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The application of NLRP3 inflammasome inhibition in Alzheimer's disease therapeutics: Clinical benefits, applications, current limitations, and future development

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Abstract. The severe dementia Alzheimer's Disease (AD) has been a neurodegenerative disorder that has troubled many for years due to its difficulty in therapeutic development. Negative regulation of the expression and activation of the NLRP3 inflammasome situated in the hippocampus, entorhinal cortex, blood, and other brain-connected tissues have been reported to contribute to the decrease of pathology and effect of AD. This concise review focuses on the various applications, characteristics, efficacy, and potential of inhibitors of the NLRP3 inflammasome at different stages of the NLRP3 activation and expression pathway in addition to their various limitations that would be places of improvement in future pharmaceutical development. NLRP3 inflammasomes such as IC100 and MCC950 are still in a stage of development, with advantages of high specificity and a large range of function, but with a variety of limiting factors such as the lack of clinical trials and deciding studies, therefore causing a therapy with large potential to be still in a position needing great progress.

keywords: Alzheimer's Disease, NLRP3 inflammasome inhibition, IC100, ODZ10117.

1. Introduction

The popular Alzheimer's Disease (AD) is a common age-correlated form of dementia and neurodegenerative disorder. Even though it has been around a century since the initial discovery of Alzheimer's Disease, the development of its target drugs has been lacking in progress. Fundamentally, the process of drug development and therapeutic targeting for Alzheimer's Disease is extremely difficult because of the transportation difficulties placed by the blood brain barrier and the lack of detailed understanding of the cause, absolute biomarkers, and pathogenesis process of this progressive disorder. Current drugs of AD can only work to inhibit the effects of AD from its beginning at the hippocampus, such as AChE inhibitors that inhibit acetylcholine turnover and restoring synaptic levels.

One of the possible fundamentally therapeutic solutions is the target therapy of the blockade of NLRP3 inflammasomes of the innate immunity system to achieve beneficial effects *in vivo* for AD patients. The NLRP3 inflammasome is an intracellular multimeric protein complex composed of a combination of the NLRP3 protein (cryopyrin), the unit that is integral in its signaling process, transcribed from genes on human chromosome 1 and adaptor protein ASC and procaspase-1, occurring predominantly in macrophages and is present in microglia for it to take an effect in AD [1].

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NLRP3 inflammasome activation can be divided into two main signal pathways. Firstly, NLRP3 inflammasome activation is induced by stimuli including lysosomal damage, ionic flux, RNA viruses, ASC, ATP, pore-forming toxins, the stimulation of which would create an inflammatory response and possibly apoptosis. At the same time, NLRP3 inflammasomes can be activated by microbial components, and endogenous cytokines, through the pathway from activation of transcription factor NF-kB and the increase of NLRP3 and pro-interleukin-1ß (pro-ILA-1ß) [1].

In AD, the deposition of Aß in the environment induces NLRP3 assembling and activation in microglia, therefore activating procaspase-1 and its assembly along with pro-interleukin-1ß (pro-ILA-1ß). The microglia with NLRP3 inflammasomes then express inflammatory M1 phenotype, in addition to an increase in procaspase-1 and ILA-1ß expression, therefore resulting in Aß deposition and neuronal loss and abnormal NLRP3 inflammasome activity. The abnormal activity and Aß deposition led to AD in a vicious cycle [1].

Currently, NLRP3 inflammasome inhibitors such as the famous MCC950 are under research in AD therapy, novel inhibitors are also being developed from healing AD from a neuroinflammation perspective. The inhibition of NLRP3 inflammasomes can inhibit the abnormal action of NLRP3 inflammasomes in AD pathogenesis and development, therefore providing a slightly easier way to fundamentally provide a therapy that can lead to AD recovery, while it still lacks clinical trials and further research. The paper will cover the real cases of application of NLRP3 inflammasome inhibition, its advantages, limitations, and possible predictions of future development.

2. Applications of NLRP3 inflammasome inhibitors

In contrary to other neurodegenerative diseases, drug development in Alzheimer's Diseases is rather difficult due to its complexity and limitations posed by research. In the scope of AD therapeutic development, drug discovery, innovation, and purposing of NLRP3 inflammasomes is still in its developing stage, restricted to some pre-clinical trials, very few clinical trials, and utilizing the inhibitors for discoveries of biomarkers of AD. Ongoing virtual and genetic screening of AD for drug discovery have also been happening for the discovery of more targets to develop inhibitors. Below is a short representative summary of the advantages and main characteristics of some of the most potent NLRP3 inflammasomes and a concise summary of innovative inhibitors that are currently still in extremely early development.

2.1. Inhibitor therapies of AD involving NLRP3 inflammasome inhibition

2.1.1. MCC950 (CRID3). Discovered in screening, MCC950, also known as CRID3, is a small molecule NLRP3 ligand and selective targeted NLRP3 inhibitor. MCC950 creates an effect of negative regulation on the inflammasome through directly binding to the NACHT domain of NLRP3 at the Walker B motif. The molecular interaction close to the at NACHT would successfully block ATP hydrolysis and therefore inhibiting the overall activation of NLRP3 and the final formation of the protein complex that would contribute to the pathogenesis of AD [2].

Pre-clinical experiments regarding mouse Alzheimer's Disease models have been completed for MCC950. Firstly, Tau seed activated NLRP3 inflammasomes and exogenous tau pathology were significantly inhibited through evidence provided images of the stained frontal cortex and hippocampus of transgenic mice [3]. In addition to that, MCC950 has been directly observed to reverse the synaptic plasticity deficiencies in CORT-treated APP transgenic mice which stimulates the issues in the brain in early Alzheimer's Disease [4].

Furthermore, studies have shown that MCC950 contribute to preventing Alzheimer's Disease in patients that have received mental damage from medication from other severe diseases. MCC950 reduced the cognitive impairment imposed on patients by chemotherapy and significantly regulated the expression of NLRP3, ASC protein, and caspase-1 in animal models, including alleviating the hazardous glial response [5]. The ability of MCC950 to achieve that implies that it may have the potential to contribute to therapies of different diseases in cooperation with Alzheimer's simultaneously.

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2.1.2. OLT1177 (dapanutrile). Greatly similar to MCC950, OLT1177 inhibits the activation of NLRP3 inflammasome by interfering with the production of ATP. OLT1177 directly binds to ATPase in NLRP3 and inhibits its activity, preventing NLRP3 signaling. In the Alzheimer's Disease animal model of APP/PS1 transgenic mice, OLT1177 inhibition proved a success in terms of phenotypic effects of the animal model, including an improvement of cognitive function and a decrease in proinflammatory cytokines that induce the pathogenesis of AD [6]. OLT1177 has already passed Phase I clinical trials for its safety in pharmacodynamics, proving to be a potent therapeutic drug to tackle AD.

2.1.3. miRNA. MicroRNAs are effective inhibitors often through directly regulating expression of certain genes. Two miRNAs show high efficacy in negative regulation of IL-1ß secretion and NLRP3 inflammasome activity, with both targeting NLRP3-3' UTR. From early times, miR-223 has proved its efficacy in NLRP3 activity mediation. miR-223 and its overexpression in macrophages derived from the THP-1 cell line decreased the expression of the NLRP3 protein and the reduction of IL-1ß production. Similarly, the virus miRNA of EBV, miR-BART 15 interfered with the NLRP3-3' luciferase construct and reduced endogenous NLRP3 protein levels and the production of IL-1ß from NLRP3 inflammasome activity [7]. In terms of miRNA transportation into the animal system, the lipid nanoparticles [8] used are a possible option for study that many finally help the microRNA to become mature therapy for AD.

In addition to applications in NLRP3 inflammasome inhibition, miR-223 can also be used for the discrimination and diagnosis of neurodegenerative diseases, such as Parkinson's Disease (PD), Alzheimer's Disease, and Mild Cognitive Impairment (MCI). The concentration of circulatory miR-223 in the different diseases serve as diagnosis markers that discriminate between the three. In AD and MCI, the concentration miR-223 decreased with the progression of disease, with AD having a smaller concentration compared to MCI, while in PD it was upregulated [9]. The ability to both diagnose, discriminate, and contribute to AD therapeutics allows miR-223 to have different effects just by adjusting the concentration that is released into the system, greatly increasing the convenience of the therapy.

2.1.4. IC100. IC100 is a monoclonal antibody that targets ASC, a particular component of the NLRP3 signalling complex. Alternative to many NLRP3 inhibitors, experiments on iBMDM (bone marrow derived macrophage) cells in vitro discovered that IC100 are internalized into iBMDM by mediation at its Fc region causing the antibody to be bound to FcRn receptors and associate with intercellular endosomes. As support, practical in vitro study on the internalization of IC100 reveals that internalized IC100 associates with TRIM21 and intracellular ASC in THP-1 cells. With the eventually causing the IC100 to be recycled and released through exocytosis [10].

In the pathway associating to the structure of ASC, IC100 prevents ASC speck formation, which is controlled by the domain PYD in ASC and the structure of ASC filaments, leading to abnormalities in the formation of a significant activator of NLRP3 and AD [11]. IC100 successfully inhibited the effects of ASC^{PYD} polymerization and the creation of ASC^{PYD} filaments by disrupting the architecture of the filaments formed.

IC100 can act upon ASC through a variety of pathways that manage to prevent neuroinflammation across a diverse variety of cell types. Unlike some inhibitors of NLRP3, IC100 can easily be transported by the circulatory system without complex alterations and penetrate the CNS through passing the blood brain barrier, as proved by an animal model, implicating that injection into the bloodstream for inhibitor transportation would be easily applicable. In a human whole blood cell inflammasome assay, IC100 binds to intracellular ASC and suppresses the secretion of IL-1ß, activators of the NLRP3 inflammasome signaling system, therefore achieving NLRP3 inhibition [10].

The antibody IC100 does not only have an inhibitory effect in Alzheimer's Disease. The antibody itself can be used for AD detection and analysis. IC100 detected the differential expression of ASC specks in neurons and microglia. IC100 can be utilized for ASC speck quantification and detection for the development and progression of AD due to its specificity to ASC. Furthermore, IC100 contributed to the discovery of the pathogenesis of AD, finding evidence that indicates that increased expression of

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inflammasomes such as NLRP3 in microglia and neurons are present in early AD, even before hippocampal damage [12].

2.1.5. ODZ10117. In addition to the inhibitors above, ODZ10117 is also a potential inhibitor for the activation of the NLRP3 inflammasome. Initially developed as a STAT3 inhibitor, drug repurposing allowed it to be used in experiments relating to AD neuroinflammation. Unlike many other inhibitors, ODZ10117 is indicated to have a high specificity to the NLRP3 inflammasome in mouse macrophages while not affecting others, such as other inflammasomes that are commonly affected in NLRP3 inflammasome drug therapeutics, such as AIM2 and NLRC inflammasome and their activation [13].

ODZ10117 creates an inhibitory effect on the NLRP3 inflammasome utilizing a unique pathway. ODZ10117 inhibited NLRP3 inflammasome activity not through inhibiting the production of its activators but through suppressing the maturation of its components. In the animal cell in vitro macrophage model, ODZ10117 prevented ASC speck formation, which serves as a significant component and signal amplification for NLRP3 [11]. Furthermore, ODZ10117 inhibited ASC oligomerization and its redistribution, proving its efficacy to be slightly higher than inhibitors that are restricted to only inhibiting the increase of quantity of NLRP3 activators such as IL-1ß.

Additionally, ODZ10117's therapeutic efficacy in NLRP3 inflammasome inhibition in Alzheimer's Disease extends to inhibiting molecular communication between mediator NEK7 and the inflammasome NLRP3. As a compulsory mediator of the activation of the NLRP3 inflammasome, NEK7 binds downstream of potassium efflux to NLRP3 and induces its oligomerization and eventual functioning [14]. The release of NLRP3 activator IL-1ß increases in positive correlation with NEK7 activity. By negatively intercepting molecular binding between NLRP3 and NEK7, ODZ successfully implicates that future studies on its efficacy in pre-clinical trials may be possible.

2.1.6. CZE ethanol extract. As of recent studies from March 2023, the ethanol extract of Chrysanthemum zawaskii (CZE) was tested on animal (mouse) model LPS-primed Bone Marrow Derived Macrophages (BMDM) in vitro. CZE is a compound composed of inflammasome-inhibiting components linarin, chlorogenic acid, and 3, 5- dicaffeoylquinic acid. Through utilization of western blotting, it is discovered that the secretion and maturation of NLRP3 inflammasome activators such as IL-1ß and activating events, especially ATP induced caspase-1 cleavage decreased immensely. In addition to inhibiting NLRP3 inflammasomes at the molecular level, CZE also achieved downregulation of NLRP3 and pro-IL-1ß gene expression in BMDM [15]. The properties and efficacy of CZE and its components can be a possible candidate of study in pre-clinical and clinical trials to further aid in drug development for AD, especially neuroinflammation.

2.1.7. RRx-001. RRx-001, otherwise known as bromonitrozidine, is an electrophile NLRP3 inflammasome inhibitor that was modified from trinitroazetidine (TNAZ) performs its negative regulatory actions via interacting covalently with the NACHT domain at NLRP3 cysteine 409 at its bromoacetyl group interferes with interactions between NLRP3 and NEK7, demolishing the pathway for NLRP3 inflammasome activation [16].

RRx-001, just discovered in 2020, has proved its efficacy in the AD animal model utilizing a comparison between non-transgenic mice and triple transgenic AD mice (3xTg-AD mice). The use of RRx-001 to these transgenic mice caused a reduction in AD hallmarks including amyloid plaque density and glutathione, implicating that RRx-001 contributes to preserving the cognitive and emotional health [17] of animals, providing insight on the possibilities of RRx-001 use in neuroinflammation therapeutics.

Due to RRx-001 previously being an anticancer NLRP3 inhibitor, it has already been applied into clinical trials for a range of different cancers, such as small cell lung cancer [16], where it is currently in phase III clinical trials. Passing the phase I trials for safety reflects its great safety in human application, therefore providing a great possibility of it being utilized effectively and safely in the AD human model.

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2.1.8. BHB. Levels increased by low-carbohydrate ketogenic diet and other actions that lead to energy deficiency, the ketone body BHB is a suppressor or inhibitor of the NLRP3 inflammasome reported through in vivo mouse models. BHB inhibits NLRP3 through preventing the K^+ (potassium ion) efflux at the beginning of the pathogenesis of AD by the pathway of NLRP3 activation and repressing ASC's oligomerization and speck formation. In addition, BHB also reduces caspase-1 activation and the release of IL-1ß [18], making it rather unique due to its target of K^+ efflux, inhibiting NLRP3 secretion and final activation more effective.

In Alzheimer's Disease patients, BHB levels are lower in brain parenchyma and red blood cells compared to healthy controls, providing a necessity for BHB to be increased for AD healing. Based on experiments on 5XFAD mice, BHB reduces AD pathology by NLRP3 inhibition, creating effects such as plaque formation, ASC oligomerization and speck formation, and a reduction in caspase-1 activation when released into the mouse system by exogenous administration, establishing it as a potent AD drug through neuroinflammation regulation [19].

2.2. Innovative artificially synthesized inhibitors in development- the upcoming studies

In addition to the inhibitors mentioned above, numerous novel inhibitors have been extracted, artificially synthesized, or made to serve as possible drugs and contributors to the therapy of Alzheimer's Disease from the perspective of NLRP3 inflammasome inhibition.

Various upcoming NLRP3 inflammasome inhibitors have already been tested in Alzheimer's Disease mouse models. The compound JC124 successfully decreased AD pathogenesis and its pathologies in transgenic wild type mice [20]. JC124 successfully decreased Aß plaques in both the mouse cerebral cortex and hippocampus and improved overall cognitive function, while also decreasing microglia activation and astrogliosis. Amazingly, JC124 also decreases cell cycle re-entry and increases the neurogenesis of the hippocampus of mice [20]. The significant effect of JC124 proves that it is a potential therapeutic drug for AD, but it still needs to be studied in clinical and primate pre-clinical trials.

Another novel inhibitor developed recently includes the AMS-17 that was just developed in 2022. AMS-17 is a sulfonylurea compound that inhibits NLRP3 inflammasome activity by inhibiting the expression of the protein NLRP3 in addition to a reduction in NO production and the secretion of substances and cytokines that are downstream in the NLRP3 activation pathway, such as caspase-1 and IL-1ß. Through testing efficacy in in vivo mouse models and in vitro cell stimulation of the N9 microglial cell, it is discovered that AMS-17 inhibited the activation of microglia cells by the NLRP3 pathway in mice and the activation of phagocytosis of lipopolysaccharide (LPS)-induced N9 microglial cells [21]. Even though AMS-17, JC124, and the collection of new artificial NLRP3 inhibitors are still in study, they show immense possibility of contributing to AD therapeutics.

2.3. The similarities and advantages of NLRP3 inflammasome inhibitors

Even though all the NLRP3 inflammasome inhibitors have rather distinct characteristics and range of functions, they have many similarities. So far, the most effective and developed inhibitors all focus on inhibiting the activation of NLRP3 from the perspective of inhibiting the production or oligomerization of its activators, such as IL-1ß and ASC. The ability to hold high specificity to NLRP3 inflammasome activators in most inhibitors allow the organism to receive less cytotoxicity due to NLRP3 inflammasome inhibitor therapy.

Furthermore, many inhibitors hold more than just a singular function relating to the NLRP3 inflammasome, with many such as IC100 and miR-223 contributing to the pathogenesis or discrimination of AD. Participating in various pathways of inhibition and function in the system allows one therapy to cover multiple aspects of AD, therefore increasing the efficiency and efficacy of the therapy on the patient. Moreover, some inhibitors such as RRx-001 and OLT1177 also show therapeutic effects for other medical issues like cancer, leading to the possibility of having a combined therapy for patients experiencing a combination of various therapeutic diseases. Generally, NLRP3 inflammasome inhibitors are relatively small in molecular size, therefore increasing the efficiency of transportation to the brain for AD.

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3. Discussion on the current Limitations and future perspectives of NLRP3 inflammasome inhibitors

3.1. The limitations and future perspectives of the NLRP3 inhibitors

In opposition to its various advantages, the limitations of NLRP3 inhibitors are also under great therapeutic concern. Due to many inhibitors targeting the same stage of NLRP3 inflammasome activation, their combined use in the animal model and their effects on the pharmacokinetics and pharmacodynamics of the inhibitors would become greatly uncertain. For example, both RRx-001 and MCC950 attach to the NACHT domain and their effects on each other is undetermined, therefore posing as a great limitation to the further development of therapies that would feature a combination of NLRP3 inhibitors in an AD therapy. Studies in that area would be greatly beneficial to increasing pharmacodynamics of the NLRP3 inflammasome inhibition therapy.

3.2. Limitations and perspectives of the development of NLRP3 Inflammasome inhibitors

Many reasons weave into the slow progression of the development of NLRP3 inflammasome inhibitors and their lack of after clinical trial application in current medicine. Primitively, the lack of research of AD biomarkers and a complete pathway and overview of AD pathogenesis causes most NLRP3 inhibitors to target the activation of NLRP3 by inhibiting the polymerization or production of its activators instead of totally inhibiting NLRP3 at the genetic level by gene knock-in or knock-out.

With the development of new screening techniques such structural proteomic profiling [22], the screening of AD genetic changes and studies on potent target sites for NLRP3 inflammasome inhibitors would be greatly helpful for the progression of drug development and discovery of NLRP3 inhibitors. Additionally, the development of the CRISPR technology has enabled the utilization of CRISPR in the diagnosis and therapeutics in AD. For example, CRISPR-Cas12a has been reported to be a biosensor for biomarker detection from experiments on miR-155 [23], therefore displaying its potential to be used in the drug discovery for AD, especially with its specialty of combinatorial screening among other CRISPR technologies.

In addition, another limitation factor for the wide use of NLRP3 inflammasomes in therapeutics is the lack of advanced preclinical trials and clinical trials. Out of the drugs provided above, only two have been in clinical trials, but for its applications in other medical uses, not in AD. One of the only NLRP3 inhibitors registered in clinical trials is Donepezil. The lack of clinical trials of NLRP3 inhibitors in AD human models causes the decrease in drug approval speed, therefore posing as an obstacle for the use and development of NLRP3 inflammasome inhibitors. Pushing for an increase in especially primate preclinical trials and clinical trials would be a potent strategy in increasing the developing speed of the NLRP3 inflammasome inhibition therapy in AD therapeutics.

4. Conclusion

NLRP3 inflammasomes and their activation are tightly connected with the pathogenesis, progression, and reduction of Alzheimer's Disease that results in loss of hippocampal and neural activity. The application of NLRP3 inflammasome inhibitors have shown great potency in the AD disease model especially through inhibiting the oligomerization or efficacy of its activators, such as IL-1ß, ATP, and ASC specks. Small molecule inhibitors such as MCC950, IC100, and OLT1177 are all some of the closest to getting onto the market, with all three having strong inhibitory effects on NLRP3 in the AD model. Other new artificially synthesized inhibitors such as AMS-17 may have not been under as much study and statistical analysis as the other slightly older inhibitors, they are still developing in the positive direction. Furthermore, NLRP3 inhibitors have a wide variety of significant functions, including having contribution to the discrimination of neurodegenerative diseases, other diseases, and the detection and analysis AD, opening the possibility of a combination therapy of NLRP3 inflammasome inhibitors to deal increase pharmacodynamic efficacy and satisfy needs of patients with multiple diseases. Despite NLRP3 inhibitors having various limitations from clinical trials and uncertainty of function when

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combined into a single therapy, NLRP3 inflammasome inhibitors still hold great potential in eventually providing a cure for AD through the perspective of neuroinflammation.

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