) [13,14]. The inflammatory response starts with a local release of cytokines, such as interleukin-6 (IL-6) and tumoral necrosis factor-alpha (TNF-α), that may spread systematically, leading to acute respiratory distress syndrome (ARDS) and multiple organ failure, the final result being death, at least in the most severe cases of COVID-19 [15,16].

Despite what is already elucidated regarding the host cell infection and the spike protein binding to the ACE2 [17], other factors may contribute to the infectivity and pathogenesis of SARS-CoV-2 that deserve further investigations [18]. The spike (S) protein’s strong interaction with human Toll-like receptors (TLRs), especially TLR-4, which is overexpressed in chronic inflammatory conditions, will be described below and may be the link between the unbalanced immune response in severe COVID-19 and cardiometabolic comorbidities.

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2. Pathophysiology, immunity, and inflammation in COVID-19

The infection process starts with the receptor-binding domain, a portion from the S protein, expressed on the surface of viral particles, binding to the ACE2 [19]. It triggers endocytosis of the SARS-CoV-2 which is then exposed to endosomal proteases [20]. The recruitment of macrophages and monocytes, the release of cytokines, and priming adaptive B and T cell immune response is usually sufficient to successfully limit the disease progression and resolve the infection [21, 22]. A dysfunctional immune response, however, may occur causing severe lung injury and systemic manifestations [23].

In severe COVID-19 cases, a disharmonic and dysfunctional immune response triggers a widespread lung and systemic inflammation by a cytokine storm [24]. The viral infection and replication induce the death of virus-infected cells and tissues during its cycle [25]. The process is marked by local inflammation and the systemic release of inflammatory cytokines [26,27]. In support of this, scientific evidence shows that increased levels of inflammatory cytokines are predictive of poor prognosis in COVID-19 patients. Patients that required intensive care showed even higher blood levels of cytokines, such as IL-2; IL-7; IL-10; granulocyte colony-stimulating factor (G-CSF); interferon-γ-inducible protein-10 (IP-10); monocyte chemoattractant protein-1 (MCP1); macrophage inflammatory proteins-1α (MIP-1α) and, TNF-α [28].

In addition, the IL-6 levels in these patients also increase over time and are relatively more elevated in non-survivors when compared to survivors [29,30]. In fact, this elevated cytokine levels could damage various end organs and prolonging the disease, promoting myocardial damage and circulatory failure as was observed in some patients [31]. This is responsible for a significant deterioration in the clinical status, and it is more likely to occur in older people (>60 years old) and those with comorbidities [32–34]. To date, since the exact immunopathological mechanism of the severe COVID-19 still not completely elucidated.
is noteworthy that the main cytokines involved in severe COVID-19 are those which are released in response to lung injury and inflammation. Among them, interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) are downstream of the TLR4 signaling pathway.

3. Toll-like receptors

The interaction between human TLRs and SARS-CoV-2 antigens may be a step to understand this host-pathogen interaction. An in-silico study demonstrated this interaction and raised the hypothesis that the TLR pathway may have a role in the inflammatory consequences of COVID-19. By a molecular docking study, the authors demonstrated a significant binding between the viral S protein and human innate immune receptors TLR1, TLR4, and TLR6, with the highest binding energy reported with TLR4 [37]. Specifically, the interaction between SARS-CoV-2 Spike protein and human TLR4 was predicted to comprise both hydrogen bond interactions as well as hydrophobic interactions (Fig. 1). While these interactions need to be confirmed with subsequent crystal structure studies, inhibitors targeting this motif of TLR4 might be developed (Fig. 1).

TLRs are prototypical pattern recognition receptors (PRRs), which recognize different microbiological substances known as either pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs) as well as endogenous substances called damage-associated molecular patterns (DAMPs) molecules responsible for triggering innate immune responses and propagate inflammation [39]. The TLR4 is known for recognizing a broad variety of substances such as lipopolysaccharide (LPS) from gram-negative bacteria, viruses, fungus, and mycoplasma [40]. On the other hand, DAMPs are endogenous substances acting as TLR4 agonists, which appear following injury and inflammation, including oxidized phospholipid (oxPL), oxidized low-density lipoprotein (oxLDL), high-mobility group protein 1 (HMGB1), heat shock proteins (HSPs), extracellular matrix (ECM), cathelicidin (LL37), hyaluronic acid, substance P, and others [41].

While facing microbiological pathogen invasions, the TLR4 activation process helps to kill the microbes by destroying pathogen substances, however, when endogenous substances activate TLRs, the radicals may harm the host’s tissues [42]. The activation process depends on two accessory proteins, cluster of differentiation 14 (CD14) and myeloid differential protein-2 (MD-2) [43,44], it initiates two internal cell signal pathways: the myeloid differentiating primary response gene 88 (MyD88)-dependent and the MyD88-independent pathway [45]. After activation, a cell internal cascade is activated leading to the release of several interleukins, interferons, and other signaling substances (Fig. 2). These signals attract macrophages, natural killer cells, mast cells, etc., which in turn may release reactive oxygen species (ROS) and reactive nitrogen species (RNS) [46].

Furthermore, viruses interact with the TLR4 complex by viral glycoproteins, which are exposed on the viral surface and mediate the fusion with host cell membranes through the hydrophobic fusion peptide [47]. Influenza-A Virus (IAV) infection activates the TLR4 complex by host DAMPs, including HMGB1 and oxPL, that usually are accumulated in response to infection and activates TLR4 through MD-2 binding [48].

Considering that host DAMPS might play a central role in acute lung injury and are detected in the lungs of patients with severe IAV or SARS-CoV infections [49,50], an important relation regarding the current SARS-CoV-2 situation underlies this interaction. To date, the roles of TLRs in human diseases are still not fully understood, however, TLR4 has shown itself as an important feature in inflammatory diseases initiation and progression [51].

3.1. Pulmonary injury and TLR4

SARS-CoV-2 infects the pulmonary system and the majority of patients with moderate-to-severe COVID-19 suffer from ARDS. TLR4 receptors play an important role in the development of inflammatory and pulmonary vascular disease. A previous study used TLR4-deficient mice to provide strong evidence for TLR4 signaling as a mediator for pulmonary injury [52]. In this study, TLR4 deletion protected the mice against various sources of acute lung injury including avian influenza. Furthermore, increased TLR4 expression by respiratory syncytial virus primes the pulmonary epithelium for endotoxin mediated damage [53].

Logically, the severity of pulmonary disease following viral infection is significantly exacerbated by increased TLR4 signaling including swine influenza infection [54] and can be protected via amelioration of TLR4 signaling [55–57]. The TLR4-NF-κB pathway is central towards promoting infection-induced lung injury. SARS-CoV-2 infection in severe COVID-19 patients is accompanied by bacterial pneumonia. In this regard, evaluating the role played by TLR4 signaling in the lungs is critical to improving the outcomes in COVID-19 patients. In the LPS-induced acute lung injury murine model of sepsis, inhibition of TLR4 signaling using monoclonal antibodies [58], pharmacological intervention [59–61] as well as miRNA-based treatments [62] could be beneficial for these patients.

An important element in SARS-CoV-2 related pulmonary disease in vascular injury is the response to hypoxia as a result of ARDS. In this regard, TLR4 modulates a wide range of inflammatory responses in the lungs to worsen pulmonary function and impair proper resolution following infection. TLR4 expression was elevated in pulmonary smooth muscle cells of rats exposed to cigarette smoke which is integral to worsened inflammation in these rats when exposed to LPS induced acute lung injury [63].

In fact, LPS exposure increases TLR4 surface expression in a Rab26 mediated fashion in human pulmonary endothelial cells which in turn increases vascular leakiness [64]. This process is accompanied by increased pyroptosis of these endothelial cells since LPS activation of TLR4 induces NLRP3-mediated inflammasome activation [64]. In line with this, suppression of TLR4 signaling in pulmonary endothelial cells using small molecular weight inhibitors are capable of alleviating the effects of LPS induced acute lung injury. On the other hand, alveolar macrophages are activated by TLR4 signaling and play an important role in the clearance of pathogens within the lung compartment. Appropriate resolution of inflammation, however, is modulated by calcium signaling via TRPV4 [65] and TRPV6 [66]. Further evaluation of strategies to promote successful and appropriate resolution of the inflammatory response in severe COVID-19 patients via suppression of TLR4 signaling could be beneficial for improving prognosis in these patients.

3.2. Atherosclerosis and TLR4

Several pathways link the destabilization of atherosclerotic plaques in acute coronary syndrome with the effect of viral infections such as COVID-19 [67]. As reported in SARS and MERS (past outbreaks of respiratory diseases caused by other coronaviruses), acute myocardial infarction has been reported in two out of five deaths [68,69]. The same is observed in COVID-19 cases [70].

The viral illness, through systemic inflammatory responses and changes of immune cell polarization towards more unstable phenotypes, is responsible for the increased risk of acute cardiovascular events or exacerbations of chronic conditions [71]. Furthermore, the IL-6, reported as a mortality predictor in severe COVID-19 cases, is an important biomarker of cardiovascular morbidity and mortality linked to atherosclerosis [72].

The presence of inflammatory cells can be observed in all stages of atherosclerosis [73]. Accumulating evidence suggests that TLR4 participates in the pathogenesis of atherosclerosis in multiple ways [74]. Different cell types in atherosclerotic vessel walls express TLR4 and its
pro-atherogenic ligands activate these cell types [75]. The activated TLR4 on macrophages can trigger a cascade of signaling events, inducing inflammatory cytokines, and proteases. OxLDL, a TLR4 agonist, is responsible for early endothelial dysfunction and its link to TLR4 contributes to the initiation of atherosclerosis [76–79]. The activation of this receptor may also promote the instability of atherosclerotic plaques and enhance their susceptibility for physical disruption and acute thrombosis [80].

3.3. Diabetes and TLR4

Type 2 Diabetes Mellitus (T2DM) is a well-known risk factor for COVID-19 severe form [81]. It was found to be an independent predictor of admission to intensive care unit, invasive ventilation, or death in COVID-19 [82]. Not enough, the SARS-CoV-2 is related to damage of pancreatic islet cell and the occurrence of acute insulin dependent diabetes mellitus mediated by ACE2-viral binding [83,84].

Recent studies proposed that T2DM is the consequence of the stimulation of TLRs [85]. The activation of TLR4 expressed in several cell types, such as β-cells and resident macrophages in the pancreatic islets, can induce both insulin resistance, pancreatic cell dysfunction, and alteration of glucose homeostasis [86]. In fact, patients with T2DM present a higher expression of TLR4 mRNA and a link between TLR4 polymorphisms and T2DM was established [87–90].

In support of this, even mild COVID-19 can present high amounts of IL-6, IL-1β, TNF-α, MCP-1, and IP-10, products of the TLR4 pathway, that can further lead to lowering of insulin sensitivity [91]. Moreover, obesity, commonly associated with T2DM is likely to further aggravate the cytokine response in a process to be described below, thereby worsening insulin resistance [92].

3.4. Obesity and TLR4

Obesity, especially visceral obesity, is known to increase the clinical risk of metabolic and cardiovascular disease [93]. In countries that had an early outbreak of COVID-19 including Italy [94,95] and the United States [96], multiple reports have emerged that implicate obesity as a comorbidity that leads to severe case of COVID-19.

It is important to highlight two mechanisms that occur in obese patients: the enhanced production of pro-inflammatory adipokines (cytokines produced by the fat tissue) and the free fatty acid activation of TLR4 signaling [97,98]. It results in a pro-inflammatory state with increased levels of IL-6 and TNF-α [99–102]. Moreover, obese individuals present an increased expression of TLR4 and its adaptor proteins [103]. Furthermore, obese and diabetic patients have a higher expression of ACE2 in adipocytes, and, regarding the SARS-CoV-2 infectivity process by binding to ACE2 to enter in the intracellular space [104,105], the adipose tissue becomes a potential target for viral reservoir, diminishing the viral clearance [106].

Taking the aforementioned into consideration, it is possible to leverage the following hypothesis: if SARS-CoV-2 targets adipocytes, especially in obese patients, with additional increased expression of TLR4, we suggest that an already inflamed and immunobalanced adipose tissue becomes a favorable environment for SARS-CoV-2-TLR4 binding escalating pro-inflammatory cytokine production.

3.5. Hypertension and TLR4

The angiotensin II role in blood pressure regulation acts through central and peripheral mechanisms [107]. Since the ACE2 receptor is the medium through which SARS-CoV-2 infects mammalian cells, early concerns were raised about treating patients with pre-existing hypertension on ACE inhibitors or angiotensin II receptor blockers infected with the virus. Continuing treatment with ACE inhibitors or angiotensin II receptor blockers, however, does not worsen outcomes in COVID-19 patients [108]. In fact, the treatment of these patients with ACE inhibitors and angiotensin II receptor blockers might actually be beneficial in reducing all-cause mortality in COVID-19 patients [109].

In hypertension, dysregulation of the renin-angiotensin system is related to elevated expression of pro-inflammatory cytokines and ROS resulting in kidney damage, endothelial dysfunction, increased sympathetic activity, eventually culminating in organ function decline [110]. Furthermore, TLR4 may participate in hypertension pathogenesis [111]. In an animal study, it was demonstrated the greater expression of TLR4 mRNA in spontaneously hypertensive rats and that angiotensin II pro-inflammatory response was directly linked to TLR4 upregulation and stimulation [112].

Nevertheless, while angiotensin II induces TLR4 with functional consequences, a review of the literature made by Biancardi et al. does not support angiotensin II as a direct TLR4 agonist. The review suggests that molecular mechanisms involved in angiotensin II-TLR4 activation may indicate a potential interaction between angiotensin type 1 receptor and TLR4 signaling downstream effectors molecules [113].

3.6. Aging and TLR4

Elder age is a risk factor for COVID-19 severe form [114,115]. Researchers demonstrated mixed results on correlations between aging and TLR4 signaling malfunction; the cytokine production after TLR4 stimulation with LPS increases [116], decreases [117,118]; and remain unchanged [119] with aging. Furthermore, it is known that the immune system changes with age, which is called “immunosenescence” [120,121].

It is well established that immune responses in older adults are less efficient, making them more susceptible to emerging infections, as COVID-19 [122]. Additionally, aging is also related to the development of chronic conditions [123], some of them are risk factors of COVID-19.

One novel role for TLR4 is to regulate autophagy within the heart in a process mediated by the Histone Deacetylase - HDAC1 [124]. Furthermore, TLR4 signaling plays an important role in promoting inflammation following ischemia/reperfusion injury in the aging heart [125]. These studies suggest that evaluating the role of TLR4 signaling within the heart of old COVID-19 patients may provide prognostic capacities to predict cardiovascular disease outcomes in these patients. Furthermore, targeting this signaling axis may be beneficial to aging patients via protecting successful resolution of inflammation to reduce progression to cardiometabolic diseases in COVID-19 patients. In the USA, 17 % of the older adults have cardiovascular disease, 26.8 % have diabetes and 63 % have hypertension [126]. All of those are considered risk factors for COVID-19 severe form [127].

4. Therapeutic perspectives targeting TLR4 pathway

The TLR4 signaling pathway and its connection to inflammatory diseases provide interesting opportunities for therapeutic targeting and clinical applications [128]. There is an intriguing variety of chemical compounds able to interact with the TLR4 pathway. Synthetic, natural compounds such as statins, ACE inhibitors, opioids, and steroids [129] were evaluated in conditions where the immune system is inappropriately overactive, such as sepsis and septic shock, lupus, rheumatoid arthritis, and atherosclerosis [130–134].

The most relevant synthetic compounds are Eritoran (E5564), TAK-242, and FP7, a drug with good bioavailability, high-water solubility, lack of toxicity, and selective TLR4 antagonist action [135–142]. In addition, Eritoran (Eisai co.) is soon to be introduced in the REMAP-COVID study, a sub-platform of the clinical trial REMAP-CAP, that evaluates specific treatments to COVID-19 [143]. Plant-based extracts are another source of natural immune modulators, several are used in Traditional Chinese and Ayurveda medicine for centuries and seem to interact with the TLR4 complex [144,145].

When facing viral infections, the use of TLR4 antagonists has consistently resulted in reduced cytokine and chemokine production.
and diminished disease symptoms in small animal models infected with viruses such as IAV, Ebola virus (EBOV), dengue virus, and respiratory syncytial virus [146,147]. Therapeutically, however, the viral-mediated TLR4 activation remains largely unexplored.

There is a variety of TLR4 drugs capable of accessing the vast range of conditions linked to the TLR4 signaling pathway [148]. Table 1 summarizes the main TLR4 antagonists and their applications. Computational techniques may provide new paths and facilitate the discovery of new therapeutic approaches to target TLR4 pathway involvement in a variety of conditions linked to inflammation and chronic pathologies.
and development of safe and effective compounds [149]. Nonetheless, during a global pandemic, since there is still no evidence supporting the use of TLR4 antagonists in COVID-19, these findings highlight the importance of controlling conditions related to a poor outcome while an effective therapy is yet to come.

5. Conclusion

In the actual context of the COVID-19 pandemic, there is an urge for effective therapy aiming at the cytokine storm responsible for many poor outcomes. In this comprehensive review, we aimed to highlight the vast scientific evidence regarding the COVID-19 severe form, TLR4, and poor outcomes. In this comprehensive review, we aimed to highlight the importance of controlling conditions related to a poor outcome while an intervention in the early stages of COVID-19 pneumonia, in: Cytokine and Growth Factor Reviews, Vol. 53, Elsevier Ltd, 2020, pp. 13-24.

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