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Review Article

A REVIEW ON MICROGLIA: ROLE IN NEUROINFLAMMATION, SCREENING MODELS AND THERAPEUTIC STRATEGIES FOR TREATMENT

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ABSTRACT

Neuroinflammation has a critical role in the pathogenesis of neurodegenerative diseases like Alzheimer's disease, Parkinson's disease. Microglia, the resident immune cells of the CNS play a key role in neuroinflammatory processes which have been a long subject of study in the neurodegenerative diseases. Though, the exact mechanism underlying the cause in Alzheimer and other neuroinflammatory diseases remains unresolved. The purpose of this review is to shed light in the role of microglia in neuroinflammation along with its features in Alzheimer's disease. In this review we provide an extensive analysis of the most important and widely used *in vitro* and *in vivo* screening models for neuroinflammation. We also summarize briefly about the various natural products, nutraceuticals along with some known anti-inflammatory agents which are undergoing clinical trials and present an overview on their therapeutic potential to treat neuroinflammatory diseases.

Keywords: Neuroinflammation, Microglia, Alzheimer, Screening models, Natural products, Nutraceuticals

INTRODUCTION

The central nervous system (CNS) and immune system are intimately coupled maintaining a homeostasis through enlightened bidirectional interference[1]. Neuroinflammation is explicated as the inflammation of the CNS, which is conceded as a prominent hallmark of many different pathological conditions[2]. The inflammatory response originates in the CNS after suffering an injury, which leads to the building of the glial cells; remarkably astrocytes and microglia responses merge soon after the injury takes place. In this event, the cellular and molecular components of the immune system such as cytokines, complement and pattern-recognition are the key actors, causing glial cell, i.e., microglia and astrocytes activation[3].

Predictably, as one ages, the brain's ability to retain the balance between protective and fatal effects of immune system is exceedingly impaired. Likewise immune system plays a pivotal role in regulating the inflammatory process, which may be advantageous in providing protection against pathogens and repair of damaged tissues which at the same time can be catastrophic when induced chronically[4]. Several studies have strongly suggested that neuroinflammation is a plethora for development of neuronal degeneration, which is an usual trait in various neurodegenerative disease which includes Parkinson and Alzheimer's disease (AD)[5].Microglia, which is the resident immune cells in the brain is an escalating factor in the brain inflammation, but the first responder in the injury is the brain mast cells rather than microglia. Microglial activation is regulated by various intracellular interaction which involves cell surface molecules and soluble mediators such as cytokines, neurotransmitters and reactive oxygen species (ROS)[6].

AN OVERVIEW OF FUNCTIONS OF MICROGLIA

Kira *et al*, in a nutshell, introduced the significant physiological effector functions of microglia- proliferation, morphological transformation, motility and migration, intracellular communication, phagocytosis, proteosis[7]. Although microglial activation provides protection to the brain throughout our lives, but its effectiveness deteriorates with age. The immune system undergoes a shift towards pro-inflammatory status upon aging, termed as inflammaging .The microglial cells display a "homeostatic" phenotype in the healthy brain that monitors the alongside environment. In such event, the surface molecules are expressed by them and soluble factors are being secreted which sequentially influences neuron propensity[8].

FEATURES OF NEUROINFLAMMATION IN AD

Diverse lines of primary and secondary evidences reveals that neuroinflammation is responsible for the pathogenesis and progression of AD. It is supported by various literature that in case of AD, the elevation in the level of microglial activation has been seen in the region of amyloid beta deposition [9].Another fact revealed that mechanistically brain inflammation is not similar to the inflammation that takes place in the periphery, as the inflammatory markers like neutrophil infiltration and perivascular mononuclear cuffing is not seen in AD brain[10].

Regardless of the fact that there are many signs for neuroinflammation in AD pathology, it still remained unclear which of these inflammatory processes are directly responsible for the progression of AD[11]. There arises the query: whether some of these processes are responsible for fighting this deadly disease. For addressing this, the role of microglia seems to be of vital importance, as these cells exert both neuroprotective as well as neurodegenerative functions.

Many animal studies as well as clinical trials have solidly proposed that nutraceuticals and the non-steroidal anti-inflammatory drugs (NSAIDs) can be considered as an interesting therapeutic regimen for AD which has been covered in the later portion of this review where focus has been made in the therapy of neuroinflammation.

ROLE OF MICROGLIA IN ALZHEIMER'S DISEASE

Microglia are a type of glial cells which plays a major role as phagocytic and also resident immunocompetent cells in case of injury and disease. Del Rio Hostiga found that microglia falls under a discrete type of glial cells which is different from astrocytes and oligodendrocytes[12]. There has been a notion that the microglial cells are immune effectors which respond to various pathological conditions. This initiates the progression of neurodegenerative diseases by releasing pro-inflammatory mediators indicating that their phagocytic functions may be a beneficial one, whereas their inflammatory functions might be fatal[13].Many studies provided an evidence that in AD brain the microglial activation due to amyloid beta fibrils is due to chemotaxis and also due to the presence of microgliosis which are present along with amyloid beta plaques in the brain of neurodegenarative disease. This outline the role of microglial cells in Alzheimer disease[14].

IN VIVO AND *IN VITRO* MODELS TO SCREEN NEUROINFLAMMATON

In vivo animal models

It is of great importance to characterize and generate an *in vivo* model of neuro-inflammation for understanding the interactions between immune system and microglial activation which is the prime cause of brain disease.

There are many models to study neuro-inflammation like aluminium chloride induction method, stress induced models, etc. Amongst these, the most popular models to study neuro-inflammation is lipopolysaccharide (LPS) induction, which proves to be a typical paragon for studying neuro-inflammation. Increasing evidence suggested that LPS induction causes a wide variety of central effects, in a rodent model, when peripherally injected, by the release of pro- inflammatory cytokines from microglial cells including the interleukin(IL)-IB, IL-6, tumor necrosis factor (TNF-α) and reactive oxygen species[15,16]. Upon single or multiple dose administration of mice with LPS, it has been found that there is an elevation in the number of F4/80, CD11, CD45 positive cells in addition to change in the morphology for activated microglias were seen in several studies[17,18].

Furthermore, a crucial point has to be taken into consideration while working with this model is the mouse strain. Numerous studies put on the view that LPS induced model showed response in case of C57BL/6J and FVB/NL mice whereas it was found to be non-responsive in case of A/J, C3H and 129S1[19,20]. Though, in another study from Yang's group, it was found that C57BL/6J mice were resistant[21]. As the mouse models for Parkinson disease have mixed C57BL/ 6Jx129S1/Sv, C57BL/6JxSJL or background, it is strenous to determine their vulnerability to systemic administration of LPS [22].

Alternative to animal models

Zebrafish (*Danio rerio*)

The zebrafish emerged as a new exciting species to study the underlying mechanisms of brain disorders. Several advantages of using zebrafish in biomedical research are its genetic homogenesity to mammals, fast development, cost effectiveness as well as ease of genetic manipulations. Liling Yang and collaborators studied the effect of Phillyrin, (PHN) which is the main ingredient in Forsythia suspense Vahl fruits on lethal LPS induced neuroinflammation in Zebrafish. Their results demonstrated that PHN was found to show potent anti-inflammatory effects by inhibiting the expression of MyD88-dependent signaling pathway in zebrafish, which also led to the suppression of NF-κB pathway[23].

Caenorhabditis elegans (C. elegans)

The C. elagans, a nematode, proves to be an interesting model organism to study the molecular cellular and system level interactions in brain. Adanna G. Alexander *et al* suggested that C. elegans can be used a promising model to study the molecular mechanism underlying the pathology of neurodegenerative disease like AD. C. elegans offers several advantages to study the pathogenesis of Alzheimer – genes showing mutation in AD have counterparts in C. elegans. Due to the well-developed neuronal connectivity in C.elegans, it also proves to be an extremely useful model for studying learning and memory impairments which is seen in course of AD[24].

Drosophila melanogaster

Drosophila melanogaster, a species of fly, has been used widely to study human brain disorders. It offers several advantages in investigating the underlying cellular and molecular mechanism involved in brain disease. Furthermore, it has a short span of life and produces large number of off springs which makes it a convenient model to study neurodegenerative diseases. This model has been exclusively used to study the deadly neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Epilepsy as well as CNS injury which was expected to provide fruitful result in molecular level therapeutic strategies to treat neurological disorders[25].

In vitro cell culture technique

In recent years a wide variety *in vitro* cell culture techniques, helped the researchers to find solutions for simulating many homeostatic or pathological states by the manipulation of these conditions. Microglial cell cultures, described as early as the 1930s but its utilization for studying microglial function did happen till a methodology was developed for attaining and culturing greater yields of microglia[26]. The homogeneity of cells in an *in vitro* cell culture technique is high when compared to that of animal models. These cells can be quantified easily and it reduces the use of animal models for scientific experimentation. To screen neuro-inflammatory activity of compounds microglial and microglial like cell lines have been utilized to perform neuro-inflammatory screening of drugs. These cell cultures may be of primary and immortalized cell culture types[27].

Primary microglia cultures

The primary microglial cells which are utilized in *in vitro* cell culture studies showcase similarities in physical and chemical characteristics attributed when compared to that of microglial cells present in the body. This encompasses the reason for the utilization of primary microglial cell cultures for neuro-inflammatory studies. Giulian and Baker cultured the microglial cell from mammalian brain which are found to be advantageous than obtaining the culture from the cortex of a mouse before or after birth. This technique provides microglial cells with enriched cell surface markers along with various secretory derivatives which is similar in nature to that of endogenous cells[28].

BV2 and N9 cells – Retroviral Immortalized Microglia

As primary microglia culture techniques are time consuming and yields low number of cells, techniques were found to yield a greater number of cells in a short duration of time. BV2 and N9 microglial cells, which are isolated from rat and mouse, respectively are the two routinely employed cell lines of this type. Both of which have been used popularly to study neuro-

inflammatory disorders. Besides, microglial cell marker analysis was performed with BV2 cells. These BV2 cell lines were found to be positive for MAC-1 and MAC-2, whereas it was negative for MAC-3 antigens. Additionally, as that of primary microglia, they were found to be negative for GFAP and GC antigens which are the markers for astrocytes and oligodendrocytes respectively[29]. The cytokines released was determined and it was found that in response to LPS stimulation, levels of IL-1 was elevated in a dose dependent manner[30]. Henn et al. further examined thatBV2 immortalized cells shown similar functions as that of primary microglia but not exactly to the same extent. This research group investigated BV2 cells as a pertinent substitute to the primary cell cultures. Their study revealed when stimulated with LPS, 90% of the genes generated by the BV2 cells were also generated by primary microglia, although, the up regulation of genes in the BV2 was much less noticeable in primary microglia[31].

The N9 microglial cells obtained from mouse brain has many similar phenotypical properties as that of primary mouse microglia which has been exemplified by various studies including one by Hickman *et al* [32]. This research group discovered that upon incubation of N9 cells with TNF the expression of scavenger receptor A and CD36 were decreased and also AB uptake was reduced, which reinforced the result derived from primary mouse microglia; which provided the affirmation that this cell line has similarities with that of primary mouse microglia. The opsonized sheep red blood cells (SRBCs) are also phagocytized by the microglia which rapidly produce cytokines; in response to LPS, IL-6, TNF-α and IL-1are produced by these cells.

NOVEL THERAPEUTIC APPROACHES TO TREAT NEUROINFLAMMATION

Nutraceuticals

An ideal stratagem to avert neuro-inflammation is based on nutritional supplements and dietary changes and nutraceuticals. In this aspect, an exciting information came from the studies with Andean Compound – a natural substance from Andes Mountain[33]. Andean Compound, which consists of major ingredient fulvic acid turned up as a potent nutraceutical for neuro-degeneartive disorders[34]. The Andean Compound shows powerful anti-inflammatory property, which proved to be a safe dietary supplement too. Studies by Cornejo *et al.* led to the fact that fulvic acid has the ability to block tau self-aggregation. This fact led tau protein therapies to emerge as a captivating target to treat neurodegenerative disorders[35]. Inelia Morales et al. has been working in a compound containing Andean Compound along with Vitamin B complex known to be Brain-Up 10, that undergone a clinical trial and showed a reduction in neuropsychological symptoms[3].

Resveratrol

Resveratrol, a known polyphenol offers neuroprotection in experimental models besides its anticancer, antioxidant and anti-inflammatory properties. Besides, a study shown it has a role in inhibition of amyloid beta peptide aggregation *in vitro*[36].
Previous studies proved that resveratrol has an excellent role in reducing interleukin mRNA expression in hippocampal region of BALB/c mice upon LPS stimulation when given as a dietary supplement treated intra-peritoneally[37]. Researchers concluded that resveratrol causes an increase in the rate of survival by eliminating no increase when compared to control which impeded LPS- induced neuro-inflammation. Resveratrol was found to have a protective effect on LPS induced memory decline in mice which suggested its probable therapeutic potential[38]. Based on the knowledge that resvaratrol has a wide variety of bioactivities, a large number of derivatives have been initiated and investigated for the treatment of AD.

Curcumin

Curcumin is a polyphenol which is isolated from *Curcuma longa* is exclusively used in Ayurvedic medicine. It is known to possess anti-inflammatory, antioxidant, anti-amyloidogenic, memory enhancing properties, which recommends curcumin to be a potent neuro-protective compound. Curcumin is shown to inhibit lipooxygenase, COX-2 and iNOS expression leading to the inhibition of NO synthesis. It also alleviates NF-κB expression leading the inhibitory effect on TNF-α expression. Due to its wide and promising effect on inhibition of release of inflammatory mediators, curcumin can be considered as a potential anti neuroinflammatory compound[39].

Cerebrolysin

Cerebrolysin, a neuropeptide preparation, has been used extensively in AD treatment. Studies by Rockenstein et al. showed that it imitates the action of endogenous neutrophic factor and it is hypothesized that this peptide mixture alongside nootropic effects can help in reducing the pathology of neurodegenerative diseases[40]. Wei et al. postulated showing the principle effect of cerebrolysin which includes neuro-immunological regulation, stimulation of nootropic effect and modifying the transportation of glucose over blood brain barrier[41].

Ginsenosides and Glycyrrhizin

Ginsenosides or panaxosides are a class of steroid glycosides and triterpene saponins exhibit a wide variety of biological effect. It is shown to possess immunomodulatory property, as well as inhibition of neuronal cell damage, mitochondrial dysfunction and cancer. Ginsenoside Rg3, the active constituent in Panax ginseng, inhibits the TNF-α and IL-6 and IL -1B expression in brain tissues of LPS injected mice. Ginsenoside Rg3 was found to attenuate the COX-2 expression and iNOS expression in brain tissue[42]. In another study, Lee and collaborators signified that ginsenoside Rb1 has a modulatory role in microglia activation by alleviating the lba 1 protein expression in brain tissue upon LPS stimulation[43]. These findings provided a rationale for the intended use of Ginsenosides in treating neuroinflammation.

Glycyrrhizin (GRZ), the chief constituent of *Glycyrrhiza glabra*, was shown to shown to alleviate cognitive deficits and neuroinflammation in a dose-dependent manner. Studies exhibited that GRZ significantly reduced the TNF-α and IL-1B expression upon LPS induction by inhibiting the release of proinflammatory mediators which supported that GRZ may be established as a potent therapeutic agent against neuroinflammation[44].

Oenothein B

Oenothein B is a polyphenol which is isolated from *Epilobium angustifolium* was found to possess immunomodulatory, oxidative stress reliever and tumor suppressing activity. Okuyama *et al*. showed that upon administration of LPS per oral (p.o.) Oenothein B showed a promising anti- neuroinflammatory property by suppressing LPS induced microglial activation and inhibiting production of COX-2 in the hippocampal and striatum region of the brain of these mice[45].

Flavonoids

Flavonoids are a group of dietary polyphenols which have been shown to possess neuroprotective properties by preventing age-

related neurodegenerative disorders. Vafeiadou and collaborators suggested that flavonoids exhibit their anti neuroinflammatory action by inhibition of microglial activation and pro-inflammatory cytokines, interleukin-1 beta, also by inhibition of inducible nitric oxide and COX-2 expression. Alongside, it has also a potential to down-regulate the expression of NF-κB[46].Considering these aforementioned facts, it can be concluded that flavonoids have the potential to represent a novel therapeutic agents against neuroinflammation.

CONCLUSION

Neuroinflammation encompasses a primordial constituent in the pathophysiology of neurodegenerative disorders, which serves as a platform for the progression of neurodegenerative process. Differential microglial activation represents a central point in regulation of neuroinflammation, which yields neurosupportive or neurotoxic environments, being unfavourable for the fate of neurons. As microglia serve as the centre of communication between the CNS and the peripheral immune system, suitable ways to protect the balance between protective and ruinous effects of these cells is of high importance.

There can be no questionable doubt about the significant role of neuroinflammation in building out AD involving a series of perturbations and variance affecting the usual functioning of the CNS. Despite scientific evidences and knowledge, it is not yet clearly known when and how the inflammation takes place in the progression of AD.

To date, as a result of ineffectiveness of current treatments for neurodegenerative diseases, search for new therapeutic targets has become a priority. The finding of novel compounds can remove the hindrance of current treatments by opening the way towards a new treatment regimen which can be positioned as a future therapeutic agent. Further studies involving genomics, and various immunological tools involved in the neurodegenerative disease are expected to contribute to the discovery of novel immune-modifying therapies for this deadly incurable disease.

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