Inflammasome activation in traumatic brain injury and Alzheimer’s disease

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Abstract

Traumatic brain injury (TBI) and Alzheimer’s disease (AD) represent 2 of the largest sources of disability and death in the United States, with an average of 1.7 million Americans. Recent studies have identified TBI as a potential risk factor for AD development, and numerous reports have shown that TBI is linked with AD associated protein expression during the acute phase of injury, suggesting an interplay between the 2 pathologies. The inflammasome is a multi-protein complex that plays a role in both TBI and AD pathologies, and is characterized by inflammatory cytokine release and pyroptotic cell death. Products of inflammasome signaling pathways activate microglia and astrocytes, which attempt to resolve pathological inflammation caused by inflammatory cytokine release and phagocytosis of cellular debris. Although the initial phase of the inflammatory response in the nervous system is beneficial, recent evidence has emerged that the heightened inflammatory response after trauma is self-perpetuating and results in additional damage in the central nervous system. Inflammasome-induced cytokines and inflammasome signaling proteins released from activated microglia interact with AD associated proteins and exacerbate AD pathological progression and cellular damage. Additionally, multiple genetic mutations associated with AD development alter microglia inflammatory activity, increasing and perpetuating inflammatory cell damage. In this review, we discuss the pathologies of TBI and AD and how they are impacted by and potentially interact through inflammasome activity and signaling proteins. We discuss current clinical trials that target the inflammasome to reduce heightened inflammation associated with these disorders.

Introduction

Traumatic Brain Injury (TBI) is a significant source of disability and death in the United States,¹ with an average of 1.7 million Americans. It is reported that 30% of people who suffer a moderate TBI report worsening symptoms over a 5 year period, with deficits in learning and memory as one of the major disabling results.²,³ These symptoms are a result of the initial acute trauma to the brain as well as homeostatic changes in the central nervous system (CNS) and chronic inflammation.⁴ TBI presents as a potent risk factor for the development of additional pathologies throughout the CNS and systemically.⁵⁻⁷ For instance, TBI is a potent underlying contributor to the pathology of Alzheimer’s disease (AD).⁸ AD is a neurodegenerative and psychiatric disorder that is one of the most common forms of dementia.⁹ AD pathology is driven by a combination of genetic and environmental factors.¹⁰ There are 2 major pathological hallmarks of AD; the formation and accumulation of amyloid beta (Aβ) plaques and hyperphosphorylated tau neurofibrillary tangles (pTau) that result in chronic inflammation and neuronal loss.¹¹

Abbreviations: Aβ, amyloid beta; AD, Alzheimer’s disease; AIM2, absent in melanoma 2; ALR, AIM2 like receptor; ApoE4, apolipoprotein E-4; APP, amyloid precursor protein; ASC, apoptosis-associated speck-like protein containing a caspase recruiting domain; ATP, adenosine tri-phosphate; BACE, β-secretase; BBB, blood-brain barrier; CARD, C terminus caspase recruitment domain; CDC, U.S. Centers for Disease Control and Prevention; CNS central nervous system CRP, C-reactive protein; DAM, disease associated microglia; DAMPs, damage associated molecular patterns; GFAP, glial fibrillary acidic protein; Glu, glutamate; GSDMD, gasdermin-D; IL, interleukin; LPS, lipopolysaccharide; MAPT, microtubule associated protein tau; NF-kB, nuclear factor-kB; NOD, nucleotide oligomerizing domain; NLR, NOD-like receptor; NLRC, NLRP, NLRP- containing caspase domain NLR, NLRP- containing pyrin domain; PAMPs, pathogen associated molecular patterns; PRR, pattern recognition receptors; PSEN, presenilin; pTau, hyperphosphorylated tau; ROS, reactive oxygen species; RhoA, Ras homolog family member A; TBI, traumatic brain injury; TLR, Toll-like receptors; TREM2, triggering receptor expressed on myeloid cells 2

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According to the United States Centers for Disease Control and Prevention (CDC), individuals with a history of moderate TBI have a 2.3 times greater risk of developing AD, and this risk may be due to the chronic nature of neuroinflammation after TBI. Moreover, there are numerous pathological features shared between TBI and AD, but most notable is the chronic neuroinflammatory response that is mediated in part by persistent inflammasome activation of the innate immune response.

The inflammasome is a multi-protein complex that activates the proinflammatory cytokines interleukin (IL)-1β and IL-18 upon activation of caspase-1, resulting in the cell death process of pyroptosis. In TBI, several recent studies have documented increased inflammasome activity after injury, primarily occurring in activated microglia. In AD, IL-1β accumulation within the CNS activates microglia resulting in the release of IL-1β. Furthermore, IL-1β plaques form as a result of ADβ monomers binding to inflammasome components. Recent studies demonstrate that formation and accumulation of tau is linked to secretion of inflammasome components from microglia. These findings collectively suggest that the main pathomechanisms of AD may be contributed in part by the inflammasome and suggest that disruption of inflammasome activation could be targeted to ameliorate AD pathology.

In this review, we discuss the pathophysiology of TBI and introduce relevant clinical and experimental findings involved with TBI induced inflammasome activity and pathology. Furthermore, we discuss TBI as a risk factor for AD development, and how these 2 pathologies interact mechanistically via inflammasome activity. Finally, we discuss current translational studies and potential therapeutic pathways for development of therapeutics that target inflammasome activation in TBI and AD pathologies.

The innate immune system

The pathophysiological processes underlying trauma are diverse and complex. Cell death, structural damage, inflammation, swelling, and infection often result from physical trauma and are either transitory components of the initial trauma and recovery or alter homeostasis in more chronic pathology. The effects of TBI are not transient, but result in chronic alterations to the CNS environment, including structural changes and a persistent elevation of inflammatory activity. One such physiological process that has been shown to be involved in acute and chronic pathology is the innate immune response.

Evolutionarily speaking, the innate immune system is one of the oldest forms of defense from invading organisms and cellular damage and is conserved in all forms of complex cellular life. The innate immune system is composed of both physical defenses, such as the skin and epithelia, and cellular agents, such as macrophages and neutrophils. The innate immune system utilizes genetically encoded pattern recognition receptors (PRR) to detect infectious pathogens, unwanted foreign matter, and cellular damage. PRR such as Toll-like receptors (TLR) and nucleotide oligomerizing domain (NOD)-like receptors (NLR) facilitate the innate immune system to recognize damage associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs), which induce macrophages to immediately react and shift to a mobile and inflammatory phenotype thus mediating phagocytosis of invaders and the secretion of inflammatory signaling proteins to alert nearby cells of potential harm. Similarly, other cells express PRR and recognize DAMPs and PAMPs, triggering activation of the innate immune response, including inflammasomes in neurons, astrocytes, microglia and oligodendrocytes.

Immunological moderators of CNS injury and disease

The CNS environment has been traditionally considered to be immunologically privileged. The blood-brain barrier (BBB), numerous antigen presenting cells, and a wide range of anti-inflammatory modulators participate in the brain’s immune response in which inflammation is highly regulated. Recent studies identified that a large array of neuroimmune interactions occurs at the CNS borders in the meningeal lymphatic system and that dysfunction of this system exacerbates TBI pathologies. Of all these mechanisms, microglia have been identified as key players in the CNS response to trauma. Interestingly, these cells play dual roles as first responders to CNS illness and injury, but also act to maintain neural homeostasis and plasticity.

In the healthy CNS environment, microglia are in a “resting” state and are identified morphologically by long processes, which sample the environment to detect deleterious changes to homeostasis. It is in the resting state microglia also clear cellular debris and contribute to the overall plasticity of the CNS through the maintenance of neuronal connections, regulation of neurogenesis, and pruning of synapses. After trauma, TLRs and NLRs on microglia detect PAMPs and DAMPs released by injured cells, and quickly shift to an “activated” state in which they assume a more ameboid morphology and migrate towards the site of injury.

Microglia are important for maintaining the health of the CNS and aid in the removal of damaged neurons and infections. In addition, they play important roles in secondary pathomechanisms of a variety of CNS disorders and interact with astrocytes and neurons in response to CNS trauma. Microglia are a well-established source of inflammatory activity within the CNS that is primarily regulated by activation and formation of inflammasomes. Activated microglia have traditionally been classified into 2 phenotypes. The M1 form is proinflammatory and expresses pro-inflammatory cytokines and chemokines, while the M2 form is neuroprotective and expresses anti-inflammatory cytokines, neutrotropic factors, and resolves the inflammatory activity of the M1 form. Although these forms are complimentary, studies have shown that the M2 form is short lived after injury, and that the M1 form plays a prevailing role in chronic inflammatory activity after injury. However, recent research has shown that these traditional phenotypic classifications of microglia are not all inclusive, and alternative and intermediate forms may exist. Studies investigating microglia activation after CNS injury or illness have noted that the M1/M2 microglial classification is simplistic, as multipurpose and alternative forms have been identified after injury. For example, the anti-inflammatory and regenerative M2 form has been further subdivided into M2a, M2b, M2c, and M2d subtypes. The M2a form is activated by IL-4 and IL-13 and plays a role in anti-parasitic responses in that it increases scavenger receptors and induces phagocytosis, IL-10 secretion, and tissue growth and repair. The M2b form is activated by IL-1R ligands and may form intermediate types that expresses pro- or anti-inflammatory activity through secretion of IL-1β, TNF-α, and IL-10. M2b interacts with B cells and regulates the M2 response that also shares characteristics of M1 microglia. The M2c form, activated by IL-10 and glucocorticoids, is considered to resolve inflammation in that it promotes the cleanup of tissue after inflammatory activity is reduced. The M2d form is unique in that it is derived from the M1 form and is alternatively activated through IL-6 and adenosine receptors and is anti-inflammatory and angiogenic in nature. Beyond the classical M1/M2 classifications, recent studies have indicated that microglial classification may be better defined along a shifting spectrum of inflammatory activity, and that microglia should instead be defined by multiple factors such as genetic expression or by the identification of multiple surface markers. Although, many current studies still use the M1/M2 classification colloquially to refer to pro-inflammatory vs anti-inflammatory microglia, new classifications are especially important in AD pathology. A new form of disease associated microglia (DAM), defined by the expression of multiple AD associated genes, is thought to play an integral role in AD pathology progression. Microglia interact with astrocytes and neurons in response to CNS trauma. Astrocytes and microglia maintain CNS homeostasis and modulate inflammatory cytokine expression regulated by assembly of the inflammasome. Astrocytes are the most numerous cell type in the brain and function in maintaining the CNS environment and...
together with neurons maintain ionic and water balances, regulate blood flow, maintain the BBB, and modulate synaptic transmission. Interestingly, astrocytes are similar to microglia in that they also have long processes that sample their environments for changes in homeostasis. Astrocytes form complex networks of gap junctions and closely adhere to neurons, and through unique end-feet adhere to blood vessels forming the BBB. Astrocytes maintain homeostasis through crosstalk with neurons via glutamatergic and GABAergic neurotransmission, calcium signaling, and ionic buffering. In the event of trauma or infection, astrocytes become activated (astrogliosis), as indicated by an increase of the cytoskeletal protein glial fibrillary acidic protein (GFAP), and like microglia, secrete numerous inflammatory products, including cytokines and chemokines such as IL-1β, TNF-α, growth factors and reactive oxygen species. There are numerous triggers of astrogliosis such as DAMPs from damaged cells, cytokines from microglia, Aβ from neurons, albumin from BBB disruption, and synaptic glutamate and adenosine triphosphate (ATP), the exact nature of astrocytic activation is still not well understood.

### Inflammasome activation and assembly

The inflammasome (Fig 1) is a multi-protein complex formed as part of the innate immune response. Inflammasomes are identified by their sensor protein, which contains either an NLR, an absent in melanoma 2 (AIM2) like receptor (ALR), or pyrin. The NLR group of inflammasomes includes NLRP1, NLRP3, and NLRC4, and is further classified by whether their nucleotide binding regions have a pyrin (NLRP) or caspase (NLRC) activation and recruitment domain. The inflammasome complex is composed of caspase-1 and typically contains an adaptor protein known as apoptosis-associated speck-like protein containing a caspase activation domain (ASC) which is activated by the inflammasome sensor proteins NLRP1 and NLRP3, and NLRC4.

#### Table I

<table>
<thead>
<tr>
<th>Microglia type</th>
<th>Activators</th>
<th>Functionality</th>
<th>Physiological response</th>
<th>Sources</th>
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<td>M1</td>
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<td>IL-1β, TNF-α, ROS</td>
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<td>IL-10</td>
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<td>Increased phagocytosis</td>
<td>33,39,41</td>
</tr>
<tr>
<td>M2d</td>
<td>IL-6, Adenosine</td>
<td>Anti-inflammatory</td>
<td>Pro-angiogenic</td>
<td>36,41,42</td>
</tr>
<tr>
<td>DAM</td>
<td>TREM2, PSEN, ApoE</td>
<td>Dysfunctional</td>
<td>Increased autophagy and Aβ phagocytosis</td>
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**Fig 1.** Inflammasome activation and formation. The NLRP3 inflammasome is activated by numerous triggers and by 2 distinct pathways. The canonical pathway is activated first by TLRs that detect the priming signal (dashed lines) which increases transcription of an inflammasome sensor and cytokine RNA through NF-kB signaling. This is followed by an activating signal including: PAMPs, DAMPs, crystalline matter, K+ efflux, ROS, and external ATP (solid lines) which activates the inflammasome sensor protein, pro-caspase-1, and ASC to form the inflammasome complex. Complex formation allows for the self-activation and cleavage of caspase-1 which in turn cleaves pro-IL-1β and pro-IL-18. Additionally, caspase-1 will cleave GSDMD allowing the N terminus to form the pyroptotic pore after which the cell undergoes pyroptosis, releasing its cellular contents, including the IL-1 inflammatory cytokines. Non-canonical activation occurs through detection of LPS or gram-negative bacteria which also induces transcriptional upregulation and caspase activation. However, this pathway utilizes caspase-4/5 in humans or caspase-11 in murine species, and unlike caspase-1, only cleaves GSDMD to form the pyroptotic pore. Pore formation allows for the release of ATP which activates pannexin channels, resulting in K+ efflux and subsequent NLRP3 activation.
recruiting domain (ASC).52 Upon inflammasome activation, the oligomerization domain of ASC allows for the binding and subsequent activation of pro-caspase-1.50,52,53 Caspase-1 activation leads to the cleavage and activation of IL-1β and IL-18, along with the formation of the pyropotytic pore through cleavage of gasdermin-D (GSDMD).53,54 The end result is pyropotytic cell death and the release of inflammatory cytokines along with the components of the intercellular environment into the extracellular space (Fig 1).

Activation of the inflammasome is specific to the respective sensor’s trigger. The NLRP1 sensor contains a function-to-find domain, and a C terminus caspase recruitment domain (CARD) and is activated by microbial associated agents such as Bacterioides anthracis lethal toxin, changes in cellular ATP levels, and double stranded RNA.55 NLRP1 binds caspase-1 directly or with the adapter, ASC.50,51,56,57 The NLRP3 sensor is unique in that it is activated through numerous triggers and by 2 distinct pathways. Traditional activation is through the canonical pathway in response to the detection of numerous triggers including PAMPs, DAMPS, extracellular ATP, increases in intracellular calcium, mitochondrial dysfunction, and cellular potassium efflux.50,56–60 The alternative pathway of activation or noncanonical pathway is activated by lipopolysaccharide (LPS), utilizing caspase-4/5 in humans or caspase 11 in mice.50,56 LPS detection results in the caspase cleavage of GSDMD and formation of the pyropotytic pore which results in ATP release and potassium efflux and subsequent activation of NLRP3.50,56 The NLRP4 sensor is activated indirectly by proteins that detect bacterial components such as flagellin and needle proteins and binds caspase-1 directly to the CARD or with ASC.51,52,57,60 NLRP6 is activated by gram positive bacteria, such as listeria and S. aureus, and has been shown to form an inflammasome complex containing ASC, caspase-1 and caspase-11.54,65 Outside of the NLR family is AIM2, which is activated by cytosolic double stranded DNA, is classified by its N terminal pyrin domain and C terminus hematopoietic interferon-inducible nuclear protein with a 200 amino acid repeat domain and requires ASC to bind caspase-1.51,52,66 Along with pyrin which is activated through Ras homolog family member A (RhoA) inactivation and contains a pyrin domain, 2 B-boxes, a coiled-coil domain, and C terminus B30.2 domain.50–52 Regardless of the unique trigger or the particular inflammasome in action, the main result of inflammasome activation is to reduce infection through pyropotytic cell death of the affected cell and alert neighboring cells to potential danger.

The ASC speck

ASC is a component of the inflammasome that acts as a scaffold of the inflammasome complex. ASC is expressed via the PYCARD gene and is structurally composed of pyrin and CARD domains that mediate binding of the inflammasome sensor protein and caspase-1, respectively.50,67 Upon inflammasome activation ASC self-oligomerizes into a 1 μm aggregate known as the ASC speck. ASC speck formation is accomplished by the binding of pro-caspase-1, to amplify the inflammatory activity and inflammatory cytokine production.50,57,68 Nagar and colleagues found that blocking ASC speck formation using colchicine in cells dosed with nigericin did not prevent inflammasome activation or subsequent cytokine maturation, but rather higher doses of nigericin were required to elicit an inflammasome response.68 These findings suggest that ASC may not be necessary for inflammasome activation, it increases the efficiency of the inflammasome by lowering the stimulus threshold necessary to induce an inflammasome response. This feature allows for a swifter and stronger response to inflammasome triggers.

ASC specks are secreted extracellularly and amplify the inflammasome response. In the CNS, ASC specks are taken up by activated microglia that also secrete inflammasome mediated cytokines.69 Thus, extracellular ASC specks propagate inflammation after release by pyroptotic cells and are ingested by activated microglia that secrete inflammatory cytokines. Moreover, ASC specks may stimulate and perpetuate inflammation after uptake by neighboring cells through recognition byTLRs. Recent studies by Cyr and colleagues showed that increased ASC protein expression in the cortical tissue is associated with the progression of the inflammatory response in aging (inflamming).52 Similarly, Kerr and colleagues showed increased ASC protein expression and speck oligomerization in the lung tissue of mice within 4 hours after brain injury that was associated with lung damage after CNS trauma.50 Johnson and colleagues also observed increased ASC protein expression in the blood serum of patients with diabetic kidney disease and lupus nephritis and showed that ASC protein levels was a reliable biomarker for predicting respective pathological outcomes with increased levels linked to more deleterious outcomes.70 Within the CNS, Johnson et al further observed this same phenomenon in the blood serum collected from hospitalized TBI patients in which ASC and other inflammasome proteins were likewise elevated after injury.71 Furthermore, Chen and colleagues identified increased levels of ASC proteins in the thrombolytic cores of patients who suffered ischemic stroke,72 and Keane and colleagues observed increased ASC and caspase-1 protein expression in patients with multiple sclerosis and that both represented potential biomarkers of pathology.73,74 Lastly, Scott et al showed that ASC protein levels was increased in the blood serum of patients diagnosed with either AD or mild cognitive impairment, and that ASC protein levels was also a reliable biomarker of the early stages of AD pathology.75 Taken together the ASC protein, and the inflammasome appears to play a pivotal role in many CNS diseases and insults, including TBI and AD.

Pathophysiology of TBI

TBI includes many different forms of CNS injury. These include concussions from sports, trauma from motor vehicle accidents, pressure damage from explosions, and penetrative trauma from gunshot wounds, and all forms of TBI may possess various levels of severity. The pathol-ogy of TBI is traditionally viewed as a 2-part event. The initial impact of trauma is termed the primary injury, while the more chronic damage is known as the secondary injury.35 Primary injury involves the damage caused by the physical blow to the brain, with the effects of injury both focal and diffuse and occurring in a relatively short period of time.35 Upon injury (Fig 2), blunt-force trauma causes immediate cell loss at the epicenter of the injury lesion, along with potential vascular injury, gliopathic/lymphatic dysfunction, edema, and diffuse injury to axons and neuronal networks.29,76 It is during the primary injury that PAMPs and DAMPS are released from damaged and dying cells that play an important role in secondary injury.

During secondary injury, the multiple pathophysiological cascades are activated by the primary injury that results in disruption of CNS homeostasis and cognitive function, chronically. At the cellular level, (Fig 2) there is a disruption in the ionic balance, resulting in energy shortfalls, dysfunctional microglia, and reactive oxygen species (ROS) production.50 After moderate or more severe TBI, errant depolarization from injured neurons results in the release of neuroexcitatory glutamate.56 Increased glutamate release is associated with worsened pathological outcomes, and results in increased intracellular sodium levels and the release of glutamate at the synaptic bouton which in turn cause a post-synaptic release of potassium ions.56,76,77 Potassium influx is met with calcium influx resulting in an increase in extracellular potassium and sodium potassium pump activity in an attempt to restore ionic balance.56,77 Resulting pump activity draws on cellular stores of ATP which may be depleted and not restored as mitochondria attempt to store the large influx of intracellular calcium and in turn become dysfunctional, resulting in hyperglycolysis and buildup of lactate.56,77 With the combination of increased calcium and decreased ATP, the cell undergoes the enzymatic processes necessary to induce cell death.34 PAMPs and DAMPS released by injured or necrotic cells trigger the activation of microglia (Fig 2), which attempt to address the injury through the dual application of increased inflammatory activity to clear damaged cells, along with phagocytic activity and neurotrophic factor release to remove and repair damaged structures.34 Astrocytes
become activated by DAMPs and release inflammatory cytokines, while also migrating to the site of injury forming a densely packed astrocytic scar. Additionally, disruption of the BBB allows for the invasion of monocytes from outside of the CNS environment, which contribute to overall inflammatory activity from injury. BBB damage and vascular inflammation also contributes to TBI pathology through the infiltration of blood directly into the cerebral tissue, resulting in excitotoxicity and oxidative stress from iron-rich red blood cells along with the infiltration of non-resident immune cells, resulting in increased inflammation, oxidative stress, and cell death. Finally, disruption of the lymphatic and systemic pathways is thought to reduce clearance of neurotoxic proteins from the CNS after injury resulting in worsened inflammatory pathology, edema, and cell death. Although these effects are seen in traumatic injury settings, they often remain present months to years after injury with chronic inflammatory activity leading to increased neurodegeneration and increased risk for the development of comorbid pathologies.

Studies have shown that damage to the CNS environment from TBI or stroke have been linked to not only loss of cognitive function, but also to psychiatric and sleep disorders, lung damage, cardiovascular disorders, and disruptions to gastrointestinal system functionality. Moreover, although TBI is mainly a pathology imposed from an external source, genetic predisposition has also been implicated as a contributor to primary and secondary injury effects. For example, a recent longitudinal study involving U.S. service members observed increased rates of self-reported decline in cognitive function and psychological wellbeing in participants who sustained a mild TBI and were positive for AD-associated apolipoprotein E-4 (ApoE). Additionally, the AD-associated microglia gene triggering receptor expressed on myeloid cells 2 (TREM2) was shown to be upregulated after TBI in rats and potentially linked to TBI neuropathology along with ApoE. These findings implicate the importance of genetic predisposition on TBI outcomes while also demonstrating how pathological outcomes are very much dependent on the individual, thus making the TBI population extremely heterogenous.

**TBI and inflammasome activity**

Changes in the extracellular environment, the release of PAMPs and DAMPS, the disruption of the BBB, and activation of microglia, all contribute to the chronic inflammatory response after TBI (Fig 2). PAMPs, DAMPS, increased intracellular calcium, potassium efflux, mitochondrial dysfunction, and extracellular ATP may trigger formation of the NLRP3 inflammasome. TLRs detect DAMPS released by injured cells and upregulate the NLRP3 sensor and IL-1β RNA transcription through nuclear factor-kB (NF-kB) signaling. In addition, changes to the extracellular environment such as K+ efflux and ROS, as well as ionic changes like Cl−, activate the inflammasome. However, although the NLRP3 inflammasome has been shown to play a major role in TBI pathology, it is not the only inflammasome that contributes to the innate immune inflammasome response after TBI. For example, the AIM2 and the NLRP1 inflammasome are also activated following TBI.

Inflammasome proteins are released into the blood and CSF following TBI and these circulating inflammasome proteins are reliable biomarkers for determining injury severity and probable pathological outcomes after TBI. For instance, Adamczak et al observed increased ASC, caspase-1, and NLRP1 in the CSF of moderate and severe TBI patients, respective amounts correlated with 5-month Glasgow Outcome Scale scores, and elevated protein levels were associated with worsened outcomes. Kerr and colleagues identified that in human TBI patients, blood serum taken at 1 and 2 days post injury showed levels of ASC and caspase-1 that were elevated after injury, and that increased ASC levels were associated with worsened pathological outcomes. In support of these findings, Pérez-Bárcena et al determined that blood serum levels of caspase-1 taken at 24 hours after hospital admission for TBI reliably predict pathological outcomes 6 months later with increased...
caspase-1 levels associated with more severe injury and worsened pathological outcomes. In a previous study, they also observed that caspase-1 levels were elevated in the CSF of TBI patients with increased intracranial pressure, and that increased levels within the CSF were also associated with worsened pathological outcomes. In addition, Johnson et al observed that increased caspase-1 and IL-10 in the blood serum of TBI patients collected between 1 and 12 hours was associated with worsened outcomes after TBI, and that IL-13 levels could be used to determine injury severity. Moreover, in a murine model of TBI, Lee et al showed that NLRP3, ASC, caspase-1, and IL-1β were all significantly increased within tissue of the injured cerebral cortex at 24 and 48 hours after penetrating injury, and that this was accompanied by increased GSDMD expression and ASC speck oligomerization. These results not only indicate that the NLRP3 inflammasome was activated after trauma, but that it also resulted in increased pyroptotic activity and subsequent cytokine release. Interestingly, IL-18 was also seen to be increased at 48 hours post injury and continued to be increased as late as 72 hours post injury.

The majority of PAMP and DAMP expression after TBI is evident within the first minutes to hours after injury, whereas the activation of microglia and the infiltration of immune cells into the injured tissue occurs later after TBI, primarily within the first few days to a week. As microglia become more activated, the levels of cellular ASC increase, thus supporting the idea that microglia are major contributors to inflammasome activity after primary injury. Indeed, TBI studies investigating the effectiveness of reducing microglia activity via chemical inhibition and replacement have observed subsequent reductions in inflammatory activity and brain injury. Although the most deleterious impacts of primary and secondary injury are seen within the first week after injury, continuous deleterious inflammation continues well past the traditional convalescent period. Chronic loss of learning and memory functionality and changes to personality and overall mental health have been observed in patients after TBI. Pathophysiologically, chronically activated microglia, autoimmunity, and inflammation are present months to years after the initial injury. Therefore, TBI is considered a risk factor for numerous CNS disorders including dementia-like disorders such as AD.

**Hallmarks and pathophysiology of AD**

AD, like many neurological and psychiatric disorders, involves a combination of genetic predisposition and environmental/lifestyle triggers that orchestrate the pathological onset and development of the disease. Increasing numbers of genetic mutations have been linked to AD pathological development. However, alterations to the genes amyloid precursor protein (APP), presenilin (PSEN1, PSEN2), and ApoE (ApoE₄) are among the most widely reported, which alter normal protein functionality resulting in the development of the hallmarks of AD pathology. The Aβ plaque is a primary hallmark of AD and results from an alternative mechanism of amyloid precursor protein (APP) cleavage and subsequent oligomerization of the released non-soluble product. APP is a transmembrane protein which is typically cleaved by α-secretase. However, in AD, APP is cleaved by β-secretase (BACE) and then released via γ-secretase as a longer, stickier peptide between 40 to 44 amino acids long, that aggregates to form neurotoxic plaques. Moreover, this description of Aβ plaque formation is overly simplified because other products of APP are generated by cleavage through caspases and other secretases into soluble forms that mediate other physiological functions.

Although the physiological role of APP in the healthy CNS environment is still not fully understood, studies suggest that it may play a role in cell growth, motility, and survival. Interestingly, some studies have suggested that Aβ in its monomeric form may be neuroprotective and found in those individuals without AD symptomology. In pathological AD, however, the insoluble Aβ plaques are deleterious, resulting in CNS cell death, microglia and astrocyte activation, and inflammation. Damage to healthy neurons has been attributed to Aβ disruption of cellular homeostasis, resulting in increased levels of intracellular calcium, increased synaptic glutamate release, and increased excitatory activity in neurons which is in turn compensated by an increase in long term depression and a reduction in post-synaptic glutamate receptors. Furthermore, Aβ plaques also affect intracellular potassium levels through the disruption of potassium channels and the increased expression and activation of voltage gated potassium channels.

Although Aβ has been the focus of many studies of AD, it does not adequately parallel the pathological properties of AD pathology progression. pTau tangles are considered another key hallmark of AD pathology and have been shown to elicit a deleterious response within the CNS similar to Aβ. In the healthy CNS, tau serves as a cytoskeletal protein and is utilized in the construction of microtubules, the growth of neurons, potential maintenance of DNA, and axonal transport. Tau is expressed via the microtubule associated protein tau (MAPT) gene and is found primarily within neurons but is also present in glia and extracellularly in small amounts. Tau has multiple isoforms and tau phosphorylation plays a role in maintaining healthy function and development of the CNS. Mutations to the MAPT gene and other environmental factors are linked to increases in Tau isoforms that are more susceptible to hyperphosphorylation and other tau pathologies such as frontotemporal dementia. In the disease state, tau does not adequately maintain DNA within the cell nucleus, contributing to cell damage, and tau hyperphosphorylation results in microtubule destruction and migration of pTau to the presynaptic terminal, causing dysfunction, vesicle release reductions, and loss of synapse and dendrites. In AD, the hyperphosphorylation of Tau makes it less efficient in binding to microtubule associated proteins and instead self-aggregates, forming pTau tangles. Thus, Aβ plaques and pTau tangles form the pathological hallmarks of AD and elicit damage to the cells of the CNS through the disruption of ionic and cytotoxic homeostasis, activation of microglia, and induction of inflammation, leading to subsequent cell death.

**Altered microglia in AD**

Microglia play an important role in the pathology of AD through the recognition and clearance of AD-associated DAMPs and subsequent inflammatory activity. Oligomerized Aβ is detected by the surface antigen receptors of microglia and astrocytes as a DAMP. Microglia scavenger receptors identify and mediate Aβ uptake, resulting in microglia activation and inflammatory cytokine release. About 25% of genes associated with immunity alterations in AD are associated with microglia. Genetic mutations, such as PSEN and TREM2 are thought to cause microglia to become dysfunctional, impacting microglial autophagy and lysosomal function. Interestingly, recent evidence suggests that a new type of microglia known as disease associated microglia (DAM) may be upregulated by AD-associated genes such as TREM2 and ApoE as well as by downregulation of genes associated with microglia homeostasis. DAM also show altered autophagy activity, and are present in regions close to Aβ plaques and contain Aβ intracellularly in murine and human samples. In addition, PSEN and TREM2 genetic alterations may increase DAM autophagy activity to increase phagocytic clearance of Aβ plaques. DAM may contribute to AD pathology through the excessive pruning of healthy dendrites and by becoming “frozen” in an activated state in order to increase inflammatory cytokine expression, resulting in a self-driving and perpetually continuous loop of inflammatory activity. Additionally, PSEN mutations may contribute to a loss of microglia lysosomal functionality in non-DAM, reducing the capacity of microglia to break down oligomerized Aβ that results in reduced Aβ clearance and increased inflammasome activation. Studies in murine models have implicated that microglia may also transport Aβ to unaffected regions of the CNS, thus increasing inflammatory activity and overall AD pathology.
The inflammasome has emerged in recent years as a key player in a number of CNS diseases and conditions, particularly AD. As noted, Aβ alters the cellular ionic balance in neurons, but acts as a DAMP in microglia and astrocytes (Fig 3). Microglia attempt to clear Aβ by phagocytosis. However, in AD, Aβ endocytosis does not result in proper degradation by lysosomes, resulting in numerous alterations of microglia morphology and functionality. Aβ aggregates are crystalline in nature, and once endocytosed, they trigger NLRP3 inflammasome activation, resulting in lysosomal damage and potassium efflux. NLRP3 activation leads to formation of the inflammasome and release of cytokines, inducing oligomerization of ASC into ASC specks. Importantly, ASC specks may act as “seeds” to encourage further polymerization of Aβ that form ASC/Aβ aggregates, which are highly toxic to neurons. Moreover, Aβ and ASC interactions increase NLRP3 activity, and Aβ/ASC aggregates hinder Aβ clearance, but also induce microglial pyroptosis. These events result in heightened microglial inflammatory activity and release of inflammatory cytokines, thereby inducing pyroptosis and accumulation of ASC and Aβ into the extracellular space that perpetuates inflammation by inducing inflammasome activation and pyroptosis in neighboring CNS cells and microglia. Additionally, murine studies observe that inflammatory cytokines such as IL-1β hamper the clearance activities of microglia, potentially reducing Aβ clearance and the removal of other cellular debris by microglia. Furthermore, IL-1β appears to increase BACE activity and alter the processing of APP, potentially increasing production of Aβ. In addition, pTau has been shown to induce inflammasome activity. Studies in murine models of AD demonstrate that reduction of NLRP3 activity may lead to a reduction in the formation of pTau and pTau tangles. On the other hand, murine models have also shown that pTau activates NLRP3 in microglia and that tau pathology is reduced in ASC knockout mice. Interestingly, Aβ deposition appears to precede tau pathology in AD, suggesting that pTau deposition may represent a downstream product of Aβ pathology. Indeed, microglia and astrocytic activation, potentially from Aβ or other sources, is thought to encourage pTau formation through the release of inflammatory cytokines such as the inflammasome product IL-1β. However, tauopathies occur in human AD that are separate of Aβ, and human imaging and postmortem studies have demonstrated alterations in microglial inflammatory activity in patients with tau pathology without the presence of Aβ.

Lastly, it should be noted that other inflammasomes beside NLRP3 have been implicated to play a role in AD. A recent study found that NLRP1 knockout in AD mouse models resulted in reduced Aβ plaque load, normalized hippocampal dendritic spines, and resulted in improved spatial and episodic memory testing performance. Increased NLRC4 expression and decreased learning and memory functionality was observed in a rat model simulating AD like pathology utilizing streptozotocin injections. AIM2 knock out resulted in murine models was associated with decreased Aβ load and reduced microglia activity, but not with improvements in memory function. Taken together, these findings indicate that several inflammasomes contribute to the inflammatory response present in AD.

**TBI as an AD risk factor**

AD is a chronic neurodegenerative disorder, and like TBI, AD is known for structural damage, neuronal loss, chronic inflammation, and behavioral abnormalities. As such, the shared aspects, and potential interactions between these 2 pathologies (Fig 3) are of paramount interest, as trauma could potentially be the pathological facilitator to AD onset in the AD predisposed brain. This is especially true as studies suggest that TBI can lead to the earlier onset of AD pathology in as much as...
4 to 10 years earlier than the traditional onset.\textsuperscript{110,111} The effects of trauma on the CNS are interesting when considering that they induce similar disruptions to cellular homeostasis, microglia and astrocyte activation, and inflammatory activity that is seen in AD pathology. For instance, NLRP1, NLRP3, AIM2, ASC speck activity, inflammatory cytokine release, pyroptosis, chronic microglia activation, and neuronal damage have all been observed after TBI in numerous studies and experimental models.\textsuperscript{11,12,15,23,83} Likewise, similar observations have been made in and are thought to contribute to the progression of AD pathology.\textsuperscript{13,69,99,105} Experiments involving TBI have observed increased levels of AD-associated proteins after injury, and human observations suggest that about 30\% of TBI patients develop Aβ after injury.\textsuperscript{112,113} In addition, TBI induced reductions to CNS g. N CIamic activity have been shown to reduce Aβ and tau clearance and increase microglia in murine AD models.\textsuperscript{28, 29}

Murine model studies of AD in the 3Xtg model have seen increased Aβ levels within 24 hours following TBI, though it should be noted that these levels often returned to sham levels at 7 days after injury.\textsuperscript{112} (Table II).

Shishido and colleagues investigating the 3Xtg AD mouse model observed increased Aβ levels within the hippocampus of injured mice 28 days post injury with accompanying decreased spatial memory function\textsuperscript{114} (Table II). In a more chronic injury model, Zysk and colleagues observed worsened learning and memory function and evidence of earlier onset of Aβ pathology in tg-ArcSwe AD mice after injury at 12 and 24 weeks post injury when compared to uninjured AD mice.\textsuperscript{8} In the R1.40 AD mouse model, Kokiko-Coehran and colleagues observed increased tissue loss and continued inflammatory activity after TBI when assessed at 3 and 120 days post injury\textsuperscript{115} (Table II).

In the APP/PS1 AD mouse model, Collins and colleagues observed increased Aβ levels in the cortex of injured 3-month-old mice. However total Aβ load, though not fibrillar Aβ load, was decreased in mice injured at 6 months of age when compared to uninjured controls at 30 days post-injury.\textsuperscript{116} Interestingly, opposite results were obtained in a subclinical blast injury model with 20-week-old APP/PS1 mice in which repeated blasts over an 8 week period, 3 times per week, did not affect overall plaque load but did reduce oligomerized Aβ levels and improved behavioral outcomes.\textsuperscript{117}

Tau pathology has been identified in as many as 1/3 of TBI patients after single and multiple injuries.\textsuperscript{118} Interestingly, a U.S. Department of Defense study led by Clark and colleagues identified increased pTau load in the CSF of Vietnam era veterans who had undergone a TBI but did not see increased Aβ expression.\textsuperscript{110} pTau is also seen in murine models after TBI, and has been demonstrated to be phagocytosed by and able to activate microglia.\textsuperscript{120} Edwards and colleagues observed increased pTau aggregation after TBI in the P301S Tau mouse model as early as 1 day after injury and noted decreased learning and memory function at 6 months post injury accompanying increased pTau aggregation.\textsuperscript{121} Additionally, disruption of the BBB secondary to TBI is also of interest as studies have shown increased plaque formation near areas of BBB damaged due to age.\textsuperscript{10} All points considered, TBI represents a potential trigger of AD development through the initiation of neuronal cell death, diffuse axonal injury, BBB disruption, microglia activation, and inflamasome activity, all of which are seen as major drivers of AD pathology and represent current areas of therapeutic research.

### New therapeutic opportunities and current clinical trials

Numerous studies and potential therapeutic interventions are currently being investigated in order to prevent, reduce, or reverse the effects of TBI and AD pathology. In both conditions, the inflamasome pathway offers attractive therapeutic targets for the reduction of damaging inflammatory secondary injury cascades. These may include the prevention of the priming phase or step 1 through targeting NF-κB, blocking the activity of the inflamasome sensor protein, such as NLRP3, prevention of ASC speck oligomerization, targeting caspase-1 activity, or blocking of GSDMD pyroptotic activity.\textsuperscript{122–124}

Therapeutics that target NLRP3 activity such as MCC950 showed initial promising results through the reduction of NLRP3 and microglia activation and increased Aβ phagocytosis in AD, and reduced caspase-1 and IL-1β activity in TBI.\textsuperscript{125} Studies with the caspase-1 inhibitor VX-765 have demonstrated reduced inflammatory cytokine and GSDM-D activity in a murine model of TBI, as well as delayed inflammatory onset in an AD murine models though without altering plaque load.\textsuperscript{126,127}

Studies involving an anti-ASC drug called ICI100 show exciting results in reducing inflammatory activity and improving functional outcomes in murine models of inflamming, multiple sclerosis, and CNS injury induced acute lung injury.\textsuperscript{8,29,125} Additionally, targeting ASC lowered the expression of caspase-1 and reduced pyroptotic cell death in rats after TBI.\textsuperscript{11} Given the unique role of ASC in the inflamasome and its interactions with AD proteins, ASC represents an interesting target in both pathologies, as hindrance of ASC speck activity could reduce plaque progression, inflamasome activation, and reduce inflammatory signaling in both AD and TBI pathologies.

Beyond the bench, numerous human clinical trials are investigating the effectiveness of targeting the inflamasome in reducing the progression of inflammatory linked pathologies within and outside of the CNS (Table II). Due to current research targets, a majority of current inflamasome clinical trials are primarily focused on treating COVID-19 infections and related pathologies such as pneumonia and lung damage. A NLRP3 antagonist known as DFV890 developed by Novartis has just finished a phase 2 clinical trial investigating its effectiveness in

### Table II

TBI outcomes in AD murine models

<table>
<thead>
<tr>
<th>AD model</th>
<th>Time post TBI</th>
<th>Observations</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Xtg</td>
<td>24h</td>
<td>Increased Aβ levels</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>7d</td>
<td>Sham Aβ levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28d</td>
<td>Increased Aβ levels</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased spatial memory</td>
<td></td>
</tr>
<tr>
<td>tg-ArcSwe</td>
<td>12w and 24w</td>
<td>Decreased learning and memory</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Earlier Aβ onset</td>
<td></td>
</tr>
<tr>
<td>R1.40</td>
<td>3d and 120d</td>
<td>Increased tissue loss</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflammatory activity</td>
<td></td>
</tr>
<tr>
<td>APP/PS1</td>
<td>30d</td>
<td>3m: Increased Aβ levels</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6m: Decreased total Aβ, same fibrillar Aβ levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8w</td>
<td>Same total Aβ, reduce oligomerized Aβ load</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced anxiety behavior, improved cognition</td>
<td></td>
</tr>
<tr>
<td>P301S (PS19)</td>
<td>1d, 1w, 2m, 6m</td>
<td>Increased Tau aggregation</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6m: Decreased learning and memory</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: d, days; h, hours; m, months; w, weeks.

* Repeated subclinical blast model.
treated severe respiratory infections of COVID-19. Provided data sug-
gests that patients who were administered DFV 890 along with standard medical care had no higher chance of dying in the intensive care unit than patients that received standard medical care alone.120 Interestingly, researchers noted that slightly less of the patients that received DFV890 required ventilator intervention and also that slightly more of these patients had reduced COVID-19 pathology.128

Another study, which instead targeted NLRC4 with the drug MAS825 also investigated the effectiveness of inflammasome targeting in treating COVID-19 patients. Results suggest that patients administered MAS825 along with standard of care had decreased levels of the inflammatory biomarker C-reactive protein (CRP) compared to placebo at 15 days post treatment.129 However, these results did not translate to an improvement in clinical outcomes or reduce the need for other interventions.129

OLT1177 (dapansutrile), a NLRP3 inhibitor developed by Olatec has undergone a few clinical trials which have shown positive results and is deemed safe for use.130 When used for the treatment of gout, which is currently being investigated for treating COVID-19 symptoms. In a clinical trial investigating the use of gout, patients administered dapansutrile 2,000mg had improved left ventricular ejection fraction and exercise time compared to placebo controls at day 14 and was deemed safe for use.130 When used for the treatment of gout, which is linked to IL-1β expression secondary to NLRP3 activation from monosom- diure crystals, patients administered dapansutrile reported reduced joint pain when compared to controls.131

Addition inhibitors of NLRP3 activity analogous to MCC950, such as IZD334 and Inzomelid developed by Infazome (Roche) are currently being assessed for safety and clinical effectiveness in autoinflammatory disease trials that have just recently been completed.132 Although these studies are not investigating CNS pathologies, given how damage to 1 organ system such as the brain and spinal cord has been shown to secondarily impact other organ systems such as the lungs or gut through inflammasome activity, any effective compound in reducing the pathology of one could be potentially effective in reducing the pathology of another.6,70 As such, attention should be paid to all types of inflamma-
some clinical trials, and their findings should be considered for potential application to CNS pathologies such as TBI and AD. Additionally, since numerous studies show that inflammasome inhibitors are well tolerated and safe, continued investigation of new targets for inflammasome inhi-
bition are encouraged. Currently, a search of clinicaltrials.gov utilizing the term “inflammasome” returns 45 studies, none of which are or have investigated inflammasome interactions in either TBI or AD pathologies, or combinations of the 2 pathologies. Future studies and drug investiga-
tions should consider the role of the inflammasome in CNS pathology, as well as more than just the products of inflammasome maturation, such as IL-1β and IL-18 but also to the individual proteins that are produced in order to build the inflammasome such as ASC specks.

Conclusion

The pathologies of TBI and AD are diverse, chronic, and psychologically debilitating for patients. Research of these 2 pathologies is of para-
mount interest and importance as incidences of both are increasing with the aging population. Emerging evidence has accumulated describes a link between TBI and AD pathologies. Cell injury in the simplest sense is the 1 true linker of AD and TBI, as the products of inflammasome activation induces pyroptotic cell death. In this scenario, heightened inflammation becomes perpetual.

In AD, the continued production and lack of Aβ clearance, and pTau activity result in cell death and the release of DAMPs, excitatory proteins, and disruptions to immune homeostasis. These disturbances to CNS homeostasis in turn trigger the activation of the innate immune sys-
tem, microglia, and the inflammasome, resulting in continued inflamma-
some activity as heightened inflammasome activation induces pyroptotic cell death. In this scenario, heightened inflammation becomes perpetual. In AD, the continued production and lack of Aβ clearance, and pTau activity feeds this inflammatory cycle thereby producing DAMPs and neuronal protein imbalance. This cycle becomes more amplified in AD in which microglia in the AD brain assume a self-perpetuating inflammatory morphology. Additionally, inflammasome products, such as ASC and IL-18 encourage Aβ pathology and in turn induces pTau pathology downstream.

Taken together, TBI represents a risk factor in AD development by enhancing inflammation and promoting AD pathological onset. Further-
more, the genetic predisposition associated with AD may impact TBI pathological and functional outcomes. TBI can be an inflammatory trigger through tissue damage, astrocyte and microglia activation and there-
fore it is not surprising that TBI would be considered a risk factor for AD. However, although these pathologies have many similarities, they also have unique signatures. Injury severity and location are major factors in determining the degree of damage and cognitive abnormalities. On the other hand, AD is associated with numerous genetic mutations and potentially can be the result of environmental factors. As such, it should

Table II
Recent clinical trials targeting the inflammasome

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Inflammasome target</th>
<th>Disorder</th>
<th>Study type</th>
<th>Results</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFV890</td>
<td>NLRP3</td>
<td>COVID-19</td>
<td>Clinical Trial</td>
<td>Reduced COVID pathology</td>
<td>128</td>
</tr>
<tr>
<td>MAS825</td>
<td>NLRP3</td>
<td>COVID-19</td>
<td>Clinical Trial</td>
<td>Decreased C reactive protein</td>
<td>129</td>
</tr>
<tr>
<td>OLT1177</td>
<td>NLRP3</td>
<td>Heart Failure</td>
<td>Clinical Trial</td>
<td>Improved left ventricular ejection fraction</td>
<td>130</td>
</tr>
<tr>
<td>Dapansutrile</td>
<td>IZD334</td>
<td>Gout</td>
<td>Clinical Trial</td>
<td>Reduced joint pain</td>
<td>131</td>
</tr>
<tr>
<td>Inzomelid</td>
<td>NLRP3</td>
<td>Autoinflammatory Disease</td>
<td>Clinical Trial</td>
<td>Trial complete</td>
<td>132</td>
</tr>
<tr>
<td>MCC950</td>
<td>NLRP3</td>
<td>AD</td>
<td>Animal Study</td>
<td>Increased Aβ phagocytosis</td>
<td>125</td>
</tr>
<tr>
<td>VX765</td>
<td>Caspase-1</td>
<td>TBI</td>
<td>Animal Study</td>
<td>Reduced cytokine and GSDM-D activity</td>
<td>127</td>
</tr>
<tr>
<td>IC-100</td>
<td>ASC</td>
<td>Aging</td>
<td>Animal Study</td>
<td>Reduced Caspase-1,8, IL-1β, ASC, NLRP-1 expression</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple Sclerosis</td>
<td>Animal Study</td>
<td>Reduced T cell, myeloid cell, and microglia activation</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS induced Lung Injury</td>
<td>Animal Study</td>
<td>Reduced IL-1β, ASC, caspase-1, AIM2 expression</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBI</td>
<td>Animal Study</td>
<td>Reduced caspase-1 and pyroptosis</td>
<td>31</td>
</tr>
</tbody>
</table>

The inflammasome represents a promising target in the treatment of numerous inflammatory fueled pathologies. Current clinical studies have shown that therapies that target inhibition of the inflammasome sensor are safe, well tolerated, and potentially effective in numerous inflammatory pathologies.

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be noted that one does not necessarily always precede the other, and that individual genetic predisposition and environmental factors must be considered when determining overall risk for chronic pathology after CNS injury.

Given the inconsistent results using murine models of AD, and that numerous AD genetic models and TBI experimental models currently exist, we must be cautious not to overgeneralize observations and extrapolate these results to humans. Regardless, the inflammasome represents a viable target for reducing the impact of each pathology, as well as reducing crosstalk between them. Current results have shown that inflammasome inhibitors appears to be a safe and potentially effective in reducing pathology in TBI and AD, and a wide variety of inflammatory-associated disorders such as MS, kidney disease, stroke, lung damage, and aging. Although current clinical trials have focused on inflammasome sensor inhibition, future studies will need to focus on other proteins associated with formation of the inflammasome complex. Given the interactions between ASC and Aβ or IL-1β and BACE in AD, and that numerous inflammasome sensors exist and are implicated in TBI and AD, future clinical studies should consider targeting multiple inflammasome sensors or adaptor molecules. In addition, neuroimmune interactions involving the meningeal lymphatic system at the CNS borders will likely provide information about the immune responses in the CNS, and potentially yield therapeutic strategies to treat neurological disorders, including TBI and AD.

In conclusion, AD and TBI individually represent complex disorders with numerous factors that play into pathological onset, development, and prognosis. As such, researchers and medical professionals must take into consideration all factors in an experimental study or individual patient’s environment in an attempt to evaluate the related pathology holistically. Since genetic predisposition has been implicated as a major factor in AD pathology and could likewise influence TBI pathology, these variables should be taken into consideration along with environmental factors when evaluating potential experimental models and injury methods. As such, while TBI represents a known source of cognitive decline, inflammatory activity, and potential AD protein development, it is not a guaranteed cause of AD. Additionally, while AD predisposition could potentially impact inflammatory activity within the CNS, it does not guarantee AD pathological development with or without TBI. Regardless, the inflammasome represents a shared characteristic of numerous pathologies and a promising target for the development of novel and effective therapeutic interventions. This is especially the case when considering the role of inflammasome-derived cytokines, activated microglia and astrocytes, as well as pyroptotic cell death induced by trauma or AD pathology.

Acknowledgments

Conflicts of Interest: JPD RV, HMB, RWK, and WDD are co-founders and managing members of InflamaCORE, LLC and have licensed patents on inflammasome proteins as biomarkers of injury and disease as well as on targeting inflammasome proteins for therapeutic purposes. JPD RV, HMB, RWK, and WDD are Scientific Advisory Board Members of ZyVersa Therapeutics. NHJ declares no conflicts of interest.

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