Parkinson's Disease and COVID-19: Role of TLR4

Subjects: Biochemistry & Molecular Biology
Contributor: Carmela Conte

Parkinson’s disease (PD) is the most common neurodegenerative motor disorder characterized by selective degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain, depletion of dopamine (DA), and impaired nigrostriatal pathway. The pathological hallmark of PD includes the aggregation and accumulation α-synuclein (α-SYN). Although the precise mechanisms underlying the pathogenesis of PD are still unknown, the activation of toll-like receptors (TLRs), mainly TLR4 and subsequent neuroinflammatory immune response, seem to play a significant role. Mounting evidence suggests that viral infection can concur in precipitation of PD or parkinsonism. The recently identified coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of ongoing pandemic coronavirus disease 2019 (COVID-19), responsible for 160 million cases that led to the death of more than three million individuals worldwide. Studies have reported that many patients with COVID-19 display several neurological manifestations, including acute cerebrovascular diseases, conscious disturbance, and typical motor and non-motor symptoms accompanying PD. The involvement of the TLR4 signaling pathway in mediating the virus entry, and the consequent massive immune and inflammatory response in COVID-19 patients has been recently explored. The strong binding of SARS-CoV-2 spike (S) protein to TLR4 and the possible interaction between SARS-CoV-2 and α-SYN suggest a potential contribute to the acceleration of neuronal death.

Keywords: Parkinson’s disease ; COVID-19 ; toll-like receptor 4 ; synuclein ; neuroinflammation

1. Introduction

According to the World Health Organization (WHO), Parkinson’s disease (PD) is the second most common neurodegenerative disease in the world, after Alzheimer’s disease, and one of the most common causes of neurological disability with a high social impact [1]. Albeit a number of genetic and environmental risk factors have been characterized, the cause(s) of PD are still unknown. A number of studies suggest that Toll-like receptors (TLRs), mainly TLR2 and 4, participate in the pathogenesis of PD as promoters of immune/neuroinflammatory responses that precede both motor and non-motor symptoms. The overexpression of TLR4 has been found in circulating monocytes of PD patients, in B cells, and in the caudate/putamen [2][3][4][5]. Studies in animal models of PD reported the potential role of TLR4 in mediating biochemical changes as well as dopaminergic cell death and α-synuclein accumulation in the midbrain [6][7]. Moreover, TLR4 has been found to play a critical role as a mediator of the neurotoxicity induced by α-synuclein oligomers [8]. Coronavirus disease (COVID-19) is an ongoing pandemic caused by a novel RNA (32 Kb genome) virus, namely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), whose worldwide cases passed 160 million. SARS-CoV-2 acts through the binding between the viral receptor S protein and different glycoprotein receptors on the cell surface. Suspected intriguing link exists between SARS-CoV-2 infection, TLR 4 and PD. Although TLR4 signaling represents one of a series of immune and inflammatory factors found activated during both PD and COVID 19, the strong interaction of TLR4 with the SARS-CoV-2 S protein as well as the possible binding between SARS-CoV-2 and α-SYN suggest triggering mechanisms of neurodegenerative processes underlying PD.

2. Toll-like receptors

TLRs are type I transmembrane glycoproteins with an extracellular leucine-rich repeat motif and a cytoplasmic Toll/IL-1 receptor (TIR) signaling domain, similar to the interleukin-1 receptor domain (IL-1R) [9]. TLRs belong to the complex pattern recognition receptors (PRRs) expressed in immune and non-immune cells, including neurons and glia, which are involved in regulating the innate immune system and inflammatory response by producing inflammatory cytokines and other mediators [10]. These processes prime immediate host-defense responses crucial for the clearance of infecting agents and following adaptive immune responses [11]. TLRs are highly specialized in sensing invading bacteria, viruses, parasites, and cell debris [12][13]. The TLR family comprises 11 members (TLR1–TLR11) in human and 12 (TLR1–TLR9, TLR11–TLR13) in mouse. They survey for the presence of structural motifs in a wide array of invading microorganisms, named pathogen-associated molecular patterns (PAMPs), in the extracellular space and within endocytic compartments.

TLRs also sense endogenous damage or danger molecular patterns (DAMPs), also known as alarmins, released by damaged cells and injured tissues or derived from apoptotic and necrotic cells [13]. The activation of neuro-inflammatory machinery starts with the binding between DAMPs/PAMPs and TLRs and advances with the dimerization of TLRs and interaction with adaptor proteins such as Myeloid Differentiation Primary Response Gene 88 (MyD88) and Toll/interleukin-1 receptor-like (TIR)-domain containing adapter-inducing interferon-β (TRIF) domain. This cascade of events leads to the recruitment of others complexes, such as IL-1R-associated kinase (IRAK) and MAP kinases, and the nuclear translocation/activation of transcription factors, including NF-kB, that ultimately trigger the downstream overexpression of pro-inflammatory genes and cell degeneration [14]. Among the 11 human TLRs members, TLR4 seems to play a critical role in the development and progression of neurodegenerative diseases, including PD [15].

3. Toll-like receptor 4 and Parkinson's disease

Analysis of transcriptomic data from human postmortem control brains reveals ubiquitous expression of TLR4 throughout the brain, with their expression being higher in the SNpc and putamen. Increased TLR4 protein levels were found in peripheral immune cells as well as in the SNpc and caudate/putamen of PD cases [16]. Additional studies in experimental models of PD and α-synucleinopathies demonstrated the important role of TLR4 and the constitutive expression in microglia [17][18][19][20]. Both neuroprotective and detrimental roles of TLR4 in PD have been suggested: acute stimuli such as posttranslational modification of α-SYN can be a trigger for TLR4 microglial activation and protein clearance. Conversely, chronic inflammation, from inside or outside the nervous system, may promote the imbalanced activation of TLR4 signaling and escalation of inflammatory response, which may contribute to the pathogenesis of PD [21][22]. A large number of molecules, including several species of α-SYN (monomer, oligomers, and fibrils, truncated and phosphorylated), released from neighboring neurons in the extracellular milieu, act as ligands for TLR4 and undergo phagocytosis, degradation, and clearance. If comprised, this mechanism can lead to further inflammatory signals that occur with the formation of aggregated forms of α-SYN in the Lewy bodies of *SNpc*.

4. Neuroinvasive potential of SARS-CoV-2 and PD pathogenesis

The concept of "Neuro-COVID-19" is being mentioned increasingly, but whether neurological manifestations in patients with COVID-19 are due to direct invasion of the virus or result from SARS-CoV-2-dependent neuroinflammatory response remains speculative.The respiratory distress caused by SARS-CoV-2 infection that emerged in December 2019 occurs in about 73% of COVID-19 hospitalized patients by a number of neurological signs associated with dysfunction of the central nervous system [23], peripheral, and enteric [24] nervous systems. The symptoms include olfactory, gustatory, dizziness, headache, confusion, encephalitis, stroke, anorexia, myalgias, and gastrointestinal disorders such as nausea and vomiting. Severe COVID 19 patients under intensive treatment exhibit cerebrovascular disease, consciousness state, and skeletal muscle injury [25][26]. SARS-CoV-2 infects cells through the interaction between its S protein previously cleaved by TMPRSS2 and ACE2. The neuroinvasive propensity of SARS-CoV-2 is probably facilitated by high expression levels of ACE2 and TMPRSS2 in neurons, astrocytes, and oligodendrocytes that, together with TLR4 activation, can predispose patients to α-SYN aggregation, neurodegeneration, and PD pathogenesis [27]. As shown in the Allen Human Brain Atlas, ACE2 mRNA is widely distributed throughout the brain with notable strong expression in areas such as the cortex, striatum, hypothalamus, medulla, and *substantia nigra* [28]. ACE2 receptors are expressed in neurons, astrocytes, and oligodendrocytes in the *SNpc* and olfactory bulb [29]. However, ACE2 may not be the only binding site involved in brain uptake [30]. SARS-CoV-2 can circumvent the host immune response and spread within the CNS directly through the olfactory nerves [31] or similar to other viruses, can reach the brainstem through the vagus nerve, infect neurons of different areas, and induce a marked systemic pro-inflammatory response associated with the overproduction of cytokines [32][33][34][35][36]. Using a human brain organoid model, Song et al. [31] showed that SARS-CoV-2 can infect cells of neural origin and cause death of nearby cells. SARS-CoV-2 particles were also detected in the cortical neurons from postmortem autopsies of patients who died from COVID-19 as well as in the cerebrospinal fluid of SAR-CoV-2-positive cases [37]. The impact that COVID-19 might have on PD pathogenesis is debated at present. PD is associated with changes in the CNS immune response, microglia and oligodendroglial activation, upregulation of histocompatibility class II, and pro-inflammatory cytokine overproduction. SARS-CoV-2 infection may be a predisposing factor for an abundant immune response. The cytokine storm during COVID-19 can cause the breakdown of the BBB and lead to virus entry and immune cell infiltration [38]. This directly can cause neuronal death and escalation of patient care towards severe neurological complications characterizing all synucleinopathies, including PD [39][40][41][42]. The possible trans-synaptic spread via the olfactory, lingual, and glossopharyngeal nerves of SARS-CoV-2 could explain the featured symptoms such as hyposmia and ageusia in many COVID-19 patients [43][44]. The presumed degeneration of dopaminergic nigrostriatal nerves could derive from immune activation in the olfactory system (without direct virus entry) that, associated with other toxic stress and the inability to activate neuroprotective responses, might promote α-synuclein misfolding, aggregation, and

neurodegeneration. Similar to PD, increased levels of IL-6 have been also found in COVID-19 patients, indicating an impact of inflammation on the progression of non-motor impairment [45][46][47]. α-SYN is the most important protein implicated in PD. Similar to West Nile virus and SAR-CoV-1, SARS-CoV-2 infection could lead to α-SYN upregulation in attempts to prevent viral replication and neuroinvasion [48][49]. However, abundant and protracted systemic inflammation could disturb the host cell proteostasis and protein quality control system, contributing to the pathological modification of α-SYN that can evolve with the formation of fibrillar structures. Although confirmation is needed, recent findings suggest that the interaction between the SARS-CoV-2 N protein and α-SYN could accelerate the protein aggregation into amyloid fibrils, leading to propagation and widespread neurodegeneration [50].

5. The Role of TLRs in inflammatory response induced by SARS-CoV-2 infection

Currently, the identification of the precise mechanism underlying the cytokine storm in hospitalized patients with severe COVID-19 is essential. The severity of COVID-19 is associated with the excessive inflammatory innate response and dysregulated adaptive host immune defense. In this context, TLRs can have a dual role. In fact, the activation of innate immune system through TLRs can be the first line of defense against invading viruses and can support their elimination. However, prolonged and dysregulated activation may contribute to the onset of the hyperinflammation and poor outcome of clinical manifestations of COVID-19 [51][52]. Systemic inflammation in patients with COVID-19 has been associated with elevated serum levels of pro-inflammatory cytokines and chemokines such as IL-2, IL-7, IL-8, IL-10, IP-10 (interferon-γ-inducible protein), MCP-1 (monocyte chemoattractant protein), MIP-1α (macrophage inflammatory protein 1 alpha), and TNFα [53]. Additionally, high levels of IgG and a high neutrophil-to-lymphocyte ratio have been found. TLRs signaling pathways have been recognized as accessory factors that may occur with the COVID-19 pathogenesis. The main members include TLR2, TLR3, TLR4, TLR6, TLR7, TLR8, and TLR9, with beneficial and harmful effects towards SARS-CoV-2 infection. The activation of TLR7/8 has been found to evoke a strong pro-inflammatory response during acute lung injury [54]. Furthermore, the binding of SARS-CoV-2 PAMPs to the extracellular domain of human TLR1, TLR4, and TLR6 seems to be crucial for COVID-19 immuno-pathogenesis [55,56]. The interaction between the SARS-CoV-2 S protein and cell surface TLRs has been investigated by molecular docking studies. The results have demonstrated a significant binding of the S protein to TLR1, TLR4, and TLR6, especially TLR-4, suggesting a potential mechanism of the cytokine cascade [55].

6. Possible link between Sars-Cov-2 and PD: role of TLR4

Although the host genetic background powerfully influences the requirement for TLR4-mediated signals during SARS-CoV-2 infection, TLR4 activation seems to represent one of the critical steps for host–virus general interaction. It has been demonstrated that TLR4 deficiency can induce resistance to acute manifestations that accompany the viral attack, suggesting an important role of TLR4 signaling in the profuse pro-inflammatory cytokine storm [56][57]. Structural analysis by molecular docking revealed the strongest binding between the native spike glycoprotein and human TLR4 compared with other TLRs present in the human cells [55]. The spike protein is a surface-exposed homo-trimeric transmembrane, heavily glycosylated complex with high binding affinity for the ACE2 receptor of human host cells 32. Another recent study found an interaction between the S protein and *Escherichia coli* LPS, the well-known activator of TLR4 [58]. A robust binding was also observed with the TLR4 accessory proteins CD14 and MD-2 that are overexpressed in inflammatory circumstances [59]. Interestingly, multi-epitopic regions of the SARS-CoV-2 S protein have been found to interact with the TLR4/MD2 complex. Therefore, it could act as a potent peptide vaccine candidate against COVID-19. Studies using surface plasmon resonance confirm the direct binding between the SARS-CoV-2 trimer and TLR4 in THP-1 cell lines, neutrophils, primary bone marrow-derived macrophages, and peritoneal macrophages [60]. Ziegler et al. [61] showed that the interaction between the S protein and TLR4 induced the overexpression of interferon-stimulated genes, which in turn provoked the upregulation of ACE2. By this ingenious strategy, the viral entry is facilitated. Although requiring confirmation, hydrogen bonds and hydrophobic interactions seem to assist the formation of the TLR4-spike complex. Together with ACE2, this event may be crucial for the activation of TLR4 signaling, NF-kB translocation, and hyperinflammation accompanied by the release of the TNF-α, IL-6 cytokines and more robustly IL1β [62]. Further studies are necessary to identify the specific TLR4 motifs involved. No interaction was observed by using the N-terminal or the receptor-binding domains of the spike protein [63] (Figure 1).

Figure 1. Toll-like receptor 4 (TLR4) signaling cascade resulting from the interaction between TLR4 and SARS-CoV-2 S protein. (a). Schematic diagram of the primary structural proteins of SARS-CoV-2.(b). The interaction between TLR4 and the SARS-CoV-2 S protein can trigger an intracellular TLR4 signaling cascade that can be one of the factors leading to the cytokine storm and neuroinflammation in severe COVID-19 patients. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; Coronavirus disease. CD14: cluster of differentiation 14; MD2: myeloid differential protein-2; MyD88: myeloid differentiating primary response gene 88; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; IRAK: interleukin-1 receptor-associated kinases; TRIF: TIR-domain containing adapter inducing interferon β; TRAM: TRIF-related adaptor molecule; TRAF: tumor necrosis factor receptor-associated factor; IFN: interferon.

In conclusion, the prolonged and dysregulated activation of TLR4 signaling, aside from the possible direct interaction between the SARS-CoV-2 N protein and α-SYN, may impair the protein quality control machinery and host cell proteostasis. The acceleration of the α-SYN aggregation into pathological multimeric protein species increases the vulnerability of nigrostriatal dopaminergic neurons, contributing to widespread neurodegeneration. Certainly, the long-term link between SARS-CoV-2 infection and PD will be demonstrated when a number of postmortem studies are performed. Moreover, future follow-up of large cohorts of patients with COVID-19 and COVID-19 survivors will be useful to clarify the impact on PD onset and other neurodegenerative disorders.

References

1. Mhyre, T.R.; Boyd, J.T.; Hamill, R.W.; Maguire-Zeiss, K.A. Parkinson’s disease. Subcell Biochem. 2012, 65, 389–455.
2. Gelders G., Baekelandt V., Van der Perren A. Linking Neuroinflammation and neurodegeneration in Parkinson’s disease.J. Immunol. Res. 2018:4784268. doi:10.1155/2018/4784268.
3. Refolo V., Stefanova N. Neuroinflammation and glial phenotypic changes in alpha-synucleinopathies.Front. Cell Neurosci.2019;13:263. doi: 10.3389/fncel.2019.00263.
4. Drouin-Ouellet J., St-Amour I., Saint-Pierre M., Lamontagne-Proulx J., Kriz J., Barker R.A., Cicchetti F. Toll-like receptor expression in the blood and brain of patients and a mouse model of Parkinson’s disease.Int. J. Neuropsychopharmacol. 2014;18:pyu103. doi:10.1093/ijnp/pyu103
5. Doorn K.J., Moors T., Drukarch B., van de Berg W.D.J., Lucassen P.J., van Dam A.M. Microglial phenotypes and toll-like receptor 2 in the substantia nigra and hippocampus of incidental Lewy body disease cases and Parkinson’s disease patients.Acta Neuropathol. Commun. 2014;2:90. doi:10.1186/s40478-014-0090-1.

6. Mariucci G., Pagiotti R., Galli F., Romani L., Conte C. The potential role of toll-like receptor 4 in mediating dopaminergic cell loss and alpha-synuclein expression in the acute MPTP mouse model of Parkinson's disease.J. Mol. Neurosci. 2018;64:611–618. doi:10.1007/s12031-018-1057-7.

7. Conte C., Roscini L., Sardella R., Mariucci G., Scorzoni S., Beccari T., Corte L. Toll like receptor 4 affects the cerebral biochemical changes induced by MPTP treatment.Neurochem. Res. 2017;42:493–500. doi:10.1007/s11064-016-2095-6.

8. Rannikko E.H., Weber S.S., Kahle P.J. Exogenous α-synuclein induces toll-like receptor 4 dependent inflammatory responses in astrocytes.BMC Neurosci. 2015;16:57. doi:10.1186/s12868-015-0192-0.

9. Anderson K.V. Toll signaling pathways in the innate immune response.Curr. Opin. Immunol.2000;12:13–19. doi:10.1016/S0952-7915(99)00045-X.

10. Vijay K. Toll-like receptors in immunity and inflammatory diseases: Past, present, and future.Int. Immunopharmacol.2018;59:391–412. doi:10.1016/j.intimp.2018.03.002.

11. Janeway C.A., Jr., Medzhitov R. Innate immune recognition.Annu. Rev. Immunol. 2002;20:197–216. doi:10.1146/annurev.immunol.20.083001.084359.

12. Hanke M.L., Kielian T. Toll-like receptors in health and disease in the brain: Mechanisms and therapeutic potential.Clin. Sci. 2011;121:367–387. doi:10.1042/CS20110164.

13. Kawai T., Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity.Immunity. 2011;34:637–650. doi:10.1016/j.immuni.2011.05.006.

14. Piccinini A.M., Midwood K.S. DAMPening inflammation by modulating TLR signalling.Mediat. Inflamm.2010;2010doi:10.1155/2010/672395.

15. Trotta T., Porro C., Calvello R., Panaro M.A. Biological role of toll-like receptor-4 in the brain.J. Neuroimmunol.2014;268:1–12. doi:10.1016/j.jneuroim.2014.01.014.

16. Hughes C.D., Choi M.L., Ryten M., Hopkins L., Drews A., Botía J.A., Iljina M., Rodrigues M., Gagliano S.A., Gandhi S., et al. Picomolar concentrations of oligomeric alpha-synuclein sensitizes TLR4 to play an initiating role in Parkinson's disease pathogenesis. Acta Neuropathol. 2019;137:103–120. doi:10.1007/s00401-018-1907-y.

17. Rueda-Carrasco J., Hong S. The jekyll and hyde of TREM2. Trends Neurosci. 2020;43:739–740. doi:10.1016/j.tins.2020.08.002.

18. Augusto-Oliveira M., Arrifano G.P., Lopes-Araújo A., Santos-Sacramento L., Takeda P.Y., Anthony D.C., Malva J.O., Crespo-Lopez M.E. What do microglia really do in healthy adult brain?Cells. 2019;8:1293. doi:10.3390/cells8101293.

19. Shin W.H., Jeon M.T., Leem E., Won S.Y., Jeong K.H., Park S.J., McLean C., Lee S.J., Jin B.K., Jung U.J., et al. Induction of microglial toll-like receptor 4 by prothrombin kringle-2: A potential pathogenic mechanism in Parkinson's disease. Sci. Rep. 2015;5:14764. doi:10.1038/srep14764.

20. Lehnardt S., Massillon L., Follett P., Jensen F.E., Ratan R., Rosenberg P.A. Activation of innate immunity in the CNS triggers neurodegeneration through a Toll-like receptor 4-dependent pathway.Proc. Natl. Acad. Sci. USA.2003;100:8514–8519. doi:10.1073/pnas.1432609100.

21. Leitner G.R., Wenzel T.J., Marshall N., Gates E.J., Klegeris A. Targeting toll-like receptor 4 to modulate neuroinflammation in central nervous system disorders.Expert Opin. Ther. Targ. 2019;23:865–882. doi: 10.1080/14728222.2019.1676416.

22. Campolo C., Paterniti I., Siracusa R., Filippone A., Esposito E., Cuzzocrea S. TLR4 absence reduces neuroinflammation and inflammasome activation in Parkinson's diseases in vivo model.Brain Behav. Immun.2019;76:236–247. doi: 10.1016/j.bbi.2018.12.003.

23. Paniz-Mondolfi A., Bryce C., Grimes Z., Gordon R.E., Reidy J., Lednicky J., Sordillo E.M., Fowkes M. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J. Med. Virol.2020;92:699–702. doi: 10.1002/jmv.25915.

24. Esposito G., Pesce M., Seguella L., Sanseverino W., Lu J., Sarnelli G. Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion?Brain Behav. Immun.2020;87:93–94. doi: 10.1016/j.bbi.2020.04.060.

25. Beyrouti R., Adams M.E., Benjamin L., Cohen H., Farmer S.F., Goh Y.Y., Humphries F., Jäger H.R., Losseff N.A., Perry R.J., et al. Characteristics of ischaemic stroke associated with COVID-19. J. Neurol. Neurosurg. Psychiatry.2020;91:889–891. doi: 10.1136/jnnp-2020-323586.

26. Li Y.C., Bai W.Z., Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients.J. Med. Virol.2020;92:552–555. doi: 10.1002/jmv.25728.

27. Chen R., Wang K., Yu J., Howard D., French L., Chen Z., Wen C., Xu Z. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains.Front. Neurol.2021;11:573095. doi: 10.3389/fneur.2020.573095.

28. Jones A.R., Overly C.C., Sunkin S.M. The allen brain atlas: 5 years and beyond.Nat. Rev. Neurosci.2019;10:821–828. doi: 10.1038/nrn2722.

29. Merello M., Bhatia K.P., Obeso J.A. SARS-CoV-2 and the risk of Parkinson's disease: Facts and fantasy.Lancet Neurol.2021;20:94–95. doi: 10.1016/S1474-4422(20)30442-7.

30. Erickson M.A., Rhea E.M., Knopp R.C., Banks W.A. Interactions of SARS-CoV-2 with the Blood–Brain barrier.Int. J. Mol. Sci.2021;22:2681. doi: 10.3390/ijms22052681.

31. Song E., Zhang C., Israelow B., Lu-Culligan A., Vieites Prado A., Skriabine S., Lu P., Weizman O.E., Liu F., Dai Y., et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain.J. Exp. Med.2021;218:e20202135. doi: 10.1084/jem.20202135.

32. Desforges M., Le Coupanec A., Brison E., Meessen-Pinard M., Talbot P.J. Neuroinvasive and neurotropic human respiratory coronaviruses: Potential neurovirulent agents in humans.Adv. Exp. Med. Biol.2014;807:75–96. doi: 10.1007/978-81-322-1777-0_6.

33. Bale J.F., Jr. Virus and immune-mediated encephalitides: Epidemiology, diagnosis, treatment, and prevention.Pediatr. Neurol.2015;53:3–12. doi: 10.1016/j.pediatrneurol.2015.03.013.

34. Mailles A., Stahl J.P., Bloch K.C. Update and new insights in encephalitis.Clin. Microbiol. Infect.2017;23:607–613. doi: 10.1016/j.cmi.2017.05.002.

35. Bohmwald K., Gálvez N.M.S., Ríos M., Kalergis A.M. Neurologic alterations due to respiratory virus infections.Front. Cell Neurosci.2018;12:386. doi: 10.3389/fncel.2018.00386.

36. Hu B., Guo H., Zhou P., Shi Z.L. Characteristics of SARS-CoV-2 and COVID-19.Nat. Rev. Microbiol.2020:1–14. doi: 10.1038/s41579-020-00459-7.

37. Huang Y.H., Jiangm D., Huangm J.T. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis.Brain Behav. Immun.2020;87:149. doi: 10.1016/j.bbi.2020.05.012.

38. Reynolds J.L., Mahajan S.D. SARS-COV2 alters blood brain barrier integrity contributing to neuro-inflammation.J. Neuroimmune Pharmacol.2021;16:4–6. doi: 10.1007/s11481-020-09975-y.

39. Alquisiras-Burgos I., Peralta-Arrieta I., Alonso-Palomares L.A. Neurological complications associated with the blood-brain barrier damage induced by the inflammatory response during SARS-CoV-2 infection.Mol. Neurobiol.2020;58:1–16. doi: 10.1007/s12035-020-02134-7.

40. Kustin T., Ling G., Sharabi S., Ram D., Friedman N., Zuckerman N., Bucris E.D., Glatman-Freedman A., Stern A., Mandelboim M. A method to identify respiratory virus infections in clinical samples using next-generation sequencing.Sci. Rep.2019;9:2606. doi: 10.1038/s41598-018-37483-w.

41. Pezzini A., Padovani A. Lifting the mask on neurological manifestations of COVID-19.Nat. Rev. Neurol.2020;16:636–644. doi: 10.1038/s41582-020-0398-3.

42. Méndez-Guerrero A., Laespada-García M.I., Gómez-Grande A., Ruiz-Ortiz M., Blanco-Palmero V.A., Azcarate-Diaz F.J., Rábano-Suárez P., Álvarez-Torres E. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection.Neurology.2020;95:e2109–e2118. doi: 10.1212/WNL.0000000000010282.

43. Ho, B.E.; Ho, A.P.; Ho, M.A.; Ho, E.C. Case report of familial COVID-19 cluster associated with high prevalence of anosmia, ageusia, and gastrointestinal symptoms. IDCases 2020, 22, e00975.

44. Tarakad, A.; Jankovic, J. Anosmia and ageusia in Parkinson's disease. Int. Rev. Neurobiol. 2017, 133, 541–556.

45. Zhang J., Hao Y., Ou W., Ming F., Liang G., Cai Q., Dong S., Hu S., Wang W., Wei S. Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: A cohort study.J. Transl. Med.2020;18:406–413. doi: 10.1186/s12967-020-02571-x.

46. Pereira J.R., Santos L.V.D., Santos R.M.S., Campos A.L.F., Pimenta A.L., de Oliveira M.S. IL-6 serum levels are elevated in Parkinson's disease patients with fatigue compared to patients without fatigue.J. Neurol. Sci.2016;370:153–156. doi: 10.1016/j.jns.2016.09.030.

47. Veselý B., Dufek M., Thon V., Brozman M., Királová S., Halászová T., Koritáková E., Rektor I. Interleukin 6 and complement serum level study in Parkinson's disease.J. Neural Transm.2018;125:875–881. doi: 10.1007/s00702-018-1857-5.

48. Beatman E.L., Massey A., Shives K.D., Burrack K.S., Chamanian M., Morrison T.E., Beckham J.D. Alpha-synuclein expression restricts RNA viral infections in the brain.J. Virol.2015;90:2767–2782. doi: 10.1128/JVI.02949-15.

49. Ait Wahmane S., Achbani A., Ouhaz Z., Elatiqi M., Belmouden A., Nejmeddine M. The possible protective role of α-synuclein against severe acute respiratory syndrome Coronavirus 2 infections in patients with Parkinson's disease.Mov. Disord. 2020;35:1293–1294. doi: 10.1002/mds.28185.
50. Semerdzhiev, S.A.; Fakhree, M.A.A.; Segers-Nolten, I.; Blum, C.; Claessens, M.M.A.E. Interactions between SARS-CoV-2 N-protein and a-synuclein accelerate amyloid formation. BioRxiv 2021.
51. Catanzaro M., Fagiani F., Racchi M., Corsini E., Govoni S., Lanni C. Immune response in COVID-19: Addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2.Signal Transduct. Targ. Ther.2020;5doi: 10.1038/s41392-020-0191-1.
52. De Rivero Vaccari J.C., Dietrich W.D., Keane R.W., de Rivero Vaccari J.P. The inflammasome in times of COVID-19.Front. Immunol.2020;11:583373. doi: 10.3389/fimmu.2020.583373.
53. Qin C., Zhou L., Hu Z., Zhang S., Yang S., Tao Y., Xie C., Ma K., Shang K., Wang W., et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China.Clin. Infect. Dis.2020;71:762–768. doi: 10.1093/cid/ciaa248.
54. Khanmohammadi S., Rezaei N. Role of Toll-like receptors in the pathogenesis of COVID-19.J. Med. Virol.2021;93:2735–2739. doi: 10.1002/jmv.26826.
55. Choudhury A., Mukherjee S. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs.J. Med. Virol.2020:1–9. doi: 10.1002/jmv.25987.
56. Root-Bernstein R. Innate receptor activation patterns Involving TLR and NLR synergisms in COVID-19, ALI/ARDS and sepsis cytokine storms: A review and model making novel predictions and therapeutic suggestions.Int. J. Mol. Sci.2021;22:2108. doi: 10.3390/ijms22042108.
57. Khanolkar A., Hartwig S.M., Haag B.A., Meyerholz D.K., Harty J.T., Varga S.M. Toll-like receptor 4 deficiency increases disease and mortality after mouse hepatitis virus type 1 infection of susceptible C3H mice.J. Virol.2009;83:8946–8956. doi: 10.1128/JVI.01857-08.
58. Petruk G., Puthia M., Petrlova J., Samsudin F., Strömdahl A.C., Cerps S. SARS-CoV-2 Spike protein binds to bacterial lipopolysaccharide and boosts proinflammatory activity.J. Mol. Cell. Biol.2021;12:916–932. doi: 10.1093/jmcb/mjaa067.
59. Bhattacharya M., Sharma A.R., Mallick B., Sharma G., Lee S.S., Chakraborty C. Immunoinformatics approach to understand molecular interaction between multi-epitopic regions of SARS-CoV-2 spike-protein with TLR4/MD-2 complex.Infect. Genet. Evol.2020;85:104587. doi: 10.1016/j.meegid.2020.104587.
60. Zhao Y., Kuang M., Li J., Zhu L., Jia Z., Guo X., Hu Y., Kong J., Jin H., Wang X., et al. SARS-CoV-2 spike protein interacts with and activates TLR41.Cell Res.2021 doi: 10.1038/s41422-021-00495-9.
61. Ziegler C.G.K., Allon S.J., Nyquist S.K., Mbano I.M., Miao V.N., Tzouanas C.N., Cao Y., Yousif A.S., Bals J., Hauser B.M. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues.Cell.2020;181:1016–1035.e19. doi: 10.1016/j.cell.2020.04.035.
62. Aboudounya M.M., Heads R.J. COVID-19 and toll-like receptor 4 (TLR4): SARS-CoV-2 may bind and activate TLR4 to Increase ACE2 expression, facilitating entry and causing hyperinflammation.Mediat. Inflamm.2021 doi: 10.1155/2021/8874339.
63. Brandão S.C.S., Ramos J.O.X., Dompieri L.T., Godoi E.T.A.M., Figueiredo J.L., Sarinho E.S.C., Chelvanambi S., Aikawa M. Is toll-like receptor 4 involved in the severity of COVID-19 pathology in patients with cardiometabolic comorbidities?Cytokine Growth Factor Rev.2020;58:102–110. doi: 10.1016/j.cytogfr.2020.09.002.