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The IL-1β phenomena in neuroinflammatory diseases

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Abstract

It is becoming increasingly clear that neuroinflammation has a causal role in the pathogenesis of central nervous system (CNS)-related diseases, and therefore therapeutic strategies targeting the regulation or availability of inflammatory mediators can be used to prevent or mitigate pathology. Interestingly, the proinflammatory cytokine, interleukin-1 beta (IL-1β), has been implicated in perpetuating immune responses and contributing to disease severity in a variety of CNS diseases ranging from multiple sclerosis, neurodegenerative diseases, traumatic brain injury, and diabetic retinopathy. Moreover, pharmacological blockade of IL-1 signaling has shown to be beneficial in some autoimmune and autoinflammatory diseases, making IL-1β a promising therapeutic target in neuroinflammatory conditions. This review highlights recent advances of our understanding on the multifaceted roles of IL-1β in neuroinflammatory diseases.

Keywords

IL-1β; neuroinflammation; multiple sclerosis; Alzheimer's disease; diabetic retinopathy; microglia

Introduction

Overview of IL-1β and neuroinflammation

The interleukin-1 (IL-1) family consist of 11 unique known ligands and antagonistic receptors (IL-1α and IL-1β, IL-18, IL-33, IL-36α, β, g, IL-1Ra, IL-36Ra, IL-38 and IL-37) which independently induce local and systemic inflammation or induce anti-inflammatory responses (Dinarello 2009). IL-1α and IL-1β were the first discovered interleukins, and exert similar proinflammatory responses through signaling via interleukin 1 receptor type 1 (IL-1R1). The biological effects of IL-1R1 signaling are regulated endogenously by interleukin 1 receptor antagonist (IL-1Ra), which competes with IL-1α and IL-1β for IL-1R1 binding. Intriguingly, both IL-1α and IL-1β are synthesized as precursor proteins, however, pro-IL-1β remains inactive until enzymatic cleavage via inflammasome activation yielding mature IL-1β (Auron et al. 1984; Mariathasan and Monack 2007). Interestingly both cytokines exert their functions extracellularly, yet they do not contain an amino-terminal signal sequence that defines a protein to be secreted through the Golgi (Auron et al. 1984). Thus they are found in the cytosol and require cell death or stimulation to be released.

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Along those lines, IL-1α is constitutively expressed by many cell types and is often a danger signal released by dying cells. Whereas, IL-1β is an inducible cytokine produced chiefly by blood myeloid cells, pathogenic lymphocytes, central nervous system (CNS) resident microglia and astrocytes during autoimmune disease, neurodegeneration, and metabolic diseases, and will therefore be the focus of this review.

IL-1β is a pivotal proinflammatory cytokine involved in the regulation of the hosts' innate immune response. Intrinsically IL-1β-mediated inflammation has evolved to combat microbes and aid in tissue repair mechanisms (Dinarello 2011). The extracellular recognition of a disturbance in homeostasis sets the stage for IL-1β processing and its ability to execute inflammatory activities. These processes begin by the host's ability to unmask microbes by recognizing exogenous pathogen-associated molecular patterns (PAMPs) via cell-surface pattern recognition receptors (PRRs). In contrast, PRRs can influence inflammatory responses by detecting endogenous damaged-associated molecular patterns (DAMPs), which can be misfolded proteins (i.e., amyloid-β peptides) or intracellular content released by stressed or dying cells such as purine metabolites (i.e., ATP) and nucleic acids (i.e., DNA and RNA) (Davis et al. 2011). PRR sensing of PAMPs and DAMPs activates the intracellular assembly of inflammasomes, which are a multiunit protein complexes that regulate the production of IL-1β (and IL-18) through caspase activity. The canonical Nod-like receptor family, pyrin domain containing 3 (NLRP3; also known as NALP3) inflammasome involves the intracellular oligomerization of the PRR NLRP3 that can trigger innate immunity by providing a scaffold for pro-caspase-1 to directly bind via the caspase activation and recruitment domain (CARD) or indirectly through a pyrin domain (PYD) by the adaptor apoptosis associated speck-like protein containing a CARD (ASC). Thus proteolytic activation of pro-caspase-1 to caspase-1 yields its cysteine proteases activity capable of cleaving the amino-terminus of pro-IL-1β to produce mature/bioactive IL-1β (Freeman and Ting 2016). The regulation of the different inflammasomes in health and disease have been reviewed in detail elsewhere (Davis et al. 2011; Hanamsagar et al. 2012). Albeit, the regulation of inflammasome activation and production of IL-1β released by cells is multifaceted and there is evidence of inflammasome-independent activation of IL-1β by other enzymes including neutrophil-derived serine proteases (Netea et al. 2015). Furthermore recent evidence has shown the evolutionary importance of IL-1β in regulating microbial defense, in which, LaRock et al. provide evidence that IL-1β acts as a sensor of bacterial infection and utilizes the microbes secreted proteases to activate mature IL-1β independently of self inflammasome activation to fight the infection (LaRock et al. 2016).

Within the nervous tissue, neuroinflammation is conventionally considered as the ability of the central (CNS) and peripheral (PNS) nervous system to mount an innate immune response during a pathological event. The tissue resident microglia and astroglia are considered the hallmark effector cells involved in mounting inflammatory responses to injury. However, the fine balance of governing neuroinflammation within the mammalian CNS is a challenging feat which is often associated with a bystander effect leading to exacerbated tissue damage. A central role of IL-1β in mediating neuroinflammation has been recognized in most CNS-related diseases including stroke, traumatic brain injury, Alzheimer's disease and multiple sclerosis and diseases that affect the ocular system including diabetic retinopathy, glaucoma and age-related macular degeneration.

IL-1β is a pleiotropic cytokine that can activate microglia and astrocytes and lead to the downstream synthesis of other proinflammatory and chemotactic mediators within the CNS (Shaftel et al. 2008), whereas in the periphery, IL-1β can lead to the expansion of encephalitogenic T cells (Dinarello 2011). Along those lines, recent work by Dror et al. demonstrated that IL-1β plays a strong role in regulating the steady-state of metabolic homeostasis by promoting glucose uptake specially in immune cells (Dror et al. 2017). Yet the overproduction or chronic exposure of IL-1β is known to contribute to disease pathogenesis in rheumatoid arthritis, gout, inflammatory bowel disease, and type 2 diabetes, in which pharmacological inhibition of IL-1β signaling directly or indirectly limits disease progression (Dinarello et al. 2012). Paradoxically, IL-1β signaling has been shown to exert neuroprotective properties following CNS damage (discussed in the sections below). As we continue to unravel the biology of IL-1β, evidence supports the notion that IL-1β is a master regulator of the physiological and pathological states; therefore, the regulation of IL-1β provides an intriguing opportunity to control neuroinflammation and mitigate tissue damage during disease. Here, we review past and more recent evidence highlighting the paradoxical role of IL-1β in diabetic retinopathy, multiple sclerosis and Alzheimer's disease.

IL-1β as a potent mediator of disease in diabetic retinopathy

Diabetic retinopathy (DR) remains one of the most enigmatic and progressive eye diseases in which neuropathy, inflammation, and vasculopathy collectively result in "retinal failure" which lead to vision impairment and ultimately blindness in patients with type 1 and type 2 diabetes (Antonetti et al. 2012; Gray and Gardner 2015). The proinflammatory and toxic effects of inflammasome activation and release of IL-1β are involved in the pathogenesis of diabetes (Maedler et al. 2002; Vandanmagsar et al. 2011; Wen et al. 2011); and systemic inhibition of IL-1 signaling by anakinra (a recombinant human receptor antagonist for IL-1R1) or neutralization of IL-1β by gevokizumab (monoclonal IgG2 antibody against IL-1β) improves pancreatic β-islet cell function and glycemia, as well as reduces the load of systemic inflammatory mediators in patients (Larsen et al. 2007; Larsen et al. 2009; Cavelti-Weder et al. 2012). Much attention has been directed to linking the diabetic milieu to retinal damage, and growing evidence suggest that IL-1β plays a critical part in driving neuroinflammation and pathology in the diabetic retina (Fig. 1). IL-1β is upregulated in the retina of rodents as early as two months of experimental diabetes (Carmo et al. 2000; Kowluru and Odenbach 2004; Liu et al. 2012; Scuderi et al. 2015) and in the vitreous of patients with early DR (Demircan et al. 2005; Patel et al. 2006). Similarly, interleukin-1 converting enzyme/caspase-1 has been shown to be elevated and biologically active in the diabetic retina of rodents and humans (Mohr et al. 2002). These above physiological levels of IL-1β have been reported to cause retinal damage, and pharmacological inhibition of caspase-1/IL-1β via minocycline can mitigate neurotoxicity (Krady et al. 2005) and vascular degeneration (Vincent and Mohr 2007) in the diabetic rodent retina. Interestingly, intravitreal administration of recombinant IL-1β into nondiabetic rat's is sufficient to promote oxidative stress and apoptosis of retinal capillary cells (Kowluru and Odenbach 2004), histopathology characteristic of DR.

Microglia are the primary cellular source of IL-1β in the diabetic retina—

Microglia, the CNS-resident immune population that originate from erythromyeloid

precursor cells from the yolk sac (Ginhoux et al. 2010; Kierdorf et al. 2013), are considered to be the primary cellular source of IL-1β in the diabetic retina (Grigsby et al. 2014). Of note, the contribution of astrocytes and müller cells to the production of IL-1β *in vitro* have been reported, but a lack of *in vivo* evidence limits their involvement. Indeed, reactive retinal microglia can synthesize and release neurotoxic levels of IL-1β *in vitro* and elicit retinal ganglion cell (RGC) death (Sivakumar et al. 2011). The mechanisms regulating overt expression of microglial-mediated IL-1β remain under investigation, but shown to be in part regulated by CX3CR1 signaling. We recently reported that CX3CR1 signaling influences the blood-retinal barrier following systemic inflammation. More specifically *Cx3cr1*$^{-/-}$ mice experienced robust perivascular clustering of IL-1β+ microglia around areas of fibrinogen leakage in the nondiabetic and diabetic retina (Mendiola et al. 2017). Moreover, in a separate study, our group showed that CX3CR1-deficiency in the Ins2^{akita} type 1 diabetic mouse strain (Barber et al. 2005) was associated with early loss of RGCs and robust microglial reactivity with specific upregulation of IL-1β protein levels in the retina following acute diabetes relative to Ins2^{akita} CX3CR1-sufficient mice (Cardona et al. 2015). Mechanistically, CX3CR1-deficient monocytes were shown to utilize exogenous ATP to signal via P2X purinoceptor 7 (P2RX7) to release IL-1β and mediate photoreceptor degeneration in an animal model of age-related macular degeneration (Hu et al. 2015). Interestingly, dying or stressed photoreceptors produce proteins that activate innate immunity and trigger the release of microglial-mediated IL-1β (Kohno et al. 2013), that in part enhance photoreceptor cell death in models of retinal degeneration (Zhao et al. 2015). Importantly, IL-1β blockade experiments were shown to be effective at mitigating photoreceptor degeneration (Zhao et al. 2015; Eandi et al. 2016).

Photoreceptors are key contributors to oxidative stress and inflammatory signals in DR by producing toxic levels of reactive oxygen and nitrosative species and cycloxygenase-2 (COX-2), that become potent induces of vascular damage and endothelial cell death in diabetes (Kanwar et al. 2007; Du et al. 2013; Tonade et al. 2016). A link between inflammation, specifically IL-1β, has been associated with inducing COX-2 in the CNS (Samad et al. 2001). Thus, it is proposed that soluble mediators released by stressed photoreceptors could activate or perpetuate microglia and astrocyte/müller cell activation and subsequent release of IL-1β (and other proinflammatory cytokines) contributing to the neuroinflammatory reactions and progressive neuronal and vascular degeneration in diabetic retina (Fig. 1). This speculation could explain why high glucose alone is not sufficient to trigger inflammasome activation and release of IL-1β in microglial cultures (Liu et al. 2012). In contrast, active caspase-1 is robustly upregulated in murine retinal endothelial cells cultured in high glucose conditions (Jiang et al. 2017) and is sufficient to upregulate IL-1β protein levels (Liu et al. 2012; Jiang et al. 2017). These data provide evidence that in response to hyperglycemia, blood vessels may contribute to the neuroinflammatory milieu in the diabetic retina as seen in models of MS (Lévesque et al. 2016). Nevertheless, chronic IL-1β exposure results in neurodegeneration (Rossi et al. 2014), endothelial cell dysfunction (Vallejo et al. 2014) and vascular degeneration (Kowluru and Odenbach 2004; Vincent and Mohr 2007) in the diabetic retina. IL-1β may also indirectly promote breakdown of the blood-retinal barrier by regulating the synthesis and release of the proapoptotic protein semaphorin 3A (Sema3A) that is produced by stressed RGCs in the ischemic retina (Rivera

et al. 2013). Indeed, Sema3A is upregulated in the vitreous of patients suffering from diabetic macular edema and in the retinas of diabetic mice (Cerani et al. 2013). Cerani et al. further showed that knockdown of Sema3A or conditional knockout of Sema3A's receptor, neuropilin-1, prevented retinal vascular permeability in diabetes.

Inhibiting IL-1β as a therapeutic approach for diabetic retinopathy—While IL-1β is known to elicit robust angiogenesis in cancer, in contrast, inhibition of IL-1β can promote anti-angiogenic properties in an experimental model of retinal neovascularization (Lu et al. 2009). On that note, a small pilot clinical trial investigating systemic IL-1β inhibition by canakinumab, a monoclonal IgG1 antibody targeting IL-1β, in patients ($n = 6$) with proliferative diabetic retinopathy (PDR) showed promising results in preventing disease progression (Stahel et al. 2016). Stahel et al. observed that following 24 weeks of repeated (one subcutaneous injection of 150 mg every 8 weeks) systemic canakinumab treatment, vascular leakage was reduced and neovascularization was stabilized in eyes of patients. However, a regression in neovascularization was not seen, and the investigators contributed this as a consequence of insufficient canakinumab in the retinal circulation and thus higher doses should be tested. The therapeutic application of intravitreal delivery of canakinumab, as currently done with anti-vascular endothelial growth factor and steroids, could also circumvent this obvious limitation in systemic administration. Given that NLRP3 and caspase-1 protein levels are significantly elevated in the vitreous of patients with late stage PDR (Loukovaara et al. 2017), the neuroprotective (i.e., preventing retinal nerve layer thinning) effects of neutralizing IL-1β remain unknown in patients with early DR and would provide compelling evidence for IL-1β-mediated damage in DR. In culmination, growing evidence has identified IL-1β as a potent mediator of DR pathogenesis, and supports the notion that neurodegeneration (Sohn et al. 2016) and neuroinflammation (Tang and Kern 2011) proceed apparent vascular degeneration, challenging the dogma that DR is solely a vasculopathy, and warrants consideration.

IL-1β in the pathogenesis of experimental autoimmune encephalomyelitis and multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease with mild, moderate or severe progression for which an exact cause is unknown. Combined actions of environmental factors in genetically susceptible individuals trigger a cascade of events that cause CNS inflammation, demyelination, and neuronal loss (Trapp and Nave 2008). Myelin destruction and axonal damage translate into unpredictable signs and symptoms often associated with motor impairment, disturbances in vision and cognitive decline. Studies in experimental autoimmune encephalomyelitis (EAE) models of MS, recapitulate important aspects of MS, including blood-brain barrier leakage, immune cell infiltration into the CNS, activation of resident CNS cells, reactivation of autoreactive T cells, and demyelination (Dendrou et al. 2015). The importance of IL-1 signaling, and specifically IL-1β-driven neuroinflammation in MS and EAE, has been established for years. However, recent evidence has guided our understanding to the specific contributions of IL-1β to the onset and progression of EAE (Fig. 2) and MS.

IL-1β drives the encephalitogenic nature of Th17 cells during EAE—In 1991, Jacobs et al. showed that neutralizing both IL-1α and IL-1β attenuates EAE disease in rats, providing the initial observation that the IL-1 system contributes to the pathogenesis of EAE (Jacobs et al. 1991). A few years later, it was shown that treating myelin oligodendrocyte glycoprotein (MOG)-immunized rats during the effector phase of disease with recombinant IL-1Ra, which competes for IL-1R1 and inhibits the actions of both IL-1α and IL-1β, delays disease onset and attenuates disease progression (Martin and Near 1995). Whereas both *Il1r1*$^{-/-}$ rats (Schiffenbauer et al. 2000) and mice (Sutton et al. 2006) are resistant to EAE pathogenesis. The next logical question is to determine if this protective effect seen in *Il1r1*$^{-/-}$ animals were due to either IL-1α, IL-1β or both. Intriguingly, a recent report has provided convincing evidence that IL-1α is dispensable in EAE development, and that IL-1β is the culprit behind IL-1/IL-1R1 mediated neuroinflammation and EAE pathogenesis (Lévesque et al. 2016); in line with literature presenting strong evidence of the involvement of the canonical NLRP3-caspase-1-inflammasome in EAE (Furlan et al. 1999; Inoue et al. 2012; Freeman and Ting 2016).

The initiation of immunopathology in active EAE begins in the secondary lymphoid organs with naive CD4+ T cells becoming activated against myelin antigen presented by major histocompatibility class-II (MHC-II) on antigen presenting cells (APCs) (Fig. 2). Autoreactive CD4+ T cells further differentiate in response to cytokines into transcriptionally defined effector subtypes that are conventionally defined as interferon-gamma producing T helper type 1 (Th1) and IL-17-producing Th17 cells with potent encephalitogenic capacity (Raphael et al. 2015). EAE disease can be independently mediated by adoptively transferring antigen-specific Th1 (Ando et al. 1989; Jäger et al. 2009; El-Behi et al. 2011) or Th17 (Langrish et al. 2005; Rangachari and Kuchroo 2013) cells. Growing evidence supports the notion that encephalitogenic Th17 cells recruited to the CNS are critical for EAE pathogenesis, and interestingly IL-1β signaling is recognized in supporting the expansion of pathogenic Th17 cells (Sutton et al. 2006; Chung et al. 2009; El-Behi et al. 2011). Sparking intrigue, *Il1r1*$^{-/-}$ mice fail to produce antigen-specific Th17 cells and are resistant to EAE (Sutton et al. 2006). Mechanistically, IL-1β signaling in Th17 cells aides in the stability and proliferation of these committed cells in part due to activation of the mTOR pathway (Gulen et al. 2010). Moreover, upon differentiation, IL-6 signaling in Th17 cells upregulates IL-23R and IL-1R1 in Th17 cells, and signaling through these cytokine receptors influence the expression of interferon regulatory factor 4 (IRF4) and retinoic acid receptor-related orphan receptor gamma (RORγt), which are key transcription factors that regulate a unique set of transcripts (i.e., *Il17a*, *Il17f*, *Il22*, *Il23r*, and *Csf2*) associated with pathogenic Th17 cells (Chung et al. 2009). Further EAE studies identified a critical role of IL-1β and IL-23 in regulating the production of Th17-derived GM-CSF (transcribed from *Csf2*), a non-redundant cytokine required for T cells to become encephalitogenic (Codarri et al. 2011; El-Behi et al. 2011; Mufazalov et al. 2016). *Csf2*$^{-/-}$ mice were shown to be resistant to CNS inflammation largely due to T cell derived GM-CSF acting on CCR2+Ly6C+ inflammatory monocytes to produce IL-1β and further expand the population of GM-CSF+ Th17 cells in an IL-1R dependent mechanism (Croxford et al. 2015). Additionally, recent evidence has shown that CCR2 mediates the cellular trafficking of these encephalitogenic GM-CSF-producing Th17 cells during the effector phase of EAE

(Kara et al. 2015). In a separate report, the author's showed that Th17 cells process their own IL-1β via a T-cell intrinsic noncanonical ASC-NLRP3-Caspase-8 inflammasome, and that IL-1β signals in an autocrine manner to further stimulate the survival and possible expansion of pathogenic Th17 cells during the development of EAE (Martin et al. 2016). This process remains to be seen in human Th17 cells and is of interest since peripheral blood mononuclear cells (PBMCs) isolated from MS patients show elevated transcripts of the canonical NLRP3-Caspase-1 inflammasome and IL-1β relative to healthy individuals, and these PBMCs were conducive of supporting Th17 cell differentiation *in vitro* (Peelen et al. 2015). Given that human Th17 cells express high levels of IL-1R1 (Mufazalov et al. 2016), this may be a likely mechanism by which IL-1 signaling expands pathogenic Th17 cells in MS. Martin et al. also confirmed the pathogenic role of IL-1β-mediated CNS autoimmunity by showing that adoptively transferred CD4+ $Il1b^{-/-}$ $Il18^{-/-}$ T cells into wild type recipients were protected from EAE pathology including reduced cellular infiltration, demyelination, and proinflammatory cytokine expression in the spinal cord (Martin et al. 2016).

In addition, it was recently shown that myelin-specific T cells that infiltrate the CNS stimulate the transcription of IL-1 signaling molecules, and specifically IL-1β was shown to be upregulated in CD11b+ microglial cells within axonal lesions (Grebing et al. 2016). Furthermore, it was demonstrated in rhesus macaques with EAE, that all IL-1β+ cells were in the perivascular space in active demyelinating lesions and colocalized primarily to IBA1+ microglia/monocytes, but not to infiltrated macrophages or T cells (Burm et al. 2016). It remains to be known if T-cell-mediated activation of IL-1β in microglia promotes their ability to present antigen (Carson 2002) or further propagates microglial neuroinflammation and ensuing neurodegeneration (Block and Hong 2005). Conversely, it was shown that at peak disease of murine EAE, 94.4% of CD45+ IL-1β-producing cells were neutrophils (approximately 28.2 %) and monocyte-derived macrophages (approximately 66.2 %) (Lévesque et al. 2016). These myeloid cells were shown to upregulate IL-1β upon transmigration across IL-1R+ endothelia of the blood-spinal cord barrier (Fig. 2). While this group has also shown that neutrophils contribute to EAE development (Aubé et al. 2014), the exact contribution of these cells and other polymorphonuclear cells in MS remain unclear.

Are microglia the primary produces of IL-1β in multiple sclerosis?—The precise cause of MS remains up for debate, however, a genetic composition has been identified in which MS patients with a higher IL-1β over IL-1Ra ratio have an increased risk for relapse-onset MS and where families have a 2.2-fold risk of developing relapsing-remitting MS (RRMS) (de Jong et al. 2002). Indeed, IL-1β protein levels are elevated in chronic active lesions of MS patients (Cannella and Raine 1995). Further evidence bolstering the involvement of IL-1β in MS comes from data correlating elevated IL-1β levels in the cerebral spinal fluid (CSF) and blood of MS patients with increased cortical lesion load and disease severity (Mellergård et al. 2010; Seppi et al. 2014). Mellergård et al. demonstrated that natalizumab treatment, a humanized mouse monoclonal antibody against the integrin late activation antigen (VLA-4) on leukocytes that selectively impedes T cells from transmigrating into the CNS, was sufficient to significantly decrease proinflammatory mediators in the CSF (including IL-1β, IL-6, and IL-8) and blood (GM-CSF, TNF-α, and

IL-6) of patients with RRMS (Mellergård et al. 2010). Morever, the two other major therapeutics used to treat MS, interferon-beta and glatiramer acetate, also influence IL-1 signaling as they increase IL-1Ra and decrease IL-1β in monocytes and serum from MS patients (Burger et al. 2009; Guarda et al. 2011). As described above, unequivocal evidence from rodents and non-human primates with EAE shows the involvement of IL-1β in disease pathogenesis; however, in MS patients the cellular source and at what stage of disease IL-1β is biologically active remains unclear. Early in RRMS, the evidence that increased cortical lesions highly correlates with IL-1β levels but not with gadolinium+ lesions (Seppi et al. 2014), suggests that IL-1β may be derived from CNS-resident cells. Activated microglia are known to be activated throughout all stages of MS and are robust producers of IL-1β and thus, chronic IL-1β exposure may be contributing to neuronal loss as reported in other neurodegenerative diseases (Cunningham 2013).

Not surprisingly, heterogeneous phenotypes of activated microglia and macrophages are found throughout brain lesions of MS patients (Vogel et al. 2013), and recent histochemical analyses of postmortem brain tissue from MS subjects (patients with RRMS and chronic progressive MS) showed that IL-1β staining was too heterogeneous amongst patients (Burm et al. 2016). In cryosections, mild IL-1β+ staining was observed in 52% of active lesions and colocalized to microglia. However, in paraffin-embedded tissues, this staining pattern was not observed in any of the 75 lesions assessed from 17 MS patients, and the IL-1β staining was primarily restricted to parenchymal microglia in areas with no apparent demyelination (Burm et al. 2016). Interestingly, Burm et al. identified a distinct population of parenchymal IL-1β+ microglial nodules that may represent “prelesions” primed for demyelination and neurodegeneration (Rossi et al. 2014) and thus needs further investigation. These data contradict another report identifying that reactive astrocytes and perivascular macrophages express the machinery of NLRP3 inflammasome and robust IL-1β staining in active lesions of four chronic progressive MS patients (Kawana et al. 2013). This discrepancy might reflect differences in histochemical approaches as the latter used paraffin-embedded tissues only and that the cellular composition of the lesions and type of MS assessed may also reveal distinct IL-1β activity.

Together, growing evidence from EAE and MS support the effort to specifically target IL-1β to treat MS; however, the cellular source and when in MS progression IL-1β is most critical for disease remains unclear. It should be noted that IL-1β signaling supports the proliferation and differentiation of myelinating oligodendrocytes *in vitro* (Vela et al. 2002) and IL-1β has been shown to be essential in CNS repair following cuprizone-induced demyelination (Mason et al. 2001). However, the cellular source of IL-1β in the context of cuprizone is primarily derived from microglia and astrocyte since cuprizone induces minimal peripheral immune infiltration into the CNS (Neumann et al. 2009). Thus the strategies to blockade IL-1β for the treatment of MS in which a complex pathophysiology exists still requires further investigation but holds a promising role in fighting MS.

IL-1β in Alzheimer’s disease and neuropathogenesis

Alzheimer’s disease (AD) is the leading cause of dementing illness and is characterized by neurodegeneration that leads to impaired cognition and memory loss. Accumulating

evidence supports the notion that immune activation and neuroinflammation in AD are at least involved in parallel in mediating pathogenesis in AD (Zhang et al. 2013; Heneka et al. 2015). Considering the strong causal role of IL-1β in obesity, a risk factor for AD (Heneka et al. 2015), chronic systemic inflammation may also contribute to neuroinflammation in the AD brain (Holmes et al. 2009). In contrast to traditional neuroinflammatory conditions (i.e., MS), the primary responders to DAMPs, which in AD involves misfolded proteins and amyloid aggregates, are tissue resident microglia and perivascular macrophages equipped with an arsenal of PRRs (Prinz et al. 2011). Microglia are tightly associated around and in close proximity to amyloid-β (Aβ) plaques in postmortem tissue of AD patients and animal models of AD (Prokop et al. 2013). The recognition and phagocytosis of soluble Aβ peptides can trigger microglial activation *in vitro* and *in vivo* and lead to subsequent release of proinflammatory cytokines and chemokines (Griffin et al. 1989; Patel et al. 2005; vom Berg et al. 2012), including IL-1β. Indeed, elevated levels of IL-1β have been detected in the CSF and brain tissue of patients with AD and AD mouse models (Griffin et al. 1989; Cacabelos et al. 1994; Blum-Degena et al. 1995; Sheng et al. 1997; Babcock et al. 2015). Interestingly neutralizing IL-1β has shown to attenuate tau pathology and restore cognition in AD mice (Kitazawa et al. 2011), however, at what stage IL-1β exerts its neurotoxic functions during AD remains unknown.

Neuroprotective versus neurotoxic microglial phenotype in AD pathogenesis —It is widely accepted that within the AD brain, an imbalance between proinflammatory microglia and a decrease ability to uptake Aβ promotes AD characteristics. It is has become apparent that microglial activation is heterogeneous not only within the same individual but across the same disease and amongst other neurological disorders. Much attention has been directed towards deciphering the mechanisms that govern the neurotoxic versus neuroprotective modalities of microglia in the CNS under neuropathological conditions. An initial report implicated the importance of the NLRP3-caspase-1 inflammasome in microglial-mediated neuroinflammation in response to exogenous Aβ (Halle et al. 2008). *In vitro* experiments showed that microglial phagocytosis of fibrillary Aβ peptides, led to cytosolic acidification and subsequent activation of the NLPR3-capasase-1 machinery and release of mature IL-1β, in addition to many other proinflammatory cytokines and chemokines (Halle et al. 2008). Interestingly, elevated levels of active caspase-1 have been detected in brain lysates from patients with AD and AD mice (Heneka et al. 2013). This study demonstrated that *Nlrp3*$^{-/-}$ and *Casp1*$^{-/-}$ in APP/PS1 AD mice have reduced levels of IL-1β and Aβ plaque burden, largely considered to be the result of anti-inflammatory microglial phenotype that is more conducive of the clearance of Aβ proteins as opposed to neurodegeneration. Interestingly, *in vivo* pharmacological inhibition of the NLRP3/Casp1/IL-1β pathway, in the TgCRND8 AD mouse, significantly decreased the accumulation of Aβ plaques but was associated with a reduction in morphological activation and cell numbers of microglia (Yin et al. 2017). Yet a commonality between the Heneka et al. and Yin et al. reports, is that both AD models showed reduced levels of oxidative stress when the NLRP3 inflammasome was inhibited, which is known to contribute to exacerbated microglial and astrocytic activation and promotes tissue damage (Heppner et al. 2015). Thus mechanisms that enhance microglial uptake of Aβ by downregulating NLRP3

inflammasome activation of IL-1β, as observed with treatment of IL-33 (Fu et al. 2016), may provide a unique therapeutic approach to attenuate cognition decline.

Utilizing an adeno-associated virus vector to deliver human IL-1β cDNA into the hippocampus of APP/PS1 mice, it was found that IL-1 β induced inflammation led to a robust upregulation of Arg1+ microglia which mediated amyloid beta plaque reduction (Cherry et al. 2015) (Fig. 3). This paradigm in which an inflammatory stimulus results in an anti-inflammatory or beneficial phenomena has been well explored by Cherry et al. proposing a mechanism by which chronic local IL-1β production recruits cells capable of producing Th2 cytokines that are then able to ameliorate inflammation (Cherry et al. 2015). These experimental models propose novel and intriguing mechanism of action of IL-1β-mediated inflammation towards resolution of plaque accumulation as previously reported (Shaftel et al. 2007a; Shaftel et al. 2007b; Matousek et al. 2012). Therefore, validation of this finding in human patients will solidify potential avenues for immunomodulatory therapies via IL-1β mediated actions.

Overwhelming evidence shows that the innate immune response mediated largely by the phenotype of microglia contributes to disease severity in AD (Fig. 3). This was recently corroborated with a novel *ex vivo* co-culture system of young and aged microglia on the ability to clear plaque formation (Daria et al. 2016). These data highlight that aged microglia are not a “lost” cause and can be manipulated to be neuroprotective. Daria et al. showed that microglia from young mice produce GM-CSF that activates and leads to the proliferation of young and old microglial cells that effectively reduce the plaque burden. Interestingly, cultured microglia treated with exogenous IL-1β do not produce GM-CSF, however, cultured astrocytes do (Lee et al. 1994). It remains unknown what phenotype GM-CSF stimulated microglial cells represent within the AD brain. Furthermore, recent evidence showed that microglia but not bone-marrow derived monocytes, are highly sensitive and reactive to aging and Aβ-induced activation (Martin et al. 2017). In which, microglial cells acquire an inflammatory profile equipment with IL-1β and TNF-α. These cytokines may be intrinsically beneficial to combat plaque burden; however, the impact of Aβ accumulation and perhaps the sustained production of inflammatory mediators results in debilitating neurodegeneration. Although microglial depletion studies have yielded little effect on plaque burden in late stages of AD (Grathwohl et al. 2009); the timing of Aβ pathogenesis has been shown to be critical for microglia to recognize and form a physical barrier to limit neurotoxicity (Condello et al. 2015). The significance of timing for intervening therapeutically to modulate the phenotype of microglia is critical and a daunting reality. Especially considering the complexing of AD pathogenesis including that AD brains are known to have compromised blood-brain barrier, and allow extravasation of fibrinogen, a potent inducer of microglial activation, that triggers neurotoxicity (Davalos and Akassoglou 2012; Paul et al. 2007; Ryu and McLarnon 2009).

The involvement of peripheral myeloid cells/macrophages in AD pathogenesis remains controversial (Simard et al. 2006; Heppner et al. 2015; Jay et al. 2015), especially in the context of cells expressing *triggering receptor expressed on myeloid cells 2* (TREM2). However, recent parabiotic experiments in both AD mice (5XFAD and APP/PS1) show that resident microglia but not peripheral monocytes are the primary phagocytes surrounding

plaques in the CNS (Wang et al. 2016). Of note, peripheral monocytes from AD patients express inflammasome components and produce bioactive IL-1β in response to Aβ stimulation *in vitro* (Saresella et al. 2016), a phenotype not observed in monocytes isolated from patients diagnosed with Mild Cognitive Impairment or healthy donors. However, the exact contribution of bone-marrow-derived monocytes, and more specifically, when and what triggers their activation of the inflammasome/IL-1β and contribution to AD pathogenesis remains unclear and needs further investigation.

IL-1β and neuronal damage—Within the CNS, regardless of the cellular source, overexposure of IL-1β causes considerable neuronal, vascular, and oligodendrocyte damage in many neurological diseases including models of stroke (Yang et al. 2014), Parkinson's disease (Mao et al. 2017; Yan et al. 2015), MS (Lévesque et al. 2016; Mandolesi et al. 2013), and AD (Heneka et al. 2013). Mechanistically, IL-1β can result in the aberrant release and accumulation of glutamate that is well known to result in neuronal cell death in most neurodegenerative diseases (Bading 2017). Glutamate is the most abundant excitatory neurotransmitter in the CNS, and proinflammatory cytokines such as IL-1β and TNF-α can independently stimulate the overproduction of glutamate in cultured human and rodent neurons via the activity of mitochondria glutaminase (Ye et al. 2013). The excessive glutamate exposure was shown to correlate with neuronal cell death, in which, N-Methyl-D-aspartate (NMDA) receptor antagonism prevented neurotoxicity *in vitro*. Furthermore, key pathological characteristics of MS are cell death of myelinating oligodendrocytes and neurons, and an imbalance between glutamatergic and GABAergic transmission represent a possible cause of glutamate excitotoxicity (excessive glutamate) observed in EAE and MS (Macrez et al. 2016). Interestingly, IL-1β alone is not sufficient to kill oligodendrocytes when cultured with microglia; however, when IL-1β is treated in mixed astrocyte/microglial cultures, extracellular glutamate builds up and causes oligodendrocyte death (Takahashi et al. 2003). This was in part due to IL-1β reducing glutamate uptake receptors in astrocytes. Interestingly, it was shown *ex vivo* that cerebellar slice preparations cultured with IL-1β alter glutamate transmission and promotes irregular synaptic events at purkinje cells, a phenotype observed in the cerebellar of EAE mice (Mandolesi et al. 2013). Thus emerging evidence continue to support the concept that proinflammatory cytokines perpetuate CNS inflammation and tissue pathology (Becher et al. 2017). In particular, modulating IL-1β both systemically and within the CNS may yield beneficial approaches to protect neurons with efforts in dampening cognitive, motor, and vision deficits during conditions such as DR, MS and AD.

Concluding remarks

There has been significant interest in modulating the interaction between IL-1β and its receptor as novel anti-inflammatory strategies. Recent research in the areas of neuroinflammation in MS, AD and DR supports the notion that a combination of approaches may provide success in ameliorating and perhaps reversing neuronal damage via utilization of IL-1β blocking strategies, targeting vascular damage and cellular infiltration to CNS tissues. Experimental models will continue to be valuable tools to test the balance of IL-1β in the CNS during health and disease. Efforts to understand how to target IL-1 signaling in

both immune and resident CNS cells still continues with the vision of applying efficacious IL-1 modulatory therapies to treat not only neuroinflammatory disorders, but also inflammatory diseases that involve systemic and peripheral tissues.

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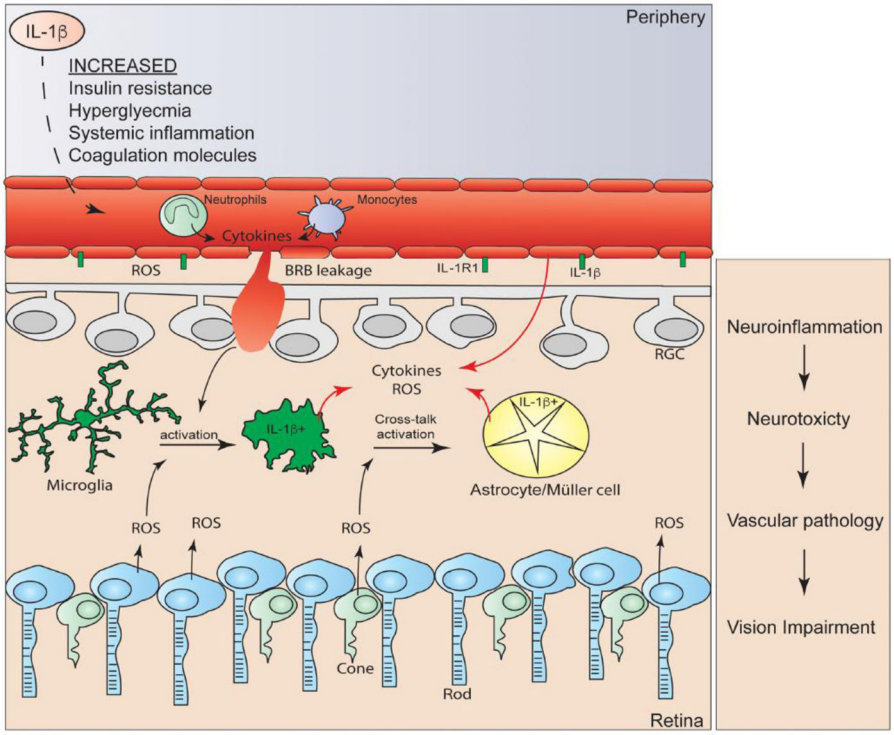

Fig 1. The role of IL-1β and neuroinflammation on diabetic retinopathy pathogenesis

Elevated levels of IL-1β contribute to diabetes susceptibility due to increasing insulin resistance and hyperglycemia. Additionally, IL-1β and many other proinflammatory cytokines contribute to the low-grade systemic inflammatory reactions associated with diabetes, including coagulation molecules such as fibrin(ogen). Early molecular changes occur in the diabetic retina that result in photoreceptor (rods and cones) stress and release of reactive oxygen species (ROS) that in part, can activate retinal microglia to produce proinflammatory mediators including IL-1β. Activated microglia can release danger-associated molecule patterns (DAMPs) such as ATP that can activate astrocytes/müller cells and contribute to the proinflammatory milieu. As diabetes progresses, systemic-induced inflammation and cytokines from inflammatory myeloid cells facilitate break-down of the blood retinal barrier (BRB) and allow the extravasation of blood content which can further activate innate immunity within the retina. Moreover, elevated IL-1β levels may act on IL-1R1+ endothelial cells which can contribute to the pool of inflammatory cytokines. Collectively, neuroinflammation in the diabetic retina can lead to cell death of retinal ganglion cells (RGCs) and contribute to vascular degeneration, setting the stage for proliferative DR.

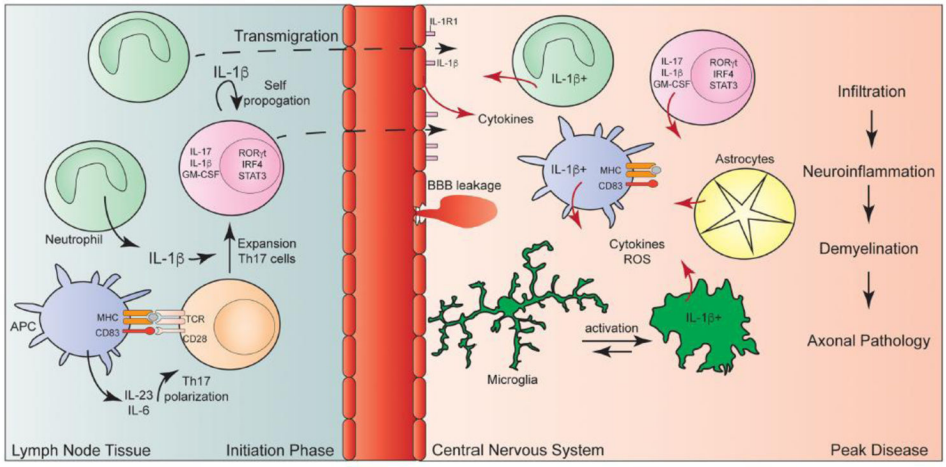

Fig 2. The role of IL-1β in the initiation and progression of EAE

During the initiation phase in the lymph node tissue, antigen presenting cells (APC; dendritic cells and macrophages) provide the necessary antigen (myelin peptides) and costimulatory signals to induce autoreactive T cell activation and provide a cytokine milieu that supports Th17 polarization. Myeloid cells and notably neutrophils contribute to releasing active IL-1β which aids in the expansion of GM-CSF producing Th17 cells. Additionally, T-cell intrinsic inflammasome production of IL-1β can contribute to the pool of encephalitogenic Th17 cells. Immune cells transmigrate from the periphery into the CNS where autoreactive T cells initiate demyelination and release cytokines (such as GM-CSF) that further perpetuate neuroinflammation. Blood brain barrier (BBB) disruption results in blood content released such as fibrin(ogen) which activates innate immunity of resident microglia and astrocytes which contribute to neuroinflammatory reactions (elevated cytokines and reactive oxygen species, ROS) and lead to further demyelination and subsequent axonal degeneration.

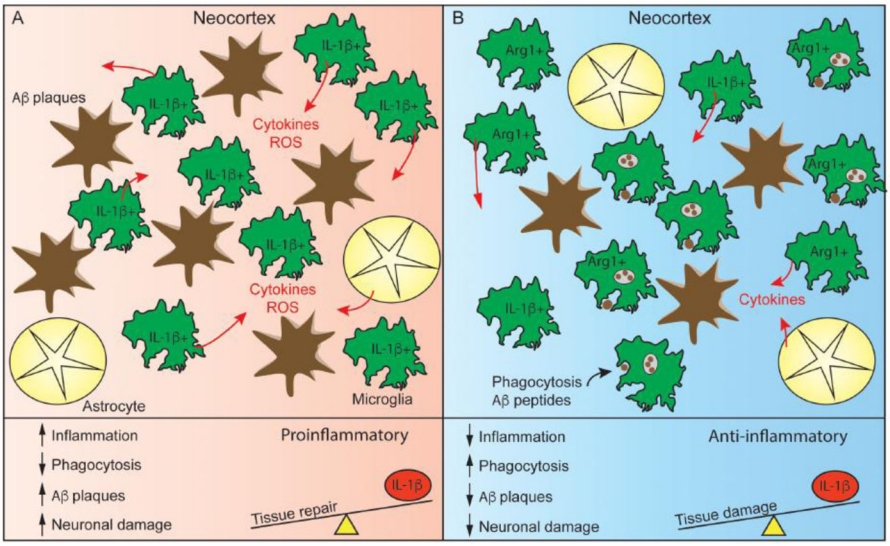

Fig 3. The paradoxical role of IL-1β in mediating neuroinflammation and neuroprotection during models of Alzheimer's disease

A threshold of IL-1β may be responsible for its mode of action within the AD brain. (**A**) Microglia are found tightly associated around Aβ plaque deposits within the neocortex and correlate with elevated levels of inflammasome machinery (i.e., NLRP3 and Caspase-1) and release of microglial-mediated IL-1β. Increased proinflammatory cytokines and ROS released by microglia and reactive astrocytes provide an environment refractory towards clearance of Aβ and conducive of neurotoxicity. (**B**) Whereas, IL-1β signaling may also regulate the physiology of microglia by upregulating anti-inflammatory mediators such as arginase (Arg1) and enhancing the phagocytic capacity and clearance of Aβ.