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Chapter

Innate Immunity and Neuroinflammation in Neuropsychiatric Conditions Including Autism Spectrum Disorders: Role of Innate Immune Memory

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Abstract

The neuroimmune network represents a dense network of multiple signals mediated by neurotransmitters, hormones, growth factors, and cytokines produced by multiple lineage cells and is crucial for maintaining neuroimmune homeostasis. Endogenous and exogenous stimuli, which are dangerous to the body, are detected by sensor cells, and they rapidly inform the brain through this network. Innate immunity is thought to play a major role in the neuroimmune network, through cytokines and other mediators released from secretary innate immune cells. Recent research has revealed that innate immunity has its own memory. This is accomplished by metabolic and epigenetic changes. Such changes may result in augmenting immune protection with a risk of excessive inflammatory responses to subsequent stimuli (trained immunity). Alternatively, innate immune memory can induce suppressive effects (tolerance), which may impose a risk of impaired immune defense. Innate immune memory affects the neuroimmune network for a prolonged period, and dysregulated innate immune memory has been implicated with pathogenesis of neuropsychiatric conditions. This chapter summarizes a role of innate immune memory (trained immunity vs. tolerance) in neuroinflammation in association with neuropsychiatric conditions including autism spectrum disorders (ASD).

Keywords: innate immunity, cytokines, neuroinflammation, neuroimmune network, immune metabolic processes

1. Introduction

It is well accepted that inflammation in the peripheral organs can influence homeostasis and immune responses in the central nervous system (CNS) [1]. In common neuropsychiatric conditions such as schizophrenia and depression, evidence indicates that neuroinflammation plays a role in the disease pathogenesis [2]. Long-lasting effects of neuroinflammation in such neuropsychiatric conditions are

implicated with altered innate immune responses in the absence of specific pathogens [2]. However, until recently, it is not well understood how innate immunity, which was thought to have no lasting memory unlike adaptive immunity, can exert prolonged actions on the CNS. The recent discovery of innate immune memory (trained immunity vs. tolerance) shed a light in a long postulated role of innate immunity in neuropsychiatric diseases [3, 4].

Since the existence of the immune system was recognized more than 50 years ago, the immune system has been thought to be comprised of two components, innate immunity and adaptive immunity. Innate immunity is the arm that mounts nonspecific, acute immune responses, by sensing microbial by-products called pathogen-associated molecular patterns (PAMPs) or by-products derived from tissue injuries called damage-associated molecular patterns (DAMPs) [5]. Signaling through PAMPs and DAMPs are thought to play a major role in plant immunity [6]. In animals, adaptive immunity is the arm that develops antigen (Ag)-specific responses. The development of Ag-specific responses requires lengthy processes including antigen (Ag) processing by Ag-presenting cells (APCs), Ag presentation to T and B cells, and TCR or immunoglobulin gene arrangements of T and B lymphocytes, respectively, which lead to the development of Ag-specific T and B cells and finally antibodies (Abs) [7]. Adaptive immunity effectively eliminates hazards from the body through Ag-specific cellular and humoral immune responses [7]. Adaptive immunity results in the development of long-lasting Ag-specific memory T/B cells [8]. In this way, the body retains immune memory against specific pathogens for a prolonged time. It is well known that individuals who have survived measles will retain measles-specific immune defense for life.

In contrast, immunology textbooks have long taught us that innate immunity does not have any lasting effects or memory, and it is mainly effective in containing infection until adaptive immunity takes over. Innate immunity has also been known to shape adaptive immunity through multiple mechanisms such as affecting actions of APCs, thereby indirectly modifying adaptive immune responses [7]. However, recent exciting research revealed that innate immunity can have its own memory, following an immune stimulus, and this depends on time, amount, and the kinds of stimuli through metabolic and epigenetic changes [3, 9]. More importantly, the stimuli that evoke innate immune memory are not restricted to microbes; nonpathogenic challenges such as stress and obesity are also found to cause innate immune memory [3, 10].

As described previously, despite the accumulating evidence, it was difficult to understand how innate immunity exerts lasting effects, in the absence of specific pathogens or other persistent environmental stimuli, in neuropsychiatric conditions. The recognition of innate immune memory (trained immunity vs. tolerance) has provided us new insights with regard to the role of innate immunity in physiological as well as pathogenic consequences in the brain. In this chapter, research efforts shaping a concept of innate immune memory (trained immunity vs. innate immune tolerance) will be discussed first. In the latter part of the chapter, a potential role of innate immune memory in neuropsychiatric conditions, especially in ASD, will be discussed.

2. Innate immune memory

2.1 Trained immunity

The presence of innate immune memory was first suspected because of unexpected, nonspecific effects of vaccinations. This is best known for a Bacillus

Calmette-Guérin (BCG) vaccine. Epidemiological studies and subsequent randomized trials showed that the BCG vaccination not only provided protection for tuberculosis but also protection against other pathogens, especially those causing respiratory infection, which resulted in a reduction in infant mortality greater than expected for reducing tuberculosis-associated mortality [11, 12]. Likewise, the measles vaccination resulted in a striking reduction in children's mortality, which was again not to be explained by the reduction in mortality caused by measles [11]. These epidemiological observations were further explored by researchers in the Netherlands. They first demonstrated that innate immune memory does exist in animal models [13]. Namely, these researchers showed that BCG provided enhanced protection against *Candida albicans* through nonspecific adaptation of innate immunity, independent of lymphocytes [13]. They proposed to name this process of innate immune memory "trained immunity." The following studies by the same group also revealed that such adaptive changes in innate immunity are present not only in monocyte-macrophage lineage cells but also in other innate immune cells such as natural killer (NK) cells [14] and progenitor cells of innate immune cells in the bone marrow [15, 16]. Further studies revealed the presence of trained immunity in humans [17–19]. It became clear that trained immunity is similar to plant immunity which does not develop Ag-specific immunity, but develops prolonged immune defense by metabolic and epigenetic modulation [20]. Mounting evidence has now repeatedly shown that trained immunity is Ag nonspecific; the second stimulus (DAMP or PAMP) causing innate immune activation can be different from the first stimulus [3].

2.2 Mechanisms of trained immunity

Adaptive changes observed in "in vitro" models of trained immunity with β-glucan, a representative PAMP from *Candida albicans*, have been extensively studied. It was revealed that ß-glucan treatment induces activation of the dectin-1/Akt/PTEN/mTOR/HIF-1α signaling pathway in innate immune cells [21]. That is, β-glucan activates dectin-1 which recruits Akt, leading to activation of mammalian target of rapamycin (mTOR) with suppression of PTEN expression and phosphorylation of the tuberous sclerosis complex (TSC) [22]. Activation of this pathway switches cellular metabolism from oxidative phosphorylation (ATP synthesis) to glycolysis, thereby reducing basal cellular respiration and increasing in glucose consumption, resulting in higher production of lactate [21]. Such metabolic changes lead to the exportation of citrate to the cytoplasm for cholesterol synthesis and phospholipid synthesis [23, 24].

This metabolic shift described above results in the replenishment of the Krebs cycle by metabolization of glutamine into glutamate and α-keto-glutamate, leading to an accumulation of fumarate [23, 24]. Higher concentration of fumarate inhibits the KDM5 family of H3K4 demethylase that eventually leads to epigenetic reprogramming [23]. It has been reported that in the initial phase of trained immunity, lysine 27 of histone 3 (H3K27) is acetylated and lysine 4 of histone 3 (H3K4) is methylated rapidly [25]. Although H3K27Ac gradually returns to the baseline over time, H3K4me3 was found to remain elevated in the trained immunity [25]. Such epigenetic histone modification (accumulation of H3K4me3) is known to lead to the remodeling of the local chromatin into an open and accessible state, resulting in the facilitation of the loading of transcriptional machinery. The remaining accumulation of H3K4me3 on chromatin has been implicated in the establishment of the epigenetic memory in the trained immunity [25, 26]. It was hypothesized that H3K4me3 increases the local hydrophobicity of the chromatin, allowing for liquid-liquid phase separated transcription factors to engage with the DNA in the aqueous

environment of the nucleus, subsequently rendering loading of transcriptional machinery onto promoters [27–29]. This will allow cells to start rapid transcription of the genes necessary for immune responses, thereby causing a much stronger Ag nonspecific pro-inflammatory response.

Long noncoding RNAs (lncRNAs) can function as a molecular scaffold where multiple protein complexes can assemble, and they also guide these complexes to specific gene loci [30]. Recent research disclosed a new class of lncRNAs named immune gene-priming lncRNAs (IPLs), and IPLs were found to have a crucial role in the accumulation of H3K4me3 on chromatin [31]. A candidate IPL, termed upstream master lncRNA of the inflammatory chemokine locus (UMLILO), was found to be crucial for trained immunity; ablation of the UMLILO transcript abolished β-glucan-induced trained immunity in both human and murine monocytes [30].

As shown in epidemiological studies of vaccinations, trained immunity, caused by metabolic and epigenetic changes, will be beneficial in providing broader immune defense and promoting tissue repair [32]. On the other hand, maladapted trained immunity can be detrimental to human health. Chronic inflammatory conditions including neuropsychiatric conditions have been implicated with maladapted changes in trained immunity [2, 9]. It should also be noted that induction of trained immunity appears to be associated with doses of PAMP, perhaps DAMP in humans; depending on the dose and the kinds of PAMP/DAMP, tolerance can be induced, instead of trained immunity [2]. It has been shown that low to moderate doses of β-glucan, tri-DAP, and muramyl dipeptides are reported to induce trained immunity [33]. It also needs to be cautioned that the effects of trained immunity are likely associated with individual's genetic and epigenetic background. For example, nonspecific effects of infant BCG vaccination are reported to be heterogeneous, affected by multiple genetic and environmental factors including age, gender, interactions with other vaccines, and exposure to infectious pathogens at the time of BCG vaccination [34].

2.3 Mediators of trained immunity

It has been reported that pre-administration of pro-inflammatory innate cytokines [interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and IL-6] provided protection against a variety of microbes [35]. Among the cytokines administered, IL-1 showed superior effects over TNF-α or IL-6 [35]. In BCG-vaccinated individuals, increase in production of these innate cytokines by monocytes in response to other microbes, other than BCG, was also found; this effect was again the most dependent on IL-1β [32]. IL-1β has also been reported to be crucial in the induction of trained immunity in NK cells [36]. On the other hand, in individuals with chronic mucocutaneous candidiasis, STAT-1-mediated type II interferon (IFN) induction was found to be crucial for induction of trained immunity [37]. The role of type II IFN (IFN-γ) in animal models was also reported by Kaufmann et al. [16]. However, in humans, innate immunity-associated protection (trained immunity) has been mainly implicated with IL-1β and other IL-1 families [38].

As detailed in the previous section, a metabolic shift from oxidative phosphorylation to aerobic glycolysis through the Hypoxia inducible factor-1α (HIF-1α) pathway downstream to mTOR is crucial for the development of trained immunity, since inhibition of this pathway is abolished induction of trained immunity [21]. Namely, in HIF-1α knockout mice, trained immunity was not induced [21]. IL-1β is known to be a direct target of HIF-1α [39], having a HIF-1α binding site in the promoter region of IL-1β gene [40]. It is now thus proposed that HIF-1α-induced

IL-1β also plays a role in epigenetic changes, through histone modifications [35]. Alternatively, IL-1β has been shown to upregulate HIF-1α [41].

Given the role of IL-1β in trained immunity, excessive, dysregulated production of IL-1β is likely to cause maladapted trained immunity and resultant pathogenic consequences. This may be observed in patients with autoinflammatory syndromes associated with gene mutation that lead to overproduction of IL-1β, including cryopyrin associated periodic syndrome (CAPS) [38, 42]. On the other hand, impaired induction of trained immunity can also cause detrimental effects. It was reported that patients with chronic mucocutaneous candidiasis exhibit impaired induction of STAT-1-dependent, trained immunity in response to β-glucan [37].

The above-described metabolic shift is not limited to glucose metabolism. Changes in glutamine and cholesterol metabolism have also shown to be crucial in trained immunity [24]. Consequently, it is thought that increased cholesterol content also plays a role in the development of trained immunity. Interestingly, increased levels of oxidized low-density lipoprotein (OxLDL) caused by dysregulated cholesterol metabolism are found to induce trained immunity in human monocytes [10]. Such a finding indicates a pathogenic role for maladapted trained immunity in atherosclerosis, since monocyte and macrophage cells are known to play a major role in plaque formation in vascular endothelium, a major histologic change in atherosclerosis [10].

2.4 Tolerance in innate immunity

As detailed in the previous section, trained immunity causes a metabolic shift from oxidative phosphorylation (OXPHOS) to glycolysis, rendering macrophage and monocyte lineage cells to classically activated cells or M1 phenotype; these cells exhibit impaired OXPHOS and anabolic repurposing of the tricarboxylic acid (TCA) cycle [43, 44]. In contrast, alternatively activated or the M2 phenotype of macrophages and monocytes has balanced processes of OXPHOS and TCA cycle activation; enhanced glycolytic generation of pyruvate fuels the TCA cycle, paralleling the induction of OXPHOS [44]. Trained macrophages via ß-glucan exposure are shown to reveal M1 phenotype [21]. Generation of M1 vs. M2 phenotypes of macrophages indicates the importance of regulating innate immune responses for prevention of excessive, potentially harmful inflammatory responses. In addition to generation of M2 phenotype, hypo-responsiveness of innate immunity has been described as endotoxin tolerance and compensatory anti-inflammatory response syndrome (CARS) [45]. Such regulatory mechanisms also have lasting effects, as observed in trained immunity.

Endotoxin tolerance in innate immunity was first shown in rodent models of sepsis. Namely, survival from sepsis is associated with diminished or absence of responses to LPS, an endotoxin [46]. Subsequently, it was shown that previous exposure to a sublethal dose of LPS led to resistance to a lethal dose of LPS in rodents [46]. Endotoxin tolerance is thought to be a result of innate immune memory with lasting immune hypo-responsiveness, even to non-LPS stimulants [47]. Phenotypic changes of tolerant innate immune cells are characterized with less production of inflammatory cytokines (TNF-α, IL-12, IL-6) and increase in production of counter-regulatory cytokines (IL-10 and TGF-β) upon stimulation [48, 49]. CARS was recognized as a clinical syndrome which is thought to represent a phase of immune "exhaustion," following initial potent immune activation, known as systemic inflammatory response syndrome (SIRS) [50]. Peripheral blood monocytes and neutrophils from CARS patients are reported to reveal similar phenotype to endotoxin-tolerant cells observed in rodent models [45, 49]. Recent research revealed that

persistent effects of endotoxin tolerance and CARS are mediated by lncRNAs as well as microRNAs (miRNAs).

LPS activates TLR4 which leads to the activation of the myeloid differentiation factor 88 (MyD88)-mediated pathway and the TIR-domain-containing adaptor-inducing interferon-β (TRIF) pathway [45]. The molecular signature of endotoxin tolerance involves downregulation of TLR4, decreased recruitment of MyD88 or TRIF to TLR4, decreased activation of IL-1 receptor-associated kinase (IRAK)1 and IRAK4, diminished nuclear factor κ chain of B-cell (NF-κB) signaling, as well as upregulation of negative regulatory molecules including SH2 domain-containing inositol phosphatase 1 (SHIP1) [51].

2.5 Regulators of innate immune tolerance

Recent research revealed a role of miRNAs in the regulation of endotoxin tolerance. Specifically, miR-155 and miR-146α have been shown to regulate endotoxin tolerance [52]. MiR-146α reduces TLR signaling, by targeting IRAK1 and TRAF6, key components of TLR signaling pathway [53]. In contrast, miR-155 is reported to inhibit expression of SHIP1 and SOCS1, negative regulators of TLR signaling, prohibiting or attenuating tolerance induction by endotoxin [54, 55]. Several other miRNAs are also implicated with regulation of endotoxin intolerance [45]. It was shown recently that miR-221/miR-222 regulates functional reprogramming of macrophages during LPS-induced tolerization [47]. miR-221/miR-222 targets brahma-regulated gene 1 (Brg1), rendering transcriptional silencing of a subset of inflammatory genes that depend on SWI/SNF and STAT-mediated chromatin remodeling [47].

Recent research also revealed a role of lncRNAs in endotoxin tolerance; lncRNAs exert transcriptional, posttranscriptional, and translational regulation of gene expression [56–58]. Multiple lncRNAs are reported to regulate target molecules of TLR4 signaling pathways. LPS-responsive lncRNAs Mirt2, THRIl, MALTAT1, NKILA, lincRNA-21, and SeT have been reported to suppress expression of pro-inflammatory mediators including TNF-α [45]. For example, Mirt2 is reported to inhibit TRAF6 ubiquitination, leading to a decrease in TNF-α production [59]. However, at this time, relationships between actions of miRNAs and lncRNA in innate immune tolerance are not well understood. Other soluble mediators such as cytokines (IL-1β, IL-10, TGF-β, and TNF-α) are also reported to induce cross-tolerance or cytokine-mediated tolerance, causing a signaling cascade similar to that observed in TLR signaling [60]. In contrast, interferons (IFN-γ, α2-IFN, etc.) are known to abrogate endotoxin tolerance [61, 62]. Again these soluble mediators exert their actions on endotoxin tolerance via modulation of intracellular lncRNAs [45].

This type of innate immune memory (tolerance) is thought to be important in maintaining brain homeostasis, and impaired tolerance of innate immunity has been suspected in chronic neurodegenerative conditions such as Alzheimer's disease [9]. Aging is associated with an increased load of gram-negative bacteria in the GI tract and mouth mucosa, resulting in an increase in endotoxin levels in the blood and the brain [62]. However, aging individuals tolerate higher LPS levels in the brain through developing endotoxin tolerance [63].

3. Role of innate immunity in the nervous system

It is known that innate immunity does exist in the brain, playing a crucial role in brain morphogenesis and homeostasis. The major innate immune cells in the central nervous system (CNS) are microglial cells which are endogenously generated in the

brain, but they can also be developed from bone marrow-derived monocytes, which are called BM-derived microglial cells (BMDM) [64, 65]. BMDM-induced inflammation has been implicated in neuropsychiatric conditions [64, 65]. It has also been reported that peripherally derived macrophages modulate microglial function after CNS injury; in this case, they are reported to exert anti-inflammatory effects [66]. Other innate immune cells in the CNS such as astrocytes are also known to exert important physiological roles [9, 67].

3.1 Trained immunity in the CNS

Inflammation in the periphery can prompt immune responses in the brain [1, 4]. Given the effects of trained immunity (activation vs. tolerance) in rodent models and humans, the development of maladapted innate immune memory in the CNS is expected to result in undesired, hazardous effects to the brain. However, reports concerning the effects of trained immunity and/or innate immune tolerance in the brain have been limited. Nevertheless, it was shown that microglial cells isolated from adult rats that were exposed to *E. coli* during the newborn period had increased expression of IL-1β mRNA [68]. The rats exposed to *E. coli* as newborns were also found to have impaired memory when they were challenged with a low dose of LPS, which was blocked by minocycline [2]. In experiments employing microglial cells obtained from sheep fetuses whose mother was given LPS intravenously, these fetal microglial cells were shown to have metabolic and epigenetic modulation, as has been reported in trained immunity [69].

Independent of the studies concerning trained immunity in the brain, persistent effects of maternal immune activation (MIA) on fetuses have been extensively studied, as one of the best studied rodent models of ASD [70]. In this model, sterile inflammation in pregnant rodents was induced with the use of PAMPs such as LPS, poly I:C, resulting in impaired neuropsychiatric symptoms in offspring in their adult years [70]. That is, offspring of MIA mothers have been shown to suffer from persistent behavioral symptoms and cognitive deficits frequently seen in ASD subjects later in life [70]. In addition, MIA also causes persistent alteration of adaptive immunity [71]. However, in this model, it is not yet well understood how innate immune memory (most likely trained immunity in this model) plays a role in a MIA model, causing persistent behavioral changes and impaired cognitive development. Children exposed to stressful events during the fetal and newborn period have also been reported to have higher levels of pro-inflammatory cytokines and neurodevelopmental impairment than control children [2]. Given the research findings in molecular mechanisms of trained immunity described in the previous section, there is a possibility that maladapted trained immunity contributes to the onset and progress of some neuropsychiatric disorders.

3.2 Innate tolerance in the brain

Tolerized innate immunity in the brain is thought to be crucial for limiting excessive inflammatory responses during brain tissue repair that involves phagocytosis of apoptotic cells and damaged tissue debris by tolerant phagocytes [72]. In rodent models, disruption of this pathway leads to neuroinflammation and subsequent neuronal damage [73]. An important regulator of this pathway is the triggering receptor expressed on myeloid cells 2 (TREM-2), which is expressed on microglial cells [74]. Blockade of TREM-2 was shown to exacerbate experimental autoimmune encephalitis (EAE), a rodent model of multiple sclerosis (MS) [75]. Apolipoprotein E (ApoE) which is a TREM-2 ligand was shown to have a role in maintaining tolerized phenotype of phagocytic cells [74]. This interaction was

found to be impaired in patients with Alzheimer's disease [9]. In animal models of Alzheimer's disease treated with trained immunity vs. tolerance inducing stimuli, it was reported that long-term modulation of brain immune responses were observed, and the authors attributed this prolonged effects on innate immune memory to reprogramming of microglial cells [4].

3.3 mTOR-related pathology in neuropsychiatric disorders

In the previous section describing molecular pathways associated with trained immunity, the importance of mTOR signaling has been repeatedly shown. One thing we learned from the research on trained immunity is that multiple lineage cells reveal metabolic and epigenetic reprogramming in the process of innate immune memory, which, in animal models, can also be applied to microglial cells [4]. Interestingly, brain dysfunction caused by dysregulated mTOR signaling has been implicated in several neuropsychiatric disorders. In the next paragraph, we summarize mTOR-related brain dysfunctions and proposed mechanisms.

One of the expected consequences of excessive mTOR signaling caused by trained immunity is the impairment of lysosomal degradation of intracellular components, since mTOR activation inhibits autophagy via inhibition of the early steps of autophagosome biogenesis [76, 77]. Autophagy is a key physiological cellular function that clears intracellular molecules and thought to be developed to adjust the state of nutrient depletion [76, 77]. However, this is also an important mechanism to remove misfolded proteins that naturally occur in living cells [22]. In addition to degradation of misfolded proteins, autophagy also degrades altered subcellular organelles, such as the mitochondria [22]. Prolonged dysfunction in autophagy can lead to detrimental effects and is implicated in the pathogenesis of multiple neuropsychiatric conditions including dementia, movement disorders, seizures, brain ischemia, ASD, affective disorder, and schizophrenia [78–82]. In rodent models of depression, tuberous sclerosis, and ASD, rapamycin (sirolimus), a representative mTOR inhibitor, has been shown to attenuate social interactions and reverse behavioral effects on their neuropsychiatric symptoms [83–86]. Thus metabolic and epigenetic changes caused by trained immunity may have profound effects through altered levels of autophagy, as a result of metabolic and epigenetic reprograming, as detailed in the previous section.

3.4 ASD and a possible role of trained immunity

In this section, we discuss a possible role for trained immunity in the onset and progress of ASD. As a clinician, the author observed that an apparent strong immune stimulus altered the responses to subsequent immune stimuli in some, but not all ASD children and these ASD children also exhibit fluctuating neuropsychiatric symptoms, following microbial infection [87, 88]. As discussed in the previous section, in the MIA model of ASD, prolonged effects of MIA on the offspring brain can be explained through a concept of trained immunity occurring to the fetus at the time of sterile immune activation in the mother. This may have also happened in ASD subjects as described above. However, it should be noted that ASD is a behaviorally defined syndrome, diagnosed on the basis of behavioral symptoms, except for a minority of ASD cases that have well-defined gene mutations [89]. Therefore, based on the author's clinical experience, it is likely that trained immunity plays a role in a subset of ASD subjects for whom neuroinflammation is associated in their ASD pathogenesis.

In ASD patients, just like in other neuropsychiatric conditions, a role of inflammation has been long suspected, and more and more evidence has been accumulating [90–92]. In the research of innate immune abnormalities in ASD children, we have

also found evidence of dysregulated innate immune responses, shifting to pro-inflammatory responses in a subset of ASD subjects [88, 93, 94]. We also experienced that these ASD subjects suffer from various comorbid medical conditions involving the gastrointestinal (GI) tract and other organs [87]. Retrospectively, our findings may be reflecting maladapted innate immunity as a form of trained immunity in such ASD subjects; these ASD subjects may fall into an ASD subset which we have called inflammatory autism, mimicking the rodent ASD model of MIA [93]. Our previous findings that may indicate altered innate immune memory in such ASD patients are as follows:

- In some but not all the ASD subjects, we found significant changes in innate immune abnormalities which are best reflected in changes in IL-1β/IL-10 ratios produced by purified peripheral blood monocytes (PBMo) [88, 93]. Namely, some patients reveal high ratios of IL-1β/IL-10, while others showed low ratios, and these rations can change from time to time, depending on their exposure to immune insults [93].

- ASD subjects who revealed high and/or low IL-1β/IL-10 ratios also revealed fluctuating behavioral symptoms following immune insults [94]. Parents of these subjects often describe more severe, prolonged illnesses and frequent respiratory infection following microbial infection [87]. They also seem to reveal significant changes in their behavioral symptoms and cognitive activity with immune stimuli not associated with microbial infection; these ASD children may exhibit worsening neuropsychiatric symptoms, following flare-ups of aeroallergen allergy, delayed-type food allergy, and adverse reactions to medications including vaccinations [87, 94].

- ASD subjects who revealed high and/or low IL-1β/IL-10 ratios also revealed changes in production of inflammatory monocyte cytokines including TNF-α and IL-6 [93, 95].

- PBMo from ASD subjects who revealed altered IL-1β/IL-10 ratios also revealed changes in miRNA expression by PBMo, as compared to cells obtained from neurotypical, non-ASD controls [93].

- We also studied changes in mitochondrial respiration in peripheral blood mononuclear cells (PBMCs) obtained from ASD subjects and non-ASD controls. Our results revealed evidence of altered mitochondrial respiration in association with changes in IL-1β/IL-10 ratios by PBMo in ASD subjects [95].

- In recent studies, we also found changes in miRNA in sera of ASD subjects, when tested by high-throughput deep sequencing. Again, changes in serum miRNA levels are closely associated with changes in IL-1β/IL-10 ratios by PBMo, production of monocyte cytokines (TNF-β, IL-6, IL-10, CCL2 mostly), along with parameters of mitochondrial respiration (manuscript submitted for publication). Interestingly, in ASD subjects, miRNA levels are mostly decreased, as compared to non-ASD controls (submitted for publication). Targeted genes by miRNAs that are altered in serum levels in ASD subjects with high or low IL-1β/IL-10 ratios are associated with pathways involved in innate immune responses, including the mTOR signaling pathway (unpublished observation).

The above-described findings may be best explained by altered innate immune responses associated with innate immune memory (trained immunity

vs. tolerance). So, if this is the case, for these ASD subjects, can clinical features that indicate an alternation of innate immune memory be detected? The author is a pediatric immunologist and, as indicated before, as stated previously, observes exacerbation of neuropsychiatric symptoms, following immune insults. Herein, a representative ASD case, in which trained immunity may be associated with the onset and progression of ASD, is presented.

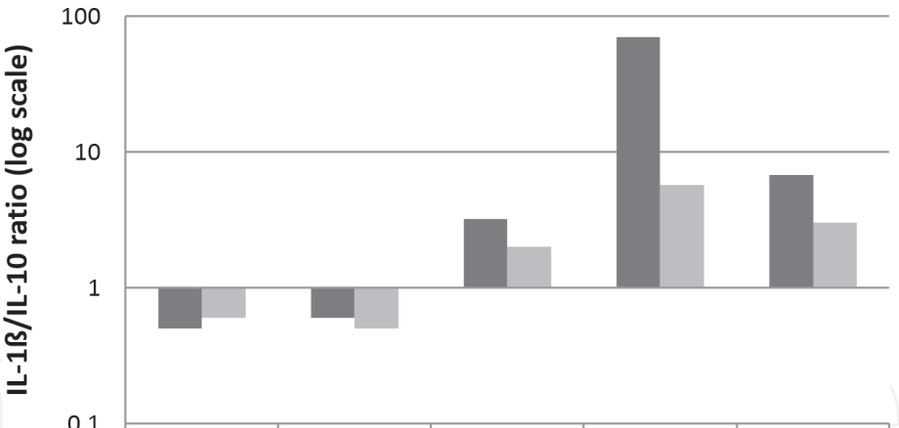
3.5 Case presentation

A 10-year-old female child presented to the pediatric allergy/immunology clinic at our institution secondary to fluctuating behavioral symptoms. Fluctuation of behavioral symptoms often occurred, following microbial infection.

The patient was born at 41 weeks of gestation via cesarean section due to breech presentation, following an uneventful pregnancy. The patient was developing typically until 24 months of age and then suffered from significant developmental regression. Prior to the onset of the developmental regression, parents took the patient to South Asia to visit other family members and friends. During this visit, the patient suffered an insect bite which was complicated by a secondary bacterial skin infection. When treated with oral antibiotics abroad, the patient developed generalized hives and severe GI symptoms (nausea, vomiting, diarrhea, and bloating): the patient then became intolerant to multiple foods. After returning to the United States, the patient was given multiple vaccinations including live vaccines to catch up the vaccination schedule. All these vaccines were given while the patient was still suffering from GI symptoms and an active skin infection. Within several days after vaccinations (multiple vaccines given all together), noticeable loss of cognitive and motor skills became apparent in the patient. The patient was eventually diagnosed with ASD around 2.5 years of age.

Eventually, the patient's GI symptoms subsided, but this subject never regained the cognitive skills that this patient had once acquired prior to the onset of developmental regression. Prior to advancing to pre-kindergarten, the patient was given booster doses of vaccines which were well tolerated. However, after starting pre-kindergarten, the patient started getting sick frequently with upper respiratory infections, which often evolved into ear infection. The patient missed many days of school, since the patient suffered a prolonged course of illness and more severe symptoms, as compared to peers. While the patient presented with symptoms of upper respiratory infection, this patient's behavioral symptoms continue to fluctuate, most evident in worsening of obsessive compulsive behaviors and frequency of "rage" episodes. Worsening behavioral symptoms would always follow immune insults, worse in a convalescence stage. Avoidance of sick contacts by placing the patient in home schooling attenuated the fluctuating behavioral symptoms. At 7–8 years of age, the fluctuating behavioral symptoms seen were mainly associated with teething. After the completion of teething, behavioral symptoms became more stable. However, the patient stopped growing, falling under the first percentile of the growth curve in height and weight. An exhausting workup for primary mitochondrial diseases, endocrine diseases, primary immunodeficiency with known gene mutations, and congenital metabolic and genetic diseases was unrevealing. However, video electric encephalogram revealed a focal epileptic activity. Family history is negative for neuropsychiatric, genetic, autoimmune, immune, and metabolic diseases.

In the case presented above, did neuroinflammation caused by maladapted trained immunity have a role in her clinical features? It is hard to prove, but it may be speculated that the initial stressful events that occurred abroad shaped trained immunity in this patient, and the subsequent multiple unrelated immune stimuli



	medium	LPS	zymosan	CL097	ß-glucan
Patient	0.5	0.6	3.2	69.7	6.8
Control	0.6	0.5	2	5.7	3

Figure 1.
IL-1β/IL-10 ratios produced by purified peripheral blood monocytes in response to medium only (no stimulus), LPS (TLR4 agonist), zymosan (TLR2/TLR6 agonist), CL097 (TLR7/TLR8 agonist), and β-glucan in the presented case (patient) and control cells from a non-ASD neurotypical subject. IL-1β/IL-10 ratios are shown in a log scale.

may have caused prolonged maladapted trained immunity, leading to persistent neuroinflammation and impairment of cognitive activity, as observed in the MIA models of ASD. Interestingly, changes in GI conditions, such as changes in microbiome, have been implicated with neuropsychiatric diseases, triggering maladapted trained immunity [96]. It is also reported that trained innate immunity can be induced in human monocytes by cow's milk [97]. Thus her severe GI symptoms and subsequent intolerance to multiple foods may be associated with excessive trained immunity in the gut of this patient.

3.6 Evidence of impaired trained immunity

As summarized in the previous section, we have found that IL-1β/IL-10 ratios produced by PBMo are altered in some ASD subjects in association with fluctuating behavioral symptoms [94]. Thus if innate immune memory (trained immunity) is associated with her above-described remarkable clinical symptoms, we may also find altered IL-1β/IL-10 ratios, as an indicator of altered innate immune responses.

Thus we assessed IL-1β/IL-10 ratios produced by PBMo in response to a panel of innate immune stimuli, including β-glucan, as reported previously [95]. As shown in **Figure 1**, the presented case revealed increase in IL-1β/IL-10 ratios in response to zymosan, CL097, and β-glucan. High IL-1β/IL-10 ratio in response to CL097, an agonist of TLR7/TLR8, was especially striking. We also observed increase in production of TNF-α and IL-6 and decrease in the production of IL-10, as well. Given these findings, it is possible that maladapted trained immunity may have caused excessive inflammatory responses to various innate immune stimuli, which then led to developmental regression and fluctuating behavioral symptoms in this presented case.

4. Conclusions

Our deepening knowledge of innate immune memory (trained immunity vs. tolerance) has shed light on the understanding of nonspecific effects of microbial infection and other immune stimuli, which have been implicated in the onset and

progress of various neuropsychiatric diseases. Recent research indicates a possibility for a role of maladapted innate immune memory in various neuropsychiatric conditions. The finding of innate immune memory is especially exciting in the field of neuroimmunology, since we now likely have better tools for addressing the long-suspected role of immune-mediated inflammation that is not associated with specific pathogens or environmental factors, in various neuropsychiatric conditions. The concept of innate immune memory will be especially important in addressing insults to the brain during the early years of CNS development, and the resultant lasting intellectual disabilities, as seen in MIA models [70]. More importantly, an improved understanding of the role of innate immune memory (trained immunity vs. tolerance) in pathogenic neuroinflammation can lead to novel therapeutic measures that are desperately needed for the treatment of neuropsychiatric diseases.

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Conflict of interest

The author has nothing to declare.

Abbreviations

Ab	antibody
Ag	antigen
APC	Ag-presenting cells
ApoE	apolipoprotein E
ASD	autism spectrum disorders
BCG	Bacillus Calmette-Guérin
Brg1	brahma-regulated gene 1
BMDM	cell, bone marrow-derived microglial cell
CAPS	cryopyrin-associated periodic syndrome
CARS	compensatory anti-inflammatory response syndrome
CNS	central nervous system
DAMPs	damage-associated molecular patterns
EAE	experimental autoimmune encephalitis
GI	gastrointestinal
HIF-1α	hypoxia inducible factor-1α
IFN	interferon
IL	interleukin
IPLs	immune gene-priming lncRNAs
lncRNAs	long noncoding RNAs
IRAK	interleukin-1 receptor-associated kinase
LPS	lipopolysaccharide
MIA	maternal immune activation
MS	multiple sclerosis
MyD88	myeloid differentiation factor 88
mTOR	mammalian target of rapamycin

NF-κB	nuclear factor of κ chain of B cells
NK	natural killer
OxLDL	oxidized low-density lipoprotein
OXPHOS	oxidative phosphorylation
PAMPs	pathogen-associated molecular patterns
PBMCs	peripheral blood mononuclear cells
PBMo	peripheral blood monocytes
SHIP1	SH2 domain-containing inositol phosphatase 1
SPUH	Saint Peter's University Hospital
TCA	tricarboxylic acid
TLR	Toll-like receptor
TNF	tumor necrosis factor
TREM-2	triggering receptor expressed on myeloid cells 2
TRIF	TIR-domain-containing adaptor-inducing interferon-ß
TSC	tuberous sclerosis complex
UMLILO	upstream master lncRNAs of the inflammatory chemokine locus

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