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SARS-CoV-2-Mediated Neuropathogenesis, Deterioration of Hippocampal Neurogenesis and Dementia

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Abstract

A significant portion of COVID-19 patients and survivors display marked clinical signs of neurocognitive impairments. SARS-CoV-2-mediated peripheral cytokine storm and its neurotropism appear to elicit the activation of glial cells in the brain proceeding to neuroinflammation. While adult neurogenesis has been identified as a key cellular basis of cognitive functions, neuroinflammation-induced aberrant neuroregenerative plasticity in the hippocampus has been implicated in progressive memory loss in ageing and brain disorders. Notably, recent histological studies of post-mortem human and experimental animal brains indicate that SARS-CoV-2 infection impairs neurogenic process in the hippocampus of the brain due to neuro-inflammation. Considering the facts, this article describes the prominent neuropathogenic characteristics and neurocognitive impairments in COVID-19 and emphasizes a viewpoint that neuroinflammation-mediated deterioration of hippocampal neurogenesis could contribute to the onset and progression of dementia in COVID-19. Thus, it necessitates the unmet need for regenerative medicine for the effective management of neurocognitive deficits in COVID-19.

Keywords

COVID-19, cytokine storm, neuroinflammation, hippocampal neurogenesis, dementia

Introduction

The severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infection accountable for coronavirus disease (COVID)-19 has become one of the leading causes of death worldwide.[1] Notably, elderly people are at a high risk of being infected with SARS-CoV-2, mainly due to the progressive physiological deficits and reduced immunogenic competence.[2] Moreover, individuals with late-onset comorbid pathogenic conditions like hypertension, diabetes and coronary heart disease are highly vulnerable to SARS-CoV-2 infection and severity of the disease.[3] While SARS-CoV-2 infection mediates cytokine storm responsible for neuroinflammation and oxidative stress in the brain, COVID-19-associated long-term neurological consequences have become increasingly evident.[4-9] A significant portion of COVID-19 patients and survivors display marked clinical signs of stress, depression, anxiety, endocrine disruption and neurodegenerative disorders accounting for a wide array of cognitive deficits ranging from mild cognitive impairment to irreversible dementia.[10] To note, the neuropathogenic signatures of COVID-19 appear to be overlapped with many brain disorders like stroke, multiple sclerosis, seizure, Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) in which progressive sensory-motor impairments, cognitive decline and memory loss in association with neuroinflammation are highly evident.[6,11,12] Besides, the incidence of SARS-CoV-2-mediated prion-like disease with cognitive impairments has become

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prominent in post-recovery state.[13,14] In addition to post-COVID-19 dementia and other brain abnormalities, rapidly progressive dementia and autoimmune encephalitis have also been reported in individuals immunized with adenovirus-based vaccines encoding SARS-CoV-2 spike protein.[15,16] While the hippocampus of the brain plays an important role in the regulation of emotions, cognitive functions and long-term potentiation, some viral infection-induced hippocampal atrophy results in neurocognitive impairments and memory loss.[17,18] Considering the facts, SARS-CoV-2-mediated neuropathogenic alterations and neuroinflammation might be linked to abnormal hippocampal plasticity leading to cognitive impairments, mood disorders and dementia. Thus, understanding the structural and functional deterioration of the hippocampus responsible for neurocognitive impairments resulting from neuropathogenic events of COVID-19 might be highly important. The hippocampus is a key neurogenic area of the adult brain that harbours neural stem cells (NSCs).[19,20] NSCs in the hippocampus are multipotent in nature that give rise to new neurons throughout life.[17,20] While NSC-derived neurogenesis in the hippocampus represents a key cellular foundation for regenerative plasticity accounting for various neurocognitive functions including learning and memory in adulthood,[17,19,21,22] impaired hippocampal neurogenesis has been established as a potential cause of progressive memory loss in ageing and many neurodegenerative disorders.[23-28] Notably, ageing, stress, depression, anxiety and neurodegenerative disorders have been characterized by various neurocognitive impairments including chronic memory deficits due to neuroinflammation-mediated pathogenic defects in hippocampal neurogenesis regardless of neuronal dysfunction and synaptic loss.[19,22] Therefore, the establishment of a potential link between SARS-CoV-2-mediated neuropathogenic changes and the regulation of hippocampal regenerative plasticity appears to be unequivocally important with reference to the incidence and degree of dementia in COVID-19 patients and survivors.

COVID-19 and Mental Disorders

Due to the expanding COVID-19 pandemic, most people worldwide suffer from different mental problems like stress, anxiety, depression and panic attacks.[10,29,30] Anxiety, stress and depression-related issues have been reported to be escalated dramatically not only in COVID-19 patients but also in frontline workers, healthcare professionals and caretakers due to unrelenting workload and for being at great risk of SARS-CoV-2 infection.[30-32] Notably, elderly people, breadwinners of the family, students and children also experience a significant level of mental health issues due to lockdown, unmanageable socioeconomic status, online mode of education, reduced physical activities, social withdrawal, loneliness and overall uncertainty.[10,33] Many cross-sectional studies and meta-analyses have revealed that a significant portion of COVID-19 survivors and the high-risk population, especially from the containment zone, have frequently been experiencing insomnia, anxiety, depression and post-traumatic stress disorder.[29,30,34-37] Considering the aforementioned facts, it is obvious that unmanaged mental health issues will lead to increased levels of stress hormones like cortisol, corticosteroid releasing hormone (CRH), epinephrine and norepinephrine in the circulation that could alter the hypothalamic–pituitary–adrenal (HPA) axis, exacerbate neuroinflammation and deteriorate neuroplasticity of the brain.[35,38,39] Therefore, identifying the COVID-19-related pathogenic determinants that affect the functional regulation of neuroplasticity has become very crucial in this unprecedented pandemic situation.

COVID-19 and Neuroinflammation

SARS-CoV-2 enters the human body via the angiotensin-converting enzyme (ACE)-2 receptor which has been found to be expressed by airway epithelia, lungs, and various subpopulations of the brain cells including the endothelial cells of the cerebral microvascular system.[40-42] In addition to ACE2, neuropilin - 1 (NRP1), a transmembrane receptor, has also been identified to facilitate the entry of SARS-CoV-2 via the olfactory epithelium.[43] Likewise, other molecular mediators that aid the entry of SARS-CoV-2 include angiotensin II receptor type (AGTR)-2, receptor for advanced glycation end products (RAGE), transmembrane protease, serine (TMPRSS)-2, cluster of differentiation (CD)-147 and peripheral olfactory receptors.[44-48] Upon infection, SARS-CoV-2 radically replicates in the tissues and organs and induces peripheral and local cytokine storm that potentially deteriorates the innate immune system.[49,50] Based on the experimental data derived from immunological assays in the plasma samples of COVID-19 patients, elevated levels of key proinflammatory determinants including different interleukins (ILs), fibroblast growth factor (FGF), interferon-gamma (IFN-γ), tumour necrosis factor alpha (TNF-α) and vascular endothelial growth factor (VEGF) have become evident.[50] Among them, the surplus levels of IFN-γ, TNF-α, IL-1 and IL-6 have been known to be associated with the dysfunction of the blood–brain barrier (BBB) as a part of priming the neuroinflammatory process in the brain.[17,51] In the neuropathological study conducted in a hamster model and post-mortem humans, disruption of the BBB has been reported in different parts of the brain, with maximum disruption in the hippocampus.[52] It is well known that peripheral immune response exerts an influence on the activation of microglial cells resulting in the surplus discharge of proinflammatory cytokines in the brain through various mechanisms including sensitising the afferent vagus nerve, stimulation of neurovascular endothelial cells and antibody-mediated humoural immune response.[53-55] As SARS-CoV-2 and peripheral proinflammatory cytokines enter the brain, microglial cells get activated and contribute to the proinflammatory secretome in the brain.[56] Moreover, the gut–brain axis has been proposed to facilitate the neuroinvasive properties of SARS-CoV-2 which could also be a pathophysiological basis for microglial activation accounting for the pathogenic establishment of neuroinflammation.[57] Moreover,

a study by Awogbindin I O et al. haves suggested that microglia could act in the clearance of the virus, but at the same time, unregulated activated forms of microglia can trigger robust neuroinflammation which could contribute to neuronal dysfunction, neurodegeneration and impaired neuroplasticity similar to PD.[58] Notably, pathological signs of microglial activation have been detected in the post-mortem brains of COVID-19 victims.[59] The SARS-CoV-2 infection has also been identified to result in pathogenic activation of microglia and neuroinflammation leading to demyelination diseases like multiple sclerosis.[60,61] Besides, enhanced levels of IL-8 and TNF-α have been reported in the cerebrospinal fluid (CSF) of a COVID-19 patient.[62] Moreover, a significant increase in the neurofilament light chain (NF-L), a molecular determinant indicating the presence of neurological disorders, has been observed in the critical COVID-19 group compared to other groups.[63] Similar to non-COVID-19 stroke controls, a prominent increase in the levels of TNF-α, IL-6 and IL-12p70 has been found in COVID-19 subjects.[63] Notably, various forms of dementia including AD have been characterized by elevated levels of TNF-α, IL-6 and IL-1.[24,64,65] To note, the hippocampus is highly vulnerable to neuroinflammation,[66,67] while previously, Jacomy H et al. demonstrated that the endemic human coronavirus HCoV-OC43 affects many brain areas and induces neurodegeneration in the hippocampus.[68] Further, based on co-immunolabeling experiments and readout of caspase signalling, it has become apparent that HCoV-OC43 infects hippocampal-derived astrocytes, microglia and neurons in vitro and induces apoptosis predominantly in primary cultures of neurons.[68] Considering neuroinflammation as a major detrimental factor for neuroplasticity, various viral infections have been reported to affect hippocampal functions due to the abnormal activation of glial cells.[69-71] Thus, SARS-CoV-2-mediated hippocampal pathology needs distinct scientific attention as it may govern dementia-related issues.

Neuroimaging Observations and Hippocampal Atrophy in COVID-19

The hippocampus is one of the important functional regions of the limbic system of the brain that contributes to the neuroregenerative process, long-term potentiation, learning process, memory formation and regulation of emotion.[19,21,72] Defects in the hippocampal structure and functions due to ageing and neurological illnesses have been directly linked to emotional disorders and memory loss.[17,73] Many neuroimaging studies have clearly established that SARS-CoV-2-mediates pathogenic alterations in various functional regions of the brain accounting for comorbid neurological deficits.[74-78] Recently, a diffusion tensor imaging (DTI)-based study on COVID-19 survivors revealed abnormal microstructural changes and hypertrophy in different brain regions including the olfactory cortex and hippocampus in parallel with memory loss.[79] A magnetic resonance imaging (MRI) based investigation on the brain of a COVID-19 patient showed hyperintensities in the unilateral ventricle and temporal lobe along with hippocampal atrophy indicating the clinical signs of encephalitis.[78] Similarly, a nuclear magnetic resonance (NMR) based case report by Chiveri L et al. reported a pathogenic lesion in the posterior portion of the hippocampus of a SARS-CoV-2 positive elderly woman with neurological deficits.[80] Meanwhile, a number of neuroimaging findings of COVID-19 patients revealed abnormalities in the medial temporal lobe in association with cerebral haemorrhage, stroke, encephalitis and seizure.[74,76,77,81,82] Based on previous retrospective studies and meta-analysis, de Erausquin GA et al. indicated that one in five recovered individuals from the previous outbreak of SARS-CoV displayed memory loss.[83,84] Presently, ample scientific evidence points towards the potential link between COVID-19 and AD as both conditions appear to share a similar pattern in the changes of the neuroinflammatory molecules like TNF-α and IL-1.[11,85] Taken together, SARS-CoV-2-mediated noticeable hippocampal pathology appears to be an underlying basis of neurocognitive impairments in COVID-19 survivors.[86-88] Thus, the neuropathogenic findings on the hippocampus of COVID-19 subjects need to be extended to understand the underlying cellular basis of dementia, as the chances for the deterioration of neurogenesis in the hippocampus of COVID-19 positive cases are highly possible, which could further result in cognitive decline in the post-recovery state regardless of neurodegeneration.

Neuropathogenic signatures in post-mortem brain samples and experimental models of COVID-19

The post-mortem analysis of the brains of COVID-19 victims revealed prominent histopathological signatures of neuronal loss in different areas of the brain including the cerebral cortex, cerebellar Purkinje layer and hippocampus.[89] Haemorrhage, acute hypoxic injury and neuroinflammation have been commonly noticed in the post-mortem brains of COVID-19 victims.[90,91] Brain ischaemic injury has also been identified in a post-mortem study conducted in SARS-CoV-2-affected individuals.[92] The histological brain slices derived from the SARS-CoV-2 positive cases have been characterized by widened gyri, narrowed sulci, flattened surface and congested meninges.[91,92] Acute neuronal injury was observed to be prominent in the hippocampal cornu ammonis (CA)-1 region, the parahippocampal gyrus and the cerebellar Purkinje cells.[92] A study by Boroujeni ME et al. revealed a reduction in the number of neurons and an increase in the number of ionized calcium binding adaptor molecule (Iba)-1-positive microglial cells and glial fibrillary acidic protein (GFAP)-positive astrocytes in the cerebral cortex of COVID-19 victims.[93] Moreover, upregulation of inflammation and immune-related genes and reduction in glutathione levels have also been reported in the cerebral cortex derived from the COVID-19 victims.[93] Neuropathological findings by Colombo D et al. have also indicated vascular changes in the cerebral cortex, neuronal loss in the cerebellum and neuronal injury in the pons and medulla.[94] Thakur and colleagues indicated the prominent vasculature pathology, hypoxic neuronal damage and presence of activated

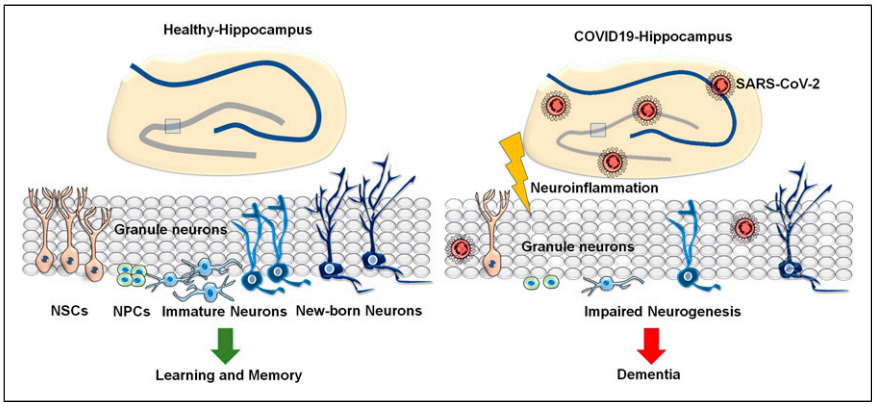

Figure 1. Schematic representation of the hippocampus in healthy vs COVID-19 condition in association with the respective cognitive status: The figure represents the neural stem cell-mediated neurogenic process in the hippocampus in healthy condition responsible for learning and memory and impaired neurogenesis in the hippocampus in COVID-19 state due to neuroinvasion of SARS-CoV-2 and neuroinflammation leading to dementia.

microglia in the hippocampus of COVID-19 victims and correlated these neuropathological outcomes with dementia.[95] In addition, post-mortem brains of COVID-19 patients have been characterized by meningitis like pathology, lymphocytic panencephalitis, microinfarcts and indication for cerebral stroke.[96,97]

Besides, experimental animal models of COVID-19 have been characterized by stress and various neurological illnesses.[97,98] A mouse model injected with the S1 subunit of the spike protein displayed stress-related behaviours and increased levels of caspase-3, C5b-9, TNF-α and IL-6 in association with neuroendothelial damage in the brain.[99] Further, murine motorneuron (MN)-1 cell line incubated with SARS-CoV-2 spike protein showed its infection and cell death.[99] Recent studies have also suggested that the S1 subunit of SARS-CoV-2 interacts with prion protein leading to the formation of homo- or hetero-polymers which results in the protein misfolding in prion disorders.[16] This could be due to the direct toxicity as a result of prolonged exposure to the spike protein of SARS-CoV-2.[16] While interaction between the spike protein and aggregation-prone proteins in the brain can leadto neurodegeneration, another possible mechanism is by the cross-reaction of anti-spike protein antibodies with the neural tissue antigens.[16] Neurotropism by pseudo SARS-CoV-2 has clearly been demonstrated in studies using human-induced pluripotent stem cell (hiPSC) derived BrainSphere model and human embryonic stem cell-derived brain organoids.[100,101] A study conducted in hiPSC-derived monolayer brain cells and brain organoids revealed that SARS-CoV-2 strongly infects epithelial cells of choroid plexus than that of cortical neurons and astrocytes.[102] Besides, a parallel study by McMahon CL et al. also showed higher infectivity of SARS-CoV-2 in glial cells and choroid plexus than neurons.[103] Meanwhile, Ramani A et al. demonstrated that SARS-CoV-2 targets neurons and causes an altered distribution and hyperphosphorylation of Tau, and neuronal cell death in the brain organoids.[104] Moreover, a recent study through two independent immunolocalization experiments has also provided the evidence for the reduced neurogenesis in the hippocampus in brains of SARS-CoV-2-infected humans and hamsters.[52] Though the reports on the regulation of neurogenesis in COVID-19 are limited now, chances for the occurrence of impairment of hippocampal neurogenesis in subjects with COVID-19 might be highly relevant to various neurocognitive impairments and dementia (Figure 1).

Possibilities for the occurrence of neuroregenerative failure in the hippocampus as a potential cause of dementia in COVID-19

Adult neurogenesis is the NSC-based neuroregenerative process that appears to be a key cellular basis for the regulation of neuroplasticity of the brain.[24,25,105] The occurrence of adult neurogenesis appears to be highly prominent in the subgranular zone (SGZ) of the hippocampal dentate gyrus, subventricular zone (SVZ) of the lateral ventricles, and hypothalamus.[20,24,25,105,106] The continuous generation and integration of new neurons in the hippocampus of the adult brain have been functionally linked to learning and memory.[20,107] However, scientific facts of neurogenesis in the adult brain have been a longstanding subject of debate. During the 1960s, the early reports on the possibilities of the occurrence of mitotic activities and neurogenesis in the dentate gyrus and olfactory bulb of the adult brain of experimental animals had largely been ignored.[108] A few decades later, with technical advancement, concurrent experimental studies validated previous data on adult neurogenesis and concluded the ongoing neurogenic process in the adult brains of rodents, songbirds and nonhuman primates.[109-112] Moreover, adult neurogenesis in the hippocampus has been linked to pattern separation, emotions and learning and memory.[113] Though there exist controversies on previous reports that highlight neurogenesis in the adult human brain due to various technical drawbacks and limitations in the availability of experimental post-mortem human brain tissue samples, recent studies have established the experimental proofs for the existence of NSCs

and neurogenesis in the hippocampus of the human brain using bromodeoxyuridine (BrdU), carbon dating, neurosphere culture and immunohistochemical methods, and further, adult neurogenesis has also been identified to occur in the hypothalamus, cortex, amygdala and striatum.[20,106,114-117] Markedly, hippocampal neurogenesis has been known to be positively regulated by many factors including physical activity, enriched environment, nutrients, cell cycle stimulating cytokines, neurotrophic factors and some antipsychotic drugs.[118-120] However, ageing, stress, depression, anxiety-like disorders and neurodegenerative disorders have been known to suppress the proliferative and differentiation capacities of NSCs in the hippocampus leading to progressive memory loss.[19,22,24,28,121] Notably, cognitive decline and memory loss noticed in AD, PD and HD have been known to be the result of impaired neurogenesis.[22,122-124] Besides, ample reports indicate that stress, neuroinflammation and viral infections lead to the inactivation of the proliferative potential of NSCs, thereby suppressing neurogenesis and cognitive function.[120,125,126] Though cerebral stroke, epileptic seizure, neurodegenerative disorders and psychiatric problems induce reactive neurogenesis in the hippocampus at an early stage of these diseases, survival and the functional integration of new neurons appear to be diminished as the disease progresses.[19,22,24,127-130] The elevated levels of proinflammatory cytokines resulting from the pathogenic process of neurological diseases and abnormal levels of stress hormones have been proposed to inhibit the proliferation and neuronal differentiation of NSCs and interfere with the functional integration of new-born neurons in the hippocampus.[24,25,27,118] Further, the decline in the level of neurogenesis has been known to be associated with memory impairment in the aforementioned neuropathogenic condition due to neuroinflammation[17] which might be highly relevant to COVID-19. Notably, experimental evidence strongly indicates that SARS-CoV-2 has the potential to infect the hiPSC-derived NSCs and the brain organoids.[101,103,131] Moreover, recent immunohistochemical examinations suggest that SARS-CoV-2 infection leads to impaired hippocampal neurogenesis in post-mortem brain samples of COVID-19 victims and SARS-CoV-2-infected experimental animals, where increased levels of cytokines like IL-1β and increased microglial activation have also been reported in brain regions including the hippocampus.[52] The increased levels of cytokines like transforming growth factor beta (TGF)-β and IFN-γ and ILs are responsible for cytokine storm and neuroinflammation in COVID-19.[132] Previously, Kandasamy et al. have demonstrated that elevated level of TGF-β signalling disrupts the proliferation and differentiation potentials of NSCs leading to aberrant neurogenesis in the hippocampus of experimental animal brains.[17,26,106] Taken together, neuroinflammation has been clearly known to affect the neurogenic potential of NSCs and integration of the neuroblast in the hippocampus, contributing to abnormal regenerative plasticity, ultimately leading to cognitive impairments.[17,106,133] While hippocampal neurogenesis is responsible for learning and memory, occurrence and progression of cognitive deficits and dementia have clearly been attributed to impairment in hippocampal neurogenesis.[20,123,134] Considering the aforementioned facts, it can be proposed that the SARS-CoV-2-mediated stress, depression, emotional and psychological trauma, sequence of comorbid neuropathological alterations and neuroinflammation might drastically alter the neurogenic potential of NSCs in the hippocampus of the brain. Further, the resulting aberrant neurogenesis in the hippocampus can be a potential cause of dementia in a significant portion of COVID-19 patients and survivors as the dysfunctional and degenerating neurons are least likely to be replenished (Fig 1). Thus, there is an urgent need of detailed scientific attention on abnormal regulation of hippocampal neurogenesis relating to cognitive impairment in COVID-19.

Conclusion

While the rising mortality resulting from COVID-19 worldwide has become an issue of serious concern, a significant portion of COVID-19 survivors appears to have an increased risk of various neurological deficits and dementia. As elevated levels of stress hormones and proinflammatory molecules in the brain have been reported to impair hippocampal neuroplasticity, clinical signs of comorbid neuropathogenic condition noticed in subjects with COVID-19 might be linked to defects in the NSC potentials accounting for aberrant neurogenesis in the hippocampus. As the failure in neuroregenerative process in the hippocampus has been identified as a major pathogenic determinant of cognitive decline , COVID-19 might represent a potential risk factor for mental health issues and dementia due to neuroinflammation and deterioration of hippocampal neurogenesis. Thus, therapeutic strategies and implementation of regenerative medicine to prevent and defend the neuroregenerative failure in the hippocampus is highly crucial to manage the possible occurrence of dementia in COVID-19 patients and survivors.

Abbreviations

ACE2, angiotensin-converting enzyme 2; AD, Alzheimer's disease; AGTR2, angiotensin II receptor type 2; BBB, blood–brain barrier; BrdU, bromodeoxyuridine; CA1, cornu ammonis 1; CD-147, Cluster of differentiation 147; COVID-19, coronavirus disease 2019; CRH, corticosteroid releasing hormone; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; FGF, fibroblast growth factor; GFAP, glial fibrillary acidic protein; HCoV-OC43, human coronavirus OC43 strain; HD, Huntington's disease; hiPSC, human-induced pluripotent stem cell; HPA, hypothalamic–pituitary–adrenal axis; Iba-1, ionized calcium binding adaptor molecule 1; IFN-γ, interferon-gamma; ILs, interleukins; MN-1, murine motorneuron; MRI, magnetic resonance imaging; NF-L, neurofilament light chain; NMR, nuclear magnetic resonance; NRP1, neuropilin 1; NSC, neural stem cell; PD, Parkinson's disease; RAGE, receptor

for advanced glycation end products; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGZ, subgranular zone; SVZ, subventricular zone; TMPRSS2, transmembrane protease serine 2; TNFα, tumour necrosis factor alpha; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor

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