

Inflammation and Treatment Resistance in Major Depression: The Perfect Storm:

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Major depression is a disease that affects approximately 20 million adults in the US and has a devastating impact on personal and public health.¹ Although successful treatment substantially reduces functional impairment and economic burden, up to one-third of depressed patients are resistant to treatment with conventional antidepressants (eg, serotonin and/or norepinephrine reuptake inhibitors), even in the context of standardized attempts such as switching medications and/or augmenting with thyroid hormone, mood stabilizers, and atypical antipsychotics.² Thus, roughly 7 million adults in the US are considered to have treatment-resistant depression (TRD), which emphasizes the need to develop new conceptual frameworks and new therapeutic targets to improve treatment outcome.

One factor that has received increasing attention regarding TRD is inflammation. A significant percentage of patients with TRD exhibit increased markers of inflammation, and clinical factors that are linked with treatment nonresponse are associated with inflammation. Inflammatory cytokines, which are critical mediators of the inflammatory response, have been found to sabotage and circumvent many of the mechanisms of action of conventional antidepressants. These findings provide powerful evidence that inhibition of inflammation or its downstream effects on mood may open up a host of new approaches to treatment for depression, especially for patients with TRD. Invaluable to survival in the short term, chronic inflammation can lead to significant damage to multiple organ systems in the body—including the brain. Recognizing chronic inflammation as a common mechanism of disease, including cardiovascular disease, diabetes, and cancer, is one of the major insights of the past decade.³ Nevertheless, psychiatry began recognizing the role of inflammation in TRD only recently—as both the problem and a solution.

The correlation between TRD and inflammation

A number of clinical factors have been associated with TRD, including obesity, childhood maltreatment, anxiety disorders, personality disorders/neuroticism, bipolar disorder, and medical comorbidities (**Table 1**). Data show a dose-response relationship between BMI and TRD—the higher the BMI, the lower the response rate.⁴ Early life stress is also associated with poor treatment outcome. Childhood maltreatment has been associated with a significantly decreased likelihood of response or remission during antidepressant treatment.⁵ Likewise, anxiety disorders, including PTSD, obsessive-compulsive disorder, generalized anxiety disorder, and panic disorder, were found to be negative predictors of response in step 1 and especially in step 2 of the STAR*D.⁶

Table 1 – Clinical predictors of treatment resistance related to inflammation	
Predictor of antidepressant nonresponse	Relationship to inflammation
Obesity	Dose-response relationship between BMI and inflammatory markers
Early life stress	Increased inflammation and inflammatory response to stress in exposed individuals
Medical illness	Increased inflammatory markers in diabetes, cardiovascular disease, and cancer
Personality disorders/anxiety	Increased inflammatory markers in patients with anxiety disorders, borderline personality disorder, and neuroticism

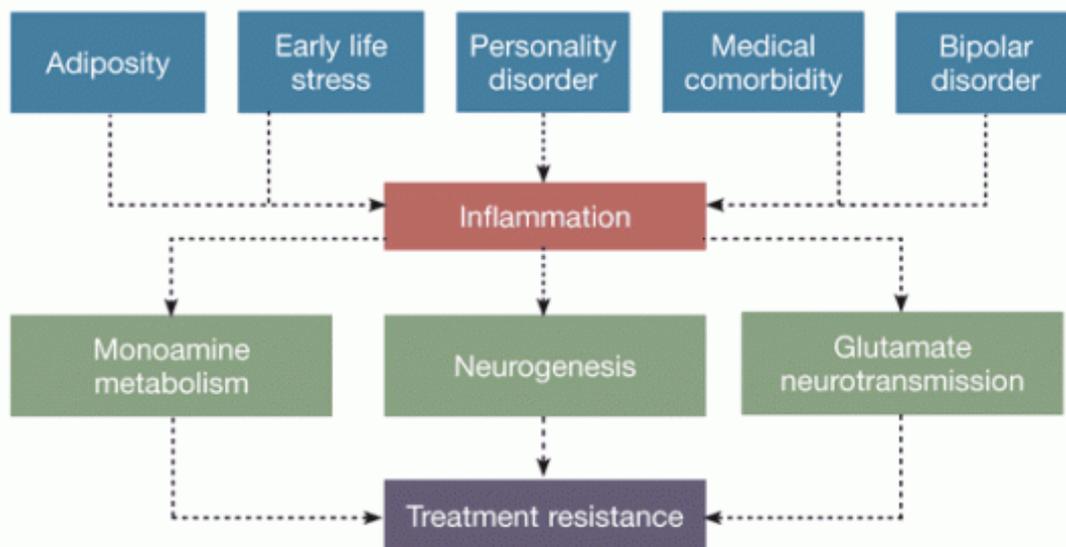
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Comorbid personality disorders and high levels of neuroticism have also been shown to predict TRD.⁷ In addition, a significant percentage of patients with TRD have hidden bipolar disorder, for which antidepressants are often less effective and poorly tolerated.⁸ A dose-response relationship appears to exist between severity or degree of medical comorbidity and treatment resistance. For each organ system affected by illness, there is an approximately 20% decrease in the likelihood of antidepressant treatment response.⁹

Not only is there a dose-response relationship between BMI and a number of inflammatory markers, but also there is an array of inflammatory mediators that are released by fat cells, including the inflammatory cytokines tumor necrosis factor (TNF)- α , and interleukin (IL)-6 as well as the chemokine monocyte chemoattractant protein-1, which is a potent attractant for macrophages that accumulate in fatty tissue and sustain inflammatory responses.¹⁰ Childhood maltreatment has also been associated with increased markers of inflammation in depression, under resting conditions, and following stress. Depressed patients with a history of childhood maltreatment were found to exhibit increased plasma levels of the acute phase protein C-reactive protein (CRP), which is released by the liver during an inflammatory response.¹¹ After exposure to a laboratory psychosocial stressor, persons with a history of childhood maltreatment showed increased plasma IL-6 levels and increased DNA binding of nuclear factor- κ B (NF- κ B) in peripheral blood mononuclear cells compared with controls.¹² NF- κ B is a lymphin signaling molecule in the inflammatory cascade.

An increase of inflammatory markers has also been seen in patients with anxiety and personality disorders. Bipolar disorder has been associated with increased blood inflammatory markers as well as increased inflammatory cytokines, NF- κ B, and markers of microglial activation in postmortem brain tissue.¹³ Patients with medical illnesses are well known to exhibit increased inflammation secondary to infection and the tissue damage and destruction that can activate the inflammatory response. The data indicate that treatment resistance may be in part a function of activation of inflammatory pathways. The clinical factors that may alert the clinician to which patients are most likely to exhibit increased inflammatory biomarkers and risk for treatment resistance include obesity, childhood maltreatment, bipolar disorder, and comorbid medical illness (**Figure 1**).

Figure 1. Routes to treatment resistance



Multiple lifestyle, environmental, psychiatric, and medical factors contribute to and are a function of an inflammatory milieu associated with increased inflammatory cytokines, which can reduce the availability of monoamines, inhibit neurogenesis, and increase glutamate. Conventional antidepressants act on monoamine pathways to increase monoamine availability and require neurogenesis for efficacy. Moreover, glutamate is not a primary target of conventional antidepressant therapy. Cytokine effects on these biological processes thus conspire to sabotage and circumvent the mechanism of action of conventional antidepressants, leading to treatment resistance.

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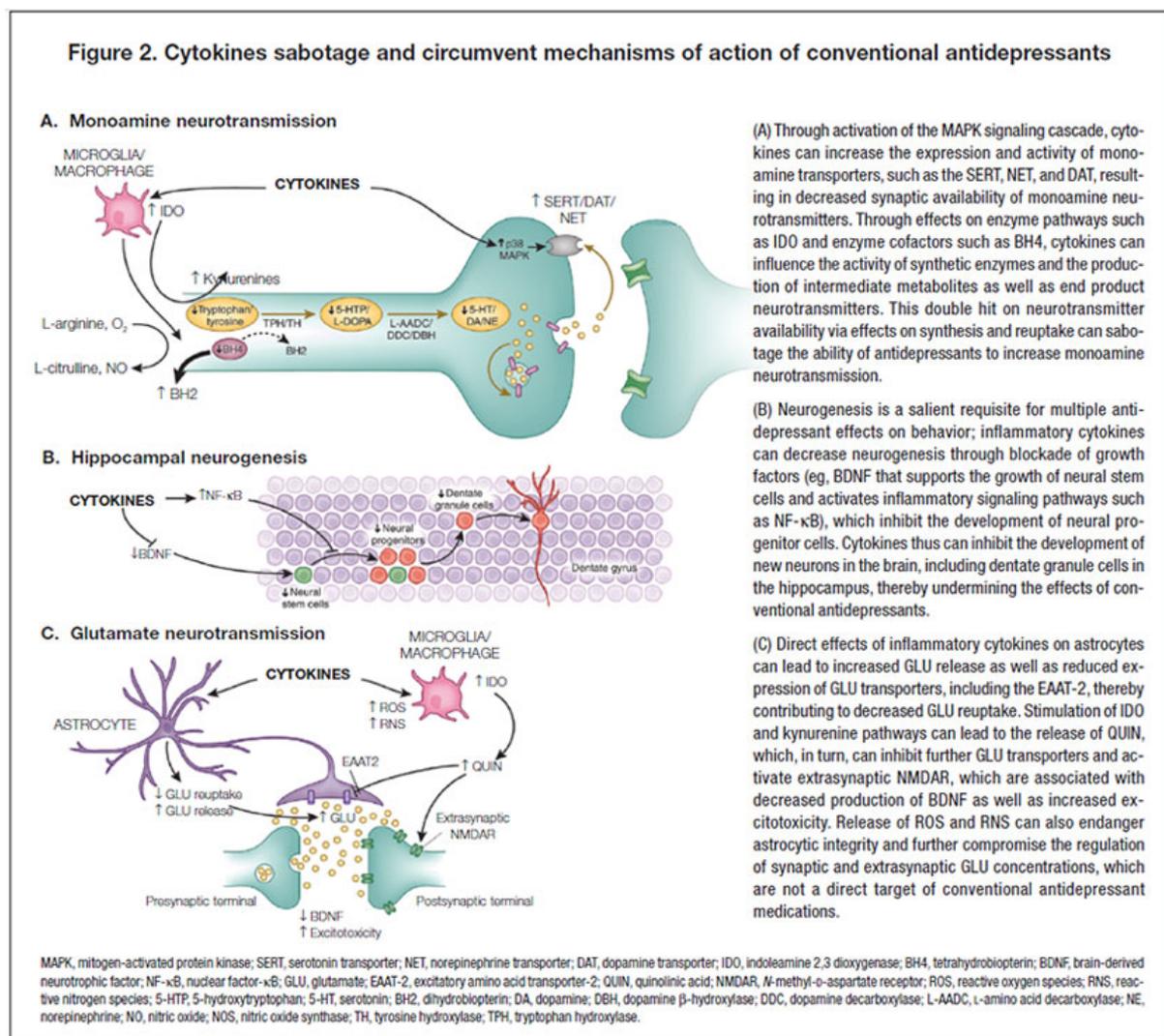
Inflammation and TRD

Compared with controls, certain patients with MDD exhibit increases in biomarkers of inflammation, including increases in inflammatory cytokines in peripheral blood and brain (cerebrospinal fluid) as well as increases in peripheral blood acute phase proteins, chemokines, and adhesion molecules.¹² Meta-analyses have identified increases in peripheral blood TNF- α , IL-6, and CRP concentrations as being some of the most reliable inflammatory biomarkers in depression.¹²

Several studies have also reported that increased inflammatory markers may have a direct relationship with TRD. Not only are patients with TRD more likely to exhibit increased levels of inflammatory markers, but also increased levels of inflammatory markers before treatment have also been found to be associated with a lower likelihood of response.^{12,14-16} In addition, data have shown a reduction of cytokine concentrations after successful antidepressant therapy. Moreover, polymorphisms in several cytokine genes, including IL-1 and TNF- α , have been associated with TRD.¹²

Neurobiological Mechanisms of Cytokines that may lead to TRD

Given the negative association between treatment response and inflammation, there has been considerable interest in the neurobiological pathways by which cytokines influence behavior and how these pathways influence the mechanisms of action of antidepressant medications (**Figure 2**).



Impact on neurotransmitter metabolism

One of the primary mechanisms by which conventional antidepressants exert their effects is through blockade of the reuptake pumps for monoamine neurotransmitters, including serotonin,

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norepinephrine, and dopamine. Blockade of reuptake is believed to increase synaptic availability of monoamine neurotransmitters, which contributes to antidepressant response. Cytokines not only influence the expression and function of monoamine reuptake pumps but also impact the fundamental availability of neurotransmitters through effects on monoamine synthesis (**Figure 2, A**).

Cytokines and monoamine reuptake.

Through activation of p38 mitogen-activated protein kinase (MAPK) in animals, both TNF- α and IL-1 have been found to increase the expression and function of the serotonin transporter, which leads to increased serotonin reuptake in vitro and in vivo.¹⁷ Similar results have been found with the norepinephrine transporter. In addition, activation of MAPK pathways has been shown to increase the surface expression and function of the dopamine transporter as reflected by increased intracellular trafficking and transport capacity.¹² Thus, by acting through their signaling pathways, cytokines can increase the expression and function of the very transporters that conventional antidepressants inhibit, thereby sabotaging their effectiveness.

Cytokines and monoamine synthesis.

Through activation of the enzyme indoleamine 2,3 dioxygenase (IDO), a number of inflammatory cytokines can increase the conversion of tryptophan, the primary amino acid precursor of serotonin, to kynurenine (KYN), which may reduce the availability of tryptophan for serotonin synthesis. IDO activation has been detected in patients with infectious diseases or cancer who have been given the inflammatory cytokine interferon (IFN)- α . In these patients, decreased tryptophan and increased KYN have been associated with IFN-induced depression.¹² Depending on the dose, IFN- α causes depression in up to 50% of patients. Increased plasma KYN concentrations have also been found in medically healthy depressed individuals.¹⁸ Pharmacological blockade of IDO or genetic targeting of IDO function has been shown to reverse depressive-like behavior in rodents following immune challenges with lipopolysaccharide or BCG vaccine.¹⁹

Another pathway by which cytokines can influence neurotransmitter synthesis is through induction of oxidative stress that can lead to depletion of tetrahydrobiopterin (BH4). BH4 is an enzyme cofactor required for the conversion of phenylalanine to tyrosine by phenylalanine hydroxylase, and tyrosine to dopamine (and ultimately norepinephrine) by tyrosine hydroxylase.²⁰ In addition, BH4 is required for the conversion of tryptophan to serotonin by tryptophan hydroxylase. BH4 is highly sensitive to oxidative stress and can be irreversibly converted to an inactive metabolite in the context of high concentrations of reactive nitrogen or oxygen species. When used as an enzyme cofactor, BH4 is broken down into dihydrobiopterin (BH2). Folate metabolism plays an important role in the regeneration of BH4 from BH2, and therefore compounds such as L-methylfolate, folinic acid, and S-adenosyl methionine may have antidepressant effect in part through enhancement of BH4.²⁰ These data suggest that through activation of inflammation, cytokines can alter BH4 availability and thereby reduce the efficiency of the enzymatic machinery necessary for monoamine synthesis. Thus, drugs that support BH4 regeneration may have antidepressant activity, especially in patients with increased inflammation.

Impact on Neurogenesis

Neurogenesis is a requirement for at least some antidepressant effects.²¹ Data indicate that cytokines can inhibit neurogenesis; thereby, cytokines provide a second major pathway that can sabotage antidepressant efficacy (**Figure 2, B**).

Administration of inflammatory cytokines and cytokine inducers can reduce the proliferation of new neurons, especially as measured in the hippocampus. Research on laboratory animals exposed to chronic stress has also demonstrated that stress-induced increases in inflammatory cytokines in the brain are associated with decreased neurogenesis and depressive-like behavior. Inhibition of inflammatory cytokines during stress has been shown to reverse these effects. Animals treated with the IL-1 receptor antagonist or the use of IL-1 receptor knock out mice has shown that the effects of chronic stress on neurogenesis as well as behavior are reversed when IL-1 is blocked or absent.²² The inhibitory effects of chronic stress on growth factors such as brain-derived neurotrophic factor (BDNF) that support neurogenesis are also reversed by cytokine antagonism.¹² In vitro and in vivo studies have suggested that cytokine effects on neurogenesis are mediated in part by activation of NF- κ B, which directly inhibits the proliferation of neural stem-like cells in the adult hippocampus.²²

Impact on Glutamate

Given the importance of glutamate in neural plasticity and excitatory neurotransmission, there has been increasing recognition of the role of glutamate in affective disorders, especially TRD.²³ The dramatic therapeutic responses of patients with TRD to the glutamate N-methyl-d-aspartate (NMDA) receptor antagonist ketamine underline the therapeutic promise of glutamate antagonists in major depression. Although conventional antidepressants were found to have some effects on glutamate receptors and inhibit stress-induced glutamate release in laboratory animals, it remains unclear to what degree these are primary or secondary to the effects of these drugs on monoamine neurotransmission.²³

Inflammatory cytokines can decrease glutamate reuptake and glutamate transporter expression in glial elements, including primarily astrocytes but also microglia (**Figure 2, C**).²⁴ One mechanism that is believed to mediate these effects is the induction of reactive nitrogen and oxygen species that have been shown to affect glutamate reuptake in astrocytes.²⁴ Inflammatory cytokine induction of nitric oxide has been shown to stimulate the release of glutamate from astrocytes, an effect that is reversed by inhibition of inducible nitric oxide synthase.²⁵ Release of glutamate by astrocytes that have access to extrasynaptic NMDA receptors may have especially detrimental consequences, given that activation of extrasynaptic versus synaptic NMDA receptors has been shown to decrease BDNF expression and increase cell death.²⁶

Inflammatory cytokine induction of the enzyme IDO may also contribute to glutamatergic excitotoxicity. IDO leads to the conversion of tryptophan to KYN, which, in turn, can access the brain and be converted to quinolinic acid (QUIN) in microglia and macrophages that infiltrate into the brain during inflammatory processes. Relative to glutamate neurotransmission, QUIN can directly bind to NMDA receptors and therefore contribute to excitotoxic activity.²⁷ QUIN also has been shown to inhibit glutamate reuptake and stimulate glutamate release by astrocytes.²⁷ In addition, QUIN is a potent inducer of oxidative stress. Of relevance to depression, increased QUIN concentrations in the cerebrospinal fluid have been correlated with depression and inflammatory markers in patients treated with IFN- α .²⁸ Increased microglial QUIN immunoreactivity also has been found in the subgenual and midcingulate regions of the anterior cingulate cortex (ACC) in postmortem brain samples from patients with depression.²⁹

Impact on the neurocircuitry of mood and anxiety

Another pathway by which cytokines may influence the brain, leading to treatment resistance, is through effects on specific neural circuits that have been associated with treatment response. Administration of cytokines or cytokine inducers has been shown to interact with the dorsal ACC (dACC) and subgenual ACC (sACC), both of which have been associated either directly or indirectly with treatment resistance.^{12,30,31} For example, administration of IFN- α to patients with hepatitis C and exposure of healthy persons to typhoid vaccination have been shown by functional MRI to increase activation of the dACC.³² The dACC is a key brain region in conflict monitoring and error detection as well as emotional arousal. It has been described as a “neural alarm system,” given its ability to detect and respond to a variety of stimuli, including emotional stimuli such as social rejection.³³ Increased activation of the dACC has been observed in a variety of disorders and personality styles that have been associated with TRD, including high trait anxiety, obsessive-compulsive disorder, and neuroticism.^{12,32,33}

Exposure of healthy persons to typhoid vaccination has been shown to activate the sACC in association with a deterioration in mood.³⁰ The sACC has been implicated as a key brain region in emotion regulation and processing, and reductions in sACC activity have been associated with treatment response to both conventional antidepressants and cognitive-behavioral therapy.³¹ Overactivation of the sACC is found in patients with treatment resistance, and targeting the sACC using deep brain stimulation has shown promise as a novel therapy for TRD.³¹ Thus, cytokines appear to interact and activate two distinct ACC neurocircuits that are related to treatment response.

Translational implications: Therapeutic targets

Numerous targets can be considered for the development of novel therapeutic strategies for patients with TRD who have high inflammation. Probably the most obvious targets are the inflammatory cytokines themselves. Findings suggest that currently available cytokine antagonists, in particular TNF antagonists used for autoimmune and inflammatory disorders, may be effective in relieving a variety of depressive symptoms, including anxiety, anhedonia, psychomotor retardation, fatigue, and alterations in sleep architecture, in both medically ill and medically healthy patient populations.^{12,16,20}

Cyclooxygenase (COX) inhibitors have also been shown to improve and/or accelerate treatment response as add-on therapy in unipolar and bipolar depression.¹² However, the high dropout rate seen in one of the few placebo-controlled trials of a COX-2 inhibitor in unipolar depression lends caution to the interpretation of the findings.¹³ Minocycline, a second-generation tetracycline that has been shown to block microglial activation and CNS inflammatory responses in laboratory animal models of cytokine-induced depression, has also shown some antidepressant efficacy as adjunctive therapy for psychotic depression.³⁷ Although they hold great promise, pharmacological agents that block p38 MAPK or IDO and the downstream enzymes that regulate the generation of molecules in the KYN pathway (eg, QUIN) have yet to be tested in depressed patients.²⁰

One limitation to current drug development efforts is the lack of neuroimaging agents to establish “target engagement” in the brain. Being able to determine whether a compound reduces inflammatory responses in the brain would greatly facilitate interpretation of negative as well as positive treatment responses. Several ligands used in positron emission tomography can bind the translocator protein (formally known as the peripheral benzodiazepine receptor [PBR]), a molecule that exhibits increased expression in activated microglia. Nevertheless, current compounds under development (including PBR28), while potentially useful in diseases with significant neuroinflammation (eg, multiple sclerosis, Alzheimer disease, Parkinson disease, AIDS dementia), have not been adequately tested in depressed patients, where more nuanced inflammatory changes in the brain might be more difficult to detect.³⁸

Translational implications: Optimal candidates for immune-targeted therapy

In the context of an inflammatory response, cytokines may have detrimental effects on multiple CNS functions; however, under physiologic conditions, these same cytokines play an indispensable role in the maintenance of neuronal integrity. Cytokines produced by multiple cell types within the brain—both glia and neurons—are involved in numerous processes essential to neural plasticity, including neurogenesis, synaptic strengthening and/or scaling, and long-term potentiation (one of the major cellular mechanisms underlying learning and memory).³⁴ Antidepressant action also may in part be dependent on CNS activation of inflammatory cytokines.³⁵ Thus, a monolithic approach to inhibition of inflammatory responses is not an ideal strategy for addressing the contribution of the immune system and inflammation to TRD.

Identification of specific subsets of patients with increased inflammation is a necessary component of any successful treatment approach. Fortunately, there are peripheral blood biomarkers of inflammation that may prove particularly useful in identifying patients with increased inflammation and ultimately selecting patients for immune-targeted therapies.

CRP has been shown to be reproducibly elevated in patients with depression and can be reliably measured in clinics and hospitals throughout the United States. Guidelines have been set forth by the American Heart Association and the CDC regarding relative degrees of inflammation based on CRP levels: a CRP less than 1 mg/L indicates low inflammation, a CRP between 1 and 3 mg/L indicates moderate inflammation, and a CRP greater than 3 mg/L indicates high inflammation.³⁶ In a recent randomized clinical trial, patients with TRD who had a CRP level greater than 5 mg/L who received the TNF antagonist infliximab showed a greater decrease in depressive symptoms as well as a greater treatment response than those who received placebo.¹⁶ Increased blood CRP levels before therapy are also one of the best predictors of treatment response to cytokine antagonists in autoimmune and inflammatory disorders.¹⁶ These data suggest that a CRP level greater than 3 mg/L may be a good biomarker for the presence of increased inflammation and its potential contribution to TRD. Individuals with this biomarker would also be the optimal candidates for immune-based therapies.

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Table 2 – Translational targets for inflammation and treatment-resistant depression

Immune system

Cytokines (eg, TNF- α , IL-1, IL-6 antagonists; IL-4, IL-10, TGF- β agonists)
 Cytokine signaling pathways (eg, p38 MAPK, NF- κ B antagonists)
 Arachidonic acid metabolites (eg, COX-2, PGE₂ antagonists)
 Chemokines (eg, MCP-1 antagonists)
 T-cell regulation (eg, increase T_{reg}/Th17 ratio)
 Monocytes/macrophages regulation (increase M₁/M₂ ratio)

Neurotransmitter systems

IDO and KYN pathway enzymes and products (eg, antagonists of IDO, KYN, QUIN, KMO)
 BH4 (eg, folinic acid, *l*-methylfolate, SAMe, BH4)
 Glutamate (eg, NMDA receptor antagonists)

Autonomic nervous system

Parasympathetic outflow (eg, α 7 nAChR agonists, efferent vagal nerve stimulation)

Lifestyle

Adiposity (eg, diet, exercise)
 Psychological stress (psychotherapy, meditation)

TNF, tumor necrosis factor; IL, interleukin; TGF, transforming growth factor; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor- κ B; COX, cyclooxygenase; PG, prostaglandin; MCP, monocyte chemoattractant protein; T_{reg}, T regulatory cell; Th, T helper cell; IDO, indoleamine 2,3 dioxygenase; KYN, kynurenine; QUIN, quinolinic acid; KMO, kynurenine 3-monooxygenase; BH4, tetrahydrobiopterin; SAMe, S-adenosyl methionine; NMDA, N-methyl-D-aspartate; nAChR, nicotinic acetylcholine receptor.

Translational implications: Prevention strategies

Inflammation may also be relevant to depression prevention and relapse. There are multiple clinical factors associated with both inflammation and TRD that can be addressed through lifestyle changes. Treating obesity with diet and exercise in patients with increased inflammation is a primary example. In a recent clinical trial of partial treatment responders, depressed patients with increased TNF levels were more likely to respond to an add-on exercise intervention than were patients who were partially responsive to an SSRI.³⁹ Another consideration is behavioral stress management including compassion meditation training, which has been shown to reduce inflammatory responses to a laboratory psychosocial stressor.⁴⁰

Exercise and meditation have been associated with an increased parasympathetic tone, which, in turn, has been associated with decreased inflammatory tone. These effects are likely related to parasympathetic activation of T cells that produce acetylcholine that binds to the α subunit of the nicotinic acetylcholine receptor, leading to inhibition of NF- κ B.⁴¹ Finally, optimizing the management of medical illnesses associated with inflammation may also reduce depression symptoms and improve treatment response.

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Conclusion

Compelling evidence indicates that an overactive immune response and the associated release of inflammatory cytokines can sabotage and circumvent the mechanism of action of conventional antidepressants. The data also indicate that not all depressed patients exhibit increased inflammation. Therefore, the opportunity exists to identify relevant patient subgroups and thereby individualize immune-targeted therapies and ultimately help obviate the long, winding road that many depressed patients travel to achieve treatment response.

Disclosures

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