Microglia and Mast Cells in Neuro-COVID

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). About 45% of COVID-19 patients experience several symptoms a few months after the initial infection and develop post-acute sequelae of SARS-CoV-2 (PASC), referred to as “Long-COVID,” characterized by persistent physical and mental fatigue. However, the exact pathogenetic mechanisms affecting the brain are still not well-understood. There is increasing evidence of neurovascular inflammation in the brain.

ACE2 brain coronavirus cytokines inflammation

1. Microglia-Induced Neuroinflammation and Mental Health

Microglia are specialized macrophage-like immune cells of the CNS and constitute about 7 percent of non-neuronal cells in the brain [1]. It has been reported that one microglial cell serves 1 to 100 neuronal cells in various brain areas with different neuronal densities [1]. Microglia are important for CNS homeostasis both in health and disease states [2], especially neurodegenerative [3][4][5][6][7][8][9] and neuroinflammatory [2][8][10][11] diseases, including COVID-19 [12][13]. During neuroinflammatory response and brain homeostasis maintenance, microglia can change their numbers, morphological characteristics, molecular pattern, and functions [13]. Activated microglia release pro-inflammatory cytokines, free radicals, and fatty acid metabolites. Cytokines and chemokines released from activated microglia induce activation of astrocytes with additional release of proinflammatory mediators that further exacerbates neuroinflammatory response. Dysregulated microglia and T-cell interactions and microglial nodules in the perivascular compartment of the brain were associated with systemic inflammatory conditions in COVID-19 [14]. Microglial activation is significantly higher in the brain stem than in non-COVID cases. Further, COVID-19 cases without dementia show more microglial activation in the brain stem [15][16]. The neuroinflammatory response is indicated by the presence of microglial reactivity indicators such as CD68-positive ameboid microglia, ionized calcium binding adaptor molecule 1 (IBA1), and human leukocyte antigen-DR (HLA-DR) in COVID-19 [13][15]. COVID-19 shows more T lymphocytes and microthromboses in the lung associated with more microglial activation in the brain stem [16]. In other words, the long-term consequences of COVID-19 could be due to persistent inflammation rather than persistent viral replication [16]. SARS-CoV-2 induces neuropsychiatric and neurological disorders such as cognitive decline, depression, dizziness, delirium, and sleep disorders that lead to neuronal damage, neurodegenerative disorders, and dementia [17]. Thus, SARS-CoV-2 can cause BBB disruption and worsen neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease, especially in aged people [17][18][19].

SARS-CoV-2 infection can cause dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [20], which may be the cause of the emotional changes observed during and after viral infection [21]. Several reports have shown the impact of the pandemic on acute and chronic mental health. Further, these studies also focused on the psycho-social factors and stress resilience of mental health and disease pathologies [22][23]. TLR4 contributes to the immune response and pathogenesis of COVID-19, and thus, TLR4 could be a therapeutic target in COVID-19 [24][25][26]. SARS CoV-2 activates TLR4 and 8 and induces cytokine release from microglia and monocytes [27]. Microglia express receptors for neurotensin (NT) [28] and corticotropin-releasing hormone (CRH), secreted under stress [29], which are especially associated with COVID-19 [30]. Microglia are typically characterized as resting (M0), pro-inflammatory (M1), and anti-inflammatory and neuroprotective (M2) phenotypes with different cytokine expressions associated with neuroinflammatory response.

Microglia are increasingly involved in the pathogenesis of psychiatric disorders [13][31][32]. In fact, microglia-induced neuroinflammation was considered a risk factor for the pathogenesis of major depressive disorder [33][34]. Moreover, SARS-CoV-2 neurotropism may increase the severity of neuropsychiatric issues [35]. A recent report indicated that the SARS-CoV-2 protein elicited a robust nuclear factor kappa B (NF-κB)/nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome-mediated pro-inflammatory response and increased Iba1 expression in a BV-2 mouse microglial cell line [36]. In addition, post-mortem reports of COVID-19 patients showed significant microglial activation and neuroinflammation associated with brain pathology [37][38][39][40]. Increasing reports indicate that elevated inflammatory cytokines and neuroinflammatory responses [8][41][42] can damage brain blood vessels [43][44] and other brain cells [41][45][46], possibly through abnormally excessive activation of microglia [47][48]. As such, long COVID could be referred to as “brain autoimmunity” [49].

2. Microglia Communicate with Mast Cells

Mast cells communicate with microglia [50][51], leading to their activation [51][52][53][54] and contributing to neuroinflammation [50][52] and neurodegenerative diseases [50][55]. This effect is not seen in mast-cell-deficient mice [56][57]. In fact, mast cell proteases can trigger astrocytes and glia/neurons and release IL-33 [58]. Stabilization of mast cells was shown to inhibit lipopolysaccharide (LPS)-induced neuroinflammation by suppressing the activation of microglia [59]. Activation of mast cells and microglia in the hypothalamus and brain [60] could lead to cognitive dysfunction [61] and neuronal apoptosis [61]. In addition, mast cells can activate the hypothalamic–pituitary–adrenal (HPA) axis [62][63][64][65] through the release of histamine [66], IL-6 [67], and CRH [68]. It is interesting that stress has been linked to the possible priming of immune cells thus contributing to neuroinflammation in AD [69][69]. Furthermore, NT [70][71] and substance P (SP) [72] induce CRH receptor-1 (CRHR1) expression in mast cells. Mast-cell-derived histamine [73] and tryptase [74] can trigger microglia and induce neuroinflammation [52]. Mast cells have been shown to be an early activator of LPS-induced neuroinflammation and BBB damage in the hippocampus [60]. In addition, food allergy that depends on mast cell activation has been shown to increase activated microglia and TNF in the hippocampus, associated with behavioral and learning impairments [75]. Another paper reported that early stress in mice and humans disrupted interactions between mast cells and glia via the involvement of

histamine [76]. As such, mast cells can participate in neuroinflammation [77][78] by releasing histamine and several inflammatory cytokines and chemokines [79].

3. Mast Cells in the CNS

Mast cells are ubiquitous in the body [80]. They are mostly known for mediating allergic and anaphylactic reactions [81], and several other diseases such as mastocytosis [82]. The functions of mast cells in health and several pathologic conditions were reviewed recently [83][84][85][86]. Mast cells respond to allergic but also to various other non-allergic stimuli [82]. Activated mast cells can secrete as many as 100 biologically powerful mediators, including pro-inflammatory molecules [79] such as bradykinin, chymase, histamine, tryptase, chemokine (C-C motif) ligand 2 (CCL2), CXCL8 [87], IL-6 [88], IL-1β, and TNF-α [89]. A particular potent stimulus of the mast cells is the peptide SP, especially when primed by the “alarmin” cytokine IL-33 [90][91][92][93]. Mast cells can also be stimulated to secrete mitochondrial DNA (mtDNA) [94], which serves as an additional “alarmin” and can trigger an auto-inflammatory reaction [95][96]. Mast cells are also found in the CNS perivascularly [97][98], especially in the meninges [99][100] and the median eminence of the hypothalamus [2][100][101], where they could have numerous functions. Functional interactions have been reported between mast cells and neurons [100][102] that are often positive for CRH [71][100]. Mast cells are the richest source of histamine in the CNS, particularly in the amygdala, hippocampus, hypothalamus, and thalamus [103][104]. Stimulated brain mast cells contribute to postoperative cognitive dysfunction (POCD) through the release of inflammatory and neurotoxic mediators from activated microglia [61][105]. Activation of mast cells [71] and microglia in the hypothalamus [106] could cause cognitive dysfunction [61] that is also seen in patients with mastocytosis [107][108][109] and may be related to brain abnormalities [110]. Allergic stimulation of nasal mast cells resulted in stimulation of the HPA axis [62][63][64][65], possibly via mast cell release of histamine [66], IL-6 [66][111], and CRH [68]. The influence of stress on mast cells has also been reviewed [21][112]. Restraint stress in rodents increased BBB permeability [101][113][114] via CRH [113][115][116]. Mast-cell-released cytokines [117][118] increased BBB permeability [101][113] and permitted mammary adenocarcinoma brain metastases in mice [115]. This process could worsen with stress, acting via CRH stimulation of mast cells [113][115] and an increase in dura vascular permeability. Meningeal mast cells affected the integrity of the BBB and promoted T-cell brain infiltration [119]. Inflammation mediated by mast cells and microglia disrupted the BBB [120]. Mast cell responsiveness may be regulated not only by the neuroimmune stimuli but also by the effects of the different receptors involved. For instance, mast cells express high-affinity neurokinin-1 (NK-1) receptors for SP [72]. Moreover, SP and NT [70] induced the expression of CRHR-1 in human mast cells. Secretion of mediators can occur by utilizing different signaling [121][122][123][124] and secretory [122][124] pathways. The regulation of mast cells by neurotransmitters and neuropeptides has been reviewed [125][126][127], with emphasis on CRH [65], hemokinin-1 (HK-1) [128], nerve growth factor (NGF [129], NT [130], SP [131], and somatostatin [132][133] acting via activation of high-affinity receptors. Activated mast cells could release a number of pro-inflammatory and vasoactive mediators that could contribute to long COVID syndrome symptoms [65][134]. Some mediators are pre-stored in secretory granules (e.g., histamine, tryptase, and TNF-α) [135][136] and are released immediately following stimulation, while others are newly synthesized and then released, such as chemokines (e.g., CCL2, CCXL8) [87], and cytokines (IL-6 [88], IL-1β [137], TNF-α [89]). Apart from allergic triggers acting via IgE, mast cells are stimulated by non-allergic agents [81][92][138],

especially neuropeptides [125], such as SP [131][137] and the SP-related HK-1 [128], which have pro-inflammatory properties. Under such conditions, especially when primed by IL-33 [92][93], mast cells can release various inflammatory mediators without the release of histamine or tryptase [139], thus contributing to inflammatory disorders [78][81]. Moreover, mouse mast-cell proteases 6 (MMCP 6) and MMCP 7 stimulated the release of IL-33 from mouse fetal-brain-derived cultured primary astrocytes in vitro [58]. A case in point is the selective release of IL-6 [88][140], which is elevated in systemic mastocytosis and correlated with disease severity [141][142][143] and can increase mast cell numbers [144].

4. Mast Cells in Long COVID

Mast cells are activated by viruses [145][146] such as SARS-CoV-2 [147][148][149][150][151][152][153][154][155][156][157][158][159][160][161]. Recent studies have also reported mast cell activation in the lungs [154] and perivascular inflammation in the brains [43] of COVID-19 patients. Two studies reported elevated serum levels of chymase in patients with COVID-19 [153][160]. Moreover, a recent study demonstrated that mast cells enhance cellular entry of SARS-CoV-2 through the generation of chymase-spike complexes [162]. Chymase converts angiotensin I to angiotensin II and may act in an autocrine fashion to increase the expression of ACE2, which then facilitate viral entry. Another paper reported that mast-cell-derived histamine can increase SARS-CoV-2 entry into endothelial cells [163]. Mast cells also release extracellular mtDNA [94], which was shown to be significantly elevated in COVID-19 patients [164]. Extracellular mtDNA can then stimulate the secretion of pro-inflammatory mediators from other immunocytes [95][96].

5. Neuroimmune Biomarkers

While a number of molecules are elevated in the blood of patients with COVID-19 [165][166][167][168], the results have been inconsistent and have focused primarily on pro-inflammatory mediators. A few studies have investigated blood biomarkers that may reflect brain injury in COVID-19 patients [169][170]. Anti-receptor antibodies and autoimmune gene expression [171] have also been reported. IL-15 is implicated in viral clearance with anti-viral properties, including in COVID-19 [172][173]. IL-18 remains elevated longer than other cytokines in inflammatory and autoimmune disorders [174][175], including COVID-19 [176]. Calprotectin (S100A8/A9) was associated with microglia activation [177] and was elevated in the serum of patients with COVID-19 [176]. Calprotectin was also in the CSF of patients with Multiple Sclerosis (MS) [178] and demyelinating polyneuropathy [179]. Neuroligins (NLGs) and neurexins are implicated in synaptic function and cognitive disease [180]. NLG1 levels were reduced in the cortex and the CSF of AD patients [181] or those with mild cognitive impairment (MCI) [182]. NLG4 was associated with cognitive decline [183], while neuropilin-1 (NRP-1) was shown to facilitate SARS-CoV-2 entry by binding to the spike protein [184]. Moreover, S100β was shown to be associated with COVID-19 severity [185] and promote microglia activation [186][187][188] and has been linked to neuroinflammation and cognitive decline [189]. Neurofilament light chain (NfL), microtubule-associated protein-2 (MAP-2), and glial fibrillary acidic protein (GFAP) indicate axonal/neuronal damage and brain injury [169][190][191][192][193]. Elevated levels of osteopontin have been associated with reduced cognition [194][195]. A recent study indicated that COVID-19 was associated with brain pathology in the

UK Biobank [196] and was associated with neuroinflammation involving primarily the chemokine CCL11 in a mouse model [197]. CCL11 has been implicated in neuroinflammatory disorders [198], while osteopontin was reported to disrupt the BBB [199]. Chemokine CCL19 and its receptor C-C chemokine receptor type 7 (CCR7) axis are involved in the immune response to viral infections [173][200]. Increased levels of CCL19 were associated with disease severity in COVID-19 patients [201].

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