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Role of the inflammasomes in HIV-associated neuroinflammation and neurocognitive disorders

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A B S T R A C T

HIV associated neurocognitive disorders (HAND) is a unique form of neurological impairment that stems from HIV. This disease and its characteristics can be accredited to incorporation of DNA and mRNA of HIV-1 into the CNS. A proper understanding of the intricacies of HAND and the underlying mechanisms associated with corresponding immune reactions are vital for the potential development of a reliable treatment for HAND.

A common phenomenon observed in CNS cells, specifically microglia, that are infected with HAND is inflammation, which is a consequence of the activation of innate immune response due to a variety of stimuli, in this case, being the HIV infection. The CNS based inflammation is mediated by the production of cytokines, chemokines, reactive oxygen species, and secondary messengers, which occurs at CNS glia, endothelial cells and peripherally derived immune cells.

Inflammasomes play a significant role with regard to neuroinflammation due to their ability to dictate the activation of various inflammatory responses. Certain stimuli can result in the activation of caspase-1; hence, leading to the processing of interleukin-1β and interleukin-18 pro-inflammatory cytokines. The processed IL-1β and IL-18 activate signaling pathways that begin the process of neuroinflammation. Due to the fact that the NLRP3 inflammasome is the most abundant in the CNS, it is the most extensively investigated inflammasome with regard to the nervous system.

Due to the importance of neuroinflammation in the evolution of HAND and proliferation of neuroinflammation due to HAND, it can be concluded that there exists a relationship between HAND and inflammasomes. The aim of our review is to consolidate current knowledge of important mechanisms in HAND, specifically related to its relationship with neuroinflammation and inflammasomes to shed light on a possible improved treatment for HAND.

1. Introduction

Human Immunodeficiency Virus (HIV) is an incurable virus that attacks the body's immune system, specifically CD4+ T cells. The damaging of these specific cells can leads to unique opportunistic infections or cancers, which are signs of late stage HIV or Acquired Immunodeficiency Syndrome (AIDS) (Bhatti et al., 2016). Antiretroviral therapy (ART) is the medicine used to treat HIV and it can potentially prolong the lives of HIV patients and significantly decreases the transmission of HIV to others. ART has successfully increased the life expectancy of HIV infected adults, leading to a near-normal lifespan for many patients (Dahabieh et al., 2015). However, because the treatment leaves many patients perpetually infected with HIV, a mounting issue of comorbidities arises. These comorbidities originate from a variety of organ systems each of which carry its own innate complexities, prompting research to address possible complications associated with HIV such as neurodegenerative conditions.

With respect to neurological disorders, HIV, unlike in the immune system, does not necessarily commandeer the functionalities of cells. Instead, the virus causes massive amounts of inflammation throughout the brain, which damages the spine/brain or stops nerve cells from working. Furthermore, certain drugs used to treat HIV and genetic predispositions can increase the likelihood for end-stage patients to contract neurological disorders. A research cohort developed a large scale research report called Central Nervous System HIV Antiretroviral Therapy Effects Research, also known as, CHAPTER (Letendre et al., 2009). The researchers examined for the occurrence and severity of distal sensory polyneuropathy (DSPN) in their patients. DSPN is the most common neurological problem in HIV and represents an advanced HIV disease or peripheral nerve damage. Despite its frequencies in HIV patients, the specific pathophysiology is not well understood in DSPN. Recent research does suggest that mitochondrial toxicity is a possible etiology of DPSN, which will be discussed at a later point in the review. Signs of DSPN include, but are not limited to: dementia, neuropathy, and diminished distal vibratory/pin sensation (Letendre et al., 2009). Another large scale study on the burden of DSPN on patients on antiretroviral therapy studied 2135 antiretroviral necessitating patients over a 7 year period. Remarkably, only 3–5% of DSPN patients were found symptomatic; hence, most of the DSPN observed in this study was actually asymptomatic (Letendre et al., 2009). These two studies

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display that the battle to treat HIV-1 does not end with antiretroviral therapy and opportunistic infections play a major role in the death and impaired livelihood of many HIV patients. The association between DSPN and HIV patients, even among those who successfully suppressed HIV with antiretroviral therapy, insinuates that neurological conditions are one of the most common conditions plaguing current HIV patients.

The spectrum of neurocognitive impairments originating from HIV is called HIV associated neurocognitive disorders (HAND) and is diagnosed using neuropsychological testing and functional status assessments (Saylor et al., 2016). Neurocognitive impairments or variations of HAND manifest in one of three different variations: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD), the most common being ANI. In the early stages of HIV, ANI can be difficult to clinically diagnose. However, through formal neuropsychological functional assessments, ANI prevalence can be deduced. According to the diagnostic criteria for cognitive impairment tests, ANI can be classified if there is identifiable impairment in at least two neurocognitive domains; these domains may include motor skills, verbal expression, or any necessity honing everyday functioning (Saylor et al., 2016). However, ANI does not need to interfere with routine/everyday functioning. Regardless of the fact of ANI being "asymptomatic," ANI can still transition to the more severe forms of MND or HAD. Just like the diagnosis for ANI, MND can be identified via functional assessments. To accurately score individuals with MND, it requires that there, again, be impairment in at least two neurocognitive domains but with modest interference with everyday functioning. Lastly, to evaluate HAD, the most severe type of neurocognitive disorder, individuals need to possess impairment in at least two neurocognitive domains with substantial interference with everyday functioning (Saylor et al., 2016).

Before combination antiretroviral therapy (cART), HAND, specifically HAD, was very common in HIV patients. However, as the widespread implementation of cART began treating many HIV patients, noticeable changes in HAND severity has been observed. For instance, a drop in the occurrence of HAD has resulted in the prevalence of milder forms of HAND; for instance, ANI now accounts for approximately 70% of all forms of HAND (Saylor et al., 2016). A plethora of studies all conclude that the introduction of ART greatly benefitted the livelihood of HAND patients. The list of cART's consequences with reference to HAND include: decrease in severity, decline in frequency, conversion from asymptomatic to symptomatic, waning relation between HAND and immunosuppression, slowed progression, and diminution in clinic severity. Therefore, the ART era, specifically the introduction of cART, has shed new light on neurocognitive impairment due to its ability to dramatically increase the lifespan of HAND patients, which in turn increases the importance of prompt diagnosis and proper care.

2. Inflammasomes

Inflammasomes are cytosolic caspase-activating multiprotein macromolecular complexes that dictate the activation of various inflammatory responses. Specifically, the inflammasome promotes the proteolytic cleavage and secretion of pro-inflammatory cytokines, such as Interleukin 1ℓ and Interleukin 18 (Latz et al., 2013). The release of these cytokines develops into a form of programmed pro-inflammatory cell death unlike apoptosis. In conjunction with the importance of inflammasomes, it is commonly recognized that this mechanism is present in numerous cell types and contributes to innate immune activation in multiple organs including the CNS (Latz et al., 2013). The specific immune responses revolving around inflammasome activation are initiated by host recognition of pathogen-associated molecular patterns (PAMPs), expressed on microbial pathogens or by danger-associated molecular patterns (DAMPs) produced by host cells. The plethora of molecules described serve as ligands for pattern-recognition receptors on cells. With relation to the CNS, these cells include microglia, macrophages and astrocytes. The binding of PAMPs or DAMPs to said pattern-recognition receptors results in the transcription of the inflammasome gene, which leads to the previously mentioned proteolytic cleavage and secretion of Interleukin 1β and Interleukin 18. These examples of cytokines are inactively present in neurological and neurological cells and require caspase-1-mediated cleavage to become activated (Latz et al., 2013).

Structurally, the inflammasome complex consists of caspase 1, PYCARD, NALP and occasionally caspase 5. However, the exact composition of an inflammasome complex depends on the activator which initiates the assembly of said complex. A paradigm of this phenomenon can be seen in dsRNA, which will trigger one inflammasome composition; however, asbestos will assemble a completely different variant of the complex (Singhal et al., 2014). Despite the variety of within the inflammasome complex, it is mainly divided into common structural domains that mediate individual functions. For instance, the nucleotide-binding domain contains leucine-rich repeat (LRR) receptors, which serve as cytosolic pattern-recognition receptors found, primarily, in macrophage cells. Other important domains, which are related to the nucleotide-binding domain, include a N-terminal effector binding domain, a nucleotide-binding oligomerization domain, and a C-terminal LRR receptor domain (Fig. 1). These domains bind to ligands and leads to the activation of inflammasomes, which is an important phenomenon that will be mentioned further along (Singhal et al., 2014).

3. Inflammasomes in the CNS

With relation to the CNS, inflammasome are present in neurological cells that can exert immune actions, which include, but are not limited to: microglia, neurons, oligodendrocytes, astrocytes and Schwann cells.

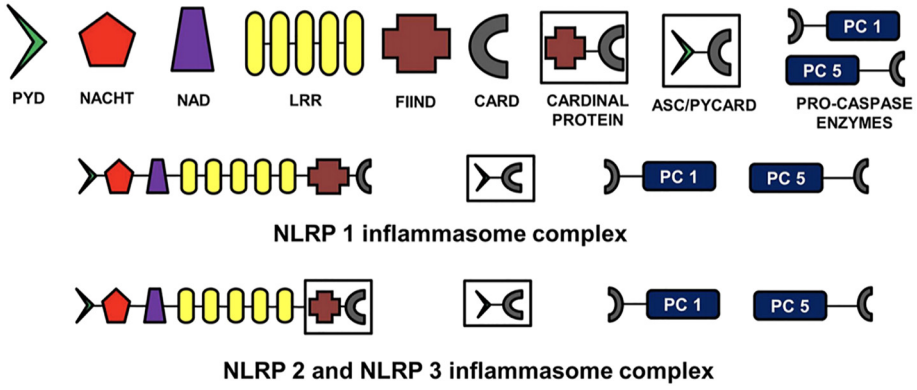

Fig. 1. Structure of NLRP inflammasomes. NLRP inflammasomes are intracellular protein complexes consisting of NLRP (NACHT, LRR, and PYD domains containing proteins 1, 2, or 3), the adapter protein ASC/Pycard, enzyme pro-caspases 1 and 5, and cardinal proteins. The structure of the NLRP1 inflammasome has a Pryin (PYD) domain on the amino (N)-terminal, which is bonded to a NACHT domain and a NACHT-associated domain (NAD), several LRRs, FIIND domain and the caspase recruitment domain (CARD) at the (C)-terminal. Similarly, the molecular structure of NLRP2 and NLRP3 closely correlate with that of NLRP1; however, LRRs are linked to a cardinal protein, which consists of FIIND domain on the N-terminal and CARD domain on the C-terminal instead of being directly linked to the FIIND domain. Figure and caption adapted from Singhal et al., 2014.

In these immune effector cells, the basal levels of the cytokines, Interleukin 1β and Interleukin 18, are vital for the for not only the physiological function of the nervous system, but also to prevent adverse outcomes. In the nervous system, the role of the cytokines is to link the learning, memory and sensory functions of inflammasome components. A paradigm of this can be seen with the increased expression of the inflammasomes NLRP1, NLRP3, and NLRC4 in the microglia, NLRP2 and NLRP3 in astrocyte and AIM2 and NLRP1 in neurons (Albornoz et al., 2018). Of these inflammasomes, NLRP3 inflammasome is the most abundant inflammasome in the CNS and, hence, is the most extensively investigated inflammasome with regard to neuroinflammation and nervous system disorders. This concept of innate immunity is an integral factor of neuroinflammation and serves as a causative agent for many different neurological diseases (Albornoz et al., 2018).

Due to NLRP3's prevalence in the CNS, it provides valuable insight into the relationship between inflammations and the nervous system. The NLRP3 inflammasome consists of three components: the NLRP3 protein (which contains the PYD, NACHT, NAD, LRR, FIIND and CARD domains), adaptor protein apoptosis-associated speck-like protein (ASC), and procaspase-1. As previously mentioned, the PAMPs and DAMPs serve an important role in the activation of inflammasomes. However, the NLRP3 inflammasome is not associated with these activating factors, such as PAMPs and DAMPs. In the absence of such factors, the LRRs and NACHT domain of the NLRP3 inflammasomes connect with each other tightly enough to nullify the interaction of the NLRP3 protein and ASC (Shao et al., 2015; Kosmidou et al., 2018). Furthermore under exposure to immunostimulation, the NLRP3 protein is activated, which leads to the interaction between ASC, procaspase-1 and caspase recruitment domain (CARD), respectively. This series of activations leads to the assembly of the NLRP3 inflammasome (Shao et al., 2015; Gambin et al., 2018).

The activation of NLRP3, like all other inflammasomes, is an important process with a multistep procedure. Firstly, a signal is triggered by specific PAMPs or DAMPs activating factors, which results in the activation of the NFκB mediated pathway. The NFκB-mediated pathway activation leads to the transcription of the NLRP3 inflammasome and its related components. This leads to the transcription of NLRP3 protein, pro-interleukin-1β (proIL-1β), and proIL-18. For step 2, upon further stimulation of inflammatory cells, the NLRP3 protein is oligomerized and follows the assembly of the NLRP3 protein, ASC and procaspase-1 (Manmeet and Christopher, 2017). These related components are then assembled to form the NLRP3 inflammasome, which triggers the transformation of procaspase-1 to caspase-1 and the formation of IL-1β and IL-18 from proIL-1β and proIL-18. These products are then secreted and lead to the inflammatory reaction (Place and Kanneganti, 2018; Shen et al., 2018). The importance of the NLRP3 inflammasome plays a vital role in this activation pathway. For instance, lipopolysaccharide (LPS) is widely considered to be a classic ligand for the activation of TLR4 and the second step of activation uses the ligands/mechanisms: adenosine triphosphate (ATP), K efflux, ROS, autophagy deficiency, and mitochondrial Ca^{2+} overload (Chen and Tully, 2018; Li et al., 2018; Meng et al., 2018; Zhao et al., 2018). However, recent literature implies that ATP may well be the sole activator, since blocking ATP release has shown to stop the assembly of inflammasomes (Mugisho et al., 2018); thereby, implying that K efflux, ROS, autophagy deficiency, and mitochondrial Ca^{2+} overload are more likely to be affects than causes (Fig. 2).

4. Neuroinflammation

Neuroinflammation is a specific type of inflammatory response located within the brain or spinal cord and is a natural response triggered as a consequence of the activation of innate immune response due to a variety of stimuli, including infection, traumatic brain injury, toxic metabolites, aggregated proteins, or autoimmunity. The CNS based inflammation is mediated by the production of cytokines, chemokines, reactive oxygen species, and secondary messengers, which occurs at CNS glia, endothelial cells and peripherally derived immune cells. Despite the similarities between inflammation and neuroinflammation, the different terms are not universally equivalent (DiSabato et al., 2016). A paradigm of this discrepancy can be seen in inflammation potentially recruiting: immune cells, edema, tissue damage and cell death at different rates than that of neuroinflammation; hence, it is important to delve into the activation mechanisms and positive & negative consequences of neuroinflammatory processes (DiSabato et al., 2016). As previously mentioned, the mediators of neuroinflammation are inflammasomes, which are commonly triggered by PAMPs and DAMPs. However, the presence of cellular death and tissue damage commonly results in the release of DAMPs and, consequently, the lethal positive feedback loop of inflammation.

The primary cells that perform the immune surveillance and macrophage role in the CNS are the microglia and a greater understanding of these cells will shed light on vital talking points regarding neuroinflammation. Microglia reside in both the white and gray matter and are approximately 10% of the cells within the CNS. Due to the fact that the cells have the same progenitor as other long-lived macrophages, microglia are long-lived cells with limited turnover rates from the myeloid cells (Ajami et al., 2007; Ginhoux et al., 2010). However, this low turnover rate would make would make the cells susceptible to proinflammatory effects of age, injury or stress (McArthur et al., 2005). Furthermore, microglia serves a vital role in the 'surveillance' of the immune system. This is shown by a study that proves microglia use their processes to survey their microenvironment and propagate inflammatory signals in the periphery (Nimmerjahn et al., 2005; Davalos et al., 2005). In diseases, microglia become activated and serve as inflammatory mediators. Upon activation, the cells undergo cytoskeletal rearrangements and produce inflammatory cytokines. All in all, microglia are vital in the protection of the CNS and benefit the host organism. However, excess microglial activation can lead to neuroinflammatory behavior and neurobehavioral complications (Norden and Godbout, 2013).

The mediation of neuroinflammatory is dictated by the cytokines (IL-1β, IL-6, and TNFα), chemokines (CCL2, CCL5, CXCL1), secondary messengers (NO and prostaglandins) and reactive oxygen species (ROS) (Gougeon, 2017). The concept of neuroinflammation, contrary to popular belief, is not necessarily negative and comprises a large range of potential consequences. For example, a study has shown evidence of active microglia and the production of respective cytokines in early brain development (Salter and Beggs, 2014), but other studies have shown active microglia providing synaptic pruning and immunological activities within the CNS. Moreover, a report shows that certain neuroinflammatory-related cytokines are vital in the regeneration of depleted microglia (Bruttger et al., 2015). Finally, another study sheds light on enhanced neuroinflammation in T-cells and CNS cells, which imply greater memory and learning (Derecki et al., 2010; Ziv et al., 2006). Hence, the term neuroinflammation inherently adopted a negative connotation, when the concept consists of a much broader range of signal communication and interaction.

Neuroinflammation can also be transient, which not only involved the activation of glia, but also the production of the cytokines IL-1β, TNFα, and IL-6.This type of neuroinflammation stems from the coordinated behavior between a potential infection and the CNS that directly affects the periphery in a beneficial way (Schain and Kreisl, 2017). Albeit the infection does not lead to significant infiltration of immune cell, blood-brain barrier breakdown or cell death. Studies have attempted and successfully harnessed this type of inflammation as a way to promote immune conditioning. The successful transient action of the immune system has been associated with the reduction of inflammatory profiles and increased neuroprotection (Gougeon, 2017).

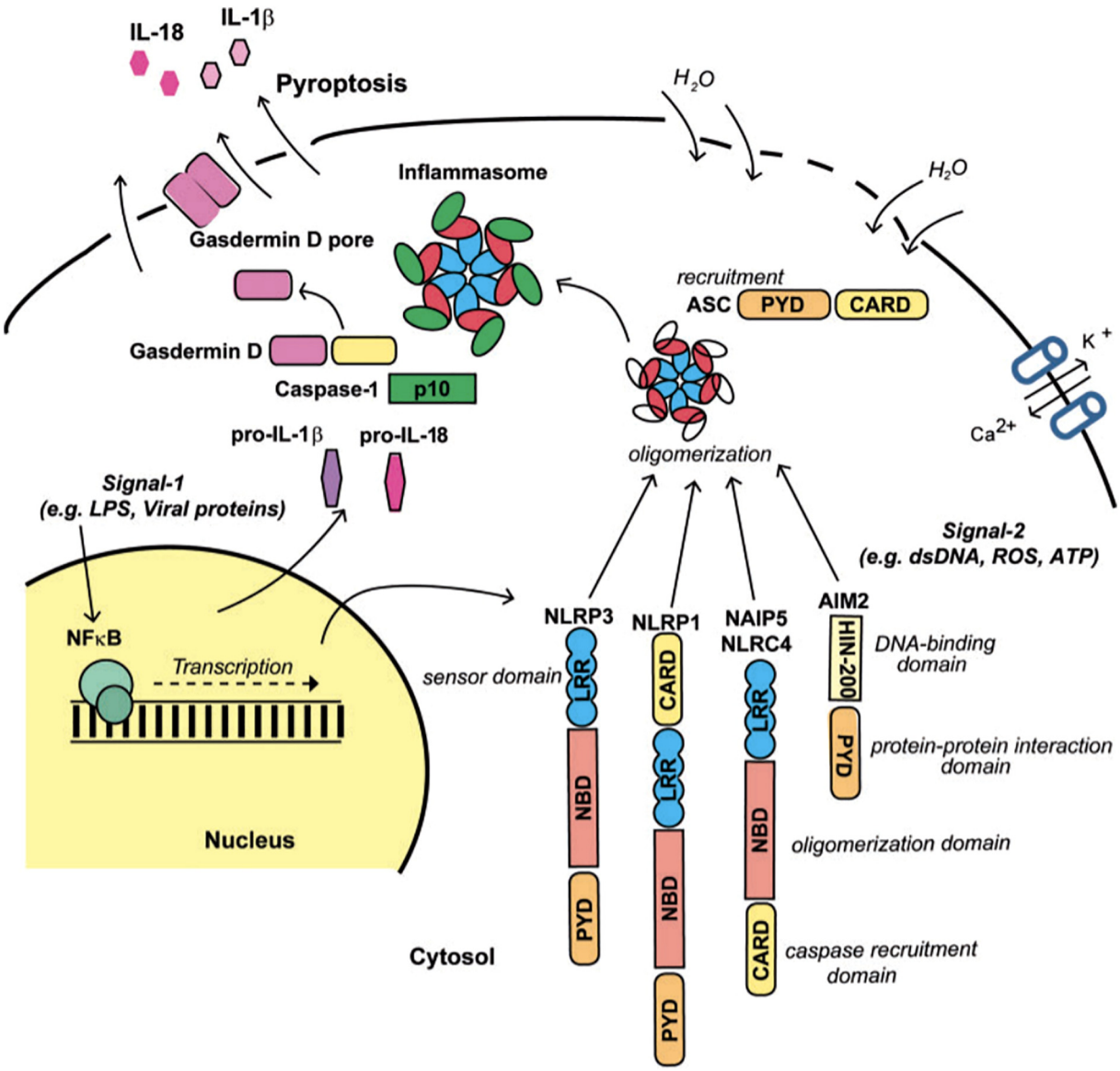

Fig. 2. Inflammasome components. Upon activation, the components of the inflammasome are transcribed and assembled into the inflammasome that serves as a platform for caspase-1 autocatalysis and activation. The activated caspase-1 then mediates proteolytic cleavage and the release of IL-1b and IL-18 cytokines. Furthermore, caspase-1 cleaves gasdermin D forming pores in the membrane, which contribute to pyroptosis. Figure and caption adapted from Manmeet and Christopher, 2017.

5. Neuroinflammation in neurodegenerative diseases

The typical pathological neuroinflammation stem from the activation of CNS glia with cytokine and chemokine production, infiltration of peripheral immune cells, edema, increased blood-brain barrier permeability and breakdown (Hawkins and Davis, 2005; Michael et al., 2015; Monahan et al., 2008). The physical damage that occurs from this kind of infection can typically lead to vascular occlusion, ischemia, and cell death. Hence, the consequence of this type of infection is, generally, life threatening and can elicit further neuropathological complications. Higher degrees of neuroinflammation are typically induced by autoimmune diseases like multiple sclerosis (MS). For instance, the experimental autoimmune encephalomyelitis (EAE) model shows the activation of CNS glia, cytokine and chemokine production, infiltration of peripheral immune cells, and presence of autoreactive T-cells (Reboldi et al., 2009; Samoilova et al., 1998). Hence, there exists significant autoimmune reaction against myelin physiology resulting in myelin loss and axonal fragmentation. The extent of the neuroinflammation is not only highly destructive, but also chronic and progressively destructive over time.

Recent studies have implied that inflammasomes are involved in the neurological processes in the brain that lead to neuroinflammation and neurodegeneration. For instance, IL-1β and IL-6 polymorphisms, which are linked to inflammasome expression, are associated with depression, migraine, MS, AD, and PD (Gougeon, 2017). Similarly, as previously mentioned, the rise of these cytokines is also strongly correlated to increased neuroinflammation. In the brain of AD and MS patients, increased caspase-1 activation was seen, which was correlated to the NLRP3 inflammasome. The same inflammasome, NLRP3, has shown evidence of contribution in the pathogenesis of CNS demyelination, prion disease and amyotrophic lateral sclerosis (ALS). Physical injuries, specifically traumatic brain injuries, have shown increased involvement from the NLRP1, AIM2 or NLRC4 inflammasomes.

Recently the prevalence of positron emission tomography (PET) has led to its use in the detection of in vivo neuroinflammation, which has sparked interest in the use of PET radioligands. These radioligands

include [^{11}C]PK(*R*)-11,195 for the 18-kDa translocator protein and [^{11}C]L-deprenyl for monoamine oxidase B; furthermore, the usage of this technology has shed light on the role of neuroinflammation in a variety of psychiatric and neurological disorders (Schain and Kreisl, 2017). The most commonly studied neurological conditions that shed light on the influence of neuroinflammation are neurodegenerative diseases; of which, Alzheimer's Disease is the most researched. In vitro and animal model studies imply that β-amyloid and hyperphosphorylated tau aggregation induce proinflammatory conditions (Papadopoulos et al., 2006; Rupprecht et al., 2010; Wilms et al., 2003). When in close proximity to β-amyloid plaques within a brain plagued with Alzheimer's Disease, it has been shown that activated microglia and reactive astrocytes are present and overexpress the translocator protein. The PET studies using [^{11}C](*R*)-PK11195 have shown increased binding in patients with a clinical diagnosis of Alzheimer's Disease and a correlation between the cortical [^{11}C](*R*)-PK11195 binding and clinical severity of Alzheimer's Disease. On the other hand, no association was discovered between [^{11}C](*R*)-PK11195 binding and amyloid binding in cross-sectional studies (Lavisse et al., 2012; Cumming et al., 2018). However, a longitudinal study implied that an increase in [11C](*R*)-PK11195 binding directly correlated with an increase in amyloid burden (Ikawa et al., 2017). Hence, neuroinflammation plays a crucial role in the many cellular mechanisms associated with the inflammasome-mediated neurological conditions presenting themselves in the CNS, which commonly manifest themselves as neurodegenerative diseases (Fig. 3).

6. Neuroinflammation & HAND

Individuals suffering with HIV were soon treated with the incorporation of cART, which lead to an extended life. However, in spite of this medical breakthrough in the field of HIV research, the rate of mild to moderate cognitive impairment remains high. This cognitive decline impacts the daily life of those infected with chronic HIV due to the impairment of ones: attention span, ability to learn, functionality and control of mood. The evidence for these affects clearly point to the monocyte and T cells in the brain that are infected with HIV, which has successfully crossed the blood-brain barrier. These viral protein that circulate the blood can induce endothelial cells to release cytokines; thereby, activating inflammation within the brain. The excess viral load within the CNS flourishes due to the difficulty of administering cART to the CNS. The HIV-infected monocytes and T cells not only infect brain cells in the CNS, but also help produce proinflammatory cytokines such as TNF and IL-1β. These cytokines, as previously mentioned, activate microglia, perivascular macrophages and astrocyte cells in the CNS, which are the main contributors to neuroinflammation in HIV infection and release neurotoxic factors such as excitatory amino acids and inflammatory mediators (Narayanaswami et al., 2018).

An affected CNS through either infiltrating viruses or HIV-infected neurocognitive disorder results in the increased activation of monocytes and macrophage, ensuing in astrocytosis and microglial activation (Hong and Banks, 2014). An examination of the postmortem brain from HAND+ patients further confirmed the relationship by expressing greater signs of neuroinflammation (Kumar and Loane, 2012). To further analyze the association between neuroinflammation and HAND certain studies have explored the effects of cART on inflammation. One such study found that the regions of the brain that exhibit neuroinflammation, during the cART era, are the hippocampus, entorhinal cortex and temporal cortex. On the other hand, the region of the brain that exhibit neuroinflammation, before the cART era, is the basal ganglia (Anthony and Bell, 2008). This shift in neuroinflammatory behavior corresponding the cART treatment timings implies that there is some correlation between HAND and neuroinflammation. Furthermore, in patients that are suffering from an HIV infection, immune

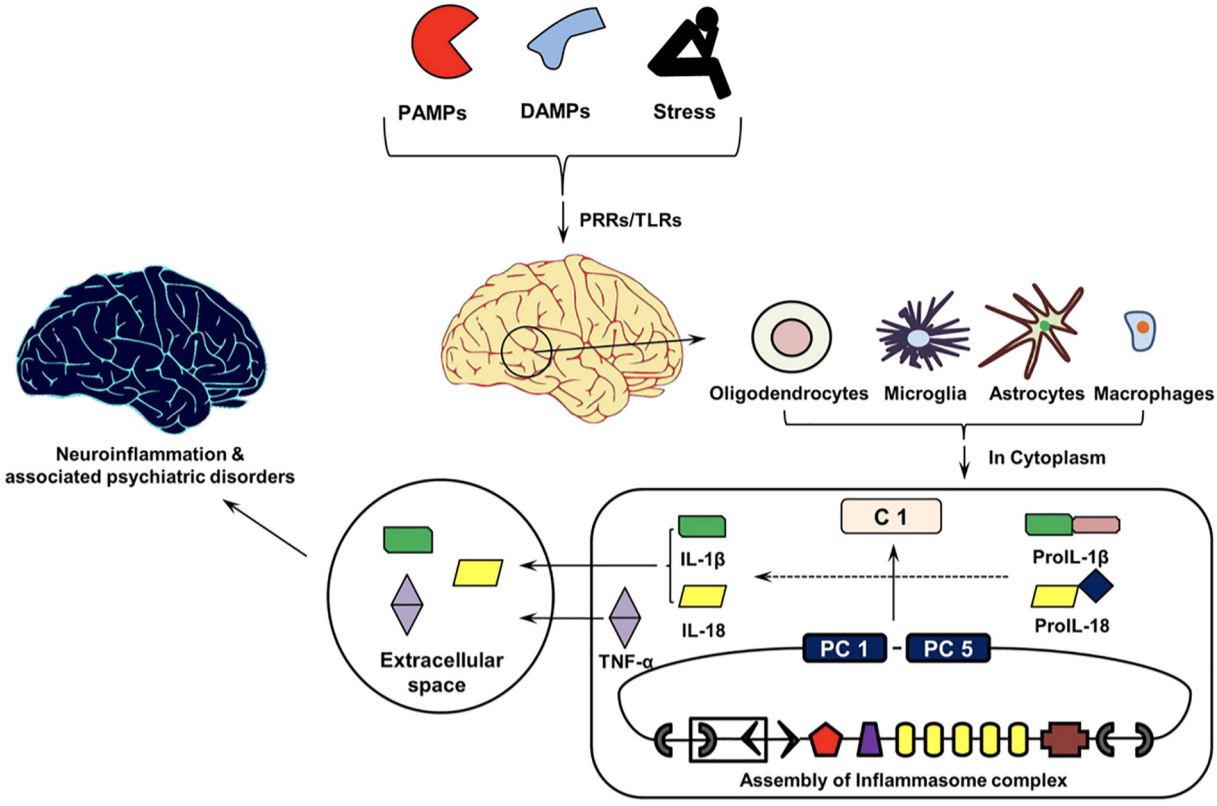

Fig. 3. Inflammasomes Cascade in the CNS. Recognition of PAMPs, DAMPs, PRRs and Toll-Like Receptors (TLRs) initiates assembly of cytosolic inflammasome complex. This leads to the activation of immune responses involving Interleukin (IL)-1 cytokines, which in addition to Tumor Necrosis Factor (TNF)-α initiate inflammatory reaction in the extracellular space. Figure and caption adapted from Manmeet and Christopher, 2017.

activation is a risk factor for the development of neuropathological conditions. Further evidence of neuroinflammation in HIV infection includes brain resident and CNS-migrating immune cells (Gougeon, 2017).

After the introduction and wide-scale prevalence of cART, HIV-associated dementia and stronger forms of HAND have decreased in prevalence, but the prevalence of mild forms of HAND have increased. This shift in HAND severity is complimented by the detection of early stage neuroinflammation through the use of biomarkers of cellular injury, even in early patients infected with chronic HIV infection (Gougeon, 2017). Furthermore, studies have shown other important evidence regarding the pathogenesis of HAND. Specifically, most patients with CNS escape in HIV, who are still neurologically asymptomatic, produce abnormally high levels of CSF neopterin, which serves as a biomarker of macrophage activation. Hence, implying a state of neuroinflammation in patients with early or underlying neurological conditions originating from their HIV infection (Lénárt et al., 2016). In similar patients with CNS escape from HIV, sequence divergence was detected between the CNS and plasma virus. This finding implies that the compartmentalized virus plays a substantial role in the rise of neuroinflammation within the patient. Through these various mechanisms, HIV-1 induces a neuroinflammatory response that is likely to be a major contributor to the cognitive changes seen in HAND.

7. Interplay between HAND, neuroinflammation & inflammasomes

As previously mentioned, rates of HIV-associated dementia has drastically decreased, since the introduction of cART as a treatment for HIV. However, the prevalence of neurocognitive disorders still remains at a staggering rate: an estimated 50% of patients with HIV on cART have some form of HAND (Lénárt et al., 2016). This phenomenon is due to the fact that many of these patients have adopted milder forms of HANDs, such as MND and ANI. A recent study regarding MND and ANI shows not only an increased risk of disease progression to symptomatic neurocognitive impairment for patients with ANI, but also continual neuroinflammation within the CNS of these patients (Lénárt et al., 2016). Hence, this sheds light on a potential pathway to prevent or cure neurocognitive impairment - the study of neuroinflammation and its relationship with neurocognitive disorders due to HIV.

To further understand the pathways with which neuroinflammation is induced and affects the CNS, researchers have attempted to understand the activation mechanisms of neutrophils and macrophages due to their pivotal roles in various neuroinflammatory processes; however, the exact mechanism for their activation is still mostly unknown. Another possible mechanism that can be investigated to establish a connection between neuroinflammation and neurocognitive disorders is DAMPs. As previously mentioned, DAMPs are released immediately after injury or impairment, which initiates a cascade of cellular and molecular immune mediators that amplify inflammation. The immune mediators that provide said cascading effect include cytokines such as TNF-a, IL-6, and IL-1β, which are upregulated rapidly by local and infiltrating immune cells in response to DAMPs (Ikawa et al., 2017). The most potent mechanism by which DAMPs initiates inflammatory signaling is through the release of cytokines, like IL-1β and IL-18, which activated the mechanistic pathways of inflammasomes.

Due to the fact that, inflammasome-associated proteins are highly expressed in the CNS, and inflammasomes assemble in glial cells and neurons, few studies have attempted to identify the priming stimulus that allows DAMPs to activate the NLRP3 inflammasome in glial cells (Savage et al., 2012). It was found that the endogenous stress proteins (such as serum amyloid A) strongly upregulated in blood at the same time as disruption of BBB occurs, primes glial cells and allows DAMPs such as ATP, monosodium urate and calcium pyrophosphate dehydrate crystals to activate the inflammasome and, consequently, IL-1b is secreted (Savage et al., 2012). Furthermore, experiments performed in IL-1a/b double knockout mice implied that that IL-1 is required for IL-6 and CXCL1 production after cerebral ischaemia. This phenomenon demonstrated the various depth with which DAMPs contributes to brain inflammation in acute brain injury: (i) by directly stimulating the production of proinflammatory mediators by glial cells, (ii) by contributing to BBB injury through induction of release of various proteases and (iii) by triggering IL-1 release from primed cells (Savage et al., 2012). Similarly, the DAMPs-driven activation of the NLRP3 inflammasome in brain injury, described above, is also correlated to the pathogenesis of neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS) (Lukens and Kanneganti, 2014; Halle et al., 2008; Meissner et al., 2010).

Specifically in HAND, HIV infects and activates macrophages in the CNS and induces chronic neuroinflammation. Certain studies attempted to establish a connection between inflammasome activation, specifically through the NLRP3-dependent manner, and HIV-1 infection of human microglia - a common phenomenon in HAND (Manmeet and Christopher, 2017). The connection is established through the prevalence of neuroinflammation that is instigated by mechanistic pathways of the inflammasomes. In vivo, feline immunodeficiency virus infection activated multiple inflammasome-associated genes in microglia, accompanied by neuronal loss in the cerebral cortex and neurological deficits (Walsh et al., 2014). With specificity to the cytokines, in this experiment, there was an increase in caspase-1 activation and IL-1β production due to the infection. Therefore, inflammasome activation in the CNS contributed to brain diseases inherited from the HIV-1 infection of the CNS (Churchill et al., 2009). Another paradigm of this can be seen in astrocytes, which express CCR5 and CXCR4, that have become infected in vivo by HIV-1 - even at lower levels. This infection of astrocytes has also shown to cause extensive modifications in the physiology of the BBB in vitro as well as in vivo, as shown in brain sections from SIV-infected macaques (Eugenin et al., 2011). Inside the CNS, the HIV-1, through the use of inflammasomes, induces the: activation of chemokine receptors, production of inflammatory mediators, synthesis of extracellular matrix degrading enzymes and induction of glutamate receptor-mediated excitotoxicity (Kovalevich and Langford, 2012). The actions listed all have severe detrimental effects on neuronal and glial functions; therefore, serving as key factors in the development of HAND in a HIV-1 infected patient (Fig. 4).

8. Conclusion

Recent reports suggest that chronic neuroinflammation from HIV-1 inhibits adult neurogenesis, thus contributing to the evolution of HAND (Ferrell and Giunta, 2014; Kaul, 2008). Neurogenesis describes the process in which neuronal and glial cells are generated from neural precursors that includes neural stem cells (NSCs) and neural progenitor cells (NPCs). This process takes place during brain development and even throughout adult life (Duan et al., 2008; Ming and Song, 2011). Neurogenesis is important to study in the context of HAND, because HIV-1 virus have been identified in the hippocampal formation of pediatric AIDS patients (Schwartz et al., 2007), and impaired neurogenesis has been observed in both HIV patients as well as SIV-infected macaques (Curtis et al., 2014; Krathwohl and Kaiser, 2004). NSCs have also been shown to be targets of active HIV- 1 infection (Okamoto et al., 2007; Fan et al., 2016; Lawrence et al., 2004; Schwartz and Major, 2006). Additionally, well-known antiretroviral drugs including AZT, efavirenz, and a tenofovir/emtricitabine/raltegravir cocktail hinder NSC proliferation and differentiation in vitro and in vivo (Demir and Laywell, 2015; Jin et al., 2016; Xu et al., 2017). The HIV-transgenic mice (Tg26) line expresses seven HIV-1 viral proteins (Dickie et al., 1991; Kopp et al., 1992; Carroll et al., 2016; Lu et al., 2006). Tg26 mice serve as an animal model for studying the long-term effects of viral proteins on the host as well as for HAND. This model is clinically relevant to ART-controlled HIV-1-infected patients who lack active viral replication, but suffer from continuous stress from HIV-1 viral protein

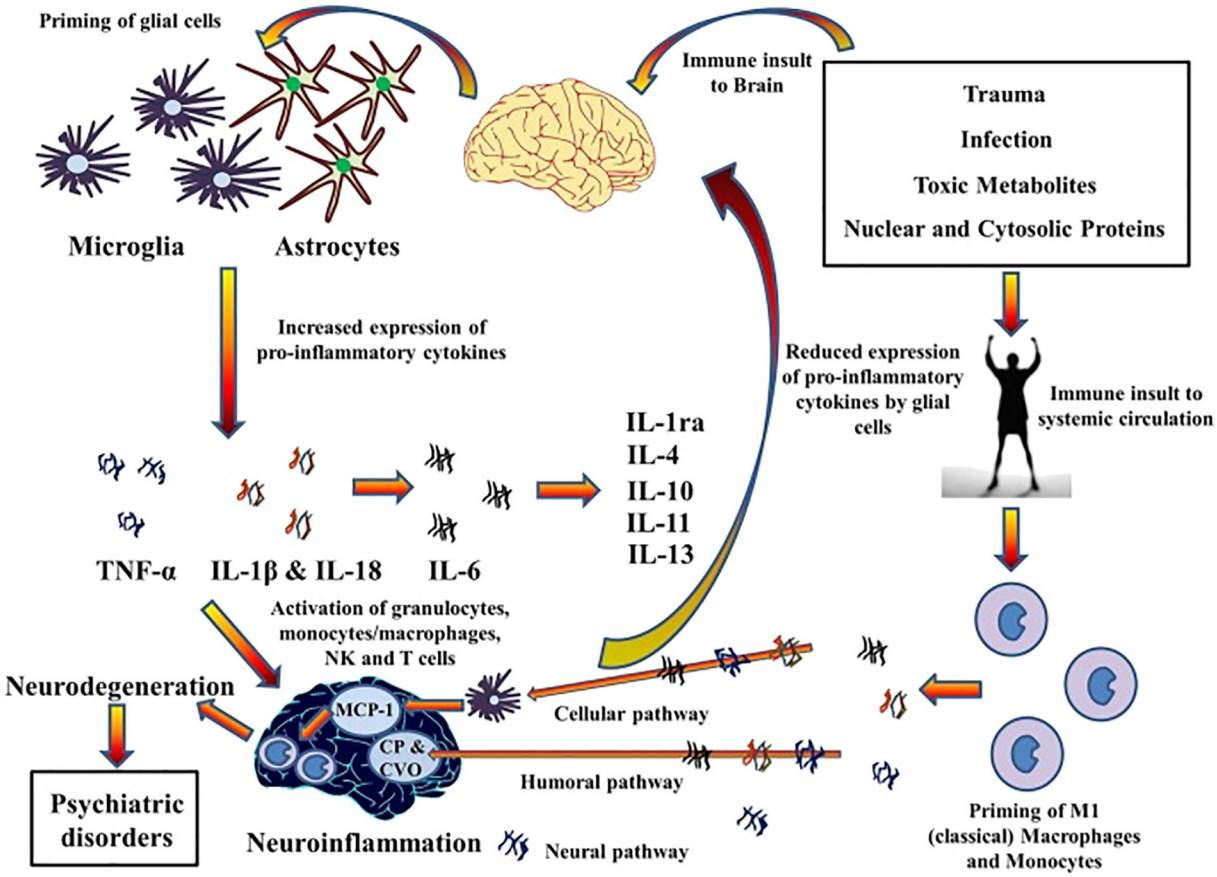

Fig. 4. Cytokines hypothesis of neuroinflammation: Implications in comorbidity of systemic illnesses with HAND. There are three pathways for the transportation of pro-inflammatory cytokines from systemic circulation to the brain: Cellular, Humoral, and Neural. PAMPs and DAMPs, due to the HIV virus, prime glial cells to express the pro-inflammatory cytokines: TNF-α, IL-1β, and IL-6. When expressed, these cytokines activate granulocytes, monocytes/macrophages, Natural Killer, and T cells to contribute to neuroinflammation. Neuroinflammation results in neurodegeneration, which leads to HAND. The cytokines also produce anti-inflammatory cytokine by glial cells that serve as negative feedback to reduce the expression of pro-inflammatory cytokines, subsiding the neuroinflammation. Figure and caption adapted from Manmeet and Christopher, 2017.

exposure. It is reported that neurogenesis is down regulated in the brain regions of TG26 mice (Putatunda et al., 2018).

On the other hand, our unpublished data have shown that neuroinflammation, CXCR4 and CCR5 expressions and astrogliosis were enhanced in the hippocampal region of three month old TG26 mice compared to normal mice. There is no report available regarding the activation of inflammasomes in the brain of TG26 mice; however, renal cortical sections of TG26 mice have shown increased expression of NLRP3, ASC (a CARD protein), caspase-1, and IL-1β proteins, confirming NLRP3 inflammasome complex formation in podocytes of Tg26 mice (Haque et al., 2016) and we also found increased level of pro-cytokines in the renal cortex of TG26 mice (Bryant et al., 2018). In this context, one group of investigators (Chivero et al., 2017) demonstrate a novel role of HIV-1 Transactivator of Transcription (Tat) protein in priming and activating NLR family pyrin domain containing 3 (NLRP3) inflammasomes in microglial cells and in HIV- Tg rats administered lipopolysaccharide (LPS). In these LPS induced rats neuroinflammation was upregulated by increasing IL-1β. Royal 3rd et al. (2012) have also reported that in the rat model of HAND, neuroinflammation significantly increased. Even White et al., 2017 (White et al., 2017) have reported that NLRP3 and NLRP1 inflammasomes have been identified as an integral in pathogenic neuroinflammation in animal models of Alzheimer's Disease. Furthermore, it is reported that Gastrodin ameliorates cognitive deficit in diabetic rat models by decreasing: endoplasmic reticulum stress, NLRP3 inflammasome activation and neuroinflammation (Ye et al., 2018). Therefore, it can be suggested that the inflammasome pathway mediators can be used as therapeutic targets to enhance or prevent neuroinflammation and, subsequently, cognitive deficiency in HIV-positive patients.

Author's contribution

The authors above have made a valuable and/or intelligent contribution to the review and agreed jointly to approve it for publication.

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