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Unveiling the Role of Microglia in HIV-Associated Neurodegeneration: Current Insights and Future Directions

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Abstract

HIV has affected approximately 84.2 million individuals to date. Antiretroviral treatment (ART) has resulted in reduced disease severity and improved quality of life for people living with HIV. Despite the effectiveness of ART, HIV-associated neurocognitive disorders (HAND) continue to present significant challenges in managing individuals with HIV. As the primary immune cells of the central nervous system (CNS), microglia play an active role in maintaining homeostasis and responding to neuroinflammatory stimuli. The virus can infiltrate the brain, establishing a persistent reservoir that leads to chronic immune activation and inflammation. Consequently, microglia undergo phenotypic and functional changes, releasing pro-inflammatory cytokines, chemokines, and neurotoxic factors. These neurotoxic substances contribute to neuronal damage, synaptic dysfunction, and ultimately the impairment observed in HAND. While ART has revolutionized HIV treatment, emerging shreds of evidence suggest that certain drugs may contribute to neurodegeneration. Understanding the mechanisms and risk factors associated with ART-induced neurotoxicity is important for minimizing long-term neurological consequences. However, challenges persist in fully comprehending the interactions between microglia, HIV infection, and ART. This review comprehensively explores the significance of microglia in HAND also investigating the effects of ART on these neurological conditions, encompassing research on HIV, HAND, and the involvement of microglial senescence.

Keywords: HIV, Neurodegeneration, Microglia, ART, Senescence

Introduction

HIV, the most enduring pandemic in history, has had a profound impact on mil-lions of individuals globally. It can be found in nearly all parts of the body, including the CNS, where it enters shortly after infection and infects brain cells [1] With advancements in ART, HIV has become a lifelong manageable chronic disease. Combination ART (cART), which includes drugs inhibiting critical HIV enzymes such as integrase, reverse transcriptase, and protease, has proven quite effective [2]. While ART has reduced mortaity rates, it cannot eliminate latent HIV from the reservoirs including the Blood Brain Barrier (BBB). The BBB confines drug permeability into the CNS. Low drug concentrations may lead to ineffective control of HIV leading to neurocognitive dysfunction in many individuals with HIV receiving ART [3-5]. HIV infection persists in brain cells and makes it difficult to eradicate.

Entry of HIV into CNS

The BBB serves as a protective wall that prevents the entry of harmful

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substances into the brain. Comprising spaced cells within the tissue surrounded by blood vessels, this tightly structured barrier regulates and restricts the movement of molecules, ions, drugs, and cells between the blood and the CNS [6, 7]. This natural process is facilitated by the attraction of these cells to inflammatory cytokines or chemokines secreted by specific brain cells [3-8]. The exact mechanism by which HIV infects brain cells remains unclear. However, the Trojan horse theory suggests, it enters the brain with the help of infected CD4+ T lymphocytes or monocytes [8].

Microglia, dendritic cells, and other cells of myeloid lineage are among those infected by HIV. The HIV-infected cells also contribute to cell-to-cell transmission of the virus. Studies have also reported that HIV can alter the permeability of the BBB through various mechanisms [Fig.1]. Notably, it can cross the barrier via transcytosis, employing the gp120 protein[9]. Furthermore, HIV modifies the expression of proteins crucial for maintaining the blood-brain barrier's epithelial junctions, with the viral transactivator of transcription (Tat) protein playing a significant role [10-12].

HIV Associated Neurocognitive Disorders

HIV is known to enter the CNS within a week of infection [1]. Many times, HIV or its proteins cause various neurological complications, including cognitive decline and motor dysfunction, etc. These alterations due to HIV in the brain contribute to the development of HAND [13]. Some antiretroviral drugs may have adverse neurological effects, increasing the risk of neurodegenerative conditions such as dementia and Parkinson's disease. The restricted penetration of ART into the CNS can result in high viral load in the brain, potentially leading to neurodegeneration [Table 1]. Alzheimer's Disease is a common neurological complication observed in HIV patients, primarily affecting synaptic function and neurodegeneration. Clinical observations of HAND include changes in behavior, forgetfulness, reduced ability to concentrate, slow thinking, depression, tremors, chorea, moment disorder, memory problems, language difficulties, coordination issues, and mood alterations. These symptoms can significantly impact daily activities and overall quality of life. Treatment for HAND may involve antiretroviral therapy to control HIV and reduce brain inflammation. Other treatment options include medications to manage symptoms and therapies to improve cognitive function, such as cognitive behavioral therapy or occupational therapy. Factors affecting the entry of antiretroviral drugs into the CNS include the permeability of the blood-brain barrier, drug solubility, molecule size, transport mechanisms, protein binding capacity, and drug metabolism. Lipid-soluble drugs are more likely to enter the CNS. Some drugs may require active transport mechanisms to cross the BBB and reach the CNS[14]. New drug designs may interact with specific receptors or enzymes in the CNS, facilitating their passage through BBB into the CNS [Table 1].

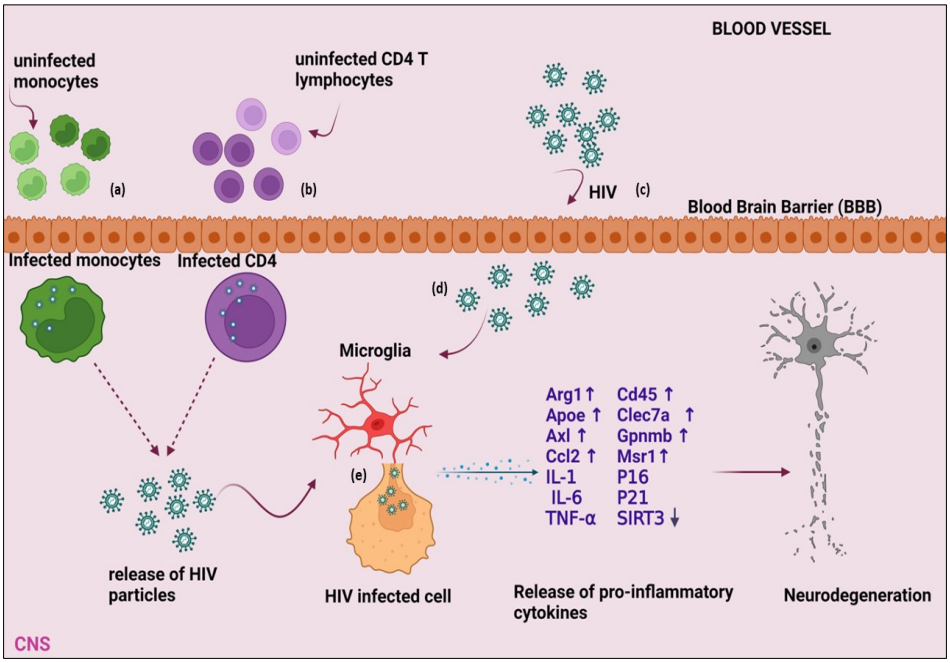

Figure 1: Pathways of HIV Infiltration into CNS and Microglial Infection Figure1: This figure illustrates a comprehensive overview of the potential pathways through which HIV could infiltrate the CNS and infect Microglial cells. (a) HIV may enter the CNS through infected monocytes, (b) infected CD4 T cells, (c) direct penetration by the HIV itself. The diagram also depicts the mechanisms by which HIV can target microglial cells within the CNS. HIV infection of microglia can occur either through (d) direct interaction with HIV (e) the transmission of the virus from infected cells to unaffected microglia in a cell-to-cell manner. Subsequently, the viral presence prompts the release of proinflammatory cytokines from the microglial cells, culminating in a cascade of events leading to neurodegenerative processes.

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Table 1: Penetration of ARVs in the brain

Class of Drugs	Low penetration	Medium penetration	High penetration
Entry/Fusion inhibitors	ENF	RAL	MVC
Integrase strand transfer inhibitor		EVG	DTG
Nucleoside Reverse Transcriptase inhibitor	TDF	3TC D4T	ZDV
		DDI	
		FTC	
		ABC	
Non-nucleoside Reverse Transcriptase inhibitor	ETR	EFV	NVP
			DLV
Protease inhibitor	NFV	APV	
	SQV	IDV	
	TPV	DRV	
	RTV	LPV	
		ATV	
		FPV	

ENF: Enfuvirtide; MVC: Maraviroc; RAL: Raltegravir; EVG: Elvitegravir; ZDV: Zidovudine; 3TC: Lamivudine; D4T: Stavudine; DDI: Didanosine; ABC: Abacavir; TDF: TenofovirDisoproxil Fumarate; FTC: Emtricitabine; EFV: Efavirenz; NVP: Nevirapine; DLV: Delavirdine; ETR: Etravirine; APV: Amprenavir; IDV: Indinavir; DRV: Darunavir; RTV: Ritonavir; LPV: Lopinavir; NFV: Nelfinavir; SQV: Saquinavir; ATV: Atazanavir; FPV: Fosamprenavir; TPV:Tipranavir [15, 16]

Microglial Cells

Microglia, essential cells of the CNS, belong to the myeloid lineage. The average age of human microglial cells is approximately 4.2 years, with some regenerating throughout life [17]. These cells exhibit slower progression compared to other brain cells. These cells play a vital role in supporting CNS development and combating infectious agents. Additionally, it has been seen that microglial cells are involved in neuroinflammation and neurodegenerative diseases, acting as connecting link between the nervous and immune systems. Microglial cells are classified as activated microglia and resting microglia. Both types are ramified cells with multiple branches[18]. Microglial cells express various pattern recognition receptors (PRRs) that detect pathogen-associated patterns (PAMPs) or tissue damage-associated molecular patterns (DAMPs) [19, 20]. Moreover, they also express chemokine receptors like CX3CR1 and CXCR4, as well as integrins such as CD11b and CD11c. Integrins facilitate the migration of microglial cells in the brain and enhance their ability to bind target cells for phagocytosis and elimination[21, 22]. CD11b is consistently expressed, while CD11c is expressed only by activated microglia. Some of the healthy brain's microglial markers include HexB, P2ry12, S100A8, S100A9, Tmem119, Gpr34, SiglecH, TREM2, and Olfml3[23].

Connecting these insights, microglial senescence denotes age-related alterations in these specialized immune cells within the brain. With age, microglia become less efficient at waste clearance and responding to injuries or infections, leading to the generation of detrimental inflammatory molecules. Microglial senescence refers to age-related changes that occur in these specialized immune cells in the brain. Microglial activation is known to protect against viruses and pathogens. However, excessive activation may lead to neuronal damage. Microglial cells interact with astrocytes to maintain homeostasis and inflammation, but this interaction may also contribute to neurodegeneration [23].

Genes responsible for phagocytosis, synaptic pruning, and remodelling, including those coding for chemokine receptors, play crucial roles. Abnormalities in these genes can lead to neurodegeneration [24]. Microglia possess receptors like FC and TOLL-like receptors (TLRs) that protect the host against infectious particles, self-injurious proteins, mutant or oxidized superoxide dismutase (SOD), and more[23]. During this process, neuroinflammatory chemicals are secreted, which may result in neurodegeneration. Any dysfunction in these processes can instigate neurodegeneration. For instance, Alzheimer, one of the most common complications of HAND, is characterized by the formation of Aβ-containing plaques, neurofibrillary tangles comprising intracellular hyperphosphorylated tau protein, and neuronal loss[25]. Microglia play a role in phagocytosing Aβ, but persistent production of Aβ can lead to over-activation of microglia, causing them to secrete proinflammatory cytokines and contribute to neurodegeneration [26-29]. Parkinson's disease, the second most common neurodegenerative disorder, is associated with α-synuclein accumulation. Microglia engulf α-synuclein and degrade, but any defect in this process can lead to an over-accumulation of α-synuclein, leading to

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microglial inflammation [27, 30]. Huntington's disease is caused by a mutation in the HTT gene, resulting in expansion of the trinucleotide CAG stretch. This gene is over-expressed in microglial cells and is associated with changes in microglial function and mRNA profile. The expression of mutated HTT in microglia leads to an increase in proinflammatory cytokines [27, 30, 31].

Role of Microglia in HAND

Microglia-mediated chronic inflammation appears to be a primary driver of cognitive deficits observed in HAND, encompassing impairments in verbal fluency, executive function, learning and memory, and motor function[32]. Notably, the HIV-1 Tat protein has been identified as a key player in activating the NOD-like receptor protein 3 (NLRP3) inflammasome pathway within microglia [33]. This pathway regulates the production of proinflammatory cytokine IL-1β through the activation of caspase-1. The activation of NLRP3 involves two steps: priming, characterized by increased levels of pro-IL-1β, followed by caspase-1-mediated cleavage and activation of IL-1β for secretion from microglia [33]. This process downregulates the NLRP3 regulator miR-223, facilitating Tat-induced microglial inflammasome activation and contributing to HAND pathology. Furthermore, the activation of NLRP3 in human microglia exposed to HIV-specific GU-rich single-stranded RNA amplifies the production of proinflammatory cytokines, neurotoxic cytokines, and complement components, including TNF-α, IL-1α, and C1q [34]. The release of these cytokines from activated microglia leads to increased cytotoxicity and cell death in human primary neurons. [35]. This disruption of mitophagy heightens caspase-1 activity, thereby mediating neurodegeneration and cognitive deficits in HIV-infected individuals [36]. Microglia-associated neurodegeneration in the context of HIV infection involves a multifaceted interplay of signaling pathways, cytokines, and HIV proteins within the CNS. Microglia, the resident immune cells of the CNS, undergo activation in response to HIV infection, adopting various phenotypes that can range from neuroprotective to neurotoxic. This activation involves key signaling pathways such as NF-κB, MAPK, and PI3K/Akt, which regulate the expression of pro-inflammatory mediators [37]. Pro-inflammatory cytokines: IL-1β, IL-6, TNF-α, TNFα receptor i.e TNFRSF1A are upregulated with HIV infection while Casp1, Transcripts associated with M2 activation, including Csf1, Sod1, Sod2 are downregulated [38] . Dysregulation of cytokine networks, including TNF-α, IL-1β, IL-6, IL-8, IL-10, and IFN-γ contributes to sustained neuroinflammation and neurodegeneration [39]. HIV and its proteins, including Tat, gp120, and Vpr, directly impact microglial function and neuronal health [40]. Tat enhances viral replication and induces pro-inflammatory cytokine production, while gp120 binds to chemokine receptors, leading to neuronal injury. Vpr induces cell cycle arrest and apoptosis in infected and neighburing cells. Collectively, these viral proteins disrupt mitochondrial function, promote apoptosis, and contribute to synaptic dysfunction, ultimately leading to neuronal damage and cognitive impairment. Understanding the intricate interactions between HIV infection, microglial activation, and neuroinflammation is critical for developing targeted therapeutic strategies aimed at mitigating neurodegenerative processes in individuals living with HIV.

Latency in HIV infection involves the virus remaining inactive within host cells, eluding detection and therapy. This latency manifests at pre-integration and post-integration stages, shaped by intricate interactions between viral and host factors. During pre-integration latency, HIV-1 RNA undergoes reverse transcription but struggles with integration into the host genome, forming the pre-integration complex (PIC) [41]. Poor reverse transcription efficiency and constraints on PIC nuclear transport contribute to this latency, as does the action of host restriction factors (RFs) like APOBEC3, SAMHD1, and MX2, which impede viral replication through various mechanisms [42]. HIV-1 accessory proteins like Vif and Vpx counteract these RFs to promote viral replication[42-44]. Post-integration latency ensues after viral DNA integrates into host chromatin, characterized by silenced HIV-1 gene expression [45]. Epigenetic modifications and transcriptional and post-transcriptional gene silencing mechanisms contribute to this state, maintaining viral dormancy despite integration [46, 47]. Understanding these latency mechanisms is pivotal to target and eradicate latent HIV reservoirs.

Models for studying Microglial cells in vitro

Models are essential for studying microglial cells due to the complexity of the brain's microenvironment and the intricate interactions involved. Direct observation and manipulation of microglia in the human brain is challenging. Thus, models provide controlled environments where researchers can investigate microglial functions, responses, and interactions with other cell types, helping to uncover insights into their role in various neurological conditions and potential therapeutic interventions. There are several model systems available for studying microglial cells in vitro, including.

Primary microglia cultures

Microglia can be isolated from the brains of neonatal or adult mice or rats and grown in culture[48]. These cultures allow for the study of microglia in a relatively pure population. Both human and rodent primary microglia cultures share similarities, with the distinction that human cultures originate from human brain tissue, while rodent cultures are sourced from rodent brain tissue [49]. The process of preparing human primary microglia cultures is more challenging due to the limited availability of human brain tissue and the difficulty of obtaining viable microglial cells from adult human brain

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tissue. The most common source of human brain tissue for primary microglia cultures is the post-mortem brain tissue of individuals who have willingly donated their brains for scientific research [50]. Human primary microglia cultures are important tools for studying the role of microglia in human brain development, function, and disease. They can be used to investigate the cellular and molecular mechanisms underlying neuroinflammatory responses in human brain tissue, as well as the effects of various therapeutic agents on microglial activity in human disease states [51, 52].

Cell lines

Microglial cell lines, sourced from microglial tumors, provide distinct benefits compared to primary microglial cultures [Table 2]. These advantages encompass an inexhaustible cell supply, simplified upkeep, and consistent reproducibility. Immortalized cell lines, while invaluable for biomedical research, are not without limitations. Continuous culturing can lead to genetic drift, resulting in mutations that may compromise experimental reliability. Loss of differentiation limits their utility for certain studies, and susceptibility to contamination or cross-contamination can hamper the results. Additionally, heterogeneity within cell cultures can confound interpretations, and altered physiology may deviate from in vivo behavior. Furthermore, dependency on specific culture conditions adds another layer of complexity.

Organotypic slice cultures

Organotypic brain slice cultures (BSCs) have emerged in 1981 as a valuable ex vivo model for studying the cellular and molecular complexity of the CNS [68]. These cultures retain a three-dimensional organization and anatomical connectivity, making them suitable for maintaining the CNS's anatomical integrity. Unlike isolated primary brain cell cultures, BSCs contain a representative mix of neuronal and non-neuronal cells, including glia and vascular cells, much similar to what is observed in vivo [69]. One of the main advantages of BSCs is that they mimic the development of cells and synapses in the brain as they would in vivo [69]. This allows researchers to study the developmental changes in cell structure, connectivity, and neuronal function. Additionally, BSCs have been used as an alternative to some in vivo experiments, reducing the number of animals required and enabling the investigation of multiple variables from a single animal. BSCs can be easily manipulated, allowing researchers to add compounds, viral tools, or other agents directly onto the slices or into the culture medium. Since BSCs lack a blood-brain barrier, they provide direct access to target engagement studies [70]. Furthermore, advanced techniques, such as long-term live imaging and electrophysiology, can be applied to BSCs, making them versatile for various experimental studies. Research studies using BSCs have contributed to our understanding of CNS proteinopathies and neurodegenerative diseases. Researchers have used recombinant adeno-

Table 2: Microglial cell lines used for invitro studies.

Species	Cell line	Immortalization methods	Reference
Human	HM06	Oncogene-Induced Immortalization (v-myc)	Nagaietal.,2001 [53]
	HMC3	SV40-dependent immortalization of human microglial cells	Janabietal.,1995[54]
	Huμglia	SV40-dependent immortalization of human microglial cells (and hTERT)	Garcia-Mesaetal.,2017[55]
	CHME-5	SV40-dependent immortalization of human microglial cells	Janabietal.,1995[54]
Mouse	BV2	Transformed, v-raf/v-myc oncogene	Blasietal.,1990[56]
	C8-B4	Naturally Immortalized Cells	Alliotetal.,1996[57]
	IMG	Transformed, v-raf/v-myc -myc oncogene	McCarthyetal.,2016[58]
	EOC-2,EOC-13.31, EOC-20	Spontaneous, M-CSF-dependentclones oncogene	Walkeretal.,1995[59]
	MG5	Transformed, p53-Deficient Microglial Transformation	Ohsawaetal.,1997[60]
	MG6	Oncogene-Induced Immortalization (v-myc)	Takenouchietal.,2005[61]
	MG20	Oncogene-Induced Immortalization (v-myc)	Iwamaruetal.,2007[62]
	N3,N9,N11,N13	Transformed,v-mycor v-miloncogenes,clones	Righietal.,1989[63]
	Muμglia	Transformed,SV40large T antigen(and hTERT)	Garcia-Mesaetal.,2017[55]
	RA2	Non-enzymatic and non-virustransformed, GM-CSF-dependent	Sawadaetal.,1998[64]
	SIM-A9	Naturally Immortalized Cells	Nagamoto-Combs etal.,2014 [65]
Rat	HAPI	Naturally Immortalized Cells	Cheepsunthometal.,2001 [66]
	MLS-9	Naturally Immortalized Cells	Zhouetal.,1998 [67]
Macaque	Mqμglia	SV40-dependent immortalization of human microglial cells (and hTERT)	Garcia-Mesaetal.,2017[55]

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associated viral (rAAV) vectors to transduce and model neurodegenerative pathologies in these cultures, leading to promising results [69].

BSCs serve as valuable experimental models for studying neurodegenerative proteinopathies, but they have certain limitations that researchers should be aware of when interpreting results. One major drawback is their limited predictive value about subsequent in vivo studies, with only a few examples of BSC findings being later validated in vivo or corroborating previous in vivo results. Another challenge lies in their moderate throughput capabilities, making it difficult to screen a large number of experimental manipulations simultaneously unless automation is improved. Additionally, BSC models are derived from rodent brain tissue, which may not fully capture the complexity of human neurodegenerative diseases, limiting the direct translatability of findings to human conditions due to species differences [71]. Many BSC models rely on the over-expression of human genes, including wild-type or mutant alleles, which may not accurately reflect the natural disease processes and can introduce non-physiological confounds. The use of 25% horse serum in BSC culture can also impact experimental outcomes, and variations in serum composition between different lots may introduce confounding factors[72]. As technology continues to advance, BSCs hold the potential to accelerate our understanding of CNS diseases and aid in the development of novel therapeutic strategies. While they are valuable tools for generating initial insights and hypotheses, further validation through in vivo studies is crucial to confirm findings. Efforts to refine and improve BSC models in the future may enhance their utility in the study of central nervous system diseases[73].

Monocyte and Induced pluripotent stem cells (iPSC)-derived microglia

Monocyte-derived microglia have been widely used as an alternative to primary microglia that is difficult to obtain and maintain in culture. In vitro, conversion of monocytes into microglia-like cells involves a stepwise process designed to mimic the transformation that occurs within the CNS. Isolating monocytes from peripheral blood and placing them in a controlled culture environment with a specialized growth medium. This medium contains factors like granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), Beta nerve growth factor (βNGF), Monocyte chemoattractant protein-1(CCL2) that induce monocyte differentiation into microglia-like cells [74]. Over several days, the monocytes change morphology and gene expression, adopting features reminiscent of microglia found in the brain. The conversion of monocytes to microglia can be assessed by upregulation of microglial-specific markers like CD11b, CD68, Iba1, and purinergic receptor (P2RY12) and downregulation of monocyte-specific markers like CD14+, CD45+ [74-76]. This analysis ensures that the cells are indeed differentiating into a microglia-like phenotype. Once the microglia-like characteristics are established, functional studies can be carried out by exposing these cells to various stimuli and replicating inflammatory conditions or disease-related factors [77]. This enables scientists to explore how these microglia-like cells respond and contribute to processes like neuroinflammation or neuroprotection.

iPSC-derived human microglia can be generated by differentiating iPSC into cells that have a similar gene expression profile and functional properties as primary microglia [78]. The utilization of iPSC-derived human microglia has emerged as a transformative approach in neurobiology and regenerative medicine, offering novel insights into neuroinflammatory processes and neurodegenerative diseases. By faithfully mirroring native human microglia characteristics, these cells offer a unique window into neuroinflammation and neurodegenerative diseases. Overall, these model systems provide valuable tools for understanding microglial biology and its role in neurological diseases.

Limitations or challenges for studying microglia

Studying microglia is essential for understanding their role in maintaining brain health, neuroinflammation, and various neurological diseases. However, one must understand several challenges and limitations associated with microglial models. Microglia, as a cell population, display remarkable diversity and heterogeneity. Their morphologies, densities, and functions are notably varied and contingent on their specific brain locale and the stimuli they encounter. This intricate variability makes it difficult to formulate sweeping conclusions about microglia behavior. Moreover, their restricted localization within the brain and spinal cord, shielded by the blood-brain barrier, limits in vivo study accessibility, necessitating specialized techniques for accurate isolation and analysis. The dynamic nature of microglia, rapidly altering their morphology and function in response to stimuli poses difficulties in capturing real-time behavior, potentially deviating from their true in vivo state [79]. Despite numerous microglial markers, lacking a singular exclusive marker can lead to misidentification or contamination during experiments [80]. Precisely defining microglial functions in healthy and diseased brains is hindered by challenges in selective targeting and manipulation in vivo. Ethical considerations and limited access to human brain samples for microglial studies, along with the potential discrepancy of post-mortem samples in representing ongoing diseases, further complicate the research. Species-specific differences in microglial behaviour impede the straightforward translation of findings from animal models to human conditions[23]. Inadequate representation of the complex in vivo microglial

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environment in traditional in vitro models limits their fidelity in replicating microglial behaviour and responses. With substantial progress, the intricate roles of microglia in various neurological conditions remain incompletely understood, underscoring the need for further comprehensive research [81]. Despite these challenges, researchers continue to make strides in microglial research, utilizing innovative techniques and collaborative efforts to better comprehend these vital cells and their impact on brain health and disease.

Future Perspectives for HIV Neurodegeneration: Nurturing Microglial Insights for Advancing Neurodegenerative Disease Therapies

To achieve a complete cure for HIV, it is crucial not only to focus on targeting CD4 cells but also on reservoirs like microglial cells. Recent studies have highlighted that microglial cells secrete specific cytokines and chemokines responsible for neurodegeneration. As HIV primarily enters the brain through infected monocytes and CD4 T cells, it is imperative to develop strategies to prevent the entry of these infected cells into the CNS. Enhancing the permeability of ART drugs in the brain can slow down the progression of CNS infection. Looking ahead, identifying HIV at an early stage and optimizing combination antiretroviral therapy to reduce neurotoxicity is crucial. It is now understood that HIV does not directly cause neurotoxicity or neurodegeneration; rather, it targets microglial cells in the CNS, which subsequently release harmful chemicals or ROS contributing to neurodegeneration. Understanding the roles of microglia in neurodegeneration and investigating the pathways that regulate their response to injury, including neuroprotective immune checkpoint pathways, are vital to keep the microglial proinflammatory response in check. New advancements should be made to target these factors and thus reduce the severity of neurodegeneration. In a distinct line of research, RK-33, an inhibitor of Dead Box RNA Helicase 3 (DDX3), was identified through an AI-based literature mining system called MOLIERE as a potential therapeutic target for HAND [82]. RK-33 demonstrates promise in reducing microglial activation and neuronal death in rodent primary cortical cell cultures treated with Tat, suggesting a potential avenue for mitigating Tat-induced toxicity by targeting DDX3. These findings collectively underscore the interplay between microglial dysfunction, inflammasome activation, mitochondrial damage, and neurodegeneration in the context of HAND, offering new insights for combating this critical condition. It is also important to develop improved in-vitro models of microglial cells for accurate interpretations. Currently, primary microglial cells or monocyte-derived microglial cells are widely used for research, and efforts are ongoing to develop such models for patients suffering from neurodegeneration. These advancements are critical steps towards harnessing the potential of microglia for the treatment of neurodegenerative diseases. By understanding their intricate functions and their role in neurodegeneration, we can pave the way for more effective therapeutic strategies in the future.

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