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Principles of inflammasome priming and inhibition: Implications for psychiatric disorders

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Abstract

The production of inflammatory proteins by the innate immune system is a tightly orchestrated procedure that allows the body to efficiently respond to exogenous and endogenous threats. Recently, accumulating evidence has indicated that disturbances in the inflammatory response system not only provoke autoimmune disorders, but also can have deleterious effects on neuronal function and mental health. As inflammation in the brain is primarily mediated by microglia, there has been an expanding focus on the mechanisms through which these cells initiate and propagate neuroinflammation. Microglia can enter persistently active states upon their initial recognition of an environmental stressor and are thereafter prone to elicit amplified and persistent inflammatory responses following subsequent exposures to stressors. A recent focus on why primed microglia cells are susceptible to environmental insults has been the NLRP3 inflammasome. Its function within the innate immune system is regulated in such a manner that supports a role for the complex in gating neuroinflammatory responses. The activation of NLRP3 inflammasome in microglia results in the cleavage of zymogen inflammatory interleukins into functional forms that elicit a number of consequential effects in the local neuronal environment. There is evidence to support the principle that within primed neuroimmune systems a lowered threshold for NLRP3 activation can cause persistent neuroinflammation or the amplified production of inflammatory cytokines, such as IL-1 β and IL-18. Over the course of an individual's lifetime, persistent neuroinflammation can subsequently lead to the pathophysiological signatures that define psychological disorders. Therefore, targeting the NLRP3 inflammasome complex may represent an innovative and consequential approach to limit neuroinflammatory states in psychiatric disorders, such as major depressive disorder.

Keywords

NLRP3 inflammasome; Microglia; Psychiatric disorders; Innate immune system; Immune priming

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8. Declaration of interest
None.

1. Introduction

The ability to prepare and strengthen a response against threats – to be primed – is a principle readily adopted throughout our immune systems. A primed immune system aims to rapidly eliminate toxins or respond to environmental insults by lowering the kinetic threshold and the time needed to produce immunological responses. This ability is apparent within the adaptive immune system in how initial exposures to viral antigens prime the immune system to quickly and effectively eliminate viruses by immune cells, a feature we have leveraged to abolish once deadly viruses (Resik et al., 2013). Meanwhile, through an evolutionarily conserved mechanism that involves non-antigen specific recognition by pathogen recognition receptors (PRRs), the innate immune system has also exhibited the capacity to become primed (Perry and Holmes, 2014). However, as a consequence of decreased response thresholds primed immune systems are susceptible to spontaneous inflammatory bursts or persistent inflammation. The consequences of persistent inflammation or hypersensitive immune systems may compound over an individual's lifetime to alter homeostatic mechanisms and generate symptomatic pathologies. When this phenomenon occurs in the brain it will lead to decreased cognitive function and neural plasticity. In order to protect the brain a tightly regulated system would be required that is able to provide proper immune protection while buffering against persistent inflammation. Therefore, this review will focus on the NLRP3 inflammasome, a unique multiprotein complex that has recently been shown to play a central role in orchestrating the initiation and amplification of neuroinflammatory responses in primed neuroimmune cells, while increased activity of this complex is associated with heightened neuroinflammation. This review will also discuss the potential therapeutic approaches that target the NLRP3 inflammasome, and that may attenuate neuroinflammation and heightened immune activity observed in patients with a number of psychiatric disorders.

2. The neuroinflammatory pathway

2.1. Priming microglia of the innate immune system

The primary mediators of neuroinflammation are the innate immune mononuclear phagocytes found in the brain parenchyma, the microglia. These glial cells are unique from other myeloid derived cells in our body in that they originate from erythromyeloid progenitors of the fetal yolk sac and maintain the local brain population via self-replication (Kettenmann et al., 2013). This makes them particularly vulnerable to injury or toxins. As the only resident immune cells in the brain, microglia arrange themselves in a grid-like mosaic and act as first responders to endogenous and exogenous insults that appear in the brain. When surveilling the parenchyma, microglia adopt a morphological state defined by a ramified morphology and highly motile processes that allow it to maximize the efficiency and total area monitored by each microglia. The extending processes of resting microglia also interact with synaptic structures in an activity dependent manner (Kettenmann et al., 2013). Whether or not surveilling microglia processes alter synaptic activity or solely monitor synaptic stability is under investigation. Upon the recognition of an environmental toxin, a sterile stress signal, or the removal of an inhibitory signal (Hamerman et al., 2006) surveilling microglia polarize into active phenotypes defined by an amoeboid morphology, the

upregulation of immunoresponsive surface proteins such as major histocompatibility complexes (MHCII), chemokine receptors and NADPH, and produce immunomodulators such as inflammatory cytokines (Aloisi, 2001) or reactive oxygen species (ROS) (Block et al., 2007). While microglia serve as the principal source of inflammatory cytokines and ROS during immune activation in the brain, neurons and astrocytes can contribute lower levels of these neurotoxic intermediaries. Activated microglia and upregulated toxic secondary messengers do serve homeostatic functions, which include synaptic pruning during development and throughout a lifespan (Schafer et al., 2012), programmed death of both progenitor neurons in the subventricular zone (SVZ) of developing primates (Cunningham et al., 2013) as well as differentiated neurons in the cortical plate (Upender and Naegele, 1999), and the clearance of pathogenic or toxic material (Salter and Stevens, 2017). However, the persistent activation of microglia produce a neurotoxic environment by promoting neuroinflammation, unregulated synaptic pruning and loss of synaptic architecture, neurodegeneration, and proteinopathies (Salter and Stevens, 2017; Wohleb et al., 2018). These neuropathologies are key signatures in patients diagnosed with a variety of neurological disorders including Alzheimer's disease (AD) (Block et al., 2007; Simic et al., 1997), autism (Lee et al., 2017), and psychiatric conditions including major depressive disorder (MDD) (Beumer et al., 2012).

Microglia activation in response to injury or stimulation vary between regions of the brain (Hart et al., 2012). The intraregional variations in microglia function results from heterogeneous transcriptomes in distinct brain regions and as a result microglia have region specific immunoregulatory potential (Grabert et al., 2016). In the murine brain for example, microglia in the hippocampus and cerebellar regions exhibited considerably greater immunoreactivity as compared to those in the cortex or striatum. This unique cellular mosaicism of microglia kinetics suggests there are intraregional susceptibilities for microglia mediated neuroinflammation, synaptic remodeling and neuropathologies. Indeed, neuropathological manifestations in AD and MDD are more pronounced in certain brain regions. In each condition, neurodegeneration and synaptic loss is most prevalent the intermediate to deep laminar layers of the dorsolateral prefrontal cortex (Drevets, 2000; Kang et al., 2012) Understanding how microglia recognize intrusions or alterations in the brain equilibrium and how they translate danger signals into responses is therefore a critical step toward integrating neuroimmune activity with the development of these disorders.

2.2. Microglia activation and the NLRP3 inflammasome

One feature of microglia is that a second exposure to an environmental insult more readily transition microglia into an activated morphology (Perry and Holmes, 2014), elicits exaggerated inflammatory responses (Frank et al., 2016b, Frank et al., 2007) and unlocks latent neuropathologies of the initial stressor (Giovanoli et al., 2013). This phenomenon can be viewed as priming of the brain resident microglia cells. Although direct microglia-ligand interaction predominates the mode of microglia priming, peripheral administration of an inflammatory stimulus in the presence of an intact blood brain barrier (BBB) similarly activated microglia and promoted consequential neuropathologies (Wendeln et al., 2018). Understanding the mechanism of microglia priming may assist in understanding psychiatric

disorders that have neuropathologies consistent with hyperactivity in immune function. One biological mechanism that may account for the apparent memory observed in primed immune systems and that is known to encode and retain previous environmental experiences is epigenetic imprinting of DNA. For example, early childhood stressors increase methylation of immunosuppressive gene promoter regions and decrease their protein expression over a lifetime (McGowan et al., 2009). This epigenetic suppression of immunomodulatory genes may in part contribute to why early life psychological stressors increase one's susceptibility to elicit heightened inflammatory responses to stressors later in life (Carpenter et al., 2010). Recently, a different perspective has highlighted a potentially new mechanism in which the previous exposure to environmental insults increases the steady-state concentration of an activated NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome complex. The activity of this NLRP3 inflammasome complex and its tight regulation largely determines macrophage or microglia morphology, the magnitude of their neuroinflammatory responses and the time elapsed between the exposure to a stressor and the initiation of an inflammatory response (Lamkanfi and Kanneganti, 2010). As an illustration of its keystone role in orchestrating neuroinflammatory states, a transgenic NLRP3 knockout in a APP/PS1 line had microglia morphologies skewed toward a surveillant, M2-like, state, rather than the activated state that defines AD related gliosis and exhibited suppressed neuroinflammatory responses (Heneka et al., 2013). The unique kinetic properties of the NLRP3 protein and its associated complex, which this review will now focus on, suggest that it is a rate-limiting protein in the production of microglia neuroinflammatory responses. Its regulation may also represent a mechanism through which environmental insults permanently alter neuroimmune responses.

3. Priming and activation of the NLRP3 inflammasome

3.1. Structure and function

As part of a class of 22 NLR proteins that recognize sterile and pathogenic danger signals and initiate inflammatory responses, the NLRP3 protein contains a pyrin domain (PYD), a nucleotide binding domain (NBD) and a leucine rich repeat (LRR) (Lamkanfi and Dixit, 2014). Under tightly regulated conditions, the NLRP3 protein, in combination with ASC and caspase-1 proteins, forms a multiprotein inflammasome complex that is responsible for translating endogenous and exogenous stress signals into inflammatory responses. Activating an NLRP3 inflammasome requires a two-step paradigm, whereby an initial signal facilitates the transcription of the NLRP3 protein, while subsequent activating stimuli remove physical and kinetic barriers to promote the step-wise assembly of the multimeric complex. In this process, a bipartite adaptor protein ASC is first recruited to the PYD domain of NLRP3 via homotypic interactions to form an ASC speck complex, this speck complex then recruits pro-caspase-1 to facilitate its auto cleavage into caspase-1 and the activation of the heterotetrameric inflammasome complex (Latz et al., 2013). Once activated, the cysteine caspase-1 of the NLRP3 inflammasome cleaves zymogen inflammatory cytokines pro-IL-1 β and pro-IL-18 into their functional conformation.

Evident in this two-step activation paradigm are event and time-sensitive properties, which can prevent the aberrant production of inflammatory cytokines and what identify it as a rate

limiting mechanism in the production of neuroinflammatory responses. Unlike other inflammasome proteins complexes that initiate caspase-1 dependent inflammation, such as NLRP1, NLRC4 or Aim2 (Kaushal et al., 2015), NLRP3 function is event sensitive because it has no baseline activity in murine neuroglia, neurons and macrophages; its activity requires a transcriptional priming step to reach a certain threshold of cytoplasmic NLRP3 mRNA (Bauernfeind et al., 2011, 2009; Sanz and Di Virgilio, 2000). The NLRP3 is also temporally regulated because its activity requires specific sequential activation signals. An activating signal that precedes priming signals will not produce an active NLRP3 inflammasome complex or significant inflammatory responses (Sutterwala et al., 2014). In addition to gating inflammatory events, the NLRP3 inflammasome can influence the magnitude of inflammatory responses by anchoring the nucleation of ASC speck complexes with increasing surface areas at the microtubule organizing center (MTOC), a process which increases the potential binding sites for ASC speck mediated caspase 1-activation, and the amplification of cytokine production (Proell et al., 2013). These studies support the principal that the magnitude and realization of microglia neuroinflammatory responses are a function of the NLRP3 protein steady-state concentration, which is proportional to the number of transcriptional priming signals, or exposures to environmental insults (Fig. 1).

A number of unique features of the NLRP3 inflammasome further differentiate it from the other characterized inflammasome complexes. Experimental evidence to date has found that the NLRP3 inflammasome activity can be stimulated by structurally diverse toxic and as well as endogenous sterile insult signals generated during metabolic or psychological stress (Lamkanfi and Kanneganti, 2010). Other scaffold forming inflammasomes that contain caspase-1 activity such as AIM2, NLRC2, and NLRC4, appear restricted in the types of environmental toxic signals they can recognize (Schroder and Tschoop, 2010). For example, some contain specific domains that recognize dsDNA or bacterial flagellin, which facilitates ligand specific inflammasome oligomerization (Storek and Monack, 2015). Furthermore, as part of the NLRP family, in addition to AIM2, NLRP3 contains a PYD domain that forms ASC speck complexes by homotypic interactions with CARD-containing adaptor proteins and allows the inflammasome to generate greater inflammasome responses (Dick et al., 2016). One final consequential difference of the NLRP3 inflammasome is that while activation of caspase-1 activity in other inflammasomes results in pyroptotic or apoptotic mediated cell death (Fernandes-Alnemri et al., 2009; Inohara and Nunez, 2003; Tan et al., 2014), activation of the NLRP3 inflammasome can result in the transient secretion of inflammatory cytokines with no concurrent cell death (Compan et al., 2012; Gaidt et al., 2016; Schmidt and Lenz, 2012). This ability to produce temporary inflammatory responses may underlie the tight regulatory dynamics of the NLRP3 inflammasome and positions it as a central player in mediating non-apoptotic neuroinflammatory responses. Furthermore, by activating non-apoptotic inflammatory pathways, the NLRP3 inflammasome may support proper immune function without permanently altering neuronal structures. This feature would be evolutionary advantageous for the development of stable neural circuits in the human adult cortex and hippocampus, as their neuronal components have a limited or no potential for replacement via adult neurogenesis (Rakic, 1985; Sorrells et al., 2018). Within this context, future studies should investigate the regulatory dynamics and activity of the NLRP3 in these neurons. It is important to recognize however that the NLRP3

inflammasome has received the most attention from investigators, and future investigations into other inflammasomes may reveal overlapping agonists and kinetics that have been primarily attributed to the NLRP3.

3.2. NLRP3 transcriptional priming

Numerous environmental stimuli have been shown to prime microglia and cells of a myeloid origin while simultaneously promoting the transcription of the NLRP3 protein (Fig. 2). Mice provided corticosterone, a molecule intuitively associated with anti-inflammatory activity (Coutinho and Chapman, 2011), increased the basal levels of microglia NLRP3 mRNA and exacerbated inflammatory responses with subsequent stimulation with LPS or ATP (Busillo et al., 2011; Frank et al., 2014). Importantly, the corticosterone inducement of NLRP3 transcription was mediated both through canonical NF- κ B pathways and through a non-canonical pathway involving the glucocorticoid nuclear receptor (GR) (Busillo et al., 2011). The presence of a non-canonical route by binding of the GR to transcriptional binding elements is also supported by studies that found glucocorticoid receptor antagonists diminish both NLRP3 expression and amplified cytokine production in response to LPS (Frank et al., 2012). There is also evidence to suggest that the positive relationship between plasma corticosterone and NLRP3 expression may be an integral mechanism linking sympathetic nervous system activation with inflammation. For example, one study found that stress induced production of neuronal IL-1 β and microglia activation could be blocked with antagonists of β -adrenergic receptors (β -AR) (Wohleb et al., 2011). Whether this observed stress induced neuroinflammation is a result of direct stimulation of microglia β -AR receptors or through sympathetic production of cortisol (Ulrich-Lai and Herman, 2009) by activation of the hypothalamic paraventricular nucleus (PVN) (Khan et al., 2007) remains an important line of future investigations. An important negative feedback loop has also been observed between an activated NLRP3 inflammasome and glucocorticoid receptors, whereby the activated caspase-1 domain cleaves the GR to decrease glucocorticoid mediated transcriptional activity in leukemia leukocytes (Paugh et al., 2015). Whether or not this process also occurs in microglia has yet to be determined, but may represent one potential mechanism that accounts for the observed hormetic properties of cortisol (Joels, 2006). In addition to LPS and ATP, corticosterone transcriptional priming of the NLRP3 in microglia generated amplified neuroinflammatory responses when mice were subsequently exposed to methamphetamine (Kelly et al., 2012) and the Gulf War Toxin diisopropyl-fluorophosphates (O'Callaghan et al., 2015).

As sentinel cells of the innate immune system, microglia and macrophages are equipped to respond to both endogenous and exogenous insult signals. When infiltrating microbes or other pathogen associated molecular patterns (PAMP's) bind with members of the toll-like receptor (TLRs) family, microglia and macrophages shift their morphologies toward active phenotypes and induces the transcription of NLRP3 via Myd88 and NF- κ B pathways (Bauernfeind et al., 2009; Daniele et al., 2015; Facci et al., 2014; Hanamsagar, 2011; Mendlewicz et al., 2006; Rapsinski et al., 2015). Extracellular TLR2 receptors preferentially recognize pathogenic endogenous proteins and gram positive bacteria, whereas TLR4 exhibits greater affinity and responses to conserved bacterial moieties, most notably LPS derived from gram negative bacteria. Myeloid-derived cells also recognize endogenous

danger-associated molecular patterns (DAMPs), or sterile insult signals, that are released from neurons during cellular stress or neurotoxic conditions. Receptors for these ligands share a high degree of homology with TLR receptors, suggesting their ligands may overlap or may activate similar intracellular pathways. As an illustration, the receptor for advanced glycation end products (RAGE) and TLR 2/4 both recognize extracellular alarmin-high mobility group box protein-1 (HMGB-1) and initiate the transcription of NLRP3 via NF- κ B pathways. Under homeostatic conditions HMGB-1 acts as a nuclear regulator in neurons and astrocytes, but transitions into an extracellular regulator of immune cells during periods of excitotoxicity (Lotze and Tracey, 2005), necrosis (Scaffidi et al., 2002), high fat diets (Sobesky et al., 2016), psychological stress (Weber et al., 2015), or after traumatic brain injury (Frank et al., 2016a; Maroso et al., 2010; Stahel, 2012). This production of extracellular DAMPs like HMGB-1 by neurons during metabolic stress not only primes NLRP3 transcription but also primes microglia into activated phenotypes, which elicit amplified neuroinflammatory responses when subsequently exposed to environmental insults (Frank et al., 2016a; Weber et al., 2015). As the production of HMGB-1 in the brain has been shown to be a function of age (Fonken et al., 2016), its persistent stimulation of microglia overtime is considered a risk factor for the development of neuroinflammatory pathologies and depression-like symptoms following traumatic brain injury (Fenn et al., 2014). Additionally, increased RAGE expression on microglia and microglia reactivity during periods of psychological stress mediated the induction of depressive phenotypes (Franklin et al., 2018). Other ligands of the TLR class capable of activating murine microglia and priming transcription NLRP3 include the analgesic morphine and fragments of extracellular matrix hyaluronic acid (Iyer et al., 2009). Neuroimmune priming of spinal cord microglia by morphine was dependent on both direct agonism of a TLR4/Myeloid differentiation complex 2 oligomer (Wang et al., 2012) and on induction of HGMB-1 by morphine in neurons. Of note, NLRP3 inflammasome activity and production of IL-1 β prolonged pain following chronic constriction injury and represents a valuable target for opioid resistant forms of pain (Grace et al., 2016).

Another apparent autocrine mechanism that amplifies neuroinflammatory responses is through the production of other cytokines by microglia, or astrocytes, which act as sterile stimuli to increase NLRP3 expression in microglia and amplify inflammatory responses. The IL-1R receptor shares evolutionary conserved intracellular homologous domains with the TLR family, notably their TIR intracellular domain. It is therefore not surprising that IL-1R stimulation licenses similar intracellular molecular pathways as the TLR. Stimulation of IL-1R by IL-1 β or IL-1 α in murine macrophages promoted NLRP3 specific activity that necessitated a two-step activation paradigm (Franchi et al., 2009). The ability of IL-1 β to prime NLRP3 indicates autocrine or paracrine activation of myeloid cells may propagate neuroinflammatory responses. Tumor necrosis factor α (TNF- α), also in potentially an autocrine manner stimulates NLRP3 transcription through NF- κ B mediated mechanisms following its binding with TNF I or II receptors in human monocytes (Franchi et al., 2009) and murine macrophages (Bauernfeind et al., 2016) and microglia (Kuno et al., 2005). Furthermore, agonists of the β -adrenergic class of receptors have been experimentally observed to increase the transcription of NLRP3 related cytokines such as pro-IL-1 β in

microglia and to amplify neuroinflammatory responses (Johnson et al., 2013). Whether it does so, however, through increased NLRP3 expression has yet to be established.

3.3. NLRP3 activation and inflammasome assembly

A set of activating signals and non-transcriptional priming events are required to initiate the translation of the NLRP3 protein and the assembly of the NLRP3 inflammasome, once the intracellular mRNA concentration of NLRP3 reaches an activating threshold (Fig. 2). One of the most potent barriers preventing NLRP3 inflammasome assembly is small non coding RNA (miRNA) that tightly regulate both pre and post-translational activation of the NLRP3. Each miRNA has cell specific expression levels that determine the transcriptional threshold required to prime NLRP3 protein expression. The brain (Lech et al., 2010), and specifically the microglia (Halle et al., 2008), have some of the highest NLRP3 mRNA expression levels of all tissues in humans. Yet, in these studies immunohistochemical validation of protein expression did not correspond to NLRP3 mRNA, which suggests that tissue specific miRNA expression plays an important function in NLRP3 kinetics. Indeed, miR-223 (Bauernfeind et al., 2012) prevents translation of the NLRP3 mRNA by binding to the 3' untranslated region of NLRP3 mRNA. In addition to regulating the NLRP3 pre-transcriptionally miR-7 binds to conserved regions on the NLRP3 to prevent NLRP3 inflammasome assembly. Further studies are warranted to investigate if priming signals increases NLRP3 inflammasome activity by downregulating miR-223 or miR-7. The potency of pre-translationally regulating the NLRP3 by interfering RNA has been evolutionarily adopted by viruses, which dampen NLRP3 activity by binding to the same target site as did the miR-233, thus circumventing the immunomodulatory capabilities of the NLRP3 inflammasome (Gregory et al., 2011; Komune et al., 2011).

Once translated, NLRP3 proteins exist in close spatial proximity in the cytoplasm and form an inactive NLRP3 oligomeric complex (Compan et al., 2015, 2012). The phosphorylation status of numerous amino acid residues on both the NLRP3 and the ASC protein can determine the rate of NLRP3 inflammasome oligomerization both by electrostatic repulsion between phosphate groups, or by facilitating conformational rearrangement to promote the recruitment of scaffold proteins (Table 1). Phosphorylation of NLRP3 side chains also regulates post-translational priming events that are critical for NLRP3 inflammasome assembly, such as the deubiquitination of the NLRP3 protein LRR domain by the deubiquitinase BRCC3 (Juliana et al., 2012). Activation of the NLRP3 inflammasome by BRCC3 deubiquitination occurs following stimulation of macrophages with ATP. This activation mechanism is another unique regulatory feature that sets the NLRP3 apart from other inflammasomes NLRP4 and AIM2 (Py et al., 2013). Another post-translational covalent modification required for NLRP3 inflammasome assembly is ubiquitination of ASC by the HOIL-1L ubiquitinase of the linear ubiquitination assembly complex (LUBAC) (Rodgers et al., 2014). Furthermore, direct ATP binding and hydrolysis by the NACHT domain of NLRP3 also is a necessary posttranslational priming step required for NLRP3 activation (Duncan et al., 2007). Other post-translational priming events that are required for NLRP3 inflammasome activation include the disassociation from the NLRP3 LRR domain of the cellular stress response proteins SGT1 and HSP90, which are believed to maintain the steady state inactive conformation of NLRP3 (Mayor et al., 2007).

Sterile danger signals produced during prolonged neurological stress are established activation signals of the NLRP3 inflammasome. Extracellular ATP, as a transmitter of the purinergic signaling pathway, is released by neurons and astrocytes following excitotoxicity and trauma (Davalos et al., 2005) and is subsequently recognized by microglia receptors P2X7 or THIK-1 (Madry et al., 2018; Yaron et al., 2015). Activation of these receptors causes potassium efflux in microglia, which is a critical event for the activation of the NLRP3 inflammasome (Lamkanfi et al., 2009). Microbial pathogens also promote potassium efflux and NLRP3 activation in microglia, but via the formation of intramembranous pores. How microglia depolarization directly activates the NLRP3 inflammasome is currently under investigation. One group observed that potassium efflux influenced the activity of the cytosolic serine/threonine kinase NEK7 that binds with the LRR domain of NLRP3 to initiate the assembly of the NLRP3 inflammasome (He et al., 2016). Other studies established that perturbations in the cellular osmotic pressure as a consequence of potassium efflux is responsible for NLRP3 inflammasome activity (Compan et al., 2012). The molecular pathway that connects NLRP3 activation with osmotic pressure differentials involves the activation of pressure sensitive membrane bound calcium channels such as TRPM7 and TRPV2, which promote the influx of calcium (Nilius and Owsianik, 2011; Yaron et al., 2015). The influx of calcium, which can also be induced in microglia following stimulation of the $G\alpha_q$ protein-coupled receptors CASR (Lee et al., 2012) and GPCR6A (Rossol et al., 2012) by the extracellular DAMP calcium, potentially activates the NLRP3 inflammasome complex in a process that potentially involves decreasing the intracellular concentration of cAMP (Lee et al., 2012), regulating the enzymatic activity of NLRP3 related calcium-dependent kinases and phosphatases (Ahn et al., 2007; Stutz et al., 2017), or by causing mitochondrial buffering of cytosolic calcium and the formation of ROS by disturbances in the mitochondrial membrane potential (Baughman et al., 2011; Murakami et al., 2012).

Mitochondrial dysfunction in macrophages and microglia is observed in psychiatric disorders (Manji et al., 2012) and results in the overabundance of ROS, potentially as a result of depleted antioxidant reserves. Both cellular stress and a number of DAMPS promote ROS formation, the loss of mitochondrial membrane potential and the activation of NLRP3 in microglia including neurodegenerative associated respiratory chain inhibitors rotenone, tebunfenpyrad (Baughman et al., 2011) and paraquat (Chen et al., 2015), high glucose levels (Fan et al., 2017), intracellular silica, asbestos (Dostert et al., 2008), gout (Martinon et al., 2006), cholesterol crystals (Freigang et al., 2011), and the fatty acid palmitate (Wen et al., 2011). Inflammasome activation by ROS is unique to the NLRP3 inflammasome, as ROS scavengers did not prevent AIM2 and NLRC4 inflammasome activation (Bauernfeind et al., 2011). While some studies have suggested a mitochondrial lineage for NLRP3-activating ROS that is dependent upon voltage-dependent anion channels (VDACs) (Zhou et al., 2011), chemical inhibitors of mitochondrial complex I and complex II had no effect on NLRP3 activation (Dostert et al., 2008). Other studies suggest that improper phagocytosis of toxic materials leads to lysosomal membrane permeabilization (LMP) and subsequently activate NLRP3 by NOX-mediated ROS production or the release of acidic lysosomal contents into the cytosol (Hornung and Latz, 2010). Consistent with the complex activation kinetics of the NLRP3, however, a separate study found that in

macrophages mitochondrial ROS production and NLRP3 activation occurred upstream of LMP (Heid et al., 2013). Other enzymatic systems apart from mitochondrial or lysosomal known to produce ROS include xanthine oxidase, lipoxygenases, cyclooxygenases, and cytochrome P450. Though they have not yet been investigated in the context of NLRP3 activity, they may also contribute to its activation via stress induced ROS production. The downstream mechanisms responsible for NLRP3 activation by ROS have received significant attention as well. Hydrogen peroxide (H_2O_2) can promote the formation of ADP-ribose, which binds with the calcium influx channel TRPM2 to promote calcium influx and NLRP3 activation (Zhong et al., 2013). Alternatively, H_2O_2 may cause the disassociation of thioredoxin (TRX)-from the TRX interacting protein (TXNIP), which when released binds directly with the NLRP3 to promote its activation (Zhou et al., 2010). It is also possible that ROS mediated increases in intracellular redox potentials may promote NLRP3 assembly by promoting the formation of the evolutionarily conserved Cys-8 and Cys-108 disulfide bond, which may serve as an essential structural component between the PYD and NBD domain of an activated NLRP3 (Bae and Park, 2011). Importantly, NLRP3 activation and IL-1 β production during partial mitochondrial dysfunction and ROS formation is a transient phenomenon, as the restoration of membrane potential decreased NLRP3 mediated IL-1 β production (Ichinohe et al., 2013). In contrast, complete abrogation of mitochondrial membrane potential resulted in cytochrome C mediated activation of NLRC4/IPAF4 pyroptosis and cell death (Zhou et al., 2011). Thus, mitochondrial activity and its production of ROS may uniquely instruct the NLRP3 inflammasome to initiate non-pyroptotic activation of cytokines, but complete loss of mitochondrial function activates pyroptotic/apoptotic cell death. Further investigations into how NLRP3 and mitochondria interact will help to understand mechanisms of stress induced neuroinflammation.

3.4. Pyroptosis versus transient secretion of NLRP3 cytokines

Activation of NLRP3 caspase-1 can lead to a non-necroptotic mode of inflammatory cell death termed pyroptosis that is found in phagocytic cells – macrophages, monocytes, dendritic cells and activated microglia. Pyroptosis causes rapid efflux of cytokines, cell swelling, and lytic cell death that causes the release of intracellular DAMP's into the extracellular milieu. In the event of pathogen infection, pyroptosis enables the clearance of infection from the cell and its removal via neutrophils. An executive event for pyroptosis is caspase-1 cleavage of gasdermin D, a pore forming protein that has a similar kinetic profile to caspase-1 processing of IL-1 β (He et al., 2015). Activation of NLRP3 caspase-1 was previously considered a binary event; if activated, pyroptosis and cell death followed. But what is now apparent is that the NLRP3 inflammasome can initiate secretion of leaderless proinflammatory cytokines independent of pyroptotic mediated cell death. Understanding what molecular events arbitrate between the induction of pyroptosis versus inflammation independent of cell death is critical to understanding the neuroinflammatory potential and reactivity of neuroglia cells.

Species-specific differences in immune regulation between murine and human myeloid cells affect their tendencies for pyroptosis. While LPS and TNF- α both primed murine macrophages and human macrophages for IL-1 β production in response to ATP and Nigericin, murine macrophages were much more susceptible to pyroptosis than human

macrophages (Bezbradica et al., 2017). Additionally, an alternative NLRP3 inflammasome activation pathway has been observed in human monocytes that results in leaderless cytokine secretion without pyroptosis. This system forgoes the well characterized classical two-step activation paradigm in murine monocytes and macrophages and does not require potassium efflux, the time-lagged NLRP3 executive activation signal (Gaidt et al., 2016). Rather, stimulation of TLR4 by LPS recruited the TRIF-RIPK1-FADD-CASP8 axis, a group of proteins involved in inflammatory responses, which regulated posttranslational maturation of the NLRP3 protein and the secretion of IL-1 β without a time-lagged secondary activation signals. As there are a multitude of ligands for TLR4, including sterile DAMPs, this alternative non-pyroptotic mode of IL-1 β production by human myeloid cells may reflect a distinct form of leaderless inflammatory responses that would support chronic inflammatory conditions.

The type of activating signal can also influence the tendency for cells to undergo pyroptotic mediated cell death. In contrast to nigericin stimulation, activation of LPS primed murine macrophages with a hypotonic solution elicited NLRP3 dependent inflammatory responses without concurrent pyroptotic mediated cell-death (Compan et al., 2015). Disruption of glucose metabolism by hexokinase disassociation from the mitochondrial membrane also activated NLRP3 mediated inflammation independent of pyroptosis in murine macrophages (Wolf et al., 2016). Although microglia and peripheral blood mononuclear cells (PBMCs), such as macrophages, act as phagocytic antigen presenting cells, their divergence early in development suggests their immune responses may be differentially regulated. Therefore, insights into the regulation of NLRP3 in macrophages may not necessarily reflect the same regulatory dynamics of NLRP3 in microglia, especially in regards to their tendencies for pyroptosis or non-pyroptotic inflammation. One study found that murine microglia primed with LPS and then stimulated with the DAMP lysophosphatidylcholine led to NLRP3 mediated inflammation; however, cytotoxicity of microglia was not dependent on NLRP3 canonical or non-canonical activation (Freeman et al., 2017). An additional study using murine microglia also found that a two-step activation paradigm regulates NLRP3 inflammasome activation in response to TLR4 stimulation (Sanz and Di Virgilio, 2000). These studies were conducted in murine microglia, and species specific molecular regulatory cascades may support alternative regulation of the NLRP3 inflammasome in human versus murine microglia, as noted between murine and human primary monocytes and macrophages (Bezbradica et al., 2017; Gaidt et al., 2016). Furthermore, of the studies analyzing NLRP3 in murine microglia, almost all take hippocampal microglia. As described earlier, microglia metabolism and function exists as a unique mosaicism throughout the brain. It is therefore unknown whether microglia NLRP3 expression and activation is similarly regulated in preference to distinct CNS anatomical locations.

3.5. Inhibition of NLRP3 inflammasome priming and assembly

Deactivation of the inflammasome is essential to maintain homeostatic balance and to prevent aberrant production of inflammatory cytokines. Transcriptional priming of the NLRP3 and IL-1 β by both TNF and TLR receptors necessitate the recruitment of the IKK complex and activation of NF- κ B dimers in microglia. Suppression of this pathway is a critical means to downregulate and inhibit transcription of *NLRP3* and prevent aberrant

inflammation. Specifically, the TNF alpha-induced protein 3 (*TNFAIP3* or A20) plays a role in inhibiting NF- κ B mediated transcription of NLRP3 in myeloid and microglia cells derived cells. The precise regulatory function of A20 is yet to be fully characterized, but evidence indicates its deubiquitinase activity controls the transduction of TNFR/TLR signals into the nucleus by regulating the activity of RIPK1, RIPK3 and TRAF2 (Onizawa et al., 2015). In the absence of A20, NLRP3 expression is increased and there are heightened neuroinflammatory states.

As phosphorylation or dephosphorylation of the NLRP3 or ASC can activate the complex, these events may also inhibit it and promote its degradation (Hara et al., 2013; Lin et al., 2017). Lymphocytes such as CD4⁺ T cells also inhibit NLRP3 activity by binding with IFN γ receptors (Guarda et al., 2009). The inhibition of NLRP3 activity by the adaptive immune system may represent an important feedback mechanism to resolve innate immune inflammatory responses. As part of the innate immune feedback mechanism, in macrophages interleukin-10 inhibits NLRP3 production of IL-1 β , not through deactivation of the inflammasome, but by decreasing the transcription of NLRP3 mRNA following stimulation with LPS (Gurung et al., 2015). Activation of D1 dopamine receptors on microglia increases intracellular cAMP levels, which as mentioned inhibits the NLRP3 and promotes its degradation via ubiquitination (Yan et al., 2015). Previous reviews have detailed the intracellular proteins and mechanisms that either prevent the formation or inhibit the activity of the NLRP3 inflammasome (Kim et al., 2017).

4. NLRP3 inflammasome cytokines and their effects

4.1. NLRP3 related cytokines are also tightly regulated and have deleterious effects

The NLRP3 activated cytokines, IL-1 β and IL-18, also possess a unique two-step activation mechanism that is distinct from the production of other cytokines secreted via classical endoplasmic reticulum and golgi apparatus mediated exocytosis. IL-1 β and IL-18 mRNA do not contain an N-terminal localization signal for the endoplasmic reticulum (ER), are transcribed as cytosolic zymogens and require enzymatic cleavage by caspase 1. Comparatively, the other two primary cytokines released from activated microglia, IL-6 and TNF- α , exist as intramembranous proteins that require cleavage by the constitutively active secretase ADAM17 (Scheller et al., 2011) or are secreted by constitutive exocytosis. Therefore, the concentrations of active IL-1 β and IL-18 depend not only on their own transcriptional kinetics, but on the tightly regulated kinetics of the NLRP3 inflammasome. Interleukin 33, as part of the same cytokine family as IL-1 β and IL-18, has been shown to be functionally dependent on NLRP3 inflammasome activity (Martin and Martin, 2016); however, the precise relationship between the two remain tenuous as experiments have shown that the full length form of IL-33 has caspase-1 independent bioactivity and capsase-1 activation by NLRP3 can dampen IL-33 production (Madouri et al., 2015). Both activated IL-1 β and IL-18 provide trophic support to neurons and even enhance long-term potentiation at homeostatic concentrations (Mori et al., 2014), but when they are persistently or abundantly secreted they can alter synaptic activity and membrane polarization in the short term (Yu and Shinnick-Gallagher, 1994), and cause cytoarchitectural changes in the brain and support synaptic remodeling in the long term (Brown and Neher, 2010; Felger and

Lotrich, 2013; Miller et al., 2009). The central nervous system is particularly sensitive to the effects of IL-1 β and IL-18 because of the widespread expression of their receptors in the CNS and across multiple neural cell types. In addition, neuronal function is not only susceptible to cytokines synthesized in the brain, but recent evidence has illustrated that systemic inflammation influences the brain by reducing the permeability of the blood brain barrier allowing the influx of plasma proteins, or by activating the nucleus tractus solitarius (NTS) via binding to IL-1R on paraganglia vagal fibers (Maier et al., 1998). The identification of the exact interactions NLRP3 activated cytokines have with the local neuronal environment and what secondary systems they activate is critical to understanding potential contributions to psychiatric disorders (Fig. 2).

4.2. Non-canonical activation of IL-1 β and IL-18

In contrast to activation by extracellular stress signals, IL-1 β and IL-18 activation by NLRP3 following endocytosis of pathogens is regulated by a separate molecular pathway, defined as the non-canonical pathway. In murine macrophages, the non-canonical pathway involved direct interaction between caspase-11 and cytoplasmic bacterial pathogens, which subsequently activated NLRP3 and the production of IL-1 β (Kayagaki et al., 2011). Similarly, the human functional ortholog to caspase-11, caspase-4, mediated IL-1 β production in response to LPS transfection in an NLRP3 and caspase-1 dependent manner (Schmid-Burgk et al., 2015). The apparent non-canonical pathway for NLRP3 activation of IL-1 β folds into the debate over whether NLRP3 can directly interact with pathogenic particles via its LRR domain to promote its activity. The singular moiety of the NLRP3 LRR, and the structural diversity of potential agonists would support that NLRP3 activation is a result of the generation of secondary signaling cascades by pathogen or danger-associated molecular patterns, such as the production of ROS. Both microglia and macrophages phagocytose $\alpha\beta$ fibrils, but the subsequent activation of the NLRP3 inflammasome results from lysosomal swelling, lysosomal permeabilization, and secretion of lysosomal proteins such as cathepsin B (Halle et al., 2008). Microglial phagocytosis of Parkinson's Disease associated α -synuclein activated NLRP3 through an identical intracellular pathway (Codolo et al., 2013). Both processes were independent of fibril-NLRP3 interaction. The direct interaction between cathepsin B and the LRR of NLRP3 (Bruchard et al., 2013) further illustrates how multiple inflammogens can license the NLRP3 inflammasome through their convergence on a single secondary messenger molecule.

4.3. Neuronal-specific consequences of NLRP3 inflammasome mediated cytokine production

Both interleukin 1 β and interleukin 18 undergo regulated exocytosis into the extracellular space and bind with their respective receptors IL-1R and IL-18R expressed throughout nervous system (Fig. 3). Upon binding of the subunit to their respective cytokines, the receptor undergoes dimerization with cell-specific intramembranous adaptor proteins (Miyoshi et al., 2008; Srinivasan et al., 2004). The downstream effects of either interleukin are dependent upon the type of adaptor protein expressed within the cell. For example, in neurons, binding of IL-1 β with IL-1R causes the recruitment of the neuron specific adaptor protein AcPb (Qian et al., 2012) which mediates NDMR 2b phosphorylation, calcium influx, and excitotoxicity (Huang et al., 2011); a potential mechanism linking IL-1 β overproduction

with exacerbated seizures (Vezzani and Baram, 2007). Meanwhile, binding of IL-1 β with IL-1R on glia lineage cells recruits the AcP adaptor protein, which is predominantly expressed on astrocytes and microglia, and promotes NF- κ B mediated transcription of other inflammatory cytokines such TNF- α (Chung and Benveniste, 1990) and IL-6 (Basu et al., 2002; Cahill and Rogers, 2008; Woiciechowsky et al., 2004) suggesting that IL-1 β plays an executive role in formation of neuroinflammatory responses. Binding of IL-1 β to IL-1R in astrocytes also activates nitric oxide synthase and the production of ROS (Lee et al., 1993). Meanwhile, the binding of IL-18 to its IL-18R α receptor recruits adaptor protein IL-18ApCl, abundant in microglia and astrocytes (Miyoshi et al., 2008), to initiate their dimerization and signal transduction of NF- κ B or STAT3 mediated transcription of pro-IL-1 β , IL-6, and TNF- α (Wheeler et al., 2003). Similar to IL-1 β , IL-18 can also induce immediate physiological changes by altering the activity of synaptic receptors. Specifically, in-vitro experiments using hippocampal neuronal cultures found that IL-18 decreased field excitatory post synaptic potential (fEPSP's) of NMDR receptors to inhibit long-term potentiation (LTP) (Curran and O'Connor, 2001).

The recruitment of IL-1R adaptor proteins by IL-1R following its stimulation by IL-1 β may mechanistically connect IL-1 β overproduction with decreased dendritic spine density (Tomasoni et al., 2017), synapse loss (Mishra et al., 2012), and impeded long term potentiation (Hein et al., 2010) and contextual and spatial memory (Prieto et al., 2015). The post-synaptic IL-1RAcP isoform binds with high affinity to the presynaptic protein tyrosine phosphatase δ to bidirectionally induce synaptic differentiation of cortical neurons (Yoshida et al., 2012). The presence of intra-synaptic IL-1 β increases the ratio of synaptic AcP/AcPb adaptor proteins and decreases synaptic plasticity (Prieto et al., 2015). Decreased synaptic stability as a result of a higher AcP/AcPb ratio may be a direct consequence of AcP having a lower affinity for presynaptic PTP δ than AcPb (Yamagata et al., 2015). Therefore, binding of IL-1 β to neuronal IL-1R may alter synaptic activity and prevent neurite outgrowth by disrupting the number or equilibrium of intra-synaptic cellular adhesion proteins. This is important to consider as alterations in homeostatic mechanisms that control the synaptic steady state, particularly in brain regions involved in emotional processing such as the limbic region, are implicated in the etiology of depression (Duman and Aghajanian, 2012). Additionally, in light of the view that neuronal inflammation is a preclinical symptom of AD (Monson et al., 2014) it is tempting to conjecture that IL-1 β mediated synaptic maladaptation may create imbalances in metaplasticity and the firing stability of cortico-hippocampal circuits, a phenomenon that is hypothesized to be a driving force of early-stage AD pathophysiology (Styr and Slutsky, 2018).

IL-1 β can also potentially elicit short term behavioral changes through its modulation of monoaminergic, GABAergic, and glutamatergic synaptic transmission. In murine models, IL-1 β facilitated the endocytosis of astrocytic glutamate transporters and decreased the reuptake of synaptic glutamate (Hu et al., 2000). The ensuing excitotoxicity caused by extracellular glutamate resulted in the production of mitochondrial ROS and neuronal atrophy (Sheng et al., 2013). IL-1 β may also promote hyper excitability by phosphorylating post-synaptic GABA $_A$ receptors and decreasing their affinity for intracellular GABA (Yu and Shinnick-Gallagher, 1994). In addition to regulating membrane-bound receptors, IL-1 β promotes the activity of serotonin reuptake receptors, which decreases intra-synaptic

concentrations of serotonin (Zhu et al., 2006). Further investigations are warranted into the relationship between IL-1 β and serotonin transmission given the putative beneficial effects of serotonin re-uptake inhibitors in treating patients with depression.

4.4. NLRP3 mediated recruitment of humoral immunity

The recruitment of the adaptive immune system by the innate immune system is a critical event for resolving threats and foreign substances. Recent investigations suggest that NLRP3 activity and its production of cytokines orchestrate the recruitment of adaptive immune cells and other peripheral monocytes into the brain (Fig. 4) when exposed to pathogenic materials or during periods of metabolic or psychological stress. The recruitment of the adaptive immune system by the innate immune system is most accurately described by a two tiered immunological response paradigm (Iwasaki and Medzhitov, 2015). In this model, the initial recognition of a stressor signal by type 1 immune cells, like microglia, promotes NLRP3 production of IL-1 β and IL-18, which are type 1 cytokines that are designed to recruit type two immune cells such as innate like lymphocytes and T-helper lymphocytes into the affected area. Once present these effector cells secrete type two cytokines such as IL-17 and interferon gamma (IFN γ) that are responsible for resolving the threat either through direct activation of intrinsic apoptotic pathways or through their ability to activate and recruit effector cells such as macrophages, eosinophils, and cytotoxic T-cells, which can then phagocytose toxic material or stressed cells (Iwasaki and Medzhitov, 2015). The recruitment of monocytes and leukocytes into the brain is implicated as an important event that drives pathologies in autoimmune disorders such as multiple sclerosis. In addition to autoimmune disorders, recruitment of peripheral monocytes into the brain parenchyma has been recently shown to be directly responsible for anxiety like phenotypes in mice following periods of psychological stress (Wohleb et al., 2018, Wohleb et al., 2013). Some debate exists over whether recruited peripheral monocytes infiltrate the brain parenchyma and directly interact with neurons or remain the perivascular space, where they generate depressive phenotypes via the production of inflammatory cytokines that diffuse across the brain parenchyma (Menard et al., 2017). When further investigating the indispensable components of monocyte infiltration into the brain using models of experimental autoimmune encephalitis (EAE) and stress-induced anxiety, it was established in both that the recruitment and activation of peripheral monocytes was dependent upon either a functional NLRP3 inflammasome or the activity of NLRP3 activated cytokines. Using a repeated social defeat paradigm as a model of psychological stress, subjected mice exhibited anxiety like phenotypes that correlated with peripheral monocyte infiltration into regions of the brain associated with emotional processing and heightened microglia reactivity; both monocyte infiltration and anxiety like phenotypes in this model were dependent upon a functional IL-1R (Wohleb et al., 2014, 2011). A putative role IL-1 β in recruiting leukocytes into the brain was further confirmed by a IL-1 β ^{XAT} transgenic mouse line, which elicits persistent hippocampal IL-1 β production, and which facilitated T_h and T_k lymphocyte infiltration into the brain parenchyma without additional stimulus (Shaftel et al., 2007). In a model of chronic herpes encephalitis, the sequential recruitment of phagocytes and neutrophils followed by CD8+ and CD4+ lymphocytes into the brain parenchyma (Marques et al., 2008) and autoimmune symptomology was dependent upon a functional NLRP3 inflammasome (Inoue et al., 2012a).

In addition to promoting the recruitment of peripheral immune cells into the brain, NLRP3 production of IL-1 β and IL-18 contributes to the polarization of undifferentiated CD4⁺ T Cells into either a Th17 or a Th1 lineage, respectively (Acosta-Rodriguez et al., 2007; Chaix et al., 2008). Once in the brain parenchyma differentiated lymphocytes act as effector immune cells and secrete a variety of cytokines or directly interact with parenchymal cells to respond to specific environmental threats. In doing so, they have detrimental effects on the tissue. Lymphocytes of the Th17 lineage promote blood-brain barrier permeability by secreting IL-17 and IL-23, two cytokines that decrease the strength of BBB epithelial tight junctions (Kebir et al., 2007). Differentiated CD4⁺ Th1 leukocytes specifically secrete interferon gamma in response to IL-18 (Okamura et al., 1998), while both IL-18 and IL-1 β can promote IL-17 production from CD4⁺ and NK killer cells (Lalor et al., 2011). In addition to causing neurotoxicity singularly by binding with neuronal FAS (Flugel et al., 2000), CD4⁺ secretion of IL-17 and IFN γ causes neurotoxic conditions through activating of CD8⁺ T lymphocytes and activating downstream inflammatory events that is suggested to drive neurodegenerative pathologies (Beringer et al., 2016; Coutinho and Chapman, 2011; Taylor et al., 2014). The differentiation of leukocytes into both Th1 and Th17 lineage leukocytes and their migration into the brain was shown to be dependent upon a functional NLRP3 in an experimental autoimmune encephalomyelitis model (Gris et al., 2010), which provides a potential therapeutic approach for brain specific autoimmune disorders.

The consequences of infiltrating and differentiating peripheral monocytes into the brain are well characterized and are known to contribute to the etiology of autoimmune disorders such as multiple sclerosis (MS). In spite of the fact that patients with MDD exhibit similar neuropathologies to patients with autoimmune disorders, much is unknown about how monocyte infiltration may contribute to MDD besides preliminary studies suggesting they may exacerbate microglia synaptic pruning (Wohleb and Delpech, 2017). Like patients with MS or other brain autoimmune disorders, patients with MDD have decreased cortical or subcortical volume. Subjects with MDD have an overall decreased volume of grey matter (Matsuo et al., 2017), and more specifically regions of the brain associated with emotional processing such as the area 9 of the dorsolateral pre-frontal cortex (Cotter et al., 2002) and the amygdala (Hamidi et al., 2004). Furthermore, in subjects with Gulf War Veterans Illness (GWVI), a set of disorders specific to veterans of the Gulf War and characterized by fatigue, memory impairment, and depression, there was an established increase of subcortical atrophy, which was increased in veterans who lacked the DRB1*13:02 HLA Allele (James et al., 2017). This MHCII allele is known to confer protection against auto inflammatory conditions such as rheumatoid arthritis (Feitsma et al., 2008) and provides an interesting link between autoinflammatory conditions and genetic contributions to pathogen recognition by the innate immune system. Future investigations should continue to explore how stress induced monocyte recruitment may alter neuronal structures and functions in a region specific manner and how the effects of this process may generate emotional susceptibilities to psychological stressors, often observed in patients with MDD. A key component toward to understanding this mechanism is the role that NLRP3 plays in facilitating the infiltration of peripheral monocytes.

5. Inflammasomes: at the nexus between inflammation and psychiatric disorders

5.1. Cytokine hypothesis of depression

The relationship between psychiatric disorders and the activation of the innate immune system is well-debated, with arguments and evidence supporting a reciprocal relationship between inflammation and brain function (Capuron and Dantzer, 2003; Raison et al., 2006). One central question in considering the extent of their relationship is whether increased inflammatory cytokines directly elicit the symptoms of psychiatric disorders, or would their altered expression levels in patient populations be a result of, or a secondary symptom to structural neuropathologies found in psychiatric populations such as altered cellular densities in the brain (Rajkowska et al., 2007), a skewed steady state of synaptic structures (Duman and Aghajanian, 2012; Rakic et al., 1994), or disruptions in the transmission or metabolism of monoamines? This begs the question, can psychiatric symptoms resolve only after the resolution of cytoarchitectural abnormalities? Addressing this question, accumulating clinical and preclinical evidence has indicated that the production of cytokines in the brain both elicits short-term oscillations in behavioral phenotypes, as well as orchestrates secondary inflammatory responses that can contribute to neuropathologies that are observed in patients with certain psychiatric disorders.

5.2. NLRP3 inflammasome cytokines influence behavior

Cytokines were first considered as an etiological root of depression in Smith's (Smith, 1991) macrophage theory of depression, and gained further traction when inflammatory cytokines were observed to mediate sickness-behavior (Dantzer et al., 2008). Based upon this, recent research has more readily adopted the function of the neuroimmune system, and specifically cytokines, in the etiology of psychiatric disorders (Schiepers et al., 2005). In addition to preclinical *in-vitro* studies that have established direct interactions between IL-1 β and IL-18 and proteins that regulate synaptic activity (see Section 4.3) clinical observations have also strengthened a neuroimmune root of psychiatric conditions. Such studies have found that 30–50% of cancer patients who received chronic treatment with interferon- α developed major depression over the course of their treatment (Capuron et al., 2002); prior admission to a hospital because of an autoimmune disease increased the risk to develop a mood disorder by 45%; prior hospital admission for infection increased the risk for mood disorders by 62% (Benros et al., 2013). Furthermore, male patients who are at a higher risk of developing MDD are more susceptible to stress induced inflammatory responses (Pace et al., 2006) and the remission of MDD symptoms is associated with the normalization of plasma cytokine levels (Hestad et al., 2003). How the production of cytokines by NLRP3 contributes to these observations will provide insight into its role in the etiology of psychiatric disorders.

Clinical studies involving patients with a subset of psychiatric disorders have found increased concentrations of NLRP3 activated cytokines in both their cerebral spinal fluid (CSF) and serum (Table 2). As outlined in Table 2, these psychiatric disorders include MDD, and bipolar disorder. Other inflammatory cytokines stimulated by IL-1 β or IL-18 through either autocrine or paracrine mechanisms, such IL-6 and TNF- α (Cahill and Rogers, 2008),

are also consistently increased in the serum of patients with MDD (Anisman et al., 1999; Howren et al., 2009; Lanquillon et al., 2000; Mikova et al., 2001; Sluzewska, 1999). Although multiple studies have found altered concentration levels of IL-1 β and IL-18 in patients with MDD, a meta study only found increased peripheral levels of IL-6, TNF- α and IL-10, whereas the levels of IL-1 β were not significantly altered (Haapakoski et al., 2015). Further studies are required to understand this discrepancy and to ensure consistent testing methodologies and sampling techniques. Of note, the magnitude of peripheral inflammation in depressive patients is marginal compared to pathogen-evoked or injury induced levels of peripheral inflammation. However, chronic subclinical inflammation is a known risk factor for diseases co-morbid with depression such as diabetes and heart disease (Herder et al., 2018), and may similarly contribute to depressive like symptoms as a function of time. There are also limitations in measuring *in vivo* neuroinflammation, the majority of clinical studies measure plasma cytokine markers to quantify systemic inflammation and a few studies take samples from the cerebral spinal fluid. Therefore, these studies may not accurately reflect neuroinflammation occurring in patients with psychiatric disorders. The most accurate gauge of neuroinflammation should come from post-mortem tissue of patients or *in vivo* radio ligand imaging. For example, tissue from the frontal cortex of patients with bipolar disorder (Rao et al., 2010) had an increased expression pattern of both IL-1 β and its receptor IL-1R. However, no studies to-date have examined IL-1 β or IL-18 expression patterns of post-mortem tissue samples of patients presenting with MDD. One *in vivo* study using the radioligand [^{18}F]FEPPA PET to measure the translocator protein binding, which is known to have increased expression levels in microglia when they are in an activated state (Rupprecht et al., 2010), found increased binding patterns in all regions of the brain in patients during a major depressive episode (Setiawan et al., 2015). This *in vivo* study complements observations using post-mortem tissue from depressive suicide patients, which found an increase in the ratio of activated vs. ramified microglia in the dorsal anterior cingulate region of the cortex (Torres-Platas et al., 2014). Combined with the observations that the NLRP3 inflammasome both steers microglia toward an activated morphology (Heneka et al., 2013) as well as is required for that stress induced depressive behavior in mice (Alcocer-Gomez et al., 2016), these *in vivo* studies of microglia reactivity in MDD patients indicate that the NLRP3 may contribute to their heightened neuroinflammatory states.

In addition to psychiatric disorders, evidence supports that NLRP3 over activity plays a role in the development of AD, as post-mortem brain tissue from these patients have both an increase in the expression of IL-1 β and IL-18 (Mrak and Griffin, 2001; Ojala et al., 2009). Additionally, mice of the APP/PS1 line crossed with a NLRP3 $^{-/-}$ or Casp1 $^{-/-}$ mouse line did not exhibit neuropathologies associated with APP/PS1 Alzheimer model including a reduction in the spinal density of hippocampal pyramidal neurons, spatial memory impairment, or $\alpha\beta$ plaque aggregation (Heneka et al., 2013). In spite of the shared inflammatory profile, synaptic loss, and studies that found depression serves as a risk factor for the development of dementia (Masters et al., 2015) no direct mechanism has been established connecting depression and neurodegenerative disorders. The precise relationship, if any, between depression and neurodegenerative disorders and the role the NLRP3 inflammasome plays in it requires further analysis.

5.3. Genetic susceptibility to depression from NLRP3 related proteins

Genetic polymorphisms of the NLRP3 gene as well as of genes that correspond to proteins associated with NLRP3 inflammasome activity often generate both autoinflammatory pathologies as well as neurological complications. For example, germline mutations in the NLRP3 gene, which cause a rare hereditary autosomal-dominant inflammatory condition labeled cyro-associated proteins syndromes (CAPS), defined by typical auto inflammatory symptoms such as rashes, fever and arthritis, also generates neurological manifestations such as headaches, migraine, fatigue, learning disability, amyloidosis, and in severe cases seizures (Arostegui et al., 2010; Kitley et al., 2010; Parker et al., 2016). CAPS can also manifest itself via somatic mutations in bone marrow derived monocytes (Arostegui et al., 2010; Gossrau et al., 2003; Looock et al., 2010). Patients presenting with these NLRP3 somatic mosaicisms also exhibit neurological complications akin to Schnitzler syndrome and supports the principle that peripheral NLRP3 activation can effect central nervous system function. In looking at the types and locations of NLRP3 mutations associated with neurological complications, the most prevalent mutations were Thr348Met, Val198Met, and Arg260Trp single nucleotide polymorphisms (SNP) (Cuisset et al., 2011). The most severe phenotypes resulted from Thr348Met and the Asp303Asn mutations (Mortimer et al., 2016; Nakagawa et al., 2015). Each of these mutations preside within the NACHT binding domain of the NLRP3 and are structurally proximate to an hypothetical ATP-binding site (Neven et al., 2004), suggesting that NLRP3 mediated complications in these disorders may be a consequence of bypassing the kinetic barrier of ATP hydrolysis in the NACHT domain. In support of this, one group found that stimulation of CAPS patients PBMCs with ATP secreted comparable IL-1 β to normal patient PBMC, but secreted higher levels when stimulated with LPS (Gattorno et al., 2007). The crystal structure for the NLRP3 NACHT domain has yet to be resolved. Targeting the ATP-binding pocket in other kinases with gain of function mutations through rational drug design of small molecule inhibitors has successfully attenuated their over activity (Liu and Gray, 2006). Therefore, future pharmacological approaches to target NLRP3 hyperactivity may necessitate resolving the NLRP3 inflammasome structure.

Genetic polymorphisms in genes involved in molecular pathways downstream or upstream of NLRP3 inflammasome function also effects brain function and increases individual's susceptibility for developing psychiatric disorders. Single nucleotide polymorphisms in the genes of cytokines activated by NLRP3, IL-1 β (Baune et al., 2010; Hwang et al., 2009; Rosa et al., 2004) and IL-18 (Haastrup et al., 2012), increase the risk to develop depression, while polymorphisms in IL-1 β also increases the risk for substance dependency (Liu et al., 2009) and schizophrenia (Clerici et al., 2009). Polymorphisms in the IL-1 β gene were located in its promoter region and resulted in the increased production IL-1 β . Given the role NLRP3 has in activating IL-1 β , it is tempting to suggest that priming of NLRP3, increased NLRP3 activity, and its production of IL-1 β may yield similar psychological susceptibilities. Polymorphisms in proteins involved in the upstream regulation of the NLRP3 inflammasome and IL-1 β secretion such as indoleamine-pyrrole 2,3-dioxygenase (Cutler et al., 2012) (IDO) and the membrane bound receptor P2X7 (Caseley et al., 2014) also generate a susceptibility to develop psychiatric disorders. As previously described in Section 3.3, the P2X7 protein recognizes extracellular ATP and when bound to it initiates signaling cascades

that activates the NLRP3 inflammasome and inflammation. Because extracellular ATP is prevalent in many neurological disorders, in addition to MDD, P2X7 is being investigated as a therapeutic target across a range of neurological disorders (Sperlagh and Illes, 2014).

6. Inhibition of the NLRP3 inflammasome and neuroinflammation

6.1. Initial attempts to target psychiatric disorders with anti-inflammatory medications

Given the evidence supporting a relationship between neuronal inflammation and psychiatric disorders, previous clinical efforts had attempted to treat depression and other psychiatric disorders with established anti-inflammatory therapies. Treating MDD patients with serotonin re-uptake inhibitor (SSRI) and adjunctive treatment of a COX-2 inhibitor was associated with a significant decrease in major depressive symptomology (Abbasi et al., 2012; Akhondzadeh et al., 2009; Mendlewicz et al., 2006; Muller et al., 2006; Nery et al., 2008). As a side note, which highlights the potential role of NLRP3 in this mechanism, neuronal IL-1 β expression is responsible for the transcriptional induction of COX-2 (Molina-Holgado et al., 2000), an enzyme that subsequently catalyzes the activation of the pro-inflammatory compound prostaglandin E2 (Williams and Shacter, 1997). Another set of clinical trials tested the antidepressant capacities of TNF- α antagonists such as Infliximab (Remicade), and found that three infusions of the medication were found to be no more effective than a placebo (Raison et al., 2013). A subgroup of patients with higher levels of C-reactive protein did experience modest benefits, however. Other clinical trials using anti-inflammatory medications for other primary indications such as psoriasis and rheumatoid arthritis also measured changes in depressive symptoms as a second outcome (Kappelmann et al., 2018). The IL-6 decoy receptor Tocilizumab (Traki et al., 2014) and the IL-4 Receptor agonist Dupilumab (Simpson et al., 2017), both showed statistically significant improvements in depressive symptoms. Collectively, the modest success of clinical trials targeting inflammatory pathway in depression provide rationale to pursue novel targets within neuroinflammatory pathways of depression.

6.2. Directly targeting NLRP3 inflammasome activity

Targeting the NLRP3 inflammasome through pharmacologic methods represents an innovative approach to decreasing neuroinflammatory responses within psychiatric conditions. Given the unique kinetics of the NLRP3 inflammasome, it would be possible to attenuate NLRP3 activity by preventing its assembly, inhibiting upstream proteins involved in its activation, or preventing transcriptional priming of NLRP3. As described in Table 3, there are numerous FDA approved therapeutics that target upstream activators of NLRP3 activation and NLRP3 transcriptional priming, as well as a set of preclinical compounds that target the assembly of the NLRP3 inflammasome. The most effective therapeutic design would likely target the assembly of the NLRP3 inflammasome, as there are diverse priming and activation signals that converge with the assembly of the NLRP3 inflammasome.

The pre-clinical small molecular entity, MCC950, inhibits the assembly of the NLRP3 inflammasome by both canonical and non-canonical pathways (Coll et al., 2015). Importantly administration MCC950 did not affect the NLRP3 priming phase, as treatment with MCC950 before stimulation with TLR ligands did not affect pro-IL-1 β levels. The

initial validation of its therapeutic ability to decrease inflammatory responses was observed using a model of experimental autoimmune encephalomyelitis, in which its administration decreased the concentration of circulating IL-18, IL-1 β and IL-6. Furthermore, using peripheral bone marrow cells from individuals with Muckle-Wells Syndrome (MWS), pretreatment with MCC950 before LPS stimulation dose-dependently inhibited processing of IL-1 β and caspase-1. The concurrent reduction in peripheral IL-6 provides additional support that NLRP3 activity and IL-1 β is an upstream regulator of IL-6. Brain penetrability and efficacy in attenuating neuroinflammation was confirmed when mice administered MCC950 24 h post traumatic brain injury had significant improvements in neurological function as well as decreased IL-1 β and caspase 3 mediated apoptosis (Ismael et al., 2018). Another molecular entity under preclinical development targeting the NLRP3 inflammasome leverages oxaborine moieties (Baldwin et al., 2017). However, in preclinical studies when compared to MCC950, the oxaborine compound failed to elicit the same dose-dependent reduction of IL-1 β in NLRP3^{-/-} mice administered LPS. Currently, MCC950 is the most advanced therapeutic that is known to directly target NLRP3 inflammasome assembly. Future pharmacological methods to inhibit the NLRP3 inflammasome may involve the targeting the ATP NACHT binding site of NLRP3, as briefly mentioned in Section 5.3.

6.3. Indirect targeting of NLRP3 inflammasome activity

Previous reviews (Baldwin et al., 2016) have detailed FDA approved and preclinical compounds that target the upstream activators of NLRP3 inflammasome assembly seen in Fig. 2. Compounds of note include glyburide which targets potassium efflux from ATP-sensitive potassium channels and has shown the ability to inhibit IL-1 β production. The compound Bay 11-7082 inhibits NLRP3 inflammasome assembly through its alkylation of catalytic cysteine residues in the NACHT ATP binding domain of NLRP3; however it exhibited poor pharmacological properties for clinical trials including low bioavailability and solubility (Juliana et al., 2010). Potassium ion channel blockers nimodipine and nitrendipine, the ROS inhibitor diphenylene iodonium and P2X7 antagonists all prevented NLRP3 mediated IL-1 β maturation, but their clinical development was discontinued due to toxicity or insufficient clinical efficacy. Ibrutinib, which inhibits the BTK kinase, prevented NLRP3 mediated neuroinflammation and infarct volume growth in a mouse model of ischemia (Ito et al., 2015). Alternative approaches to limiting NLRP3 activity involve targeting transcriptional priming of the NLRP3 inflammasome. An antibody against the RAGE1 receptor, which facilitates HMGB-1 signaling in microglia, significantly attenuated neuroinflammation, microglia reactivity, and maintained the integrity of the blood barrier in a mouse model of traumatic brain injury (Kim et al., 2006). Inhibiting the RAGE1 receptor with BoxA similarly inhibited HMGB1 transcriptional priming of NLRP3 and IL-1 β maturation in mice microglia when exposed to chronic stress (Weber et al., 2015). More recent approaches involve using antagonists of the glucocorticoid receptor (Busillo et al., 2011) or of the TNF α R (McGeough et al., 2017) to prevent NLRP3 transcriptional priming. However, given the polymorphic forms of NLRP3 transcriptional priming it would be difficult to prevent NLRP3 transcription by inhibiting one pathway or even two of these pathways.

Certain immunotherapeutic approaches have shown preclinical and clinical efficacy in inhibiting the NLRP3 inflammasome in autoinflammatory conditions. Both IFN γ and interferon beta (IFN β) inhibit NLRP3 inflammasome activity via the stimulation of nitric oxide production by nitric oxide synthase and increased NLRP3 S-nitrosylation that inhibits ASC speck formation and inflammasome assembly (Guarda et al., 2011; Mishra et al., 2013). Importantly, type 1 interferons selectively inhibit caspase 1 activity of an activated NLRP3 inflammasome over other inflammasomes AIM2 and NLRC4, potentially due to the NLRP3 C-terminal susceptibility for S-nitrosylation (Hernandez-Cuellar et al., 2012). Interferon beta may also inhibit the NLRP3 inflammasome activity indirectly via the production of IL-10 and autocrine reduction of pro-IL-1 β . In clinical settings, the therapeutic efficacy of IFN β in multiple sclerosis is believed to be partially a result of its ability to inhibit the NLRP3 inflammasome, as its efficacy was dependent upon gain of function NLRP3 mutations. (Inoue et al., 2012b; Inoue and Shinohara, 2013).

7. Conclusion

Neuroinflammatory priming is designed to protect the brain against psychological stressors and several environmental insults across a lifespan. Recent studies have keenly illustrated how the NLRP3 inflammasome may play a keystone role in facilitating this process. However, priming of neuroinflammatory responses is double edged. It may be more readily capable of responding the threats, but by removing certain barriers that prevent aberrant inflammation it also increases the susceptibility to elicit inflammatory responses. The contributions the NLRP3 inflammasome has towards primed neuroinflammatory responses may therefore represent a novel therapeutic approach to target heightened neuroimmune activation that can play an important role in the etiology of psychiatric disorders, in particular major depressive disorder.

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Fig. 1.

Priming of NLRP3 in microglia cells, neuroimmune function, and clinical implications: while the initial exposure to an insult (either a pathogen or a sterile signal) may not elicit a pronounced neuroinflammatory response, subsequent insults elicit amplified neuroinflammatory responses. This phenomenon is related to transcriptional priming of the NLRP3 mRNA by the initial insult, which lowers the kinetic threshold for NLRP3 inflammasome assembly and activity. Evident in Fig. 1 is the principal that neuroinflammatory response thresholds are inversely related to NLRP3 mRNA expression. While symptoms may not necessarily appear immediately, overtime the persistent stimulation of inflammatory pathways may produce neuropathologies that are consistent with major depressive disorder.

Fig. 2.

The molecular mechanisms involved in priming and activation the NLRP3 inflammasome: the activation of the NLRP3 inflammasome is dependent upon two a step mechanism: a priming signal is required to initiate the transcription of the NLRP3 inflammasome to above a certain threshold, which may be a function of miR-223 levels, while a second signal is then required to remove kinetic and physical barriers to promote the oligomerization of the NLRP3 and its recruitment of ASC and pro-caspase-1 proteins. An activated NLRP3 inflammasome is then capable of cleaving pro-IL-1 β and pro-IL-18 into their active conformations; it also can cleave cytosolic glucocorticoid receptors (GR) into inactive conformations. Transcriptional priming of NLRP3 mediated through NF- κ B mechanisms can result from the stimulation of membrane bound receptors by a number of signals associated with cellular or metabolic stress such as TNF- α , DAMP's such as HMGB-1, and PAMP's such a LPS; corticosterone (CORT) may also stimulate the transcription of NLRP3. Evidence also suggests that stimulation of microglia with β -AR agonists also prime neuroinflammatory responses; however, the precise mechanism through which this occurs is uncertain. The A20 protein plays a critical role in regulating the RIPK1-RIPK3 complex. Once the NLRP3 protein is transcribed however, multi-layered regulatory steps prevent its activation without further stimuli. The proteins HSP90 and SGT1 maintain the steady state inactive conformation of NLRP3. Secondary messengers and activating steps that promote an active NLRP3 inflammasome include extracellular ATP stimulation of membrane bound receptors and potassium efflux, extracellular calcium stimulation of GPCRs, osmotic

pressure differentials (π) the formation of reactive oxygen species (ROS) by improper phagocytosis or hyperglycemia, phosphorylation/dephosphorylation of key amino acid residues, or the removal of an ubiquityl group by BRCC3. Once the NLRP3 has assembled with its components including ASC and caspase-1 it can be inhibited via a number of mechanisms including interferon- β mediated nitrosylation of the NLRP3 protein that facilitates its degradation, increased intracellular cAMP levels from dopamine receptor D2 (D2R) stimulation by dopamine (DA), or miR7 mediated inflammasome deactivation.

Fig. 3.

IL-1 β and IL-18 and the neuronal local environment: following the cleavage of IL-1 β and IL-18 by the caspase domain of the NLRP3 inflammasome, the cytokines are released into the extracellular space where they bind with receptors or activate pathways involved in synaptic function and immune regulation. When IL-1 β binds with the IL-1R on neurons, it recruits the IL-1RAcPb adaptor protein to facilitate the phosphorylation of NMDR receptors in glutamatergic neurons and increased activity of the serotonin receptor (SERT) in serotonergic neurons via MAPK activation, which decreases intra-synaptic serotonin interactions with serotonin receptor 5-HT_{2A}. Non-dimerized IL-1RAcPb acts a synaptic adhesion protein with PTP σ and promotes differentiation of glutamatergic synapses. Binding of IL-1 β to IL-1R on glia lineage cells recruits the IL-1RAcP adaptor protein to promote NF- κ B mediated transcription of inflammatory cytokines, astrocyte hypertrophy and the production of ROS via induction of nitric oxide synthase (NOS). Extracellular IL-1 β also decreases glutamate uptake by EAAT1 and decreases GABAergic transmission by phosphorylating GABA_A receptors and decreasing their affinity for GABA. The IL-18 binds with IL-18R β on astrocytes and recruits the adaptor protein IL-18R α , which promotes the production of TNF α . IL-18 may also bind with presynaptic NMDA receptors to decrease calcium reuptake. Both IL-1 β and IL-18 also play a critical role as effector cytokines by recruiting peripheral monocytes and leukocytes into the brain parenchyma; recruited monocytes propagate neuroinflammation by secreting other inflammatory cytokines that resolve the infection or environmental stressor.

Fig. 4.

Neuroinflammatory propagation and amplification by primed neuroimmune systems: in primed neuroimmune systems, subsequent exposures to insults can lead to amplified neuroinflammatory responses, which result in the degradation of the blood brain barrier as well as the recruitment of peripheral monocytes into the brain parenchyma. In this process, microglia are signal recognizing cells that upon stimulation generate type 1 cytokines such as IL-1 β , IL-18, IL-6 and TNF- α , which recruit type two immune cells such as leukocytes and phagocytes into to the injured area. Not only do these cells have neurotoxic effects, but they secrete effector cytokines such as IFN γ and IL-17 that also have neurotoxic features. The degradation of the blood brain barrier that occurs concurrently with neuroinflammation and peripheral monocyte recruitment removes a physical barrier between the plasma and the brain parenchyma and furthers neuroinflammatory loads.

Table 1

Covalent regulation of NLRP3 activation by phosphate groups: the identified phosphorylation sites on the NLRP3 protein that regulate its activity and the enzymes which are responsible for catalyzing the phosphorylation or dephosphorylation events. These enzymes may serve as potential targets to decrease the activity of the NLRP3 inflammasome in autoinflammatory and neuroinflammatory conditions.

Residue	Enzyme	Effect
Serine 5	Phosphatase 2a (Stutz et al., 2017)	Dephosphorylation→Inflammasome Assembly
Serine 194	JNK (Song et al., 2017)	Phosphorylation→NLRP3 BRRC3 Deubiquitination
Serine 295	PKA (Mortimer et al., 2016)	Phosphorylation→Inhibits Inflammasome Activity
Tyrosine 861	PTPN22 (Spalinger et al., 2016)	Phosphorylation→Inhibits Inflammasome Assembly
Tyrosine 918	Lyn (Lin et al., 2017)	Phosphorylation→NLRP3 Ubiquitinase/Degradation

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Table 2

NLRP3 activated cytokines and other major cytokines in psychiatric disorders: a list of inflammatory cytokines in the NLRP3 priming pathway sampled in patients with major depressive disorder and bipolar disorder.

Psychiatric Disorder	Inflammatory Protein (+/-)	Sample-Type	Source
Major Depressive Disorder	(+) IL-1 β	CSF	(Levine et al., 1999)
	(+) IL-1 β	Serum	(Anisman et al., 1999; Howren et al., 2009; Maes et al., 1993; Owen et al., 2001; Thomas et al., 2005)
	(+) IL-18	Serum	(Kokai et al., 2002; Merendino et al., 2002)
	(+) IL-6	Serum	(Howren et al., 2009; Lanquillon et al., 2000; Sluzewska, 1999)
	(-) IL-6	CSF	(Levine et al., 1999)
Bipolar Disorder	(+) TNF- α	Serum	(Anisman et al., 1999; Hestad et al., 2003; Lanquillon et al., 2000)
	(+) IL-1 β	Post-Mortem Tissue	(Rao et al., 2010)

Table 3

Targeting the NLRP3 inflammasome: a list of currently FDA approved therapies or preclinical compounds that target the NLRP3 inflammasome, either through inhibition of transcriptional priming, inflammasome assembly, or NLRP3 activated cytokines. These treatments may be leveraged to target neuroinflammatory states in patients with major depressive disorder or other psychiatric disorders.

Current Immune Treatments	Target (Effect)	Type (Mimicked Protein)
Anakirna	IL-1R (Antagonist)	IL-1 β
Rilonacept	IL-1 β (Trap)	IL-1R/IgG1
Pegilodecakin	IL-10R (Agonist)	PEGylated IL-10
Mifepristone	GR (Antagonist)	Prostaglandin Analogue
MCC-950	NLRP3 (Inhibits Assembly)	Small Molecule Compound
Avonex	IFN- β R (Agonist)	Interferon Beta-1
Etanercept	TNF- α (Trap)	TNFR-II/IgG1 Fc
G5	Deubiquitinases (Inhibitor)	Small Molecule Compound
Azeliragon	RAGE (Inhibitor)	Small Molecule Compound
Ibrutinib	BTK (Inhibitor)	Small Molecule Compound
TAK-242	TLR-4 (Inhibitor)	Small Molecule Compound
Oxaborine Derivatives	NLRP3 (Inhibits Assembly)	Small Molecule Compound