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Microglial response to viral challenges: Every silver lining comes with a cloud

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1. ABSTRACT

Microglia, the resident macrophages of the Central Nervous System (CNS) mediate key innate immune responses against foreign invasions within the CNS and clear the debris after any damage to the nearby tissue. Blood Brain Barrier (BBB) segregates the CNS from the rest of the lymphatic system and prevents the entry of foreign molecules into the brain. Pathogens still cross the BBB via different mechanisms and can cause severe infections of the CNS. Viral encephalitis is the most common form of brain infection and the causative agents include Japanese Encephalitis Virus (JEV), West Nile Virus (WNV), Murray Valley Encephalitis Virus (MVEV), Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV) and Hepatitis C Virus (HCV) among several others. Microglia expresses various Pattern Recognition Receptors (PRRs) to identify viral signatures called Pathogen Associated Molecular Patterns (PAMPs) to which microglia respond by releasing several pro and anti-inflammatory cytokines like MCP1, IL-1beta, Type I IFN, IFN-gamma, TNF-alpha etc. This review discusses the various viral infections of the brain and strategies employed by microglia to detect them.

2. INTRODUCTION

Central Nervous System was considered to be 'immune-privileged' for long as the earlier demonstrations showed it to react poorly to allogenic grafts and foreign tumors (1, 2). Moreover, its anatomical separation by the virtue of BBB makes it inaccessible to larger molecules and peripheral leukocytes. Although, the existence of phagocytic cells within the CNS was reported by several workers including Nissl in 1899, Alzheimer in 1904, Cajal in 1913 and del Rio-Hortega in 1932 among several others, it took several decades for glial biologists to acknowledge the fact that these brain macrophages termed as 'microglia' form the backbone of innate immunity within the CNS. Microglial origin has also remained a controversial topic for decades and now it's currently accepted that microglia are monocytic in their origin which migrate to CNS during early embryonic development (3, 4). Microglia may constitute 10%-15% of the brain cells and are found as a distinct cell type within the CNS with a characteristic morphology and specialized staining which differentiates them from glial cells and neurons (5). On the basis of their location, three different microglia subtypes have been characterized: parenchymal, which is actually the

population that migrates during embryonic development to the CNS and is involved in the surveillance of the parenchyma and perivascular and leptomeningial microglia which are usually replenished by the circulating macrophage population which occasionally move to parenchyma in case of brain injury (6-8).

Microglia share many phenotypical and functional characteristics with peripheral macrophages (9, 10) and communicate with other cells of CNS by means of cytokines and chemokines thereby contributing to both defense against CNS infections as well as neuropathogenesis. It has a characteristic 'ramified' morphology in their non-activated state within the brain parenchyma which is a unique property that distinguishes it from resident macrophages of any other tissue (9, 11). Upon activation, microglia become amoeboid and migrate to the site of injury where they may proliferate and release pro-inflammatory cytokines to recruit other cells in order to the prevent any further damage to the infected brain (9).

The most common infections of brain include meningitis and encephalitis which can be both bacterial and viral in nature. While bacterial encephalitis is not uncommon, it is the viral encephalitis that takes a toll on majority of the world population and its pathology is generally associated with seizures, stroke, fever and even death. Encephalitis, as the name suggests is the inflammation of the brain and can be caused by a wide variety of virus species. The causative viral agents include arboviruses (viruses that are transmitted by mosquitoes, tick or any other arthropod), herpes viruses or even Human Immunodeficiency virus (HIV). The most common arboviruses responsible for brain pathology belong to the family of flaviviruses which include JEV, WNV and MVEV among several others (12) The members of herpes group, HSV and CMV are also implicated in significant number of CNS infections (13). Upon infection, these viruses can lie latent for many years and can cause opportunistic infections in immunocompromised individuals as commonly reported in cases of HIV, and therefore co-infections are also common (14, 15) It is important for us to understand how viruses gain entry into the CNS and how do the cells respond to an acute or chronic viral infection.

The CNS viruses invade through peripheral routes and are initially encountered by the peripheral arm of the immune system of within a host. The entire process involves the production of reactive B- and T-cells against the viral pathogens along with a surge in circulating antibodies, complement proteins and cytokines. Peripheral macrophages play an important role in combating these infections that pose a threat to the health of an individual. These macrophages can cause decreased viremia and reduction of viral infection. However, most of the neurotropic viruses escape their way to the CNS and the routes of entry of these viruses can range from accessing the neuronal pathways to directly crossing the blood brain barrier or by a 'trojan horse' mechanism through infiltrating macrophages and leukocytes. In case of HIV-1 infection, it is very well understood that this virus enters the CNS by infecting CD4+ cells and macrophages (16-19). However, the routes of entry for most of the CNS viruses are not clearly understood. For example, in case of WNV infection, it is hypothesized that this virus either crosses via axonal retrograde transport through peripheral neurons or via hematogenous pathways involving the direct breach of BBB or by endothelial infiltration (20, 21) but the mode of entry is not well defined. Similarly, in case of JEV, the possibility of macrophage as a putative carrier has recently been evaluated and it was found out that this virus has the capability to reside within these macrophages and therefore there is a possibility that JEV may also employ 'trojan horse' mechanism to cross the BBB (22). However studies are further required to understand in detail about its transport to CNS. Other viruses like CMV can use leukocytes as a means of transport to the CNS (23). A recent *in vivo* study using a recombinant mouse CMV expressing a green fluorescent protein reporter gene has shown that CMV is found in peripherally circulating as well as infiltrating leukocytes and therefore concluded that CMV uses this method to gain entry into the CNS (23). Another member of herpes family, HSV-1 lies latent for years after primary infection in the epithelial mucosal surface. In immunocompromized state, HSV-1 can enter the CNS via a retrograde axonal transport through the trigeminal ganglia and can establish a latent infection for the rest of the life (24).

Identification of viral pathogens within the CNS takes place by specific surface receptors as well as intracellular receptors present within microglia. Astrocytes and oligodendrocytes are also known to immunomodulate the outcome of several infections, however, the role of microglia is well defined in identification of viral pathogens and they are the primary cells that respond to infections within the CNS. The microglial cells identify viral pathogens by the virtue of pattern recognition receptors (PRRs) which are specific for PAMPs like specific protein sequences, nucleic acids or carbohydrate structures (Figure 1) (25, 26). Several extracellular and intracellular receptors present in the host cells have the responsibility of identifying viral ligands (26, 27) which include double stranded RNA (dsRNA), single stranded RNA (ssRNA) and double stranded DNA (dsDNA). Toll like receptors (TLRs) like TLR2 andTLR4 are generally involved in viral recognition extracellularly (27, 28) while TLR3, TLR7, TLR9, Retinoic acid inducible gene (RIG-I) and Melanoma Differentiation-Associated Gene 5 (MDA5) as well as Nod like receptors like NLRP3 are involved in intracellular viral antigen recognition in macrophages/microglia (26). Once the pathogens are identified, microglia gets activated and secretes several factors to alert the nearby cells about a possible threat. The focus of this review is to bring forth the recent developments that have taken place in our understanding of viral infections of the CNS and strategies employed by microglia to combat them.

3. COMMON AGENTS CAUSING VIRAL ENCEPHALITIS

3.1. Human immunodeficiency virus-1 (HIV-1)

Individuals with Acquired Immunodeficiency Syndrome (AIDS) often suffer from severe neurological

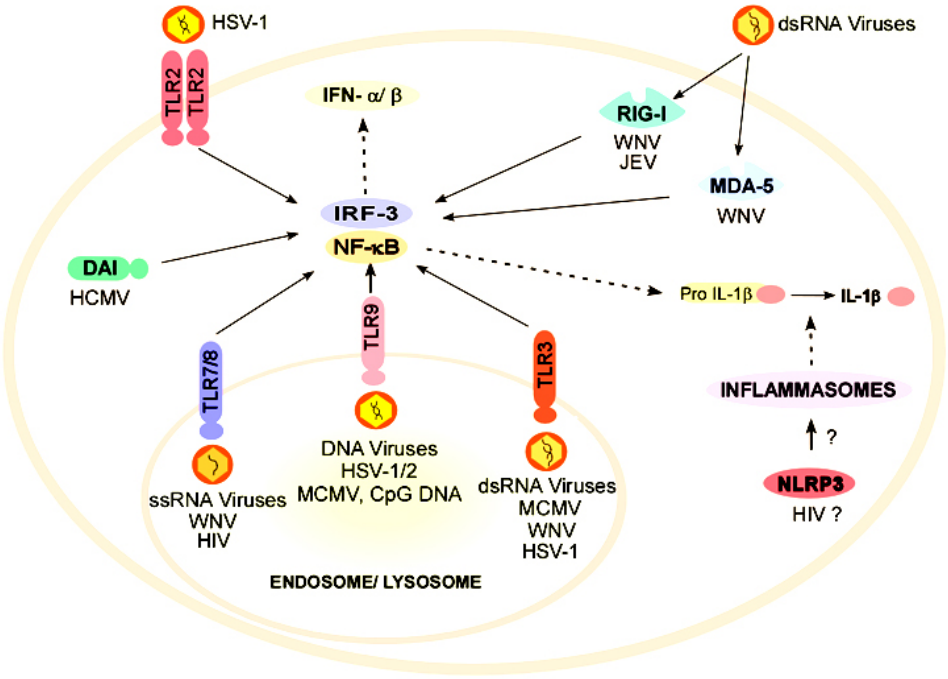

Figure 1. Schematic showing PRRs within microglia which are involved in anti-viral signaling within CNS. PRRs are shown with a list of potential viral ligands. There are various extracellular (TLR2) and intracellular (Endosomal; TLR3, TLR7/8, TLR9) membrane bound toll like receptors engaged in antiviral signaling. Antiviral responses are also generated by RIG-I, MDA5, DAI and NLRP3 which are cytosolic receptors and can potentially identify various viral nucleic acids. While TLR7/8 have been shown to identify HIV RNA, role of NLRP3 in HIV mediated IL-1beta production is not well defined. WNV is a single stranded RNA virus which is identified by RIG-I, MDA5 as well as TLR7/8 and TLR3 which are classical receptors known to identify dsRNA viruses. RIG-I is also associated with identifying JEV ssRNA genome. While DAI has been reported to be important for the identification of HCMV, TLR3 and TLR9 are known to identify MCMV genetic material. HSV1/2 are recognized by TLR3 receptors on the endosomal membrane. Once activated, signaling cascade initiated by these receptors converge on IRF-3/7 and NF-κB which are subsequently responsible for the production of Type I IFNs and IL-1beta respectively. The PRRs for many other CNS viruses in microglia are still unknown.

dysfunctions. These deficits generally occur at later stages of the HIV pathology and this condition is widely known as HIV associated neurocognitive disorders (HAND) (29). HIV infects CD4+ lymphocytes as well as macrophages in the peripheral system while in CNS, microglia and perivascular macrophages are the key cell types that are infected by HIV (18, 19). As neurons are not directly infected by this virus, loss of neurons is not an early event during HIV-1 infection but they fall victim to several pro-inflammatory cytokines and soluble factors that are produced by microglia and macrophages in response to viral infection (30, 31). The histopathological hallmarks of HIV infection include the formation of microglial nodules and giant multinucleated cells along with the onset of astrogliosis which are brought about by inflammation resulting from the activation of microglia and peripheral macrophages (32). These symptoms are collectively referred to as HIV encephalitis (HIVE) (32, 33). Interestingly, during the early stages of infection, activated microglia and perivascular macrophages release factors that are neuroprotective in nature (34, 35), but these events are short-lived and as the infection progresses, the balance shifts towards the secretion of neurotoxic cytokines that subsequently result in bystander neuronal death.

HIV-1 infected monocytes and peripheral macrophages enter the CNS after crossing the BBB (16). The BBB is either breached by induction of apoptosis in the BBB endothelial cells (36) or by disruption of tight junctions(37, 38) in case of HIV infection. This is the most popular theories of HIV entry into the CNS and is often called as 'trojan horse' hypothesis (17). After reaching the CNS, peripheral macrophages harboring the virus differentiate into microglia (39). The studies showing peripheral cells to bethe major reservoirs for the HIV further support the trojan horse mechanism of CNS entry (39, 40). Once inside the CNS, virus starts replicating within the microglial population or monocytic cells that have differentiated into macrophages. Microglia once activated release Monocyte Chemoattractant Protein-1 (MCP-1), a CC-chemokine which increases in case of HIV infection in patients with progressive HIVE which is also observed *in vitro* (41, 42). The major source of MCP-1 was found to be the infected microglia or peripheral macrophages which subsequently recruit other resident microglia and astrocytes to the site of viral entry as well as peripheral macrophages to the CNS via inflamed BBB (43). In addition to microglia, other cell types including endothelial cells and astrocytes also contribute to

inflammation by secreting MCP-1 which then attracts monocytes, memory T lymphocytes, natural killer (NK) cells to the site of viral entry (44). HIV-1-infected macrophages and microglia are also the major source of toxic molecules which further result in the neurological dysfunction often referred to as HIV Associated Dementia (HAD) (45). Production of NO, which is a key signaling molecule, is also associated with neurodegeneration and its production in turn depends upon the levels of another pro-inflammatory enzyme, Inducible Nitric Oxide Synthase (iNOS) which also increases in HIV infection (46). The expression of other inflammatory mediators like interleukin-1beta (IL-1beta), Tumor Necrosis Factor-alpha (TNF-alpha) and caspase-1 also increases upon HIV infection by macrophages and microglia (46, 47).

Microglia has several receptors and co-receptors to which HIV can bind (48). One of the HIV envelope proteins, Glycoprotein120 (gp120) binds to the co-receptors CCR5 and/or CXCR4 to gain entry into the cells (49, 50). Microglia get activated after the binding of gp120 to its receptors and release TNF-alpha and other chemokines. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) is also upregulated in activated microglia and infiltrating peripheral macrophages which further mediate the pathology of HIVE (51). A transactivator protein, Tat, which is involved in transactivation and stabilizing viral genes is also implicated in the pathogenesis of HIV and neuronal death (30). Upon infection with HIV, microglial migration takes place and Tat is one of the important proteins which is involved in this migration of human fetal microglia in a MCP-1 dependent manner (52, 53). Tat protein also stimulates iNOS and subsequent NO production in a dose dependent manner in microglial cultures (54). *In vivo* experiments using transgenic mice expressing Tat have shown that Tat is toxic to oligodendrocytes which in turn results in increased turnover of oligodendrocytes (55). Infact, myelin loss is a key feature observed in patients with HIV-1. Recent anatomical and ultrastructural investigation carried out in HIV-1 infected brains revealed a significant reduction of nerve fibers and axons, as well as a reduced myelin sheath thickness (56). Apart from Tat, few other proteins that are implicated in HIV mediated neurotoxicity include Nef and Vpr (31, 57, 58). These proteins also significantly increase the production of pro-inflammatory cytokines and also cause cell death within the CNS. In a study carried out by Cosenza-Nashat et. al., Granulocyte Macrophage Colony Stimulating Factor (GMCSF), which elevates during HIV-1 infection within the CNS, reduces the proliferation of productively infected primary microglia by arresting them in the G1/M phages of the cell cycle at least *in vitro* (59). This study focuses on the preventive measures taken by the microglia to contain viral replication within the CNS. It was further observed that the infection with Vpr mutant virus did not arrest this GMCSF induced proliferation indicating a role of this protein in maintaining HIV reservoirs upon suppression of host cell proliferation (59).

PRRs within the microglial cells are involved in host response to many viral pathogens (Figure 1). Single stranded RNA (ssRNA) is natural ligand for TLR7 (60, 61) and studies have shown that responses to HIV-1-encoded TLR7 ligands significantly differ between male and female plasmacytoid dendritic cells and this is now thought to be one reason for known differences in HIV-1 disease progression between men and women (62). A cytosolic receptor, NLRP3 which belongs to NOD-like receptor (NLR) family has been implicated in several viral infections (63-65). NLRP3 interacts with other adaptor proteins to form a multiprotein complex called as inflammasome where autocatalysis of caspase-1 from its pro-forms occur which further cleave the pro-forms of IL-1beta and IL-18 to their mature and active forms that are anti-viral in nature and are also known to have neurotoxic effects (65-67). A study carried out on HIV patients demonstrated that the allelic distribution in NLRP3 gene were differently placed when compared to controls (68). Moreover, susceptibility to HIV-1 infection was found to be associated with a 3'UTR NLRP3 single nucleotide polymorphism (SNP) indicating the potential role of this host cell receptor in mediating antiviral effects (68). It is likely that NLRP3 plays an important role in mediating the production of IL-1beta during HIVE as well, but further work is needed to elucidate the inflammasome mediated IL-1beta production and subsequent neuronal death in case of HIVE.

Currently, there is no cure available for AIDS and its associated cognitive dysfunctions which is an irreversible phenomenon (69). With the introduction of Highly Active Anti-Retroviral Therapy (HAART), incidents of HAD have significantly lowered and these dysfunctions are more prevalent in milder forms of HAND frequently referred to as Asymptomatic Neurocognitive Impairments (ANI) and Minor Neurocognitive Disorders (MND) (29, 70, 71). The limitation of many anti-retrovirals to cross the BBB is one of the biggest challenges in the introduction of anti-HIV therapeutics. Lentiviral vector-based techniques are therefore being tested for improved gene transfer into the CNS (72). In a study carried out on human monocytes-derived macrophage (MDM) cultures, the cells transformed with concentrated HIV-1-based defective lentiviral vectors demonstrated a significant protection of transduced MDM from super-infection with wild-type HIV-1 (72). These measures only aim to alleviate the disease but cannot be used for the total containment of this virus. Further research is required to understand the role of other PRRs including the inflammasomes that may be involved in HIV-mediated inflammation.

3.2. Herpes simplex virus (HSV-1)

Primary infection with HSV-1 typically occurs during early life cycle of an individual during childhood or adolescence and is usually mild or asymptomatic in healthy and immunocompetent individuals (24). HSV-1 infection of the brain results in necrotizing encephalitis which is a deadly CNS disease (73). CNS infection with HSV-1 triggers neuroinflammatory responses leading to the infiltration of peripheral immune cells into the CNS (73). Studies carried out on rats infected with HSV-1 showed that the virus moves along neuronal pathways, and spreads

across the brain within 8-10 days (74). Granulocytes, T-lymphocytes, and monocytes get infiltrated to sites of infection following HSV-1 inoculation while reactive microglial cells near the sites of infection increase the expression of MHC class I and class II glycoproteins (74).

Chemotactic cytokines or chemokines play a crucial role in the development of immunological resistance to HSV-1 replication. Microglial cells secrete TNF-alpha, IL-1beta, CXCL10, MCP-1 and CXCL9 chemokine in response to HSV infection (24, 75). As observed in other cases of viral infection, the production of these innate immune mediators could be both protective as well as potentially detrimental during HSV infection to the brain. Infact, a study carried out on mice revealed that these responses were not sufficient to protect from HSV-1 brain infection (75, 76). Moreover, HSV-1 infection results in the upregulation of ROS (73), iNOS and heme oxygenase (HO-1) thereby causing oxidative damage to the brain tissue (77). The role of glutamate transporter GLT-1is also studied whose expression increases in HSV-1 infection (78). GLT-1 increases the uptake of glutamate and convert it to glutathione and it was observed that inhibition of glutathione synthesis via GLT-1 resulted in increased HSV infection indicating that GLT-1 plays a major role in self defense against viral infection (78).

Chemokine expression during HSV-1 infection is initiated by recognition of viral PAMPs by PRRs. Four different TLRs are known to play an important role in host resistance to HSV-1 infection: TLR2/6 heterodimer recognizes lipopeptides while TLR3 recognizes double stranded RNA and TLR9 is associated with identifying CpG DNA motifs (Figure 1) (79, 80). TLR3 plays a protective role in human viral infections and it was found that children with HSV-1 encephalitis have a dominant-negative TLR3 allele (80). Although TLR3 was seen to be redundant in host defense to HSV-1 in epithelial and dendritic cells, expression of TLR3 in the CNS was found to be essential for immunity to HSV-1 (80). Other TLRs such as TLR9 are also known to act as receptors for genomic DNA from DNA viruses such as Herpes Simplex Virus-2 (HSV-2) immune cells (81). Studies on murine models have revealed that HSV-1 can induce pro-inflammatory cytokine production through TLR2 (Figure1) (82, 83). Infact, in microglia isolated from $TLR2^{-/-}$ mice, there is a delayed and attenuated ROS production following viral infection (73). Moreover, HSV-infected $TLR2^{-/-}$ microglia produced less neuronal oxidative damage to mixed neural cell cultures when compared to HSV-1 infected wild-type microglia (73). Direct signaling via TLR2 also resulted in apoptotic cell death in microglia isolated from wild type mice whereas it was significantly lowered in the cells isolated from $TLR2^{-/-}$ mice indicating the role played by this receptor in HSV mediated inflammation (84).

The recent discoveries of TLRs that interact with HSV-1 nucleic acids have intiated studies that involve designing antiviral agonists of TLRs. A TLR3 agonist, poly I:C when given 24 hours prior to the infection resulted in increased survivability mainly by priming the immune system (85). Many antiviral drugs like Acyclovir can interfere with HSV-1 replication and significantly reduce the mortality associated with HSV-1 encephalitis. The neurological sequelae that are generated during the course of the disease are however, often irreversible.

3.3. Cytomegalovirus (CMV)

During early development and in the immunocompromised adults, CMV causes neurological deficits and serious neurodevelopmental sequelae, including mental retardation, cerebral palsy, and sensorineural hearing loss (86, 87). In a study on several patients of Human cytomegalovirus (HCMV), 97 % percent of the cases were found to be among AIDS patients (88). The disease is characterized by micronodular encephalitis or ventriculoencephalitis within the brain. Micronodular encephalitis is characterized by multifocal, diffusely scattered micronodules which result from the aggregation of macrophages and glial cells within the CNS (89) and is responsible for progressive delirium, cranial nerve deficits, ataxia and even death (90).

There are different reports of different cell types that become the target for HCMV. The key cells that are known to generate responses against HCMV include microglia and astrocytes (91). CMV-infected astrocytes do not produce antiviral cytokines but secrete large quantities of the chemokines, MCP-1 and IL-8 in response to viral infection. In culture systems, CMV-stimulation of purified microglial cells show a marked increase in the production of TNF-alpha and IL-6, as well as chemokines which suppresses HCMV replication in astrocytes (91). CMV treated microglial cells also release a T-cell chemoattractant protein, CXCL10 (gamma interferon-inducible protein 10) which brings T-cells to the site of injury and results in their activation. These activated T lymphocytes can then secrete interferon-gamma (IFN-gamma), which also inhibits HCMV replication in astrocytes (92). There are various ways by which CMV tries to modulate host responses. For example, CMV expresses a homologue of human IL-10 which is known to suppress CXCL10 production by microglial cells thus enabling CMV to suppress host immune response because T-cell recruitment is crucial for viral clearance (93). There are also evidences that exposure of microglia to IFN-gamma 24 h before infection markedly suppresses Mouse CMV (MCMV) production and resultant cytopathic effects in a dose-dependent fashion (94). In the human CNS, HCMV primarily infects astrocytes and ultimately leads to their destruction via apoptosis (95). Neuroepithelial precursor cells, differentiating astrocytes and neurons are also permissive to cytopathic HCMV infection, suggesting that the fetal human CNS is vulnerable to HCMV-induced neuronal injury (96, 97)

As with other viruses, microglia possess various PRRs to identify CMV DNA. A relatively lesser known PRR, DAI (DNA-dependent activator of IRFs) was shown to be associated with identification of MCMV (98). When DAI was overexpressed in murine fibroblasts, enhancement of induction of type-I IFN and other innate immune genes occurred in response to CMV DNA (98) indicating that

DAI mediates the anti-inflammatory cascade after identifying viral DNA. Very recently, DAI has been shown to be important for the anti-viral immune response to Human cytomegalovirus (HCMV) (99). It was observed that DAI was essential for IRF3 activation and IFN-beta expression in response to HCMV, which could inhibit replication of HCMV via Z-DNA binding protein-1 (ZBP1). Another important pathway, TLR9/MyD88 mediates antiviral cytokine responses by dendritic cells (DC), and possibly other cell types, which are coordinated to promote effective NK cell function and MCMV clearance (100).

The magnitude of CMV infection demands an immediate attention. As of now, current therapeutic measures include the administration of several antiviral drugs like ganciclovir, foscarnet etc. that target CMV DNA polymerase and provide relief of symptoms in immunocompromised individuals (87). However, there is limited information about the ability of antiviral therapy to limit the neuropathogenesis of congenital CMV infections.

3.4. Japanese encephalitis virus (JEV)

Japanese encephalitis virus is a major cause of viral encephalitis in Asia. It belongs to the family *flaviviridae* and genus Flavivirus which contains approximately 70 arthropod-borne enveloped RNA viruses many of which cause severe disease (101). Annually 30,000-50,000 incidences of the JE infections are reported (102) and the infection is fatal in 25-30% of cases and approximately half of these cases result in neuropsychiatric sequelae (103). The main mode of transmission of Japanese Encephalitis Virus (JEV) is via *Culex tritaeniorrhynchus* that breeds in irrigated rice fields (103). CNS, upon JEV infection, is manifested with fever, headache, vomiting and signs of meningeal irritation resulting in high mortality (104). Poliomyelitis like flaccid paralysis and parkinsonian syndrome may also occur in the later stages of the disease (105). The changes in pathology in fatal cases of JEV are polymorphic and diffuse wherein the brain develops severe degree of vascular congestion, microglial proliferation, formation of gliomesenchymal nodules, cystic necrosis and cerebral edema (103, 106).

JEV crosses the BBB probably by the increase in the expression of Matrix metalloproteinase 9 (MMP9) on endothelial cells which compromises the integrity of BBB (107). Microglia is one of the major sources of cytokine and chemokine production upon JEV infection in the CNS (108-110). These cytokines and chemokines initiate the recruitment of other immune cells to the site of infection to clear the debris and help in the repair process (111, 112). However, uncontrolled regulation of this phenomenon could lead to bystander neuronal damage (110, 113, 114). Although, the mechanism of the inflammatory responses being initiated in the CNS in response to JEV infection are not well understood, many studies have delineated important pathways being triggered in the process. RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted) an important chemoattractant has been shown to be secreted by the microglia and astrocytes upon JEV infection (115). The expression of this chemoattractant recruited other immune cells to the area of infection, thereby increasing the magnitude of inflammation. It was also demonstrated that the induction of RANTES was dependent upon the activation of ERK and NF-kappaB signalling pathways as well as upon the replication of JEV (115). Studies by Ghoshal *et al.* show that the number of activated microglia significantly increases upon JEV infection (110). These activated microglial cells express various pro-inflammatory molecules such as MCP-1, IL-6, TNF-alpha as well as other pro-inflammatory enzymes, Cyclooxygenase-2 (ox-2) and iNOS. Their studies further demonstrated that neuronal death occurs as a result of the inflammatory responses initiated during JEV infection (110, 116, 117). Raung *et al.* show that activated microglia upon JEV infection express pro-inflammatory cytokines and cause neurotoxicity via Src/Ras/Erk pathway (118). JEV infection in animals as well as *in vitro* also results in the induction of pro-inflammatory cytokines, IL-1beta and IL-18 (119). These cytokines further result in expression of other pro-inflammatory modulators from microglia and astrocytes like MCP-1, IL-6, TNF-alpha and also cause neurotoxicity (119).

Several host responses aim to alleviate inflammatory processes in JE infection. Earlier, microglia has been shown to express IL-10 in CNS which is anti-inflammatory in nature and inhibits the production of pro-inflammatory molecules like TNF-alpha and IL-6 (120). *In vitro* studies with JEV have shown that treatments of microglial cells with IL-10 results in reduced levels of pro-inflammatory cytokines, IL-1beta and TNF-alpha (121). Further, IL-10 also prevented neuronal cell death that occurs post the inflammatory processes initiated by JEV (121).

A Recent study has shown that TNFR associated death domain (TRADD) is important in mediating JEV induced microglial activation and the release of pro-inflammatory cytokines (122). TRADD knock-down in mice resulted in significant reduction in the activation of microglia and macrophages and subsequent production of pro-inflammatory cytokines and chemokines upon JEV infection (123). Also, the recruitment of peripheral leucocytes was reduced to the site of infection and the expression of chemokine receptors and cell adhesion molecules was attenuated (123). Recent studies by Thongtan *et al.* show that mouse microglial cells permit JE replication and result in extra-cellular infectious viral production which could successfully infect the mouse neuroblastoma cells (124).

JEV has a ssRNA genome which can potentially be identified by several PRRs. However, till date, not many PRRs are known to provide protection against JEV infection. RIG-I, a cytoplasmic pattern recognition receptor which has been shown to be important for identifying other flaviviruses has also been shown to be essential for JEV induced IRF-3 and IFN-alpha/beta activation pathways (125). This study was however carried out in carcinoma and neuroblastoma cell lines and there is no information about the role of PRRs on microglia in mediating the viral

responses. Since microglia are progressively infected by JEV, it is therefore of utmost importance to find out the role of potential TLRs and helicases responsible for viral identification within the microglial population.

In developing countries like India and other Southeast Asian countries, JEV poses a severe threat and therefore we need to look for strategies to manage JEV epidemics. There is no specific treatment available for JEV infection as of now and neither are any anti-viral drugs available. In this context, our lab has recently shown that microglial activation upon JEV infection significantly decreases upon treatment with a tetracyclic compound, Minocyclin (116). In animal studies, this drug has been found to confer complete protection upon JEV infection (116). Many more studies and clinical trials are to be carried out in order to test the efficacy of this drug before it is intended for human use.

3.5. West nile virus (WNV)

WNV, another flavivirus, is prevalent in certain regions of Europe, Asia, the Middle East, Africa and North America (126). WNV Infection is often asymptomatic, but high fever, meningitis, encephalitis, or acute flaccid paralysis may occur in 20 to 40% of infected individuals (127). Although more severe symptoms are associated with infections in young children, the elderly, transplant patients or immunocompromized individuals, healthy young adults have recently been shown to be afflicted with neurological disease (128, 129). The virus replicates possibly in the Langerhans cells of the skin and then spreads sequentially to draining lymph nodes and to the blood where it causes viremia. Virus in blood disseminates the infection to visceral organs, particularly the kidney and spleen, then to the CNS (130).

WNV can enter the CNS by breaching the BBB which is achieved by the action of Matrix metalloproteinase9 (MMP9) as suggested by studies with MMP9 $^{-/-}$ mice (131). Once inside the CNS, neurons become the primary target of WNV infection (132, 133) and neuropathological findings from human autopsies show accumulation of inflammatory infiltrates that consist predominantly of nodules of activated microglia, T and B cells, and macrophages (134, 135). Apart from the neurons, the astroglia and microglia have also been found to take part in immunological responses to WNV by releasing various cytokines and chemokines (136, 137). There are reports that WNV virions align along the lamellae of the myelin sheath but it was not found to be associated with any severe damage to the axon or to the myelin sheath (138). While there are studies demonstrating the ability of rodent peritoneal macrophages and dendritic cells to support the proliferation of WNV, recent studies suggest that human microglia are unable to support WNV replication (139-141). Cheeran *et al*. demonstrate that microglia produce robust levels of chemokines CXCL10, MCP-1 and CCL5 in response to WNV infection (141). These chemokines may be involved in raising an alarm by attracting other immune cells like monocytes and lymphocytes to the site of infection in the brain.

Activated microglia was also shown to produce inflammatory cytokines like TNF-alpha and IL-6 post WNV infection *in vitro* (141). A recent study has reported that upon WNV infection, inflammatory monocytes are recruited from periphery in the CNS and these cells act as precursors for microglia (142). Interestingly, the migration of these monocytes occurs independent of BBB breach or radiation preconditioning (142). Furthermore, the neutralization of MCP-1 chemokine resulted in marked decrease in the microglia numbers in WNV infected brains suggesting that the inflammatory monocyte migration in CNS is influenced by the MCP-1 secretion (142). Microglial activation upon WNV activation also depends upon a Toll/Interleukin-1 Receptor (TIR) adaptor molecule called Sterile alpha and HEAT/Armadillo motif (SARM). Increased neuronal damage, decreased levels of inflammatory cytokine TNF-alpha and reduction in microglial activation is seen upon WNV infection in SARM $^{-/-}$ mice (143).

TLRs play an important role in mediating responses against WNV (Figure 1). A replication defective WNV strain was shown to be ineffective in inducing inflammatory responses by microglia suggesting that accumulation of viral nucleic acids are required for triggering TLR signaling to induce the production of cytokines and chemokines (141). The TLR pathway converges on IFN regulatory factor 3 (IRF-3) which then stimulates Interferon-stimulated gene (ISG) response which is crucial for the production of type I interferons. IRF-3 generation has been found to be critical for host responses against WNV. Several receptors are known to induce IRF-3 and subsequent ISG stimulation including RIG-1 and MDA5 helicases. RIG-I plays a critical role in initiating innate immunity against WNV as a knockdown of RIG-I disrupts the immune responses against WNV (144). Disruption of MDA5, another helicase also abrogated activation of the antiviral response to WNV, suggesting a role of MDA5 in mediating host's defense against WNV infection (144). In addition to RIG-I and MDA5 helicases, TLR3 has recently been shown to induce the production of IRF-3 in presence of WNV (145). Studies on TLR3 knockout mice have shown that upon WNV infection, these mice had increased mortality rate with respect to wild type mice indicating the role of TLR3 in mediating protection against WNV infection (145). Recent studies have also suggested a role of TLR7 in initiating response to WNV infection. TLR7 and IL-23 can stimulate a vital host defense mechanism that operates by affecting immune cell homing to infected target cells in response to WNV infection (146, 147).

There is no specific therapy available for WNV infection as of now. One major problem in designing drugs involves their passage through the CNS to the WNV infected regions. However many novel strategies are being devised and being tested for their ability to combat the infection. Inhibitors of guanosine biosynthesis like Ribavarin and Mycophenolic acid have been found to be effective against WNV infection in cell cultures but enhance the mortality in animal models (148, 149). RNA interference is also found effective *in vitro* as the cells

expressing SiRNA become resistant to the WNV infection (150, 151), however administration of SiRNA in mice post WNV infection does not result in significant number of survivals (152). Given the lack of an effective therapy against WNV, the ongoing studies should help in providing clues to a novel strategy that can help in containing the infection.

3.6. Hepatitis c virus (HCV)

Hepatitis C virus (HCV) is an important etiological factor of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (153, 154). In a study on 59 liver transplant recipients, Singh *et al.* (155) showed that the recurrent HCV hepatitis in these recipients is associated with reduced quality of life, functional status, and higher psychological distress compared with patients who did not have HCV and those without HCV recurrence. It was found that HCV infection is also associated with cognitive dysfunctions (156). HCV traffics into the HIV-infected brain, where it might lead to a productive coinfection with HIV which can be correlated with cognitive impairment (157).

Radowski *et al.* showed that HCV sequences are present in the autopsy brains of Hepatitis C patients and also that these sequences were similar to the sequences from lymph nodes (158). Since HCV RNA sequences were detected in PBMC and hematopoietic progenitor cells by *in situ* hybridization (159) studies also, it was proposed that this virus may infect the cells from monocyte/macrophage lineage. Very recently, using Laser Capture Microscopy (LCM), different cell populations were isolated from autopsy brains of HCV patients and it was found that upto 95% of cells were positive for HCV non structural protein 3 (NS3) and CD68 (a marker for microglia/macrophage) positive in contrast to only 4% to 29% which were GFAP (a marker for astrocytes) positive (160). Neurons and oligodendrocytes were NS3 negative indicating that majority of the cells that are infected by HCV are microglia/macrophage and a very few astrocytes are infected in the CNS (160).

HCV infected macrophages/monocytes also enter the brain through blood-brain-barrier via 'trojan horse' mechanism as seen in the case of HIVE (161). Recent findings from CSF analysis of HCV infected patients support this hypothesis (162). It was found that the RNA sequence of CSF derived virus was similar to that found in Peripheral Blood Mononuclear Cells (PBMC) in nearly half of the patients, which suggests that PBMC could carry HCV into the brain (162). Another report from PCR and sequencing studies on autopsy brains also revealed the presence of negative-strand HCV RNA in brain which confirms that HCV replicates within the CNS and moreover Internal Ribosomal Entry Sites (IRES) polymorphisms are also present which prove to be important viral strategy to favor latency in the CNS (163).

HCV infection is also reported to have severe impact on the metabolic activities within CNS. Gene expression studies using differential display and reverse Northern hybridization on autopsy brains from HCV infected patients showed that there was a considerable downregulation of mitochondrial oxidative phosphorylation genes, some ribosomal protein genes and several genes involved in transcription regulation which reflect reduced metabolic activities (164). These findings suggest a biological basis for the neuropsychiatric symptoms and cognitive impairment associated with HCV infection. HCV core proteins are also known to play an important role in the immunopathology in CNS (165). HCV core protein can cause oxidative injury within the brain by the generation of ROS both *in vitro* and *in vivo* by directly interacting with mitochondria (165).

Role of PRRs on microglia and the mechanism for HCV evasion or activation of the immune system within the CNS is not clear. Peripherally, TLR2 and TLR6 mediated innate immune signaling pathways are activated by HCV core and NS3 proteins which induce the production of TNF-alpha and IL-10 in human monocyte-derived macrophages, which was found to be impaired by knocking down bothe TLR2 and TLR6 (166). However, this study is limited to peripheral systems and role of TLRs in mediating CNS inflammation during HCV infection is not understood. Further studies are therefore required to find out HCV specific PRRs on microglia.

3.7. Murray valley encephalitis virus (MVEV)

MVEV is also an arthropod-borne virus and is another member of the Flavivirus genus (12). MVEV causes age-dependent encephalitis in mice after peripheral inoculation (167). The neuronal injury and destruction in Murray Valley Encephalitis (MVE) is associated with adherence of inflammatory cells, neutrophils and macrophages to infected neurons (168). The histological and ultrastructural features of CNS infection using electron microscopy with MVEV in mice revealed neuronal necrosis in the olfactory bulb and hippocampus of MVE infected brains (169). Inflammatory cells such as macrophages, lymphocytes and especially neutrophils were found to be responsible for these pathological changes (169). The mortality rates of MVE treated mice also correlates with the intense polymorphonuclear and mononuclear leucocyte infiltration within the CNS. This response is prominent in perivascular regions and in the CNS parenchyma (168) which precedes the expression of TNF-alpha and neutrophil-attracting chemokine N51/KC within the CNS. Increase in neutrophil population within the CNS is also correlated with expression of the iNOS enzyme (168).

Flavivirus resistance locus (Flv^r) found on chromosome 5 resists the spread of MVEV in mice that are transgenic for this locus (170). This resistance to viral replication is NO independent (171). Significant reduction in viral RNA is seen in these MVEV resistant mice within the cortex, olfactory bulb, thalamus and hypothalamus. The low virus titers within brains of resistant mice coincide with decreased inflammation and low counts of infiltrating inflammatory cells. Resistant mice also show lower IFN I/II and TNF-alpha gene induction than susceptible mice suggesting the immunopathological nature of MVEV infection (171).

MVEV has not been studied in details in terms of their pathogen recognition in CNS. There are no known pathogen recognition receptors that are identified for MVEV on microglia. The possibility of MVEV having TLRs common with other flaviviruses cannot be ruled out. Therapy for curing MVE is also lacking and there are currently no known effective anti-viral agents available to treat Murray Valley encephalitis. The lack of knowledge about the PRRs for MVEV poses a hurdle in developing strategies against MVEV. Emphasis should be laid on identifying novel PRRs within microglia that identify this pathogen.

4. CONCLUSIONS AND PERSPECTIVES

Infections of CNS are not common, yet not very uncommon.Viruses have posed a challenge to mankind since ages and they have constantly evolved their ways to robustly invade the host. Viral infections pose a much bigger threat to the health of an individual as CNS is devoid of an inbuilt humoral immune system actively participating in the clearance of pathogens. The major role of microglia initially is to alert the system in case it encounters a virus or any other pathogen. In due course this 'system alert', in addition to pathogenic clearance can lead to irreversible damage to neurons which can result in severe cognitive and neuromotor dysfunctions, impaired learning and memory etc. Our review discusses the different viral infections of the CNS and the challenges that underlie in viral resolution from the CNS.

The response to any infection is a very complex event. Infact, in addition to microglia, cell types including oligodendrocytes and astrocytes can have a modulatory function during viral invasions. Astrogliosis or the activation of astrocytes is also a very common observation in CNS viral infections. For example, during HIV-1 infection, astrocytosis, which is usually accompanied with an increase in Glial fibrillay acidic protein (GFAP) expression within the astrocytes is commonly observed (172, 173). As already mentioned, Tat protein, in addition to directly resulting in neuronal death can cause increased GFAP expression in astrocytes (172) indicating that astrocytes may play an important immunomodulatory role during infections of CNS. Genomic studies have also shed some light on the possible role that astrocytes play in HIV-1 infection (174). Infection of astrocytes has also been reported in case of other infections such as JEV, however, direct JEV infection of astrocytes does not result in neurotoxicity, it is microgliosis that promotes neuronal death by the activation of astrocytes (175, 176). As already mentioned, in case of CMV, astrocytes secrete MCP-1 and IL-8 which further help recruiting microglia (91). These studies emphasize on the immediate need to evaluate the cross-talk that occurs between microglia and astrocytes.

In addition to neuronal degeneration and astrogliosis, loss of myelin and degeneration of oligodendrocytes is also reported in some cases. For example, loss of myelin is observed in the case of HIV-1, HSV-1 and also in cases of WNV (55, 138, 177). CMV infection also result in demyelination, or at least is responsible for immunomodulation in case of HIV-1 (178). Loss of myelin results in the dysfunction of normal neuron-to-neuron communication as well as axonal degeneration (179). Demyelination induced by viral infections results from a direct viral infection of oligodendroglia or indirectly by the activation of microglia that release cytokines and other immune mediators which result in direct damage to the oligodendroglia or the myelin sheath (180). These studies clearly indicate the complexity of immune system within this organ. While the immunomodulatory role played by astrocytes and oligodendrocytes cannot be ruled out, it is the microglial population along with the circulating lymphocytes that orchestrate the events of neuropathogenesis.

The presence of PRRs confers microglia with a sense of specificity. Different pathogens are either identified by different receptors or have similar epitopes which makes them identifiable by a single receptor. The discovery of newer PRRs constantly improves our knowledge about the functioning of immune system and antiviral mechanisms within the CNS. We have discussed various intracellular and extracellular TLRs that identify the molecular signatures of different viral pathogens. As illustrated in Figure 1, stimulation of TLRs by viral PAMPs can result in the activation of NF-kappaB (25, 26) which is involved in the upregulation of several pro-inflammatory cytokines. TLR pathways also converge on Interferon regulatory factors like IRF-3 and IRF-7 that are known to induce ISGs like IFN-alpha and IFN-beta which play a very important anti-viral role (26, 181). Identification of viruses by several pattern recognition receptors on microglia (Figure 1) is generally associated with secretion of pro-inflammatory cytokines and chemokines (see Table 1). As illustrated in Figure 2, these pro-inflammatory mediators released during microglial activation result in neuronal damage. Neurons once damaged can also secrete several death associated products such as laminin, neuromelanin and MMP3 which cause reactive microgliosis (182). This cyclic phenomenon ultimately proves detrimental for CNS health and many more nearby neurons then succumb to inflammatory response. Microglial activation is also suggested to be associated with neuron survival and repair (183), but there is hardly any evidence suggesting the neuroprotective role of microglia during viral encephalitis.

With the recent discoveries of inflammasomes and their implications in different kinds of infections, our understanding of the pathways leading to the production of many pro-inflammatory cytokines has greatly benefitted. As mentioned earlier, many studies have provided direct evidences while others have indirectly provided information about the role of these inflammasomes during viral invasions. For example, a study on several Brazilian HIV infected patients and HIV-seropositive Italian individuals showed that a 3' UTR NLRP3 SNP was associated with HIV-1 infection in the studied groups (68). This study at least provides us with a preliminary information about the role of NLRP3 in mediating HIV-1 infection and it is likely that in case of HIV infection, NLRP3 inflammasome might be responsible for the production of IL-1beta and/or IL-18. In-depth studies are

Table 1. List of cytokines and chemokines released by microglia in response to different viruses

Viral Agents in CNS	Major effector molecules released during viral infection	Effector functions
HIV	MCP-1 TNF-alpha, iNOS, IL-1beta GM-CSF	Chemoattraction of monocytes/ peripheral lymphocytes; Neuronal apoptosis; Reduced microglial proliferation
HSV	MHC I/II TNF-alpha, IL-1beta CXCL10, MCP-1 and CXCL9 iNOS/ Hemeoxygenase	Increased antigen presentation; Antiviral effects; Increased inflammation; Oxidative damage
CMV	TNF-alpha and IL-6 MCP-1 and IL-8, CXCL10	Antiviral effects/ Increased inflammation; Chemoattraction of monocytes and T-cells
JEV	RANTES, IL-1beta and IL-18 MCP-1, IL-6, TNF-alpha, Cox-2 and iNOS, IFN- alpha/beta	Chemoattraction of monocytes and lymphocytes; neuronal damage; Increased inflammation;
WNV	CXCL10, MCP-1 and CCL5 TNF-alpha, IFN-alpha/beta	Chemoattraction of monocytes and lymphocytes; Antiviral effects
HCV	ROS; metabolic disturbances	Oxidative damage, Neuronal apoptosis
MVE	TNF-alpha; N51/KC iNOS	Chemoattraction of monocytes and neutrophils; Oxidative damage

Microglial activation is associated with the enhanced production of pro-inflammatory cytokines and chemokines Most of the cytokines and chemokines that are listed here are small signaling molecules that are used by microglial cells to communicate with and attract peripheral macrophages and lymphocytes to the site of viral entry. These responses, however, prove to be detrimental to the cells of CNS.

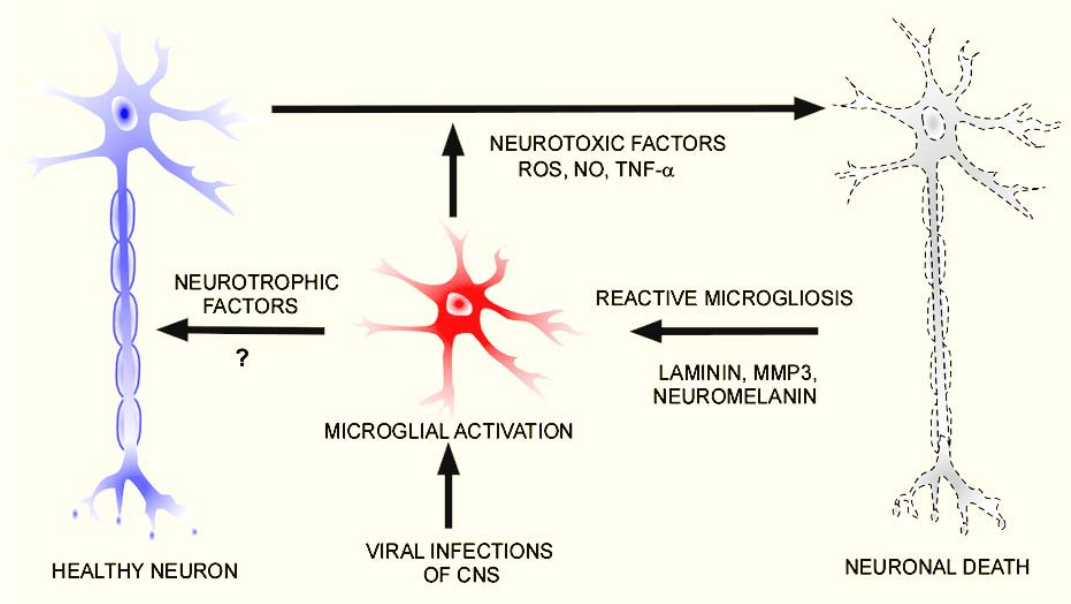

Figure 2. Schematic representing microglial activation and subsequent neuronal death in response to pro-inflammatory mediators. Viruses can be identified by PRRs on microglia resulting in their activation which is associated with the release of pro-inflammatory mediators including TNF-alpha, IL-1beta, NO, ROS etc. Activation of microglia can also occur in response to stimulation from neuronal injury (reactive microgliosis) which results from the secretion of Matrix metalloproteinase 3 (MMP3), neuromelanin and laminin etc. by damaged neurons. Secretion of neurotoxic molecules either way can result in bystander neuronal death.

required for the better understanding of such mechanisms which may lie at the core of several viral infections.

In the light of current knowledge about the role of cytokine receptors and chemokines along with complex molecular events that take place downstream to identification of a pathogen by microglia, many therapeutic agents targeting the production of pro-inflammatory cytokines are being looked into (184, 185). For example, a naturally found antagonist for IL-1Receptor (IL-1Ra protein), or anakinra, a recombinant IL-1Ra that has been approved for rheumatoid arthritis, works by blocking IL-1 signaling by competitively inhibiting the binding of IL-1beta to its receptor (185, 186). It therefore prevents the formation of inflammasome complex and further production of IL-1beta. Direct administration of some of the pro-inflammatory cytokines also exhibit anti-viral properties. For example, studies in mice with type I IFN receptor or IFN-beta gene deficiency have revealed an important role played by type I IFNs against CNS viral infections. Many anti-inflammatory agents like neuropeptides (187, 188) and anti-inflammatory cytokines including IL-10 (121) and TGF-beta (189) also result in decreased microglial activation and subsequent neuronal

protection. IL-10 has been reported to reduce the synthesis of pro-inflammatory cytokines and the receptor of certain cytokines in the brain (190). The synthesis of Cox2 and ROS mediated by pro-inflammatory cytokines IL-1beta and TNF-alpha has also been shown to decrease upon in-vitro IL-10 treatment (121). A recent class of type III IFN, IFN-lambda has been shown to have anti-viral properties (191). Treatment with IFN-lambda inhibits the HSV-1 infection in primary neurons and astrocytes (191). The potential of neutralizing antibodies is also been explored. Recent work with neutralizing antibodies has shown remarkable reduction in viral loads. A recent study on macaques suggested that administration of neutralizing antibodies at suboptimal concentrations against simian-HIV resulted in increased production of neutralizing antibodies and subsequent reduced viremia in plasma (192) which indicates about the potentials of this approach. These molecules are of great therapeutic importance which can subsidize microglial activation and prevent a potential neuronal damage and subsequent cognitive loss.

Inflammation has always been associated with body's need to parry away the pathogens and therefore generally considered as 'good' for the host. Excess of anything can be harmful and this is what we witness during viral mediated neuroinflammation. We have come a long way from the times that microglia was discovered and today we have plethora of information regarding the mechanisms employed by CNS to combat infections. Antiviral therapy has also witnessed a metamorphosis in its approach over several decades. However, most of the viral infections of CNS are still incurable and therefore, the future research will need to continue to identify the molecular events and novel receptors involved in the vigilance against viruses and designing novel strategies for the prevention and treatment of neuronal damage.

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