NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | MINI-REVIEW ISSN: 2576-828X

Interleukin 1 receptor antagonist and neurodegenerative diseases: the future treatment strategy

Thaarvena Retinasamy and Mohd. Farooq Shaikh *

Neuropharmacology Research Strength, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway 47500, Selangor, Malaysia.
* Correspondence: farooq.shaikh@monash.edu; Tel.: + 603 5514 4483

Received: 25 May 2022; **Accepted:** 15 October 2022; **Published:** 11 February 2023
Edited by: Sharmili Vidyadaran (Universiti Putra Malaysia, Malaysia)
Reviewed by: Phalguni Anand Alladi (NIMHANS, Bangalore, India);
Masriana Hassan (Universiti Putra Malaysia, Malaysia)
https://doi.org/10.31117/neuroscirn.v6i1.164

Abstract: Neurodegenerative disorders encompass a range of conditions affecting the central nervous system (CNS) in which alterations in the neuronal structure and cellular dysfunction lead to progressive deterioration. Activation of microglia and expression of the inflammatory cytokine interleukin-1 (IL-1) in the CNS have become almost synonymous with neuroinflammation. Additionally, the relentless activation of the IL-1 signalling pathway has been linked with the pathogenesis of various CNS disease states, ranging from Alzheimer disease (AD), Parkinson disease (PD) to amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Moreover, a growing body of evidence has inferred that impeding the IL-1 signalling either pharmacologically or genetically in various CNS disease models could reduce neuroinflammation or delay disease progression. This review will therefore aim to study the role of IL-1 in neurodegenerative diseases and highlight the key aspects that warrant IL-1Ra as a promising target for developing a novel treatment for various CNS conditions.

Keywords: Interleukin1; Interleukin 1 receptor antagonist; Neurodegeneration; Neuroinflammation; CNS

1.0 INTRODUCTION

Neurodegenerative disorders are debilitating conditions that primarily impact the central nervous system (CNS), where neuronal structure and cellular dysfunction deterioration occur progressively (Suescun et al., 2019). In most of these neurodegenerative diseases, an inflammatory response is observed following a CNS insult to shield and restore the damaged tissues and ultimately re-establish homeostasis. However, in most neurodegenerative disorders, the insult persists over time, triggering a progression from acute into chronic neuroinflammation (Kwon & Koh, 2020; Suescun et al., 2019). Brain inflammation is characterized by both astrocytes and microglial activation as well as key inflammatory mediators, which in turn trigger the release of toxic molecules, escalate blood–brain barrier (BBB) permeability, enabling peripheral immune cell attack, thus ultimately compromising brain cells (Kwon & Koh, 2020). Cytokines serve as one of the critical mediators of the inflammatory response where one of the most extensively studied cytokines is the pro-inflammatory cytokine IL-1 (interleukin-1), which has been implicated in various chronic neurodegenerative disorders

2.0 THE IL-1 FAMILY

Interleukin-1 (IL-1) family are pro-inflammatory cytokines capable of multiple phenotypic effects on a range of cells and play key roles in both acute and chronic inflammatory disorders (Ren & Torres, 2009). The IL-1 family consists of two essential agonists, IL-1α and IL-1β. Both agonists are encoded by distinct genes but produce analogous biological actions (Shaftel et al., 2008). Both these agonist proteins, IL-1α and IL-1β, upon binding to the specific membrane receptors, tend to prompt cell activation. IL-1 facilitates its actions via an 80 kDa cell surface receptor termed type I IL-1 receptor (IL-1RI) (Glaccum et al., 1997). These receptors are present throughout the brain, with higher levels reported within the neuronal-rich regions like the hypothalamus, hippocampus, and dentate gyrus (Cunningham et al., 1992; Farrar et al., 1987). The IL-1 family demonstrates an imperative role in inflammation where IL-1β overproduction has been linked to the pathophysiology of various neurodegenerative conditions like Alzheimer disease (AD) and multiple sclerosis (MS) (Braddock & Quinn, 2004; Ren & Torres, 2009). Studies have reported rapid generation of IL-1β in rodent brains subjected to insults that ultimately led to neuronal damage. Additionally, these observations were further corroborated by supportive clinical studies that displayed enhanced expression levels of IL-1 present in patients from several neurodegenerative conditions both in post-mortem brain tissues and in their cerebrospinal fluid (Rothwell et al., 1997).

The IL-1 family holds an additional member termed IL-1 receptor antagonist (IL-1Ra) which is encoded by the *IL1RN* gene. It serves as the single example of a naturally occurring antagonist molecule that competes with both IL-1α and IL-1β, thus decreasing inflammatory signalling and inhibiting them from further prompting the expression of other pro-inflammatory molecules (Chakrabarti et al., 2021; Sims et al., 1988). Based on the ability of IL-1Ra to inhibit neuronal loss could be an invaluable effective therapeutic agent for neurodegenerative diseases.

3.0 ROLE OF IL-1 IN THE CENTRAL NERVOUS SYSTEM

Inflammation of the CNS appears to be notable due to its normal mammalian CNS appearing "immunoprotected" with the presence of resident immune cells and a highly specific blood-brain barrier (BBB). Pattern recognition receptors expressed mainly on microglia, the resident macrophages of the brain, are the initial responders to tissue damage, following which astrocytes and reactive microglia produce various molecules to recruit other glial cells and peripheral immune cells to the site of injury (Griffiths et al., 2007). Increased glial activation, pro-inflammatory cytokine concentration, BBB permeability, and leukocyte invasion are common events following brain injury and have been documented in neurodegenerative diseases. One key player that is believed to drive this neuroinflammatory process is interleukin (IL)-1 beta, which is found to be increased in AD, Parkinson disease (PD), MS, and other neurodegenerative disorders (Griffin et al., 1994a; Rothwell & Luheshi, 2000).

IL-1 signalling occurs via the type I IL-1 receptor/IL-1 accessory protein complex, leading to nuclear factor kappa-B (NF-κB)-dependent transcription of pro-inflammatory cytokines like tumour necrosis factor (TNF)-alpha, IL-6, interferons, and neutrophil-recruiting chemokines (CXCL1 and CXCL2) in glia (Kwon & Koh, 2020). When IL-1 binds to the IL-1R1, a conformational change triggers the IL-1R1 accessory protein (IL-1R1AcP) to form a trimer that stimulates the Toll and IL-1R-like (TIR) domains to initiate two crucial proteins, the myeloid differentiation primary response gene 88 (MYD88) and the interleukin-1 receptor-activated protein kinase (IRAK) (Weber et al., 2010) **(Figure 1)**. These actions further stimulate the IL-1 signalling pathway causing the activation of two separate pathways leading to transcription (Huang et al., 2011). In the first pathway, the IκB subunit of the NF-κB is phosphorylated, leading to the NF-κB release (Huang et al., 2011; Qian et al., 2012). The activation of NF-κB causes the release of other pro-inflammatory cytokines like IL-6 and TNFα, thus making it a key component in the inflammation process (Srinivasan et al., 2004). The second pathway activates three MAP kinase pathways: p38, JNK, and ERK. Each pathway significantly functions in the inflammatory response as they are initiated by stress and can diminish cell functioning, leading to neuronal cell death (Cao et al., 2004; Park et al., 1996; Qian et al., 2012).

IL-1 plays crucial roles in a vast range of physiological and pathological processes within the CNS, varying from memory consolidation and neurodegeneration right to sleep regulation (Liu et al., 2019). IL-1 has been identified as one of the earliest cytokines discovered to have effects on the brain. Its ability to elicit fever after peripheral administration led to early descriptions of IL-1 as the "endogenous pyrogen" (Berkenbosch et al., 1987; Besedovsky et al., 1986). IL-1 is also implicated in a diverse array of physiologic and pathologic processes within the mammalian CNS, earning IL-1 status as a prototypic pro-inflammatory cytokine (Gosselin & Rivest, 2007; Rothwell, 2003). Infection and cellular

injury are the two principal stimuli that provoke inflammation. Detection of infectious agents and danger signals by pattern recognition receptors orchestrates a coordinated series of events that ensure the removal of the insult and promote tissue repair. IL-1 can stimulate sterile inflammatory disease pathogenesis at multiple levels. For instance, IL-1 directly causes tissue destruction, altered fibroblast proliferation, and collagen deposition (Ishida et al., 2006; Lukens et al., 2012). IL-1 receptor signalling also potently provokes the production of secondary inflammatory cytokines and chemokines such as IL-6, TNFα, KC, and G-CSF, which ultimately indicate the central role of IL-1 in sterile inflammation.

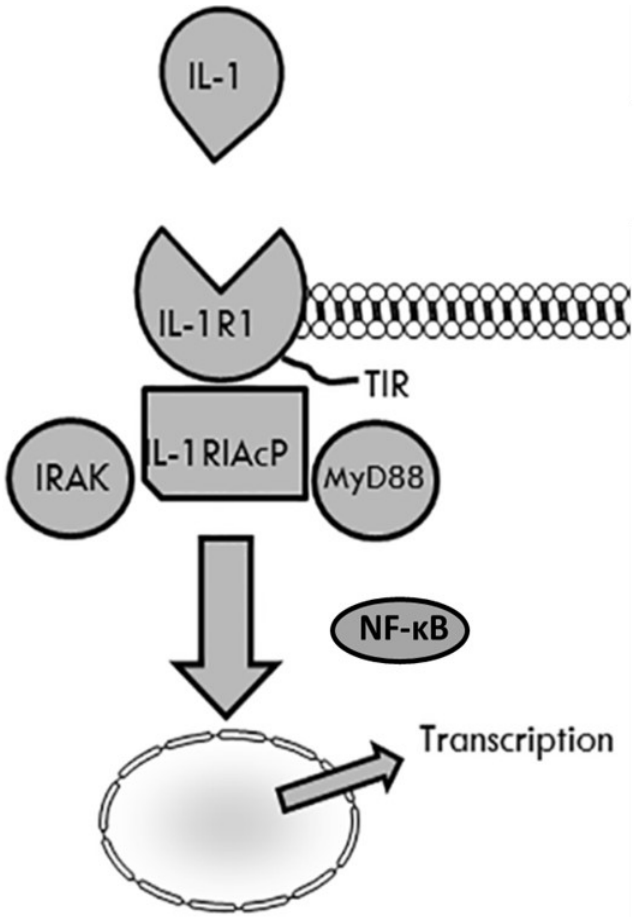

Figure 1: IL-1 Signaling Pathway. The binding of IL-1 to IL-1R1 receptor activates two kinase pathways triggering transcription. In the first pathway, the IκB subunit of the nuclear factor kappa-B (NF-κB) is phosphorylated leading to the NF-κB release whereas the second pathway activates three MAP kinase pathways: p38, JNK, and ERK where each pathway plays a significant role in the inflammatory response.

4.0 EVIDENCE OF IL-1 IN NEURODEGENERATIVE DISEASES

The role of IL-1 in the physiological, immunological, and neural activities within the brain region was examined via *in vivo* studies. Different cell-type-specific IL-1R1 signalling was found to be primarily involved. Notably, endothelial IL-1R1 drove leukocyte conscription to the CNS, triggering impaired neurogenesis. On the other hand, ventricular IL-1R1 regulated monocyte conscription and the non-inflammatory ventricular, astrocyte, and neuronal-mediated neuromodulatory activities (Liu et al., 2019). Initiation of pro-inflammatory cytokine synthesis within the brain has been elucidated in various neuroinflammation-related brain conditions like CNS autoimmunity, AD, Parkinson disease (PD), acute brain injury, post-infectious neuropathology, temporal lobe epilepsy, schizophrenia, febrile convulsions (Khazim et al., 2018; Liu & Quan, 2018). Generally, the IL-1 expression levels in a healthy animal brain have been reported to be low. However, IL-1 also demonstrates a key function in neuroimmune interactions and facilitates various responses to systemic and cerebral diseases (Haddad et al., 2002). IL-1 on its own appears harmless to healthy neurons or brain tissues, but it significantly increases injury at low concentrations (Allan & Rothwell, 2001).

Preliminary evidence of the possibility that IL-1 could be involved in local brain tissue reactions arose from high expression levels of IL-1 observed in a myriad of CNS diseases. Studies have previously demonstrated that elevated amounts of IL-1 were observed in brain tissue and cerebrospinal fluid (CSF) of brain injury and stroke patients (Griffin et al., 1994b). This expression pattern was further extrapolated to in-vivo models where parenchymal IL-1 mRNA and protein levels were also heightened. Moreover, IL-1 levels that were hardly visible in the brains of healthy humans and rodents were observed to increase rapidly following an acute injury (Allan et al., 2005; Patel et al., 2003). Upsurge in IL-1 levels has also been reported in conditions like Down syndrome and HIV-associated dementia (Griffin et al., 1989; McGuinness et al., 1997; Stanley et al., 1994). These findings further corroborate the key role IL-1 plays in diseases like AD, MS and Creutzfeldt-Jakob disease (CJD). In addition, depending on the concentration, IL-1 was shown to facilitate neuronal survival by promoting the expression of nerve growth factors (NGFs) and other neurotrophic factors or impairing neurogenesis, for instance, by favouring the astrocyte rather than neuronal lineage (Garber et al., 2018).

It is well-reported that activation of microglia inflammasome and production of IL-1 can lead to neuroinflammation and neurodegeneration. Rodents deficient in NLRP3 or caspase-1 are protected from neuroinflammation and cognitive decline (Heneka et al., 2013). Coherent with the animal studies, in selected human ethnic groups, IL1A allelic polymorphisms that lead to augmented IL-1α expression have been linked with increased susceptibility to AD due to its dependence on the production of amyloid precursor protein and further IL-1α and IL-1β production by activated microglia (Khazim et al., 2018). Also, NLRP3 inhibition has been reported to reduce stroke-induced neural damage and functional deficits (Liu & Quan, 2018). Furthermore, treatment with IL-1Ra was found to be valuable in diminishing infarct size in animal models of stroke, stress-induced depression, and anxiety, as well as in enhancing clinical outcomes in experimental epilepsy (Koo & Duman, 2009; Vezzani et al., 2000). These findings were also further supported by *in vitro* studies which demonstrated that IL-1 (and TNF-α) induces neuronal death directly or indirectly by activating glial production of neurotoxic substances (Liu & Quan, 2018). These preclinical experiments paved the way for the use of IL-1Ra to treat neuroinflammation-related conditions. For instance, a randomized, double-blind, placebo-controlled trial of Anakinra was carried out in patients with acute stroke, whereby Anakinra treated group demonstrated lower systemic inflammation (white blood cells, neutrophil counts, C-reactive protein [CRP], and IL-6 levels) and cognitive impairment as compared to the placebo-treated group (Wong et al., 2019). In addition, Anakinra has also been employed in treating autoinflammation-associated epilepsy syndrome (DeSena et al., 2018).

5.0 ENDOGENOUS REGULATORS OF IL-1

During the development of a neuronal injury that typically occurs during neurodegenerative diseases, expression levels of IL-1 are observed to be heightened rapidly (Allan et al., 2005). Thus, regulators of IL-1 are crucial to act as modulators for IL-1-related inflammatory responses and diseases. The utmost powerful and selective inhibitor of IL-1 actions is its antagonist, IL-1Ra. This antagonist is known to compete with both IL-1α and IL-1β, thereby decreasing inflammatory signalling transduction and inhibiting them from prompting pro-inflammatory molecules expression (Chakrabarti et al., 2021). Moreover, it was IL-1Ra that first demonstrated clear resistance towards neuronal injury, which typically occurs due to cerebral ischaemia, provoked by cerebral occlusion, and against damage caused in rodents by intracerebral administration of excitotoxins like *N*-methyl-D-aspartate (NMDA) (Relton & Rothwell, 1992). *In vivo* studies have shown that when either exogenous or endogenous IL-1RA are overexpressed, the neural injury appears to be significantly impeded by other types of cerebral ischaemia (Rothwell, 2003). Rodent studies also reported the effects IL-1RA have on epileptic seizures and similar results were also observed in studies done using rabbits where its ability to regulate brain injury stimulated by heat stroke was apparent (Lin et al., 1995; Vezzani et al., 2000). These effects of IL-1RA further corroborate the possibility that IL-1 could be mediating these types of neurodegenerations. Additionally, when expression levels of IL-1Ra in rodent brains following a lateral fluid percussion trauma, which causes localized cortical damage were analysed, the expression levels of IL-1Ra were observed to be at minimal levels in both the hippocampus and cortex region. However, following a fluid percussion trauma, a remarkable build up in IL-1Ra levels were observed, specifically in the CA2-CA3 layers of the dentate gyrus in the hippocampus, and in the injured cortex neurons. The IL-1Ra expression levels were most apparent in regions closest to the lesion where neuronal death did not take place. These findings were consistent with the proposed endogenous protective action of IL-1Ra (Rothwell et al., 1997). Thus, targeting the various factors that regulate IL-1 and IL-1Ra expression may lead to a valuable therapeutic strategy.

6.0 THERAPEUTIC IMPLICATIONS OF IL-1 RECEPTOR ANTAGONIST

Inflammation has become a key hallmark for various neurodegenerative diseases (Akiyama et al., 2000; Streit, 2004). Although microglia play a crucial role in neuroprotection, immune surveillance, and phagocytosis, incessant activation could serve to be unfavourable (González-Scarano & Baltuch, 1999; Rock et al., 2004; Streit, 2006). For instance, when microglia are persistently activated over prolonged periods, the production of IL-1β, a key pro-inflammatory cytokine largely involved in neuron degeneration, is observed to be augmented (Simi et al., 2007). The absence of IL-1 signalling has also been shown to protect against neuroinflammation and neurodegeneration. Additionally, coherent with the enhanced inflammatory response and memory deficits observed in various neurodegenerative conditions, these augmented IL-1β levels impede synaptic strength and LTP in vivo and appear neurotoxic *in vitro* (Bellinger et al., 1993; Katsuki et al., 1990; Viviani et al., 2003). Since IL-1 mediates various host responses to systemic disease, which are accountable for destroying pathogens and infected

cells, thus IL-1 is most likely to exert similar effects on CNS diseases. Studies have shown that IL-1 functions upstream as a signal for multiple pro-inflammatory cytokines, chemokines, prostaglandins, and other inflammatory mediators (Basu et al., 2004). Therefore, the progress and execution of a novel mechanism, like developing an antagonist to IL-1 signalling by which healthy neurons can be protected from inflammatory insults, serves as a critical target.

There have been several strategies employed experimentally to diminish IL-1-mediated inflammation. However, a key regulator, IL-1Ra, which has been shown to provide a significant and robust defence against IL-1 signalling, could defend the cells from insult. Hyperactivation of the IL-1 pathway due to IL-1R8-deficiency or IL-1 treatment can cause the upregulation of the mechanistic target of the rapamycin (mTOR) pathway and improved levels of the epigenetic regulator methyl-CpG-binding protein 2 (MeCP2). MeCP2 is a protein implicated in neurological conditions that causes changes in the morphology of the dendritic spine, synaptic plasticity, and plasticity-related gene expression. IL-Ra can restore these MeCP2 levels and spine plasticity and ultimately ameliorate cognitive deficits (Tomasoni et al., 2017). Extensive toxicity studies have demonstrated favourable outcomes of IL-1Ra in both in-vivo and human studies, and IL-1Ra has now been successfully licensed to be used in rheumatoid arthritis treatment where it is subcutaneously administered (Basu et al., 2004). Although it is imminent that IL-1Ra provides its anti-inflammatory outcomes by competitively attaching to IL-1R1, the intracellular signalling cascade via which the production of IL-1Ra is controlled remains to be elucidated (Arend, 2002). Thus, the intracellular pathways essential to impart the signal from the cell surface to the nucleus to modulate IL-1Ra serve as an active area for research since compounds adept at carrying out such signalling may exert beneficial effects in IL-1-mediated pathophysiological conditions.

7.0 CONCLUSION

IL-1, IL-1Ra and its downstream mediators appear to engage pivotal roles in the modulation of inflammatory responses. The promising *in vitro* and *in vivo* studies put ahead a strong case for IL-1Ra whereby several studies have demonstrated remarkable protection in diverse experimental models of neurodegeneration and have been observed to be effective even following an insult. An increasing impetus for exploring IL-1Ra as a therapeutic target is due to the cumulative evidence that has exhibited a significant decrease in disease-linked microgliosis and astrogliosis, as well as diminished levels of pro-inflammatory players in various neurodegenerative diseases.

Author Contributions: MFS and TR conceived the idea and TR wrote the paper. MFS provided critical inputs and edited the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M., Cooper, N. R., Eikelenboom, P., Emmerling, M., Fiebich, B. L., Finch, C. E., Frautschy, S., Griffin, W. S., Hampel, H., Hull, M., Landreth, G., Lue, L., Mrak, R., Mackenzie, I. R., McGeer, P. L., O'Banion, M. K., Pachter, J., Pasinetti, G., Plata-Salaman, C., Rogers, J., Rydel, R., Shen, Y., Streit, W., Strohmeyer, R., Tooyoma, I., Van Muiswinkel, F. L., Veerhuis, R., Walker, D., Webster, S., Wegrzyniak, B., Wenk, G., & Wyss-Coray, T. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging, 21*(3), 383-421. https://doi.org/10.1016/s0197-4580(00)00124-x

Allan, S., & Rothwell, N. (2001). Cytokines and acute neurodegeneration. *Nature Reviews Neuroscience, 2*, 734-744. https://doi.org/10.1038/35094583

Allan, S. M., Tyrrell, P. J., & Rothwell, N. J. (2005). Interleukin-1 and neuronal injury. *Nature Reviews Immunology, 5*(8), 629-640. https://doi.org/10.1038/nri1664

Arend, W. P. (2002). The balance between IL-1 and IL-1Ra in disease. *Cytokine & Growth Factor Reviews, 13*(4-5), 323-340. https://doi.org/10.1016/s1359-6101(02)00020-5

Basu, A., Krady, J. K., & Levison, S. W. (2004). Interleukin-1: A master regulator of neuroinflammation. *Journal of Neuroscience Research, 78*(2), 151-156. https://doi.org/https://doi.org/10.1002/jnr.20266

Bellinger, F. P., Madamba, S., & Siggins, G. R. (1993, Nov 19). Interleukin 1 beta inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. *Brain Research, 628*(1-2), 227-234. https://doi.org/10.1016/0006-8993(93)90959-q

Berkenbosch, F., van Oers, J., del Rey, A., Tilders, F., & Besedovsky, H. (1987, Oct 23). Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. *Science, 238*(4826), 524-526. https://doi.org/10.1126/science.2443979

Besedovsky, H., del Rey, A., Sorkin, E., & Dinarello, C. A. (1986, Aug 8). Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science, 233*(4764), 652-654. https://doi.org/10.1126/science.3014662

Braddock, M., & Quinn, A. (2004, Apr). Targeting IL-1 in inflammatory disease: new opportunities for therapeutic intervention. *Nature Reviews Drug Discovery, 3*(4), 330-339. https://doi.org/10.1038/nrd1342

Cao, J., Semenova, M. M., Solovyan, V. T., Han, J., Coffey, E. T., & Courtney, M. J. (2004). Distinct requirements for p38alpha and c-Jun N-terminal kinase stress-activated protein kinases in different forms of apoptotic neuronal death. *Journal of Biological Chemistry, 279*(34), 35903-35913. https://doi.org/10.1074/jbc.M402353200

Chakrabarti, S., Prorok, T., Roy, A., Patel, D., Dasarathi, S., & Pahan, K. (2021). Upregulation of IL-1 Receptor Antagonist by Aspirin in Glial Cells via Peroxisome Proliferator-Activated Receptor-Alpha. *Journal of Alzheimer's Disease Reports, 5*, 647-661. https://doi.org/10.3233/ADR-210026

Cunningham, E. T., Jr., Wada, E., Carter, D. B., Tracey, D. E., Battey, J. F., & De Souza, E. B. (1992). In situ histochemical localization of type I interleukin-1 receptor messenger RNA in the central nervous system, pituitary, and adrenal gland of the mouse. *Journal of Neuroscience, 12*(3), 1101-1114. https://doi.org/10.1523/jneurosci.12-03-01101.1992

DeSena, A. D., Do, T., & Schulert, G. S. (2018). Systemic autoinflammation with intractable epilepsy managed with interleukin-1 blockade. *Journal of Neuroinflammation, 15*(1), 38. https://doi.org/10.1186/s12974-018-1063-2

Farrar, W. L., Kilian, P. L., Ruff, M. R., Hill, J. M., & Pert, C. B. (1987). Visualization and characterization of interleukin 1 receptors in brain. *Journal of Immunology, 139*(2), 459-463.

Garber, C., Vasek, M. J., Vollmer, L. L., Sun, T., Jiang, X., & Klein, R. S. (2018). Astrocytes decrease adult neurogenesis during virus-induced memory dysfunction via IL-1. *Nature Immunology, 19*(2), 151-161. https://doi.org/10.1038/s41590-017-0021-y

Glaccum, M. B., Stocking, K. L., Charrier, K., Smith, J. L., Willis, C. R., Maliszewski, C., Livingston, D. J., Peschon, J. J., & Morrissey, P. J. (1997). Phenotypic and functional characterization of mice that lack the type I receptor for IL-1. *Journal of Immunology, 159*(7), 3364-3371.

González-Scarano, F., & Baltuch, G. (1999). Microglia as mediators of inflammatory and degenerative diseases. *Annual Review of Neuroscience, 22*, 219-240. https://doi.org/10.1146/annurev.neuro.22.1.219

Gosselin, D., & Rivest, S. (2007). Role of IL-1 and TNF in the brain: twenty years of progress on a Dr. Jekyll/Mr. Hyde duality of the innate immune system. *Brain Behavior and Immunity, 21*(3), 281-289. https://doi.org/10.1016/j.bbi.2006.12.004

Griffin, W. S., Sheng, J. G., Gentleman, S. M., Graham, D. I., Mrak, R. E., & Roberts, G. W. (1994a). Microglial interleukin-1 alpha expression in human head injury: correlations with neuronal and neuritic beta-amyloid precursor protein expression. *Neuroscience Letters, 176*(2), 133-136. https://doi.org/10.1016/0304-3940(94)90066-3

Griffin, W. S., Sheng, J. G., Gentleman, S. M., Graham, D. I., Mrak, R. E., & Roberts, G. W. (1994b). Microglial interleukin-1 alpha expression in human head injury: correlations with neuronal and neuritic beta-amyloid precursor protein expression. *Neuroscience letters, 176*(2), 133-136. https://doi.org/10.1016/0304-3940(94)90066-3

Griffin, W. S., Stanley, L. C., Ling, C., White, L., MacLeod, V., Perrot, L. J., White, C. L., 3rd, & Araoz, C. (1989). Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proceedings of the National Academy of Sciences of USA, 86*(19), 7611-7615. https://doi.org/10.1073/pnas.86.19.7611

Griffiths, M., Neal, J. W., & Gasque, P. (2007). Innate immunity and protective neuroinflammation: new emphasis on the role of neuroimmune regulatory proteins. *International Review of Neurobiology, 82*, 29-55. https://doi.org/10.1016/s0074-7742(07)82002-2

Haddad, J. J., Saadé, N. E., & Safieh-Garabedian, B. (2002). Cytokines and neuro-immune-endocrine interactions: a role for the hypothalamic-pituitary-adrenal revolving axis. *Journal of Neuroimmunology, 133*(1-2), 1-19. https://doi.org/10.1016/s0165-5728(02)00357-0

Heneka, M. T., Kummer, M. P., Stutz, A., Delekate, A., Schwartz, S., Vieira-Saecker, A., Griep, A., Axt, D., Remus, A., Tzeng, T.-C., Gelpi, E., Halle, A., Korte, M., Latz, E., & Golenbock, D. T. (2013). NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature, 493*(7434), 674-678. https://doi.org/10.1038/nature11729

Huang, Y., Smith, D. E., Ibáñez-Sandoval, O., Sims, J. E., & Friedman, W. J. (2011). Neuron-specific effects of interleukin-1β are mediated by a novel isoform of the IL-1 receptor accessory protein. *Journal of Neuroscience, 31*(49), 18048-18059. https://doi.org/10.1523/jneurosci.4067-11.2011

Ishida, Y., Kondo, T., Kimura, A., Matsushima, K., & Mukaida, N. (2006). Absence of IL-1 receptor antagonist impaired wound healing along with aberrant NF-kappaB activation and a reciprocal suppression of TGF-beta signal pathway. *Journal of Immunology (Baltimore, Md. : 1950), 176*(9), 5598-5606. https://doi.org/10.4049/jimmunol.176.9.5598

Katsuki, H., Nakai, S., Hirai, Y., Akaji, K., Kiso, Y., & Satoh, M. (1990). Interleukin-1 beta inhibits long-term potentiation in the CA3 region of mouse hippocampal slices. *European Journal of Pharmacology, 181*(3), 323-326. https://doi.org/10.1016/0014-2999(90)90099-r

Khazim, K., Azulay, E. E., Kristal, B., & Cohen, I. (2018). Interleukin 1 gene polymorphism and susceptibility to disease. *Immunological Reviews, 281*(1), 40-56. https://doi.org/10.1111/imr.12620

Koo, J. W., & Duman, R. S. (2009). Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression. *Current Opinion in Investigational Drugs, 10*(7), 664-671.

Kwon, H. S., & Koh, S.-H. (2020). Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Translational Neurodegeneration, 9*(1), 42. https://doi.org/10.1186/s40035-020-00221-2

Lin, M. T., Kao, T. Y., Jin, Y. T., & Chen, C. F. (1995). Interleukin-1 receptor antagonist attenuates the heat stroke-induced neuronal damage by reducing the cerebral ischemia in rats. *Brain Research Bulletin, 37*(6), 595-598. https://doi.org/10.1016/0361-9230(95)00046-h

Liu, X., Nemeth, D. P., McKim, D. B., Zhu, L., DiSabato, D. J., Berdysz, O., Gorantla, G., Oliver, B., Witcher, K. G., Wang, Y., Negray, C. E., Vegesna, R. S., Sheridan, J. F., Godbout, J. P., Robson, M. J., Blakely, R. D., Popovich, P. G., Bilbo, S. D., & Quan, N. (2019). Cell-type-specific interleukin 1 receptor 1 signaling in the brain regulates distinct neuroimmune activities. *Immunity, 50*(2), 317-333.e316. https://doi.org/10.1016/j.immuni.2018.12.012

Liu, X., & Quan, N. (2018). Microglia and CNS interleukin-1: Beyond immunological concepts. *Frontiers in Neurology, 9*, 8. https://doi.org/10.3389/fneur.2018.00008

Lukens, J. R., Gross, J. M., & Kanneganti, T. D. (2012). IL-1 family cytokines trigger sterile inflammatory disease. *Frontiers in Immunology, 3*, 315. https://doi.org/10.3389/fimmu.2012.00315

McGuinness, M. C., Powers, J. M., Bias, W. B., Schmeckpeper, B. J., Segal, A. H., Gowda, V. C., Wesselingh, S. L., Berger, J., Griffin, D. E., & Smith, K. D. (1997). Human leukocyte antigens and cytokine expression in cerebral inflammatory demyelinative lesions of X-linked adrenoleukodystrophy and multiple sclerosis. *Journal of Neuroimmunology, 75*(1-2), 174-182. https://doi.org/10.1016/s0165-5728(97)00020-9

Park, D. S., Stefanis, L., Yan, C. Y., Farinelli, S. E., & Greene, L. A. (1996). Ordering the cell death pathway. Differential effects of BCL2, an interleukin-1-converting enzyme family protease inhibitor, and other survival agents on JNK activation in serum/nerve growth factor-deprived PC12 cells. *Journal of Biological Chemistry, 271*(36), 21898-21905. https://doi.org/10.1074/jbc.271.36.21898

Patel, H. C., Boutin, H., & Allan, S. M. (2003,). Interleukin-1 in the brain: mechanisms of action in acute neurodegeneration. *Annals of the New York Academy of Sciences, 992*, 39-47. https://doi.org/10.1111/j.1749-6632.2003.tb03136.x

Qian, J., Zhu, L., Li, Q., Belevych, N., Chen, Q., Zhao, F., Herness, S., & Quan, N. (2012). Interleukin-1R3 mediates interleukin-1-induced potassium current increase through fast activation of Akt kinase. *Proceedings of the National Academy of Sciences of USA, 109*(30), 12189-12194. https://doi.org/10.1073/pnas.1205207109

Relton, J. K., & Rothwell, N. J. (1992). Interleukin-1 receptor antagonist inhibits ischaemic and excitotoxic neuronal damage in the rat. *Brain Research Bulletin, 29*(2), 243-246. https://doi.org/10.1016/0361-9230(92)90033-t

Ren, K., & Torres, R. (2009). Role of interleukin-1beta during pain and inflammation. *Brain Research Reviews, 60*(1), 57-64. https://doi.org/10.1016/j.brainresrev.2008.12.020

Rock, R. B., Gekker, G., Hu, S., Sheng, W. S., Cheeran, M., Lokensgard, J. R., & Peterson, P. K. (2004). Role of microglia in central nervous system infections. *Clinical Microbiology Reviews, 17*(4), 942-964. https://doi.org/10.1128/cmr.17.4.942-964.2004

Rothwell, N. (2003). Interleukin-1 and neuronal injury: mechanisms, modification, and therapeutic potential. *Brain Behavior and Immunity, 17*(3), 152-157. https://doi.org/10.1016/s0889-1591(02)00098-3

Rothwell, N., Allan, S., & Toulmond, S. (1997). The role of interleukin 1 in acute neurodegeneration and stroke: pathophysiological and therapeutic implications. *Journal of Clinical Investigation, 100*(11), 2648-2652. https://doi.org/10.1172/jci119808

Rothwell, N. J., & Luheshi, G. N. (2000). Interleukin 1 in the brain: biology, pathology and therapeutic target. *Trends Neurosci, 23*, 618-625.

Shaftel, S. S., Griffin, W. S. T., & O'Banion, M. K. (2008). The role of interleukin-1 in neuroinflammation and Alzheimer disease: an evolving perspective. *Journal of neuroinflammation, 5*, 7-7. https://doi.org/10.1186/1742-2094-5-7

Simi, A., Lerouet, D., Pinteaux, E., & Brough, D. (2007. Mechanisms of regulation for interleukin-1beta in neurodegenerative disease. *Neuropharmacology, 52*(8), 1563-1569. https://doi.org/10.1016/j.neuropharm.2007.02.011

Sims, J. E., March, C. J., Cosman, D., Widmer, M. B., MacDonald, H. R., McMahan, C. J., Grubin, C. E., Wignall, J. M., Jackson, J. L., Call, S. M., & et al. (1988). cDNA expression cloning of the IL-1 receptor, a member of the immunoglobulin superfamily. *Science, 241*(4865), 585-589. https://doi.org/10.1126/science.2969618

Srinivasan, D., Yen, J. H., Joseph, D. J., & Friedman, W. (2004). Cell type-specific interleukin-1beta signaling in the CNS. *Journal of Neuroscience, 24*(29), 6482-6488. https://doi.org/10.1523/jneurosci.5712-03.2004

Stanley, L. C., Mrak, R. E., Woody, R. C., Perrot, L. J., Zhang, S., Marshak, D. R., Nelson, S. J., & Griffin, W. S. (1994). Glial cytokines as neuropathogenic factors in HIV infection: pathogenic similarities to Alzheimer's disease. *Journal of Neuropathology and Experimental Neurology, 53*(3), 231-238. https://doi.org/10.1097/00005072-199405000-00003

Streit, W. J. (2004). Microglia and Alzheimer's disease pathogenesis. *Journal of Neuroscience Research, 77*(1), 1-8. https://doi.org/10.1002/jnr.20093

Streit, W. J. (2006). Microglial senescence: does the brain's immune system have an expiration date? *Trends in Neuroscience, 29*(9), 506-510. https://doi.org/10.1016/j.tins.2006.07.001

Suescun, J., Chandra, S., & Schiess, M. C. (2019). Chapter 13 - The Role of Neuroinflammation in Neurodegenerative Disorders. In J. K. Actor & K. C. Smith (Eds.), *Translational inflammation* (pp. 241-267). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-813832-8.00013-3

Tomasoni, R., Morini, R., Lopez-Atalaya, J. P., Corradini, I., Canzi, A., Rasile, M., Mantovani, C., Pozzi, D., Garlanda, C., Mantovani, A., Menna, E., Barco, A., & Matteoli, M. (2017). Lack of IL-1R8 in neurons causes hyperactivation of IL-1 receptor pathway and induces MECP2-dependent synaptic defects. *Elife, 6*. https://doi.org/10.7554/eLife.21735

Vezzani, A., Moneta, D., Conti, M., Richichi, C., Ravizza, T., De Luigi, A., De Simoni, M. G., Sperk, G., Andell-Jonsson, S., Lundkvist, J., Iverfeldt, K., & Bartfai, T. (2000). Powerful anticonvulsant action of IL-1 receptor antagonist on intracerebral injection and astrocytic overexpression in mice. *Proceedings of the National Academy of Sciences of USA, 97*(21), 11534-11539. https://doi.org/10.1073/pnas.190206797

Viviani, B., Bartesaghi, S., Gardoni, F., Vezzani, A., Behrens, M. M., Bartfai, T., Binaglia, M., Corsini, E., Di Luca, M., Galli, C. L., & Marinovich, M. (2003). Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *Journal of Neuroscience, 23*(25), 8692-8700. https://doi.org/10.1523/jneurosci.23-25-08692.2003

Weber, A., Wasiliew, P., & Kracht, M. (2010). Interleukin-1 (IL-1) pathway. *Science Signaling, 3*(105), cm1. https://doi.org/10.1126/scisignal.3105cm1

Wong, R., Lénárt, N., Hill, L., Toms, L., Coutts, G., Martinecz, B., Császár, E., Nyiri, G., Papaemmanouil, A., Waisman, A., Müller, W., Schwaninger, M., Rothwell, N., Francis, S., Pinteaux, E., Denés, A., & Allan, S. M. (2019). Interleukin-1 mediates ischaemic brain injury via distinct actions on endothelial cells and cholinergic neurons. *Brain, Behavior, and Immunity, 76*, 126-138. https://doi.org/https://doi.org/10.1016/j.bbi.2018.11.012