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Review

Depression as a Microglial Disease

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Despite decades of intensive research, the biological mechanisms that causally underlie depression are still unclear, and therefore the development of novel effective antidepressant treatments is hindered. Recent studies indicate that impairment of the normal structure and function of microglia, caused by either intense inflammatory activation (e.g., following infections, trauma, stroke, short-term stress, autoimmune or neurodegenerative diseases) or by decline and senescence of these cells (e.g., during aging, Alzheimer's disease, or chronic unpredictable stress exposure), can lead to depression and associated impairments in neuroplasticity and neurogenesis. Accordingly, some forms of depression can be considered as a microglial disease (microgliopathy), which should be treated by a personalized medical approach using microglial inhibitors or stimulators depending on the microglial status of the depressed patient.

Major Depression and Microglial Homeostasis

Major depression, which afflicts one in six people at some point in life, is one of the main causes of human suffering and the leading global cause of years of life lived with disability (www.who.int). Despite recent progress in understanding the molecular, cellular, and circuit-level correlates of depression, the biological mechanisms that causally underlie this disease are still unclear, and therefore the development of novel effective antidepressive procedures has been slow and frustrating. A possible reason for this situation is that most research to date focused on neuronal dysfunction, while studies on the role of glial cells in depression have lagged behind. Recent data suggest that glia play important roles in normal brain processes, such as synaptic transmission and neural plasticity, as well as in pathological brain processes including neuropsychiatric diseases [1–3]. However, the specific role of microglia in major depression is only beginning to be explicated [4–7] and will be the topic of the current review.

In recent years our knowledge regarding the origin, structure, and function of microglia has been increasing rapidly [2]. Microglia, which comprise about 10% of all brain cells, play crucial roles in normal development and in the regulation of ongoing structural and functional processes, from individual synapses to neural circuits and behavior [3,8]. During pathological conditions (e.g., infection, injury, and neurodegeneration) microglia are activated and serve as the major orchestrators and executors of the inflammatory, protective, recuperative, and toxic processes that affect neurons and other brain cells (Box 1).

The essential roles of microglia under resting, quiescent conditions depend on exquisitely tight spatial and temporal regulation of their structure and function. Therefore, although the morphological and functional changes associated with microglial activation are essential for coping with external or internal pathogenic challenges, these changes compromise and interfere with the normal physiological functioning of microglia. Interference with microglial functioning can also

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Microglia are best known as the immune cells of the brain, but emerging data indicate that they also influence brain development, synaptic plasticity, neurogenesis, memory, and mood under quiescent physiological conditions.

Deviation from microglial homeostasis, caused either by microglial activation during inflammatory conditions (e.g., infections, stress, stroke, or neurodegenerative diseases) or by microglial decline and senescence (e.g., during aging or chronic unpredictable stress), can lead to depression.

Conventional antidepressant drugs and electroconvulsive therapy modulate microglial structure and function, suggesting a novel mechanism of action for these treatments.

Microglia represent a promising therapeutic target for the treatment of depression; either microglia-suppressing or -stimulating drugs can serve as antidepressants, depending on the microglial status of the patient.

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Box 1. The Emerging Roles of Microglia in Developmental, Physiological, and Pathological Brain Processes.

During embryonic development, microglial progenitors arise from primitive myeloid precursors in peripheral mesodermal tissue, in contrast to neurons, astrocytes, and oligodendrocytes which are derived from the neuroectoderm. The microglial progenitors migrate from the extraembryonic yolk sac into the developing CNS and disperse almost evenly throughout the entire brain [172]. After the embryonic period and throughout life, microglial maintenance and local expansion are almost exclusively dependent on self-renewal of CNS-resident microglia, and progenitor recruitment from the circulation occurs only in special conditions [173].

In the developing CNS, microglia regulate the neuronal precursor cell pools as well as synaptogenesis and neural network formation [174,175]. In the adult CNS, the processes of 'resting' microglia are highly motile even under normal quiescent conditions. Frequent brief contacts of microglial processes with presynaptic and postsynaptic neuronal elements contribute to the regulation of synapse formation and elimination (pruning) [3,8]. The microglial–neuronal interactions depend on neuronal activity, particularly in specific environmental contexts such as sensory stimulation/deprivation and specific learning and memory tasks [176,177].

Under conditions of disturbed brain homeostasis, including infection, injury, neurodegeneration, or markedly altered neuronal activity, microglial structure and function are rapidly and profoundly altered, and they assume an 'activated' status characterized by (i) rapid and targeted movement of microglial processes toward the site of infection or injury; (ii) proliferation and resultant increase in the density of microglial cells; (iii) morphological alterations, including enlargement of the soma, increase in the diameter of primary processes, shortening of distal processes, and, in fully activated microglia, complete retraction of all processes and assumption of an amoeboid morphology; (iv) enhanced phagocytic activity; and (v) production and secretion of inflammatory cytokines and other mediators. It is now evident that microglial activation is not an 'all or none' process; in other words, microglia can undergo multiple functional alterations or programs, which confer specific adaptation for coping with diverse pathological conditions [2].

The microglial activation process is controlled by exogenous and endogenous 'alarm' molecules ('on' signals) or by suppressed production of microglia-inhibitory molecules that are constitutively produced in the brain, usually by neurons ('off' signals) [178]. Microglial activation and associated neuroinflammation evolved as an adaptive process, allowing the elimination of pathogenic challenges; however, under many circumstances, including neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, activated microglia become neurotoxic and damage neurons and glial cells [179,180].

occur in conditions that induce microglial suppression, decline, and senescence. These interferences produce changes in behavior, cognition, and mood, which are usually transient but may be long-lasting if the microglial changes are enduring, for example, in association with chronic infections, stroke, trauma, neurodegenerative diseases, or chronic psychological stress. A pathological condition in which aberrant microglial structure and function is the main trigger of the disease symptoms may be considered a 'microgliopathy' [7]. In the following we review evidence for the notion that some forms of major depression are caused by either intense activation or by decline and suppression of microglial functioning in specific brain areas, and therefore can be regarded as microgliopathies.

The Role of Microglial Activation in Illness-Associated Depression

Various bacterial and viral infections (e.g., influenza virus, Epstein–Barr virus, herpesvirus, cytomegalovirus, Borna disease virus, and gastroenteritis-related viruses) are associated with a range of depressive symptoms [9]. Many of these infectious pathogens have a special affinity for the brain, where they induce microglial activation [10]. These pathogens also induce the secretion of proinflammatory cytokines [11], whose plasma levels are correlated with depressive symptomatology [12,13]. Consistently, experimental administration in humans of immune challenges that are known to activate microglia [e.g., endotoxin (lipopolysaccharide, LPS) or *Salmonella typhi*] induces depressive symptoms, whose severity is highly correlated with elevated blood levels of inflammatory cytokines [14–16].

Experiments in animal models provide more direct evidence for a role of microglia in depression, mainly by using LPS administration, which induces microglial activation together with a depressive-like episode in rodents that can be prevented by treatment with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) [17,18]. Several lines of evidence support

the involvement of microglia in LPS-induced depression: (i) LPS-induced depressive-like symptoms can be attenuated by treatment with the microglial inhibitor minocycline [19]; (ii) activation of the enzyme indoleamine 2,3-dioxygenase (IDO) in microglia is essential for the development of depressive-like symptoms and microglial activation induced by LPS and other immune challenges [19–22]; and (iii) mice with microglial hyper-reactivity, induced by a microglia-specific mutation [23] or by traumatic brain injury [24], exhibit exacerbated LPS-induced depressive-like symptoms.

Infection with the human immunodeficiency virus (HIV) is associated with a twofold increase in the prevalence of major depression [25]. Microglia-induced neuroinflammation may be particularly responsible for this depression, given that the virus rapidly gains access to the brain where it infects mainly microglia (but not neurons) and induces their activation [26]. Studies in experimental animals show that the virus sheds two specific proteins, gp120 (glycoprotein 120 kDa) and Tat (transactivator of transcription), which induce marked microglial activation [27,28] together with a depressive-like neurobehavioral syndrome [25,27–30] that can be attenuated by anti-inflammatory drugs [28,29].

The Role of Microglia Activation in Depression Not Associated with Overt Inflammatory Challenges
Microglial Status in Depressed Patients
Microglial status in major depression patients without a comorbid medical condition was assessed in postmortem and positron emission tomography (PET) imaging studies. In general, the results of these studies were negative or inconclusive, probably because depression may be associated with either microglial activation or decline, and therefore averaging microglial status for entire samples can lead to null results. Specifically, one postmortem study demonstrated the presence of activated microglia in one of six affective disorder patients [31], and three additional studies reported no differences between depressed patients and controls in microglial density [32–35]. In contrast to depression *per se*, suicide (committed by psychiatric or non-psychiatric individuals) was associated with microglial priming and activation as well as elevated density of perivascular macrophages around blood vessels ([32,33], but see [34]).

Studies on the association between *in vivo* microglial activation and depression utilized PET ligands for the neuroinflammation marker translocator protein 18 kDa (TSPO). This protein is localized primarily in the outer mitochondrial membrane and is involved in mitochondrial function, including in the synthesis of steroids and neurosteroids, as well as in cell proliferation and apoptosis [36]. In the brain TSPO is mainly (but not exclusively) expressed in microglia. Expression levels are low in the healthy brain, but are markedly upregulated locally during neuropathological conditions, providing the rational for assessing the binding of labeled TSPO ligands by PET imaging techniques to visualize and quantitate various neuroinflammatory conditions [36]. It should be noted, however, that results from studies with this method should be interpreted cautiously because different TSPO PET ligands have distinct binding affinity patterns, and because the sensitivity of the current methodology, which has been validated only in neuropathology, may be insufficient for detecting changes associated with psychiatric illness. The first PET imaging study, using the ligand [^{11}C]PK-11195, revealed no difference between depressed and control groups in any brain region [37], whereas a more recent study, using the PET ligand [^{18}F]FEPPA, reported significant depression-associated elevations in TSPO volume distribution in the prefrontal cortex, insula, and anterior cingulate cortex (ACC) that correlated positively with the severity of depression [38]. Furthermore, elevated TSPO binding by the [^{11}C] PK-11195 ligand was found in the right hippocampus of euthymic bipolar disorder patients, compared to healthy controls, with trends for increased TSPO binding in the left hippocampus and decreased binding in the left dorsolateral prefrontal cortex (PFC) [39]. Finally, a recent preliminary report suggested that, in multiple sclerosis patients increased, microglial activation in

the hippocampus (reflected by elevated [^{11}C]PK-11195 binding) is correlated with depressive symptomatology [40].

Microglial Status in Animal models of Stress-Induced Depression

In humans and in experimental animals stress is causally related to the development of depression [41–43]. Ample evidence demonstrates that exposure to stress can induce microglial activation (Table 1). Acute stressors [44–47] induced microglial activation in many brain areas. Consistently, minocycline administration completely blocked the effects of foot-shock stress on hypothalamic interleukin (IL)-1β production [48]. Semi-chronic (2–6 days) repeated restraint or unpredictable stress also induced a dramatic increase in the proliferation of hippocampal microglia together with increased mRNA expression and immunoreactivity of several microglial activation markers [43,49,50]. Mice subjected to repeated social defeat or foot-shock stress also exhibited microglial activation, recruitment of peripheral macrophages into the brain, and anxiety behavior [51–56]. Chronic stress, which induces a depressive-like condition in rodents, was also found to alter microglial number, morphology, and functioning. Daily exposure of rats to restraint over 14–21 consecutive days induced depressive-like symptoms which were accompanied by increased microglial number, hyper-ramification (i.e., branching) of processes, and expression of the activation marker IBA1 (ionized calcium-binding adapter molecule 1, also known as allograft inflammatory factor 1, AIF1), but not of type II major histocompatibility complex molecules (MHC-II), in many stress-responsive brain areas [57–60]. A recent study demonstrated that exposure to chronic unpredictable stress (CUS) in rats resulted in microglial activation, stimulation of the microglial NLRP [NLR (nucleotide-binding domain and leucine-rich repeat) family, pyrin domain containing] inflammasome and increased IL-1β production in the PFC [61]. In the context of neuroinflammation, exposure to CUS exacerbated microglial activation induced by intracerebral administration of LPS [62]. Importantly, the effects of chronic stress on microglial activation are heterogeneous and depend on several parameters, including the age of the animals (e.g., one study revealed larger stress-induced microglial activation in young than in old animals) [63], and the nature of the stress regimen (e.g., one study demonstrated microglial activation following chronic restraint but not CUS) [64].

Early-life stress, trauma, and adversity are major risk factors for the development of depression [65]. Early stress alters immune functioning at the time of exposure, but it can also change immune, endocrine, neural, and behavioral responsiveness to various stressful challenges later in life and contribute to various psychopathologies [66,67]. Given the important role of microglia for brain and behavior development (Box 1), early stress-induced alterations in microglia may be particularly important for conferring vulnerability to depression. Indeed, prenatal stress, which is known to promote subsequent depressive-like symptomatology in the offspring, was shown to induce long-lasting basal hippocampal microglial activation together with an exacerbated microglial responsiveness to systemic LPS administration [68]. Furthermore, adult mice that were exposed to neonatal maternal separation displayed increased number and motility of microglial processes [69], as well as increased microglial activation (reflected by elevated IBA1 immunoreactivity) in the PFC following exposure to chronic food-restriction stress at adolescence [70]. Future studies should examine the causal relations between the early stress-induced lifelong changes in microglial structure and function and vulnerability to depression.

Microglia-Suppressive Properties of Antidepressant Drugs

Recent studies suggest that in addition to their classical effects on neurotransmission, antidepressant drugs can also inhibit the production of proinflammatory cytokines and suppress microglial activation [71]. Specifically, several SSRIs were found to inhibit the ability of cultured murine or rat microglia to produce tumor necrosis factor α (TNFα) and the free radical nitric oxide [71–75]. Other classes of antidepressants [including TCAs, serotonin/norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase (MAO) inhibitors] were also found to have

Table 1. Effects of Acute and Chronic Stressors on Microglial Structure and Function in Experimental Animals[a,b]

Stress Regimen	Total Stress Exposure Duration	Species/Strain	Microglial Status Measurements	Stress-Induced Changes in Microglial Structure/Function	Brain Areas Involved	Refs
Acute water immersion	1 or 2 h	Rats/Wistar Mice/C57	IHC of microglial markers mRNA expression	↑ CD11b IR ↔ IL-1β, IL-6, or iNOS mRNA	HPC, thalamus, Hyp, PAG	[44,45]
Acute tail shock	~2 h	Rats/SD	IHC of MHC-II expression mRNA expression in LPS-stimulated freshly isolated microglia (ex vivo)	↑ Number of MHC-II+ microglia ↑ Iba-1, MHC-II, CD11b, IL-1β, IL-6, and NF-κBIα mRNA ↔ CD163 or TNFα mRNA	HPC	[46,47]
Repeated unpredictable stress (cage shaking, cage tilt, wet cage, stroboscopic light, cold room, mild restraint, noise)	Three different stressors/day for 2 days	Mice/C57, CX3CR1+/−-GFP, Rats/SD	IHC of Iba-1 Visualization of CX3CR1–GFP labeling Microglial proliferation (GFP and BrdU double labeling) mRNA expression	↑ Proliferation, density (cell number per HPC) and soma area ↓ Process length ↑ Iba-1, MHC-II, IL-1 receptor-1 mRNA ↔ CD11b, IL-1β mRNA ↓ IL-1ra mRNA	HPC (DG)	[43]
Repeated immobilization stress	15 h daily for 2–6 days	Mice/C57	FC of CD11b+/CD45low microglia, as well as proliferating cell nuclear antigen-positive and annexin-positive (apoptotic) microglia	↑ Microglial numbers (only on day 4 post stress initiation) ↑ PCNA-positive microglia (proliferation) on days 4 and 6 ↑ Annexin-positive microglia (apoptosis) on day 6	HPC and whole brain	[49]
Repeated immobilization stress	2 h daily for 4 days	Mice/ICR	IHC of OX-42 (CD11b), as well as IL-1β within the OX-42 labeled microglia	↑ CD11b and IL-1β IR	HPC (CA1), striatum, PVN	[50]
Repeated foot-shocks (FS), or witnessing other mice receiving FS	1 h daily for 5 days	Mice/C57	IHC and counting of Iba-1-labeled cells, as well as GFP-labeled infiltrating monocytes FC analysis of surface markers	↑ Number of Iba-1-labeled microglia ↔ microglial morphology ↑ Infiltration of monocytes that acquire ramified morphology (but are still different molecularly and morphologically from resident microglia)	Ventral HPC, PVN	[55]

Table 1. (continued)

Stress Regimen	Total Stress Exposure Duration	Species/Strain	Microglial Status Measurements	Stress-Induced Changes in Microglial Structure/Function	Brain Areas Involved	Refs
Repeated social disruption stress	2 h daily for 6 days	Mice and rats/C57 and SD	FC of brain macrophages versus microglia, and activation markers on these cells IHC of Iba-1 IR mRNA of activation markers in freshly isolated microglia (ex vivo) Protein levels in supernatants of enriched microglial cultures	↑ Percentage of infiltrating macrophages/ microglia ↑ CD14, TLR4 and CD86- labeled cells ↔ MHC-II-labeled cells ↑ Iba-1 IR ↑ IL-1β, TNFα, iNOS mRNA ↓ GILZ and FKBP51 mRNA ↑ IL-6, TNF-α, and MCP-1 protein levels	HPC, PFC, Am, and PVN, for histology Whole brain for other analyses	[57–54]
Chronic variate stress in the context of neuroinflammation (forced swimming, restraint, cold room, social isolation, water/food deprivation)	One different stressor/day for 9 days	Rats/Wistar	IHC of activation markers, followed by cell counting mRNA expression IHC and mRNA following LPS administration in CUS-exposed animals	↑ Number of MHC-II (OX-6)$^+$ microglia ↔ TNFβ, IL-1β, IL-6, iNOX Potentiation of the effects of LPS on the above parameters by CUS	SN	[62]
Chronic restraint stress	2 × 30 min daily restraint for 14 days	Rats/SD	IHC of Iba-1 and MHC-II-labeled cells	↑ Number and IR of Iba-1-, but not MHC-II-labeled cells ↓ Cell size	HPC, PFC, Am, NA, BNST, PVN	[59]
Chronic restraint stress	6 h daily restraint for 21 days	Rats/SD	IHC of activation markers, β-integrin (a marker of microglial ramification), and P2X7 (a purinergic receptor) Reconstruction of Iba-1-labeled microglia followed by morphometric and Scholl analyses	↑ Iba-1 IR ↔ MHC-II, CD68 IR ↑ β-integrin IR ↓ P2X7 IR ↑ Branch points (nodes), intersections, and process length in large microglia (top 25%)	PFC	[57,58,60]
Chronic unpredictable stress (cage shaking, cage tilt, wet cage, intermittent, continuous, or stroboscopic illumination, mild restraint, cold room, noise, water deprivation)	2–3 different stressors/day for 5 weeks	Mice/C57 and CX3CR1–GFP$^{+/–}$ Rats/SD	IHC of Iba-1 Visualization of CX3CR1–GFP-labeled microglia, cell counting and morphological analysis mRNA expression	↓ Number of Iba-1- and GFP-labeled microglia ↓ Soma size, processes length (dystrophic morphology) ↓ Iba-1, Cd11b, ICE mRNA ↔ IL-1β, IL-1R1, IL-1ra mRNA	HPC (DG), but not in cortical microglia	[43]

Table 1. (continued)

Stress Regimen	Total Stress Exposure Duration	Species/Strain	Microglial Status Measurements	Stress-Induced Changes in Microglial Structure/Function	Brain Areas Involved	Refs
Chronic unpredictable mild stress (cage tilt, wet cage, intermittent, continuous, or stroboscopic illumination, intruder rat, noise, water/food deprivation)	Two different stressors/day for 12 weeks	Rats/Wistar	IHC of activation markers mRNA expression and protein levels (ELISA) of inflammasome and other microglia-related markers	↑ Iba-1 and CD11b IR ↑ Colocalization of NLRP and Iba-1 ↑ IL-1β, NLRP, ASC Caspase-1, P2X7, TLR2 mRNA and protein levels ↔ TLR4 mRNA	PFC	[61]

[a]The stress regimens are ordered according to the stressors exposure period, that is, from acute to subchronic (repeated stress for 2–6 days) to chronic (9 days and above). Immunoreactivity was assessed by labeling of microglial surface markers (e.g., CD11b, Iba-1, MHC-II, CD68), followed by 'thresholding' procedures and measurements of the relative area occupied by immunoreactive material. mRNA expression levels were assessed by RT-PCR.

[b]Symbols and abbreviations: ↑, increased; ↔, no change; ↓, decreased; Am, amygdala; BNST, bed nucleus of the stria terminalis; C57, C57 BL/6; FC, flow cytometry; HPC, hippocampus; Hyp, hypothalamus; ICE, interleukin-1 converting enzyme (caspase-1); IHC, immunohistochemistry; IR, immunoreactivity; NA, nucleus accumbens; PFC, prefrontal cortex; PVN, hypothalamic paraventricular nucleus; PAG, periaqueductal grey matter; SD, Sprague–Dawley; SN, substantia nigra.

microglia-suppressive effects in microglia cultures [72,76,77]. At least some of the effects of antidepressants were found to depend on their ability to increase intracellular cAMP because inhibition of cAMP production or the production of the associated enzyme protein kinase A (PKA/cAMP-dependent protein kinase) diminished the microglia-suppressive effects of some antidepressants [72,78]. Antidepressants were also found to attenuate microglial activation [79] and promote resilience of injured neurons [80] during neuroinflammatory conditions *in vivo*. Finally, long-term antidepressive treatment (with either imipramine or fluoxetine) prevented the development of microglial alterations *in vivo*, as well as the depressive-like behavioral alterations induced by CUS [43,61].

Antidepressant Properties of Anti-Inflammatory/Microglial-Inhibiting Drugs

Ample studies examined the antidepressive properties of anti-inflammatory drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs), as add-ons to conventional antidepressants. A recent meta-analysis of 14 randomized clinical trials (RCTs) (10 with NSAIDs, three with TNFα inhibitors, and one with an IL-12/IL-23 blocker) demonstrated that overall, anti-inflammatory drugs produced a significant reduction in depressive symptoms [81]. Most of the studies reporting significant antidepressive effects of NSAIDs utilized the cyclooxygenase 2 (COX-2) inhibitor celecoxib. In general, many of these studies were conducted in the context of a physical medical comorbidity (e.g., osteoarthritis or psoriasis), suggesting that depression associated with medical conditions may be particularly affected by anti-inflammatory drugs [81]. Another meta-analysis revealed that selective COX-2 inhibitors, particularly celecoxib, may have antidepressive efficacy (observed in four of six studies), whereas administration of other (non-selective) COX inhibitors, particularly aspirin, had no antidepressive effects [82]. The highly heterogeneous results with NSAIDs as antidepressants suggest that their effectiveness depends on the condition and characteristics of the patients.

The microglial inhibitory drug minocycline was also found to have antidepressive properties. Evidence in humans is limited to one successful case report [83] and one open-label study which demonstrated that 6 weeks of minocycline treatment resulted in significant improvement in both depressive and psychotic symptoms in adult inpatients with psychotic depression [84]. By contrast, minocycline administration produced no effects on the levels of depressed mood and quality of life in patients with diseases other than depression, including acne, AIDS, and resistant obsessive–compulsive disorder [85].

Studies in experimental animals demonstrated antidepressant-like effects of minocycline in the following models of depression: (i) in the forced swim test, acute administration of minocycline (either systemically or directly into the nucleus accumbens) reduced immobility (considered to reflect behavioral despair) and potentiated the antidepressive effects of desipramine and glutamatergic receptor antagonists [86]. However, another study found no antidepressant-like effects of minocycline (albeit at somewhat lower doses) in the forced swim test [87]; (ii) in the LPS model of depression in rats, administration of minocycline completely prevented the development of depression-like symptoms, as well as the LPS-induced increase in 5-HT turnover [19,20]; (iii) in the interferon (IFN)-α model of depression, minocycline prevented depression-like behavior and suppressed neurogenesis [88]. It should be noted that in the three models mentioned above minocycline was administered as a preventive (prophylactic) treatment, commencing before the exposure to the depression-inducing challenge. However, in the following two models minocycline was found to reverse existing depressive-like symptoms; (iv) In the learned helplessness model, depressed-like rats showed recovery of normal escape behavior after a single intracerebroventricular administration of minocycline [89]; (v) in the olfactory bulbectomy (OB) model of depression, chronic administration of minocycline attenuated the depression-like behavior in association with a decrease in microglial activation status in the PFC [90].

Source of Microglial Activation in Depression

Microglia Activation Induced by Infectious and Noninfectious Inflammatory Responses

As noted above, peripheral and central inflammatory challenges can affect behavior and lead to the development of depression. Conserved pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) elicit infectious or noninfectious (sterile) inflammatory responses, respectively, and induce peripheral immune cells to secrete inflammatory mediators, which in turn relay information on the body's immune status to brain microglia via humoral and neural pathways [91,92] (Figure 1). Under normal conditions, the interactions between peripheral immune cells and microglia are regulated by the choroid plexus (the blood–CSF barrier) and the blood–brain barrier [93,94]. Under pathological conditions (e.g., viral
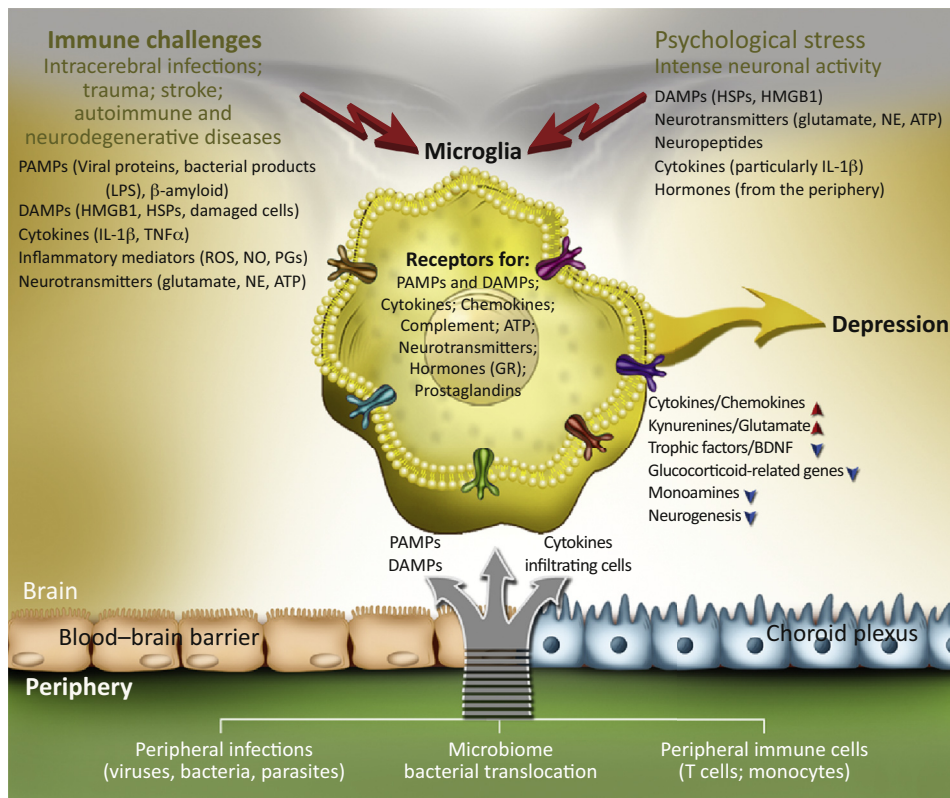
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Figure 1. Sources of Microglial Activation in Depression. Peripheral and central molecular triggers of microglial activation can induce the development of depression. Peripheral sources of microglial activation include pathogen-associated molecular patterns (PAMPs) and damage (or danger)-associated molecular patterns (DAMPs), inflammatory cytokines, and other mediators produced by damaged/inflamed cells, as well as alterations in the gut microbial composition. These molecules can have effects on microglia via humoral and neural periphery-to-brain pathways. Some of the interactions between these molecules and the parenchyma are based on the cellular environment and functioning of the choroid plexus and blood–brain barrier. Under particular inflammatory or stressful conditions, peripheral immune cells can infiltrate the brain and influence microglial activation status. Central sources of microglial activation include brain-derived PAMPs, DAMPs, cytokines, chemokines, inflammatory mediators [reactive oxygen species (ROS), nitric oxide (NO) or prostaglandins (PGs)], as well as various neurotransmitters, neuromodulators, and hormones associated with these inflammatory challenges. Exposure to psychological stress can also induce the production of DAMPs [such as heat shock proteins (HSP) and high mobility group box 1 (HMGB-1)], cytokines (particularly IL-1), neurotransmitters, neuropeptides, and centrally-acting peripheral hormones such as glucocorticoids. All of these molecular triggers bind to specific receptors, leading to microglial proliferation and activation, which result in further production and secretion of cytokines, chemokines, kynurenines, and glutamate (Figure 2), and reductions in trophic factors [particularly brain -derived neurotrophic factor (BDNF)], expression of glucocorticoid-related genes [e.g., glucocorticoid-induced leucine zipper (GILZ) and FK506 binding protein-51 (FKBP51)], monoamine neurotransmission, and hippocampal neurogenesis. The sum of these processes induces the development of depression.

infection, stroke, trauma) barrier functions become compromised, and infiltrating immune cells from the periphery enter the brain parenchyma and modulate the inflammatory response from within.

Regardless of their source, once in the brain PAMPs and/or DAMPs, as well as the inflammatory mediators and neurotransmitters that they induce, directly stimulate microglial activation via specific receptors, promoting the secretion of additional inflammatory mediators (such as cytokines) which in turn result in further microglial activation and the development of depressive symptomatology.

Stress-Induced Microglial Activation

Most depressed patients do not display an overt inflammatory condition. Nevertheless, many of these patients have elevated levels of inflammatory biomarkers [12,13] whose source is not clear yet. Endogenous processes, particularly as a result of exposure to stress, may account for the elevated inflammatory state and increased microglial activation. The hypothalamus–pituitary–adrenal (HPA) axis is the major neuroendocrine system that controls and regulates stress responses. Although glucocorticoids are normally anti-inflammatory, they become proinflammatory under special conditions, particularly within the brain [95]. Specifically, following exposure to stress, glucocorticoids induce microglial activation in preparation for subsequent immune challenges such as injury, trauma, or infection which are more likely to occur during fight/flight conditions [96]. The role of glucocorticoids is evidenced by findings that corticosterone administration increases microglial number, while blockade of corticosterone production or actions abolishes acute or chronic stress-induced microglial proliferation and activation [47,49,62]. Chronic stress also reduces the microglial gene expression of glucocorticoid-induced leucine zipper (GILZ) and FK506 binding protein-51 (FKBP51) [52], which are mediators of glucocorticoid actions and in humans contribute to stress reactivity and depression [97,98].

The gut–brain axis is another system that may be involved in stress-induced microglial activation. In general, the gut microbiota is known to influence the structure, migration, and functions of various immune cell subsets. Consistently, the gut microbiota has been shown to control the maturation and functioning of microglia under normal steady-state conditions [99]. Accordingly, disturbances in gut bacteria can result in neural, hormonal, and behavioral alterations. For example, germ-free animals are hyper-responsive to stress, showing exaggerated HPA responses to restraint or novel environmental stressors [100], while probiotic treatment in animal models was shown to reduce depression-like behaviors and reverse the depression-like symptoms induced by maternal separation [101]. The communication pathways between the gut and the brain are still not fully elucidated, but under certain conditions exposure to stress was found to increase intestinal permeability, allowing gut bacteria or their products (e.g., LPS) to translocate across the intestinal mucosa, stimulate the immune-to-brain mechanisms mentioned above, and result in microglial activation together with depressive symptomatology [4].

Activation of the noradrenergic system has also been proposed to mediate stress-induced microglial activation, mainly because all psychosocial stressors induce the release of norepinephrine, which signals in many types of immune cells as well as in microglia via β-adrenergic receptors. A role of this signaling in stress-induced microglial alterations was demonstrated by findings that β-adrenergic receptor antagonists can block the effects of repeated chronic defeat stress on microglial activation [52].

In addition to peripheral effects, psychological stress can induce direct microglial activation via the release of DAMPs (also termed alarmins) within the brain [102]. These molecules can signal via microglial Toll-like receptor 4 (TLR4) and translate psychological danger signals into

stress- and depression-associated microglial alterations. Specifically, acute stress induces the production of the DAMP high mobility group box 1 (HMGB1), which is both necessary and sufficient for microglial activation [103]. HMGB1 primes microglia for the secretion of inflammatory cytokines and upregulates the expression of microglial matrix metalloprotease 9 [104]. The latter was found to be upregulated in depressed patients [105]. Stress can also alter the levels of heat-shock protein 70 (HSP70) [103,106], which also binds to TLR4 and which, together with its regulating chaperone BCL2-associated athanogene 1 (BAG1), has also been associated with depression [107,108].

The proinflammatory cytokine IL-1, which is produced in the brain during exposure to many types of acute and chronic stressors, plays an important role in the development of depression [41], evidenced for example by findings that mice with genetically impaired IL-1 signaling display no chronic stress-induced microglial activation, depression, or anxiety [43,52,53,109,110]. Finally, intense stress can induce the infiltration into the brain of bone marrow-derived monocytes which can themselves become microglia-like or alter the functioning of existing microglia [54–56].

Microglia Activation Induced by Intense Neuronal Activity

Microglia can become activated after sensing stress-induced increases in neuronal activation. This is not surprising considering that microglia have receptors for many stress-related neurotransmitters, including glutamate, norepinephrine, and serotonin receptors [111]. Specifically, the relations between neuronal and microglial activations were demonstrated by the following findings: (i) in the periaqueductal grey (PAG) (which plays important roles in behavioral responses to uncontrollable stress, threat, anxiety, and pain), stress-associated microglial activation occurs adjacent to active neurons [44]. Interestingly, LPS treatment induced PAG microglial activation even in the absence of neuronal responses, demonstrating that the classical neuroinflammatory reaction is different from the response to stress; (ii) the stimulatory effects of chronic restraint stress on neuronal and microglial activation are highly correlated [58]; (iii) pharmacological blockade of NMDA glutamatergic receptors prevents stress-induced microglial activation [49]. Similarly, in mice exposed to chronic defeat stress, administration of the β-adrenergic receptor blocker propranolol concurrently blocked both neuronal and microglial activation [52]. Interestingly, in this study mice with impaired IL-1 signaling due to deletion of IL-1 receptor-1 demonstrated stress-induced neuronal activation but no microglial changes, suggesting that noradrenergic-supported neuronally-induced IL-1 production mediates stress-induced microglial activation [52].

Mechanisms by which Microglial Activation Induces the Development of Depression

Microglial Activation-Induced Suppression of Neurogenesis and Neuroplasticity

Impaired hippocampal neurogenesis is considered as an important mechanism underlying major depression and is a target for antidepressant actions [112,113]. Several lines of evidence implicate microglial activation as a key mechanism of neurogenesis suppression under inflammatory and stressful conditions [114–116]. Specifically, treatment with LPS or irradiation resulted in marked suppression of hippocampal neurogenesis, whereas treatment with minocycline counteracted this effect [117,118]. The detrimental effects on neurogenesis were primarily due to effects on the maintenance of newborn neurons rather than on their proliferation. A specific role for microglia in neurogenesis suppression is suggested by the negative correlation between the number of newborn neurons and the number of activated microglia under various inflammatory conditions [117,118]. Furthermore, *in vitro* experiments demonstrated that conditioned media from LPS-challenged microglia induced apoptosis of hippocampal neuroblasts, mediated by the secretion of IL-6 [118] or TNFα [119] into the medium, while medium from non-activated microglia increased neuroblast survival. The effects of microglia on neurogenesis may

be mediated by the secretion of IL-1 because both acute and chronic IL-1β administration impaired hippocampal neurogenesis [109,110], whereas pharmacological, surgical, or genetic procedures for IL-1 blockade prevented both the neurogenesis suppression and the depression-like effects induced by acute and chronic stressors [109,110,120,121]. Microglia-derived IL-1 can exert its detrimental effects on neurogenesis via its stimulatory effects on the HPA axis and the secretion of glucocorticoids, as evidenced by the abrogation of the IL-1-mediated neurogenesis-suppressive effects of CUS by adrenalectomy [43]. In addition, IL-1 can directly activate the type 1 IL-1 receptors expressed by hippocampal neural progenitor cells, resulting in decreased cell proliferation that is mediated by the nuclear factor-κB (NF-κB) signaling pathway [110].

As presented in Box 1, in addition to their role in neurogenesis, microglia also control other mechanisms of neuroplasticity. Therefore, it is expected that microglial activation during inflammatory and stressful conditions will interfere with this control. Indeed, exposure to CUS impaired neurobehavioral plasticity [e.g., spatial memory, hippocampal long-term potentiation (LTP)] via inhibition of GluR1 phosphorylation (a component of the AMPA glutamate receptor), which is required for synaptic plasticity and retention of spatial memory [122]. Importantly, administration of minocycline throughout the CUS exposure period prevented the alteration in GluR1 phosphorylation and the neurobehavioral effects, suggesting that microglial activation-associated depression in rodents may be related to alterations in glutamatergic neurotransmission.

Elevated IDO Activity

Several lines of evidence implicate the activation of the enzymes IDO and signaling via the kynurenine pathway (KP) in major depression. The KP was proposed to serve as the switch from acute (sickness-like) effects of inflammatory challenges and stress to the development of depression [4,123,124]. Microglial IDO is activated by inflammatory cytokines (predominantly IFN-γ, but also IL-1β, IL-6, and TNFα) and their inducers [e.g., LPS, CpG, HIV Tat protein, and Bacillus Calmette–Guérin (BCG)] [21,125,126]), as well as by psychological stress and glucocorticoids [127] (Figure 2). The enzyme tryptophan-2,3-dioxygenase (TDO) is also involved in the conversion of tryptophan to kynurenine, and is also activated by glucocorticoids. However, this enzyme is expressed mainly in neurons and not in microglia, and its expression is inhibited by IFN-γ [128], implying that, although a role for TDO in depression should not be dismissed, this enzyme is not directly related to microglia-associated depression.

The involvement of the microglial KP in mediating inflammation and stress-induced depression is supported by clinical studies demonstrating that IFN-α immunotherapy increases tryptophan metabolism through the KP pathway, both in the periphery and in the CSF, and this increase is significantly correlated with the development and severity of IFN-α-induced depression [129–133]. Furthermore, common polymorphisms in the IDO gene were found to be associated with greater IFN-α-induced depression in hepatitis C patients [134], as well as with antidepressant treatment outcome [135]. Finally, postmortem analysis of brains from unipolar depressed patients revealed a significant increase in the numbers of quinolinic acid (QUIN)-positive microglia. This increase was particularly evident in the subgenual anterior cingulate gyrus and anterior mid-cingulate cortex, which contain a high density of NMDA receptors (which mediate QUIN signaling) [136].

Studies in rodents provide even more specific evidence for the role of microglial IDO and KP activation in inflammation-induced depression, evidenced by the following findings: (i) the depressive-like symptoms induced by LPS and other immune challenges were attenuated by administration of the IDO competitive antagonist 1-methyl-D,L-tryptophan (1MT). Conversely, exogenous administration of L-kynurenine to naive mice dose-dependently induced depression-like behavior [20–22]; (ii) exposure to repeated psychological stress resulted in
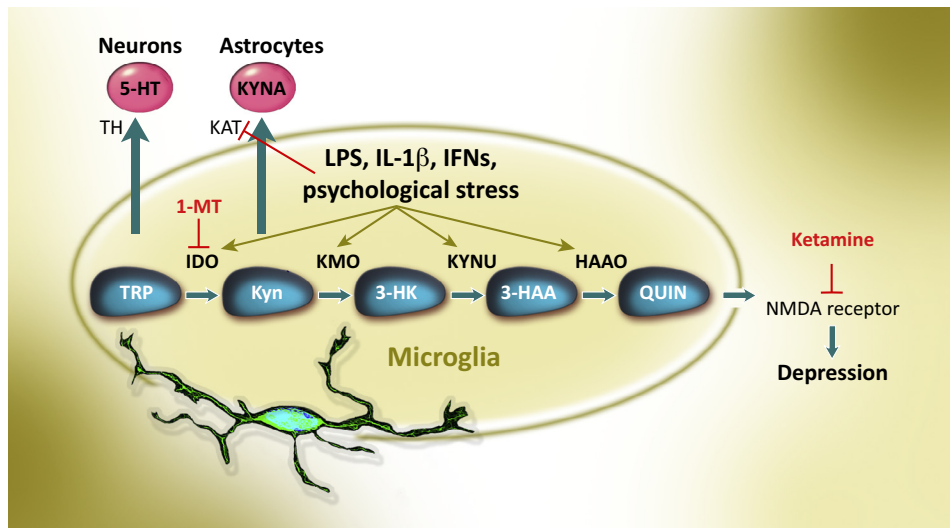
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Figure 2. Involvement of Microglial Indoleamine 2,3 Dioxygenase (IDO) and the Kynurenine Pathway in Major Depression. Activation of the enzyme IDO diverts the metabolism of the essential amino acid tryptophan (TRP) in the brain from the pathway culminating in the neurotransmitter serotonin (5-HT – the main pathway in neurons) to an alternative metabolic pathway termed the kynurenine (Kyn) pathway (KP). IDO is primarily expressed by microglia, but also by astrocytes and possibly also by neurons. Subsequent biochemical steps in the KP are entirely cell specific. Astrocytes produce kynurenic acid (KYNA) by the enzyme kynurenine aminotransferase (KAT). In microglia the enzymes kynurenine monooxygenase (KMO), kynureninase (KYNU), and 3-hydroxyanthranilic acid oxygenase (HAAO) produce the metabolites 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), and quinolinic acid (QUIN), respectively. Importantly, the end products of the KP in microglia and astrocytes induce opposite neuroactive effects: QUIN serves as an agonist of the glutamatergic NMDA receptor, whereas KYNA serves as an antagonist of this receptor (and therefore is considered to be neuroprotective). Inflammatory challenges, including the cytokines interleukin (IL)-1β and interferon (IFN)-γ, as well as psychological stress, facilitate the microglial KP while inhibiting KAT (thus reducing KYNA production). The elevated QUIN levels intensely stimulate NMDA receptor signaling, leading to depression. Blockade of the KP activation and the neurobehavioral consequences of this activation can be achieved by the IDO inhibitor 1-methyl-D,L- tryptophan (1MT) as well as by NMDA receptor antagonists such as ketamine.

cytokine-mediated induction of the KP, and blockade of this induction by 1MT abrogated the stress-induced behavioral symptoms [127]; (iii) in parallel with its effects on depressive-like symptoms, the microglial blocker minocycline blocked the LPS-induced IDO induction [19]; (iv) mice with a microglia-specific mutation that induces microglial hyper-reactivity exhibited exacerbated LPS-induced depression-like symptoms, which were found to depend on exaggerated IDO activation [23]; (v) LPS-induced depression-like symptoms could be blocked by inhibition of QUIN-mediated NMDA receptor signaling using the NMDA antagonist ketamine [125] which exerts potent and fast-acting antidepressant effects in depressed patients [137].

The Role of Microglia Decline/Suppression in Depression

While the studies discussed above provide strong evidence for the involvement of microglial activation in depression, other studies do not lend support to the inflammatory/microglial-activation hypothesis of depression and even suggest that decreases, rather than increases, in the inflammatory status in general and in microglial activation in particular may be associated with depression. Specifically, although in many studies depression was found to be associated with significant increases in plasma levels of cytokines and other inflammatory markers, such as C-reactive protein (CRP), in other studies depressed patients were reported to have normal or even reduced levels of such inflammatory markers [12,138–141]. Similarly, in a genetic rat model of depression (Flinders sensitive line), CRP levels were found to be significantly lower than in control animals [142].

Box 2. Microglial Decline and Senescence

Many conditions that induce intense and prolonged microglial activation end up showing the opposite phenomenon, specifically microglial decline, senescence, and dysfunction. Human postmortem studies reveal that with aging an increasing proportion of microglia display an abnormal (dystrophic) morphology, consistent with cell senescence, leading to impaired functioning [181]. In Alzheimer disease (AD) microglia appear to play a causal role in the pathogenesis of the disease [179,180,182]. Similarly to normal aging, several lines of evidence indicate that AD (or specific phases of this disease) is associated with microglial dysfunction, rather than activation, and with the assumption of a dystrophic/senescent microglial morphology. These microglial changes interfere with the normal physiological functions of microglia and reduce their beneficial neuroprotective effects such as phagocytosis of Aβ and the production of neurotrophic factors [180–182].

Microglial decline has been also found following exposure to certain regimens of chronic stress in rodents [43,49]. For example, using the CUS model of depression in mice we recently found that following an initial period of repeated stress-induced microglial proliferation and activation, some microglia in the hippocampal dentate gyrus, but not other brain areas, underwent apoptosis, leading to a reduction in microglial number and assumption of a dystrophic morphology (characterized by smaller soma size and shorter and thinner processes) [43]. The CUS-induced microglial decline probably resulted from the initial stress-induced, IL-1-mediated microglial activation, because blockade of this initial microglial response by minocycline or transgenic IL-1 receptor antagonist overexpression rescued the subsequent microglial apoptosis and decline, and prevented the development of CUS-induced depressive-like behavior and suppressed neurogenesis [43]. Consistent with these findings, chronic administration of glucocorticoids (GC) (mimicking the GC levels in stress-induced depression-like conditions) reduced the number of proliferating microglia in various regions of the hippocampus [156]. A decrease in another important microglial marker – the purinergic P2X7 receptor – was also found following chronic restraint stress [57]. This receptor constitutes an important mechanism for microglial status regulation and for the processing and release of mature IL-1β by microglia. Interestingly, specific single-nucleotide polymorphisms within the P2X7 receptor gene were found to be associated with clinical depression [183].

As noted above, postmortem and PET studies comparing microglial numbers and activation in depressed versus control subjects reported mixed or negative results. Evidence for suppressed microglial status in some depressed patients was provided by demonstrating reductions in glial cells (but not in neurons) in the subgenual anterior cingulate [143–145], as well as lower (albeit not significant statistically) microglial activation status (detected by PET imaging with the TSPO ligand [^{11}C]PBR28) in many brain areas in depressed patients versus controls [37].

Microglial decline and senescence, in humans and in experimental animals, have been found in several conditions including aging, Alzheimer's disease, and chronic stress (Box 2). Importantly, these conditions have been associated with high prevalence of major depression [42,43,146,147].

Inflammatory Effects of Antidepressants and Electroconvulsive Therapy (ECT)

Although under some circumstances antidepressant drugs, particularly SSRIs, were shown to exhibit anti-inflammatory effects, these results are highly heterogeneous, and in many studies antidepressants induced an increase, rather than decrease, in TNFα and IL-6 levels [148]. Consistently, administration of the SSRI drug citalopram in mice induced significant increases in the expression of the proinflammatory cytokines IL-1β, IL-6, TNFα, and IFN-γ in the frontal cortex [149]. The latter findings are consistent with the demonstration that under particular *in vitro* conditions many SSRIs and the MAO inhibitor phenelzine potentiate LPS-induced cytokine production [78,150].

Treatment with ECT, which constitutes one of the most effective treatment strategies for depression [151], provides another notable example of the microglia-activating effects of antidepressive procedures. ECT was found to induce a rapid and transient elevation of proinflammatory cytokines in the plasma of depressed patients [152,153], together with increases in absolute numbers of granulocytes, monocytes and natural killer (NK) cells. Similarly, studies in rodents demonstrated that electroconvulsive shock (electroconvulsive stimulus, ECS – the experimental term for ECT in animals) induces a marked increase in the proliferation, metabolic,

and phagocytic activity of macrophages [154,155]. Importantly, repeated ECS administration in rodents induced marked and long-term increases in microglial proliferation and activation in several brain areas, including the hippocampus, PFC, amygdala, and hypothalamus [156–159]. Furthermore, ECS treatment counteracted the suppressive effect of chronic corticosterone administration on microglial proliferation [156]. A different type of brain stimulation (repeated transcranial direct current stimulation) was also found to increase the number and activation status of cortical microglia [160].

Finally, the antidepressive effects of deep brain stimulation (DBS) in the subgenual cingulated gyrus of depressed patients may at least partly depend on microglial activation. This is evidenced by results showing that the early antidepressant effect induced by this procedure can occur even without any current delivery (i.e., only due to the DBS electrodes insertion, which certainly induces microglial activation). Furthermore, this antidepressive effect could be blocked by treatment with NSAIDs [161].

Anti-inflammatory Drugs Are Not Always Antidepressant and May Even Be Depressogenic

As noted above, studies on the antidepressive effects of NSAIDs yielded mixed findings. In fact, several case reports and clinical studies demonstrated that treatment with NSAIDs for pain due to rheumatoid arthritis, osteoarthritis, or other musculoskeletal syndromes could elicit a moderate to severe major depressive episode in otherwise psychiatrically healthy individuals [162–164]. The depressive symptoms remitted when the drugs were stopped, and returned upon re-use. Furthermore, administration of NSAIDs in some depressed patients was found to exacerbate the depressive symptoms, which remitted when the drug was stopped [165], and to decrease the antidepressive effectiveness of SSRIs (i.e., induce treatment resistance) [149]. Consistently, treatment of experimental animals with SSRIs stimulated proinflammatory cytokine production, and this effect (along with the behavioral antidepressive effects of SSRIs) was blocked by administration of NSAIDs [149].

The findings that COX-1 inhibitors can produce depression (as opposed to the antidepressant effects of COX-2 inhibitors) is important, considering that COX-1 is predominantly active in microglia, whereas COX-2 is mainly active in neurons and astrocytes [166]. Thus, it may be suggested that in some inflammatory conditions reductions in prostaglandins by COX-2 inhibition can be antidepressive, but in other conditions the specific inhibition of microglial COX-1 contributes to the decline in the inflammatory status of these cells, and results in increased depression and non-responsiveness to antidepressant drugs.

The ability of anti-inflammatory drugs to either counteract or exacerbate depression was demonstrated not only in studies with NSAIDs but also by a recent study using the TNFα inhibitor infliximab. Specifically, treatment with this drug for 12 weeks produced antidepressive effects in depressed patients with high (above 5 mg/L) baseline levels of the inflammatory biomarker CRP, but exacerbated depression severity in patients with low (below 5 mg/L) baseline levels of these marker [167].

Antidepressive Properties of Microglia-Stimulating Drugs

Evidence for the possible antidepressive effect of immune stimulation in humans has been provided by only one study [168]. This study demonstrated that a single administration of endotoxin to severely depressed patients, which induced a short-term elevation in IL-1, IL-6, and TNFα levels, significantly but transiently improved their depressed state for 24 h. Importantly, a high correlation was found between the endotoxin-induced increases in cytokine levels and the mood improvement [168]. Similarly, in experimental animals, administration of TNFα or IFN-γ decreased the immobility time in the tail suspension test (i.e., reduced 'despair-like' behavior),

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Box 3. Microglia, Neuroplasticity, and Depression

Microglia play an important role in neuroplasticity processes, such as alterations in synapse structure and functioning, neurogenesis, and neurotrophins action. The key involvement of impairments in these processes in the pathogenesis of depression [112,113,184] suggests that a decline in microglial functioning may induce depression via its detrimental effects on these processes. Specifically, appropriate microglial functioning is essential for neurogenesis under normal physiological conditions, evidenced by findings that (i) microglia are crucial for the rapid clearance of apoptotic newborn neurons through phagocytosis [185], and inhibition of this clearance is detrimental for neurogenesis [186]; (ii) under particular conditions microglia secrete pro-neurogenic cytokines, which induce the proliferation, differentiation, maintenance, and migration of newborn neurons [187–190]; (iii) microglia activated by LPS induce neuronal proliferation via the production of protease serine 2 (PRSS2) [191]; (iv) the basal level of microglial proliferation in the neurogenic region of the subventricular zone (SVZ) is much higher than in surrounding forebrain areas [192]; (v) environmental enrichment, which confers resilience to stress and exerts antidepressive effects, not only increases neurogenesis but also induces proliferation and mild activation of microglia [193,194]; (vi) treatment with LPS, M-CSF or GM-CSF, which induced a rapid and significant microglial proliferative response, produced concomitant behavioral antidepressive effects and facilitated neurogenesis in depressed-like mice [43].

Microglial BDNF is an important mediator of microglia-to-neuron communication [195], particularly via local interactions between microglial processes and TRKB (neurotrophic tyrosine kinase receptor type 2) receptors on synaptic elements [177]. This communication contributes to normal synaptic and behavioral plasticity, as evidenced by impairments in glutamatergic synaptic components, memory functioning, and learning-induced spine formation in mice with specific deletion of BDNF in microglia [177]. Microglial BDNF may also be involved in the neurobehavioral plasticity and neurogenesis facilitated by environmental enrichment and exercise [193,194], and therefore may underlie the resiliency to depression observed under these conditions.

In conclusion, the disruptions in neuroplasticity and neurogenesis that contribute to some depressive conditions may be downstream to the decline in microglia, which are necessary for the normal functioning of these processes. The fact that microglial stimulators, such as LPS, promote microglial BDNF production (even in situations in which total brain BDNF is reduced) [196–199] may underlie our recent finding that microglial stimulators (e.g., LPS, M-CSF) produce antidepressive effects in mice with CUS-induced microglial decline [43].

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and this effect depended on the cytokine-induced elevation in p11, which is considered an important mechanism of action for antidepressant medications [149]. Recent work in our laboratory, using an animal model of CUS-induced depression in association with microglial decline and dystrophy, demonstrated that treatment of 'depressed-like' mice (i.e., following 5 weeks of CUS exposure) with compounds that stimulated microglial proliferation and activation, including endotoxin (LPS), macrophage colony stimulating factor (M-CSF), or granulocyte-macrophage colony stimulating factor (GM-CSF), partially or completely reversed the depressive-like behavior and dramatically increased hippocampal neurogenesis [43], possibly by inducing brain-derived neurotrophic factor (BDNF) and other neuroplasticity- and neurogenesis-facilitating molecules (Box 3). Interestingly, treatment with imipramine or minocycline (which could reverse the development of depression when given throughout the CUS exposure period, probably via suppression of microglial activation during the first few days of stress exposure), had minimal antidepressive effects when given to the depressed-like mice (whose microglia were already suppressed/declined) [43].

Concluding Remarks Determining the Appropriate Microglia-Related Personalized Medical Approach for the Individual Depressed Patient

Based on the data presented in this review, we postulate that at least some forms of depression can be considered as microgliopathies in which either microglial activation or microglial decline and suppression constitute the direct etiology of the depressive syndrome (Figure 3). Accordingly, deviations from microglial homeostasis should be regarded as important therapeutic targets for major depression. This implies that depression cannot be treated uniformly, but should instead be treated by a personalized medical approach based on the microglial status of the individual depressed patient. The data reviewed above leave many outstanding questions regarding the significance, mechanisms, diagnosis, and translation of the notion that depression is a microglial disease (see Outstanding Questions). At present, the only methodology to monitor microglial status in patients involves PET assessment of various TSPO ligands binding. This
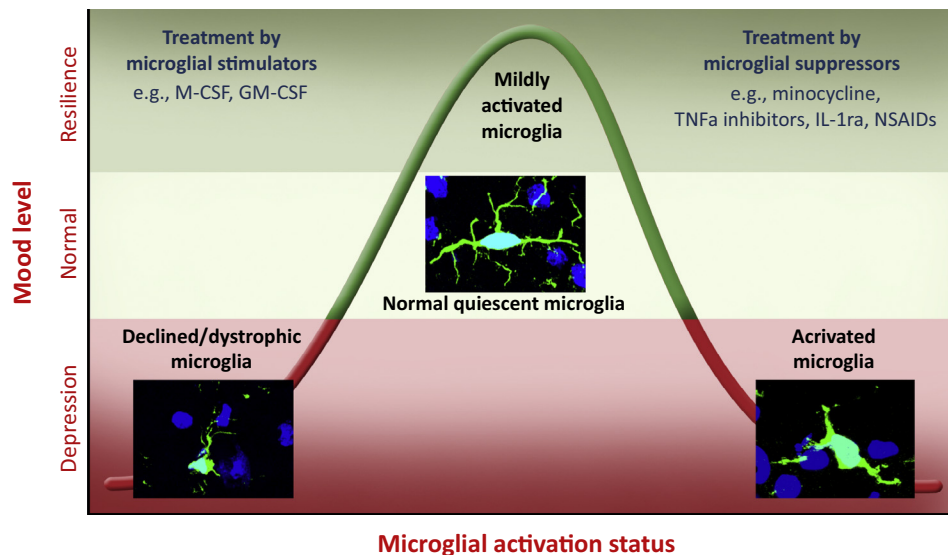
Figure 3. Deviations From Microglial Homeostasis Induce Depression: Therapeutic Implications. Normal physiological functioning of microglia is essential for normal mood levels. Accordingly, extreme deviations from the normal microglial activation status may be the cause of some forms of depression. Such deviations include microglial activation associated with peripheral and central infections, autoimmune and neurodegenerative diseases, trauma, stroke, and acute psychological stress (Figure 1). Microglial decline, senescence, dystrophy, and suppression, which sometimes occur following long periods of microglial activation, for example due to aging, Alzheimer's disease, or some chronic stress regimens, also represent a deviation from microglial homeostasis. The alterations from the normal quiescent microglial morphology, represented by the ramified microglia in the center of the figure [green, genetic labeling of microglia with GFP, blue, DAPI (diamidinophenylindole) nuclear staining] are exemplified by the activated microglia from the brain of an acutely stressed mouse and the dystrophic microglia from the brain of a mouse exposed to chronic unpredictable stress (CUS; right and left sides of the figure, respectively). In contrast with the consequences of extreme microglial states, mild microglial proliferation and activation, which can be induced by environmental enrichment or physical activity [193,194], is associated with resilience to depression [200]. According to this model, depression should be treated by a personalized medical approach based on the basal (pretreatment) microglial status (declined vs fully activated) of the individual depressed patient, using microglia-stimulating or -suppressing drugs, respectively.

methodology is not adequate for routine use and future studies should focus on diagnostic procedures that will allow identification of microglial status. In view of the substantial correlation between peripheral and central inflammatory states [169], the levels of peripheral inflammatory markers can serve as surrogate markers for microglial status. Therefore, it may be suggested that patients with high levels of inflammatory markers (e.g., CRP, TNFα, IL-1, and IL-6) should be treated with microglia-suppressive drugs, such as minocycline, TNFα inhibitors (e.g., infliximab), IL-1 inhibitors (e.g., IL-1ra) or COX-2 inhibitors (e.g., celecoxib). On the other hand, patients with low levels of these inflammatory markers should be treated with microglia stimulating drugs, such as M-CSF or GM-CSF.

Clinical experimental evidence for this personalized medical approach is still limited, but was recently provided by the findings of a study revealing that depressed patients with high basal levels of CRP and TNFα benefited from treatment with the TNFα inhibitor infliximab, whereas in patients with low levels of these inflammatory markers the depression was exacerbated following infliximab treatment [167]. In principal, it is likely that specific types of depression may be more frequently associated with higher or lower microglial activation status. For example, patients with depression due to a general medical condition were found to have high levels of inflammatory markers and microglial status, whereas patients with melancholic depression exhibited lower levels of inflammatory cells and markers than patients with non-melancholic depression [170,171]. Future research should further establish the relationship between clinical

Outstanding Questions

Are there specific mood disorder subtypes in which disturbed microglial homeostasis plays a pivotal role? For example, does microglial activation underlie 'depression due to a general medical condition' whereas microglial decline underlies melancholic or chronic stress-induced depression?

What are the major triggers of the microglial alterations that induce depression? For example, what is the contribution of stress-induced changes in the microbiome, infiltration of peripheral immune cells into the brain, neuronal activation, central cytokines, chemokines, hormones, and neurotransmitters to the depression-inducing microglial alterations?

What are the mechanisms that link the changes in microglial status to the neuronal substrate of depression? For example, are changes in microglial status causally related to impairments in neuroplasticity, neurogenesis, neurotrophins production, monoaminergic transmission, or glucocorticoid signaling, which in turn are the cause of the depressive symptoms?

What is the contribution of microglia-related transcriptome changes to the vulnerability or resilience to depression? Specifically, are the incidence, severity, and treatment responsiveness influenced by alternations in microglial-related gene expression?

Does restoration of microglial homeostasis constitute an important mechanism of action of conventional antidepressive procedures (such as SSRIs and ECT)?

How should microglial status be diagnosed in depressed patients? This diagnosis (e.g., by sensitive PET imaging technologies or novel peripheral markers) is crucial for tailoring the appropriate personalized antidepressant treatment (i.e., via suppression or stimulation of microglia). Can similar diagnostic tools be used repeatedly and efficiently for monitoring the microglial changes induced by such treatments?

depressive subtypes and the corresponding microglial/inflammatory status, aiding in the implementation of the microglia-modulating personalized antidepressive approach.

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