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Review

Increased IL-6 trans-signaling in depression: focus on the tryptophan catabolite pathway, melatonin and neuroprogression

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Abstract:
Depression has been conceptualized as a disorder driven by immuno-inflammatory pathways and oxidative and nitrosative stress. These factors couple to the induction of neuroregulatory tryptophan catabolites *via* the activation of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). Oxidative damage to neoepitopes increases autoimmune responses, changing the nature of the neural substrate of recurrent depression, which leads to neuroprogression and drives treatment resistance. A number of pro-inflammatory cytokines are linked to these processes. Here, we focus on the role of interleukin (IL)-6 in depression and its associated disorders; we highlight the progress made since the first paper showing increased IL-6 levels was published 20 years ago by Maes and colleagues. When coupled with increased levels of the soluble IL-6 receptor in depression, higher levels of IL-6 may indicate increased IL-6 trans-signaling, whereby IL-6 receptor signaling occurs in cells not normally expressing the IL-6 receptor. It has been suggested that IL-6 is intimately associated with two crucial aspects of depression, as well as central inflammation more broadly. First, the regulation of the local inflammatory response *via* its interactions with macrophage and glia melatonin production is coupled to local epigenetic modulation *via* methyl CpG-binding protein 2 (MeCP2). Second, the more systemic regulation of tryptophan availability occurs *via* the IL-6 induction of IDO. Coupled to its role in the regulation of autoimmune associated T-helper 17 cells and IL-17 production, IL-6 has wide and differential impacts on processes driving depression and a wider range of psychiatric and neurodegenerative conditions.

Key words:
depression, interleukin-6, indoleamine 2,3-dioxygenase, cytokines, melatonin, inflammation, oxidative stress, neuroprogression

Abbreviations: ADAM – a disintegrin and metalloproteinase, AHr – aryl hydrocarbon receptor, BBB – blood brain barrier, BDNF – brain-derived neurotrophic factor, CMI – cell-mediated immunity, CNS – central nervous system, HPA – hypothalamic-pituitary-adrenal, IDO – indoleamine 2,3-dioxygenase, IFN-γ – interferon γ, IL-1 – interleukin-1, IL-2 – interleukin-2, IL-6 – interleukin-6, IL-17 – interleukin-17, kyn – kynurenine , KYNA – kynurenic acid, MAPK – mitogen activated protein kinase, MeCP2 – methyl-CpG-binding protein 2, NAD+ – nicotinamide adenine dinucleotide, NAS – N-acetylserotonin, NF-κB – nuclear factor-κB, O&NS – oxidative and nitrosative stress, PARP – poly(ADP-ribose) polymerase, PGC-1α – peroxisome proliferator-activated receptor γ coactivator-1α, PI3K – phosphatidylinositol-3 kinase, QUIN – quinolinic acid, S1P – sphingosine-1-phosphate, sIL-6R – soluble interleukin-6 receptor, SNPs – single nucleotide polymorphisms, TDO – tryptophan 2,3-dioxygenase, TGFβ – transforming growth factor-β, Th – T-helper, TLR4 – Toll-like receptor 4, TNF-α – tumor necrosis factor-α, Trk – receptor tyrosine kinase, TRYCATs – tryptophan catabolites

Introduction

Depression is a common disorder with increasing prevalence across various cultures. Although many theoretical perspectives have tried to explain the genesis of depression, including psychoanalytic and cognitive models, recent studies on the biological underpinnings of depression have highlighted the important role played by oxidative and nitrosative stress (O&NS) in conjunction with cell-mediated immunity (CMI). CMI associated immuno-inflammation and pro-inflammatory cytokines production coupled to O&NS have been shown to mediate their depressive effects *via* the activation of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), leading to the induction of neuroregulatory tryptophan catabolites (TRYCATs), such as kynurenic acid (KYNA) and quinolinic acid (QUIN) [1, 23]. The activation of IDO and TDO drives tryptophan to TRYCAT pathway products and away from serotonin, N-acetylserotonin (NAS) and melatonin [1, 21].

Recent work on depression has also suggested that it is a neuroprogressive disorder, with changes over time that lead to increased apoptosis, autoimmunity and O&NS driven damage coupled to decreased neurogenesis. Such shifts in the biological underpinnings of depression over successive episodes have implications for the conceptualization of staging and early intervention, which highlights the potential of individualizing treatment of recurrent *versus* first-presentation depression, as well as the factors that drive treatment resistance [1, 18]. Conceptualizing depression as a neuroprogressive disorder has produced a shift in how depression is thought to interact with other disorders. Depression is being viewed less as a comorbidity of conditions such as Alzheimer's disease, Parkinson's disease and schizophrenia and more of an intimate part of the biological processes driving the etiology and course of interaction conditions that share elements of common pathways [1, 18].

Another condition very closely associated with depression is somatization, which is the presentation of medically unexplained somatic symptoms [21]. Many questionnaires used to measure depression incorporate items of somatization, often as a part of a somatization subscale of the overall depression measure. However, we recently showed that somatization can be biologically differentiated from depression on the basis of increased kynurenine (kyn)/tryptophan and kyn/KYNA ratios [21]. Increases in these ratios are associated with somatization when they occur concurrently with depression or chronic fatigue syndrome. Given the close association of somatization and depression and the infrequent measurement of somatization in published studies on depression, many previous studies examining biological indices of depression may have conflated biologically differentiated subgroups. That said, the biological processes altered in somatization suggest that it contributes to driving the central changes underlying depression [21].

Overall, depression is strongly associated with O&NS, CMI and TRYCAT pathways, which intimately link depression to other medical conditions [1, 18]. Here we examine the role of interleukin (IL)-6 in the etiology and course of depression, suggesting that it may be intimately associated with the local regulation of the immuno-inflammatory response (Fig. 1).

IL-6

IL-6 is constitutively expressed or can be induced in many cells. The highest levels of IL-6 production are found in adipocytes, highlighting the nexus between diet, obesity and depression, although central nervous system (CNS) cells and immune cells are also a significant source. Other pro-inflammatory cytokines,

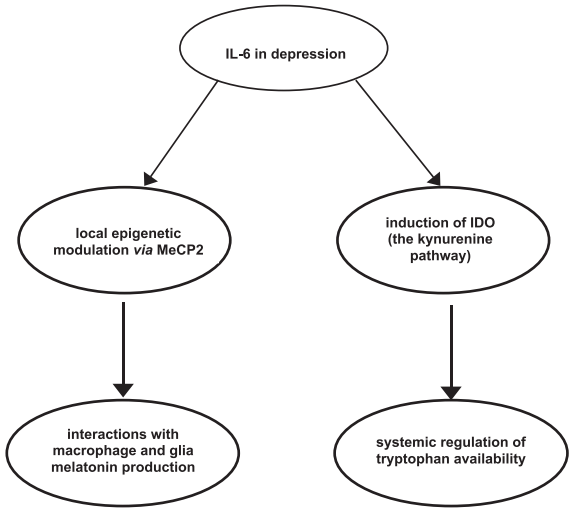

Fig. 1. Proposed role of interleukin-6 in depression

including tumor necrosis factor-α (TNF-α) and interferon γ (IFN-γ), can induce IL-6, although this process differs among various CNS cells [5, 18]. Thus, IL-6 is typically increased as part of a wider pro-inflammatory process [5]. IL-6 receptor (IL-6R) activation predominantly activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and, to a lesser extent, the mitogen activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K) pathways. For IL-6 to activate IL-6R induced signaling, gp130 must be recruited. A soluble IL-6R (sIL-6R) response also occurs, usually as the result of cleavage by metalloproteases, including a disintegrin and metalloproteinases (ADAM)10 or ADAM17, but also *via* alternative splicing of IL-6R mRNA. Both IL-6 and gp130 can bind to sIL-6R and lead to IL-6R signaling pathway activation in cells without endogenous IL-6R. This is known as trans-signaling. Such trans-signaling can be inhibited by soluble gp130 [18].

CNS cells, such as astrocytes, microglia, neurons and endothelial cells, express IL-6 and its receptor, and IL-6 is normally induced *via* the activation of the transcription factor nuclear factor κB (NF-κB). However, in astrocytes, the activation of the cAMP pathway can also increase IL-6, allowing common cAMP inducers, such as norepinephrine, to increase astrocyte IL-6 release [24]. Synthetic ceramides and sphingomyelinase also increase astrocyte IL-6, as does the depression and pain associated with neuropeptide substance P *via* the activation of NF-IL-6.

IL-6 and depression

Increased levels of IL-6, sIL-6R and other cytokines, including IL-1 and TNF-α, are evident in depression [3, 18], as well as in associated psychiatric disorders, including bipolar disorder, post-traumatic stress disorder, schizophrenia and autism spectrum disorders [18]. Increased IL-6 and sIL-6R in depression, coupled to an absence of changes in the levels of soluble gp130, indicate that IL-6 trans-signaling is increased in depression and allows IL-6 to modulate signaling in cells where the plasma membrane IL-6R is not typically expressed. Such differential effects of IL-6 signaling are evident in posttraumatic stress disorder, depending on the presence of concurrent depression [18]. Generally, increased IL-6 levels in depression are related to increased hypothalamic-pituitary-adrenal (HPA) axis activity, increasing cortisol, which in turn activates TDO and leads to decreased tryptophan availability for serotonin, NAS and melatonin synthesis. Thus, IL-6 has a role in the co-ordination of important biological pathways underlying stress and stress induced depression.

Increased IL-6 and IL-6 single nucleotide polymorphisms (SNPs) also modulate depression-associated conditions such as Alzheimer's disease [10]. Typhoid vaccination increases plasma levels of IL-6, which correlate with levels of depression and psychomotor retardation [2]. An increased ω-6/3 ratio in depression contributes to prostaglandin production, in turn increasing pro-inflammatory cytokine levels, including IL-6. Recent conceptualizations of depression have emphasized the role of O&NS-driven neoepitopes that lead to autoimmunity, thereby changing the nature of the immune responses occurring during depression [1, 18]. IL-6 in the presence of transforming growth factor-β (TGF-β) increases IL-17 producing T-helper (Th)-17 cells, which are classically associated with a more prolonged and often damaging immune response that is strongly linked to autoimmune disorders [26]. In conjunction with O&NS, IL-6 may then contribute to the changing nature of recurrent depression, linking it to neuroprogression and treatment resistance, as well as to the association of depression with neurodegenerative disorders such as Alzheimer's disease [1, 18]. Higher IL-6 levels are increased in association with treatment resistance [18].

IL-6 is also significantly increased in animal models of depression [18]. Plasma IL-6 levels are elevated

in high-anxiety rats, and IL-6 injection into the amygdala and hippocampus induces behaviors indicating depression. Over-expression of IL-6 also increases neurodegeneration, suggesting the relevance of IL-6 to depression's association with neurodegenerative disorders, as well as to the neuroprogressive processes in depression *per se* [18].

Antidepressants generally improve redox status and decrease proinflammatory cytokine production, including IL-6, in animal models, as well as in brain cell cultures, although the results are somewhat mixed [16]. These mixed results may indicate a more complex role for IL-6. Kubera and colleagues have repeatedly found that antidepressants increase IL-6 in animal models and in humans with depression [16]. Given that IL-6 is associated with emergent treatment resistance [16], this finding suggests that monitoring IL-6 may provide an indicator of emerging alterations in the biological underpinnings of depression. It is important to clarify this possibility, including whether the adjunct use of antioxidants and/or anti-inflammatories may prevent antidepressant-induced increases in IL-6.

Overall, IL-6 is strongly associated with a number of important processes in depression and depression-associated neurodegenerative conditions. IL-6 effects can be viewed as part of a wider pro-inflammatory response, as well as specific in regard to the regulation of Th-17 cell responses [26]. However, many of its effects on the changing nature of neuronal activity and patterning in depression may be mediated by its induction of neuroregulatory TRYCATs.

IL-6 and TRYCATs

In rodents, IL-6 increases IDO *via* the JAK/STAT pathway both *in vitro* and *in vivo*, contributing to both pain and depression [14]. Hippocampal IL-6 and IDO inductions drive both pain and depression in rodent models [14]. Pain is frequently reported in depression, a diagnosis of comorbid somatization represents depression's most common 'comorbidity'. Increased peripheral kyn in somatization is relevant to the maintenance of decreased pain threshold in somatization and results in enhanced kyn availability for brain uptake and, *via* its conversion to neuroregulatory TRYCATs, for the modulation of brain neuronal activity and patterning [21].

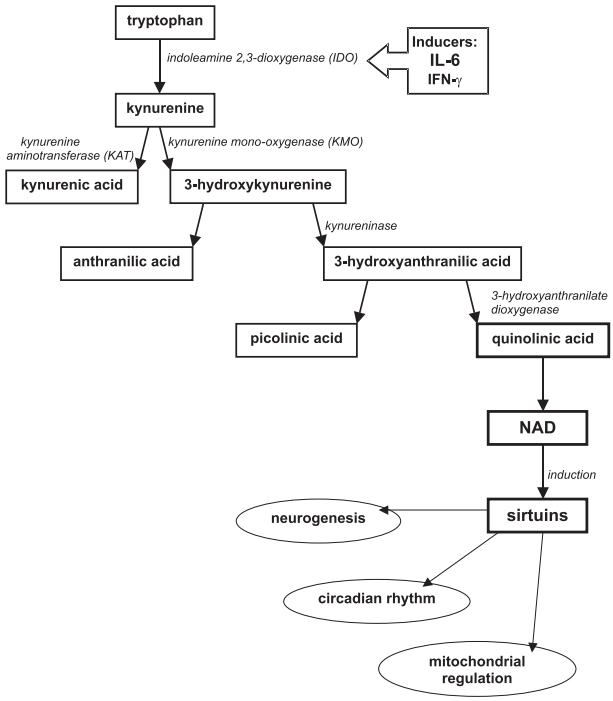

Fig. 2. Diagram of the kynurenine pathway

Increased peripheral kyn can cross the blood-brain barrier (BBB), thereby contributing to central TRYCATs, including the production of neuroregulatory KYNA and QUIN (Fig. 2). Thus, peripheral IL-6 that drives IDO induction of kyn may contribute to the peripheral manifestations of somatization, as its impact centrally contributes to altered neuronal regulation and interarea patterning. This may also be a mechanism whereby peripheral and central IL-6 contribute to chronic pain [6] and chronic pain-induced depression [14]. In the presence of IFN-γ, which is the major inducer of IDO and increases IL-6, IDO induction is potentiated and contributes to further decreases in serotonin, NAS and melatonin. Overall, the induction of IDO by IL-6 contributes to both the central and peripheral processes linked to depression, somatization, inflammation and chronic pain.

IDO induction may have evolved as a mechanism for the maintenance of nicotinamide (NAD+), which is the final product of the IDO and TRYCAT pathways. NAD+ is important to the induction of the sirtuins, which contributes to many of the processes that are dysregulated in depression, including neurogenesis, circadian rhythms and mitochondrial regulation. The latter occurs *via* both mitochondria-associated

sirtuin-3 and master mitochondrial coordinator peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) regulation by sirtuin-1. However, O&NS-induced DNA damage leads to the induction of poly(ADP-ribose) polymerase (PARP), which catabolizes NAD+ and decreases sirtuins, in turn contributing to mitochondrial dysregulation in depression and depression-associated conditions [1]. The induction of IDO by IL-6 may be in part an attempt to maintain sirtuin levels and mitochondrial function, which is thwarted by the high levels of O&NS, lipid peroxidation and DNA damage.

As with other pro-inflammatory cytokines, IL-6 increases the activation of the HPA axis [18]. By increasing cortisol levels, IL-6 contributes to cortisol's induction of TDO. TDO exhibits high hepatic expression but is also present in central astrocytes and some neurons. When TDO is knocked out in rodents, there is a twenty-fold increase in central serotonin, with a concurrent decrease in anxiety and an increase in neurogenesis, highlighting the importance of TDO in the regulation of key changes associated with depression [8]. The indirect regulation of stress hormone-induced TDO is another means by which IL-6 acts to induce neuroregulatory TRYCATs. In astrocytes, TDO leads only to the production of kyn and KYNA. The activation of the cAMP pathway also increases astrocyte KYNA production [20], suggesting that cAMP induced IL-6 may be coordinated with increased KYNA release.

cAMP regulation of KYNA may be important to neuronal regulation, given that KYNA, *via* the inhibition of the α7 nicotinic acetylcholine receptor (α7nAChr), inhibits cortical ACh, glutamate and dopamine release and concurrently lowers the glial and mast cell reactivity threshold, in turn contributing to increased BBB permeability [1]. Given that cAMP levels are often altered in depression and that cAMP also has a role in the regulation of the aryl hydrocarbon receptor (AHr) and the coordination of the AHr with the circadian genes Period1 and Period2, it is important to investigate how cAMP-induced IL-6 interacts with the significant oxidant and circadian regulation by the AHr.

IL-6 and neuroinflammation

Dysregulated serotonin is classically associated with depression, although recent work suggests that the induction of neuromodulatory TRYCATs may be a principal mediator of altered neuronal activity and patterning in depression [1, 18]. Serotonergic activation of the astrocyte 5-HT_{7r} can also lead to the release of IL-6 [19], which suggests that serotonergic activation of astrocytes, in addition to providing a substrate for melatonin and NAS synthesis, also contributes to local IDO and TRYCAT induction. Thus, IL-6 has local as well as systemic effects on the regulation of TRYCATs and tryptophan availability, respectively.

The loss of melatonin and NAS due to wider IL-6-induced IDO is also important to depression associated processes, including the decreased neurogenesis that is evident in depression. Melatonin and NAS, as well as serotonin, increase neurogenesis [4, 27]; the effects of NAS are mediated, at least in part, by its activation of the brain-derived neurotrophic factor (BDNF) receptor tyrosine kinase (Trk)B [13]. Astrocytes and immune cells produce melatonin and NAS, which may be relevant to the local regulation of neurogenesis by IL-6-induced IDO and associated serotonin, melatonin and NAS depletion. The results regarding the effects of IL-6 on neurogenesis are mixed. These discrepancies may be explained by variations in the effects of local and systemic IL-6 on local melatonin and NAS production, with astrocyte melatonin and NAS possibly being enhanced under mild inflammatory conditions, as occurs in other cells. However, IL-6 is generally thought to decrease hippocampal neurogenesis.

The local production of melatonin and NAS is thought to be a major modulator of local inflammatory responses. Melatonin and NAS, *via* their anti-inflammatory and antioxidant effects, as well as their induction of prosurvival pathways and mitochondrial oxidative phosphorylation, are protective against O&NS, CMI and TRYCAT-driven neuronal toxicity. Given that melatonin increases a non-inflammatory, phagocytic phenotype in phagocytic cells, such as monocytes and macrophages, local decreases in melatonin may then contribute to heightened local inflammatory responses in depression. Such increases in O&NS and immuno-inflammation are crucial to depression, including its association with a neuroprogressive course and its high level of co-occurrence with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [1]. As such, IL-6-induced IDO may alter the local melatonin and NAS regulation of inflammatory processes that are crucial to the local biological underpinnings of depression, as well as to the regulation of neurogenesis.

However, it should be noted that in Jurkat T cells, activation of melatonin MT1r interacts with IL-6-induced STAT3 signaling [17] *via* STAT3 phosphorylation. Whether this is relevant to the autocrine and paracrine effects of local melatonin in astrocytes and microglia requires investigation. This possibility suggests more direct effects of IDO- and TDO-driven decreases in serotonin, melatonin and NAS on IL-6 signaling.

The efficacy of melatonin may be mediated in part by its regulation of epigenetic processes [25], including in the induction of methyl-CpG-binding protein 2 (MeCP2). The loss of MeCP2 function is classically associated with Rett syndrome, although decreased MeCP2 is evident in many disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia and autism spectrum disorders [7]. These conditions are all associated with increased levels of stress responsivity and depression. Decreased MeCP2 Ser421 phosphorylation increases stress responsivity, with antidepressant efficacy partly mediated by increased MeCP2 Ser421 phosphorylation [11]. Such mechanisms indicate that stress and depression are intimately involved in the etiology and course of the varied conditions that are linked to decreased MeCP2 function. When wild-type MeCP2 is replaced only in glia in MeCP2 KO rodents, the massive regression that would normally occur in this model of Rett syndrome is prevented. The efficacy of MeCP2 in microglia is mediated by an increase in their phagocytic activity [7]. Whether the induction of a phagocytic phenotype by autocrine melatonin in macrophages [22] is evident in microglia and linked to melatonin induction of MeCP2 requires investigation. In addition to modulating local inflammatory processes *via* the systemic regulation of IDO and melatonin availability [28], IL-6 is likely to have significant local impacts on the intercellular interactions occurring among astrocytes, microglia and neurons.

The interactions of melatonin and MeCP2 may be relevant to the effects of IL-6, given that MeCP2 in some cells represses IL-6 transcription [5]. Whether this occurs in CNS cells requires investigation, as it may suggest that the genetic and epigenetic increases in O&NS and CMI in depression may contribute to increased IL-6 *via* decreased MeCP2 levels and functioning by driving down local melatonin. In such a scenario, locally increased IL-6 would contribute to increased IDO and neuronal regulating TRYCATs, as well as to wider inflammatory responses in CNS cells. Given the association of depression with neuroprogression and the etiology and course of many neurodegenerative disorders, IL-6 may be intricately linked to depression's overlap with these degenerative conditions *via* its regulation by local inflammation.

The activation of the inflammatory transcription factor NF-κB is required by macrophages to induce melatonin and its autocrine effects that lead to a phagocytic phenotype. This is dependent on the specific subunit dimers that form NF-κB [22], suggesting that particular NF-κB subunits in different cells determine the interactions of IL-6 and melatonin. NF-κB activation is also a significant inducer of many pro-inflammatory cytokines, including IL-6. It will be important to clarify whether IDO and TDO induction of TRYCATs, by driving down available melatonin production by macrophages and perhaps glia, leads to a desynchronization of melatonin with IL-6 and wider cytokine production [28]. This could suggest that TRYCAT-driven depletion of local melatonin and NAS might be associated with alterations in the nature of local immune and glia inflammatory responses. However, it should be noted that melatonin increases levels of IL-6, as well as IFN-γ and IL-2, in human circulating T-lymphocytes [9], suggesting that local melatonin production may have variable effects depending on the presence of specific types of immune cells. This also suggests that the pro-inflammatory cytokine inhibition of pineal melatonin production may be temporally synchronized, *via* IDO and TDO induction, with a decrease in local melatonin and NAS. In turn, this process would bias the relative contributions of monocytes/macrophange/glia *versus* Th-1 lymphocytes while also modulating the type of macrophage/monocyte phenotype induced. Thus, IL-6 and variations in melatonin may be significant modulators of immuno-inflammation patterning.

A recent model of depression utilized repeat toll-like receptor (TLR) 4 activation to induce depression [15]. Lipopolysaccharide (LPS) activation of TLR4 increases NF-κB, IL-6, nitric oxide and mitochondrial dysfunction, which can be prevented by melatonin. Whether melatonin's effects involve the induction of MeCP2 and its suppression of IL-6 transcription, including the regulation of IDO and neuroregulatory TRYCATs, should be investigated. TLR4 induced IL-6 is also regulated by microRNAs, including miR-181, with miR-181 KO increasing LPS induced IL-6 in astrocytes [12]. MeCP2 is a significant gene target for miR-181 [12]. As such, IL-6 may be regu-

lated by factors modulating miR-181, at least in part, *via* the regulation of MeCP2; thus, miR-181 may be a potential treatment target in the regulation of local inflammatory responses in depression and associated degenerative conditions.

Another factor associated with the regulation of TLR4, as well as O&NS, plasma membrane plasticity and neurogenesis, is sphingosine-1-phosphate (S1P). *Via* its activation of S1P1r *versus* S1P3r in different cells, S1P can decrease or increase TLR4 induced NF-κB, as indicated by Anderson and Maes [1]. It appears likely that variations in S1Pr subtype activation may interact with the effects of TLR4 activity, as well as other NF-κB inducers, in the regulation of IL-6 and wider inflammatory transcriptions. It will be interesting to determine whether the S1Pr subtype interacts with specific NF-κB subunits to modulate local melatonin and IL-6 production in macrophages and glia.

Conclusions

Overall, the role of IL-6 in depression may be intimately associated with the regulation of local inflammation *via* its interactions with macrophage and glia melatonin production and MeCP2 regulation. By systemically contributing to IDO and TRYCATs, IL-6 may decrease levels of serotonin, melatonin and NAS production, thereby impacting key immuno-inflammatory processes that underpin depression and its associated conditions. The plethora of data linking increased IDO and kyn/tryptophan ratio to depression/somatization and neurodegenerative disorders may then be closely linked to the regulation of IL-6 induced local and systemic IDO. In recurrent and neuroprogressive depression, IL-6 may contribute to increased immuno-inflammation *via* the induction of Th-17, thereby increasing levels of autoimmunity.

Understanding the nature of IL-6 effects locally, systemically and in T cell subset differentiation has the potential to contribute to improved treatment of depression and its associated conditions.

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Declaration of financial interests:
None.

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