Virus and Accelerated Brain Aging

Subjects: Neurosciences

Contributor: Alexey LARIONOV

Accelerated brain aging is often related to enhanced neurodegeneration, which includes loss of neuronal cell structure and function due to (1) metabolic changes, (2) neuronal cell death (3) decline in the neuronal network, (4) neuronal functional deficiency, (5) decline in neuronal regeneration, or (6) a combination of the mentioned reasons. It also includes functional and structural changes of the glial cells, resulting in demyelination and gliosis. Neurodegeneration is aggravated by neuroinflammation, which contributes substantially to accelerated brain aging. Neuroinflammation usually correlates with the activation of microglia, the resident macrophages and innate immune cells of the brain.

brain aging microglia neuroinflammation neurotropic virus HIV flavivirus SARS-CoV-2 human herpes virus

1. Overview

Microglia are the resident immune cells of the central nervous system contributing substantially to health and disease. There is increasing evidence that inflammatory microglia may induce or accelerate brain aging, by interfering with physiological repair and remodeling processes. Many viral infections affect the brain and interfere with microglia functions, including human immune deficiency virus, flaviviruses, SARS-CoV-2, influenza, and human herpes viruses. Especially chronic viral infections causing low-grade neuroinflammation may contribute to brain aging. This review elucidates the potential role of various neurotropic viruses in microglia-driven neurocognitive deficiencies and possibly accelerated brain aging.

2. Brain Aging

Aging is a programmed biological process, affecting all biological systems, controlled by genetic [1] and epigenetic mechanisms [2], and influenced by environmental factors [3][4]. The principles of aging apply also to humans [5], to all organ systems and to the brain [6]. Physiological aging of the healthy brain is an age-dependent biological process and consists of deterioration of structure and function [7][8][9][10][11][12]. However, brain aging can be accelerated by multiple factors, due to traumatic events [13][14], following neurovascular conditions [15][16][17], or related to specific brain diseases, including Alzheimer's and Parkinson's disease. Accelerated brain aging is often related to enhanced neurodegeneration, which includes loss of neuronal cell structure and function due to (1) metabolic changes [18], (2) neuronal cell death [19] (3) decline in the neuronal network [20], (4) neuronal functional deficiency [21], (5) decline in neuronal regeneration [22][23][24], or (6) a combination of the mentioned reasons. It also

includes functional and structural changes of the glial cells, resulting in demyelination and gliosis [25][26][27]. Neurodegeneration is aggravated by neuroinflammation, which contributes substantially to accelerated brain aging. Neuroinflammation usually correlates with the activation of microglia, the resident macrophages and innate immune cells of the brain [28][29]. Thus, the role of microglia in neuroinflammation and brain aging will be explored. Neuroinflammation is often induced by viral infections culminating in encephalitis, which is an inflammatory process of the brain that usually involves the microcirculation, neurons and glia cells, including microglia, as well as infiltration of brain tissue by other cells of the innate and acquired immune system like monocytes, dendritic cells, granulocytes and various subpopulations of T lymphocytes [30][31][32][33]. Encephalitis can be mild, with reversible functional deficiencies, but it can also result in severe structural damage with corresponding functional defects and sequelae [34]. Viruses that affect the brain and may contribute to accelerated brain aging will be reviewed. Finally, the role of microglia in viral brain infections and corresponding accelerated aging of the brain will be unfolded [35].

3. Neuroinflammation in Brain Aging

Neuroinflammation relates to a pathological immune response in the brain. It can be sudden and excessive, or subliminal, as well as short-lived or chronic. It may include a cellular immune response of the innate [36] and/or the acquired immune system [37], as well as humoral (antibodies) [38] and soluble factors (chemokines, cytokines) [39][40][41]. It certainly includes general basic cellular responses to inflammatory inducers and mediators (toxins, microbial products, metabolic or other damage-related cellular molecules), recognized by corresponding receptors, i.e., Pattern Recognition Receptors (PRRs) for Pathogen-Associated Molecular Patterns (PAMP) and/or Damage-Associated Molecular Patterns (DAMP) [42][43][44][45][46]. In that respect, all cells of the brain may respond to inflammatory signals, including neurons, astrocytes, oligodendrocytes, microglia, and the cells of the blood vessels (endothelial cells, pericytes, myofibroblasts, vascular dendritic cells, etc.) and the meninges.

There is increasing evidence that the aging immune system is skewed towards a more inflammatory status, increasing the probability and intensity of neuroinflammation [47][48][49]. In addition, a strong systemic inflammatory immune response may influence the brain function and cause corresponding syndromes and disease, as well as induce or aggravate neuroinflammation [50][51][52].

Neuroinflammation interferes with the brain function, may cause structural damage, influence regeneration, and modulate remodeling. It may induce neuronal cell death directly by acting on neurons, or indirectly through actions via astrocytes, oligodendrocytes and microglia, mediated by various neural and inflammatory factors [25][53]. Neuroinflammation and its consequences contribute to physiological brain aging and certainly enhances and accelerates the aging process [19][54]. Neuroinflammation has been shown to contribute to Alzheimer's and Parkinson's disease [29][55][56]. It may also play a role in certain psychiatric diseases, including depression, schizophrenia, autism spectrum disorders, etc., some with increasing incidence in aged individuals [57][58][59][60][61].

A plenitude of inflammatory cytokines may contribute to neuroinflammation and its pathological consequences in the brain, including interferons, interleukin-1, 6, 17, 23, and 34, tumor necrosis factor and related cytokines and receptors [62][63][64][65][66][67][68][69][70]. Interestingly, there is evidence that certain cytokines may affect specific brain

regions or functional structures. For example, interferon-gamma has been correlated with effects in the hippocampus, where decreased neurogenesis and neuronal apoptosis has been shown in a mouse model [71], whereas interleukin-6 has been shown to disrupt synaptic plasticity [72]. The inflammatory cytokines may enter the brain from the blood circulation through the disrupted blood–brain barrier, or may be produced by infiltrating immune cells, as well as by the local immune cells, i.e., the microglia.

4. Conclusions

The more we age, the more our immune system gets toward a more inflammatory status. The increased systemic inflammatory immune status also affects microglia, resulting in decreased physiological neuroregeneration and remodeling [49][73]. The inflammatory status is certainly enhanced and accelerated through frequent or chronic viral infections. The increased and chronic inflammatory status in the brain may contribute to neurodegeneration due to increased neuronal cell death and reduced neurogenesis, reduced remodeling and irreparable damage to the neuronal network, resulting in an enhanced or accelerated brain aging process. In the context of microglia and viral infection, most research has been done in HIV, where the association has been shown for neurocognitive decline [74][75][76][77]. However, there is little information available about the cellular and molecular mechanisms that contribute to or influence the chronic HIV infection and corresponding involvement of microglia, which requires more future research. The same accounts for other viruses, including flaviviruses, human herpes viruses and SARS-CoV-2.

References

1. Foo, H.; Mather, K.A.; Jiang, J.; Thalamuthu, A.; Wen, W.; Sachdev, P.S. Genetic influence on ageing-related changes in resting-state brain functional networks in healthy adults: A systematic review. Neurosci. Biobehav. Rev. 2020, 113, 98–110.
2. Delgado-Morales, R.; Agís-Balboa, R.C.; Esteller, M.; Berdasco, M. Epigenetic mechanisms during ageing and neurogenesis as novel therapeutic avenues in human brain disorders. Clin. Epigenet. 2017, 9, 67.
3. Palmer, A.L.; Ousman, S.S. Astrocytes and Aging. Front. Aging Neurosci. 2018, 10, 337.
4. Vaiserman, A.M.; Koliada, A.K.; Jirtle, R.L. Non-genomic transmission of longevity between generations: Potential mechanisms and evidence across species. Epigenet. Chromatin 2017, 10, 38.
5. Ostojic, S.; Pereza, N.; Kapovic, M. A Current Genetic and Epigenetic View on Human Aging Mechanisms. Coll. Antropol. 2009, 2009, 687–699.
6. Lupo, G.; Gaetani, S.; Cacci, E.; Biagioni, S.; Negri, R. Molecular Signatures of the Aging Brain: Finding the Links Between Genes and Phenotypes. Neurotherapeutics 2019, 16, 543–553.

7. Beck, D.; de Lange, A.-M.G.; Maximov, I.I.; Richard, G.; Andreassen, O.A.; Nordvik, J.E.; Westlye, L.T. White matter microstructure across the adult lifespan: A mixed longitudinal and cross-sectional study using advanced diffusion models and brain-age prediction. Neuroimage 2021, 224, 117441.
8. Cox, S.R.; Harris, M.A.; Ritchie, S.J.; Buchanan, C.R.; Valdés Hernández, M.C.; Corley, J.; Taylor, A.M.; Madole, J.W.; Harris, S.E.; Whalley, H.C.; et al. Three major dimensions of human brain cortical ageing in relation to cognitive decline across the eighth decade of life. Mol. Psychiatry 2021.
9. Fu, T.; Kobeleva, X.; Bronzlik, P.; Nösel, P.; Dadak, M.; Lanfermann, H.; Petri, S.; Ding, X.-Q. Clinically Applicable Quantitative Magnetic Resonance Morphologic Measurements of Grey Matter Changes in the Human Brain. Brain Sci. 2021, 11, 55.
10. Hrybouski, S.; Cribben, I.; McGonigle, J.; Olsen, F.; Carter, R.; Seres, P.; Madan, C.R.; Malykhin, N.V. Investigating the effects of healthy cognitive aging on brain functional connectivity using 4.7 T resting-state functional magnetic resonance imaging. Brain Struct. Funct. 2021.
11. Lin, H.-Y.; Huang, C.-C.; Chou, K.-H.; Yang, A.C.; Lo, C.-Y.Z.; Tsai, S.-J.; Lin, C.-P. Differential Patterns of Gyral and Sulcal Morphological Changes During Normal Aging Process. Front. Aging Neurosci. 2021, 13, 625931.
12. Zhang, Y.; Wang, Y.; Chen, N.; Guo, M.; Wang, X.; Chen, G.; Li, Y.; Yang, L.; Li, S.; Yao, Z.; et al. Age-Associated Differences of Modules and Hubs in Brain Functional Networks. Front. Aging Neurosci. 2020, 12, 607445.
13. Breunig, J.J.; Guillot-Sestier, M.-V.; Town, T. Brain injury, neuroinflammation and Alzheimer's disease. Front. Aging Neurosci. 2013, 5, 26.
14. DeKosky, S.T.; Asken, B.M. Injury cascades in TBI-related neurodegeneration. Brain Inj. 2017, 31, 1177–1182.
15. Beishon, L.; Clough, R.H.; Kadicheeni, M.; Chithiramohan, T.; Panerai, R.B.; Haunton, V.J.; Minhas, J.S.; Robinson, T.G. Vascular and haemodynamic issues of brain ageing. Pflug. Arch. 2021, 1–17.
16. Hort, J.; Vališ, M.; Kuča, K.; Angelucci, F. Vascular Cognitive Impairment: Information from Animal Models on the Pathogenic Mechanisms of Cognitive Deficits. Int. J. Mol. Sci. 2019, 20, 2405.
17. Winder, N.R.; Reeve, E.H.; Walker, A.E. Large artery stiffness and brain health: Insights from animal models. Am. J. Physiol. Heart Circ. Physiol. 2021, 320, H424–H431.
18. Noori, A.; Mezlini, A.M.; Hyman, B.T.; Serrano-Pozo, A.; Das, S. Systematic review and meta-analysis of human transcriptomics reveals neuroinflammation, deficient energy metabolism, and proteostasis failure across neurodegeneration. Neurobiol. Dis. 2021, 149, 105225.

19. Landfield, P.W.; Thibault, O.; Mazzanti, M.L.; Porter, N.M.; Kerr, D.S. Mechanisms of neuronal death in brain aging and Alzheimer's disease: Role of endocrine-mediated calcium dyshomeostasis. J. Neurobiol. 1992, 23, 1247–1260.
20. Vecchio, F.; Miraglia, F.; Maria Rossini, P. Connectome: Graph theory application in functional brain network architecture. Clin. Neurophysiol. Pract. 2017, 2, 206–213.
21. Schlachetzki, J.C.M.; Toda, T.; Mertens, J. When function follows form: Nuclear compartment structure and the epigenetic landscape of the aging neuron. Exp. Gerontol. 2020, 133, 110876.
22. Beckervordersandforth, R.; Rolando, C. Untangling human neurogenesis to understand and counteract brain disorders. Curr. Opin. Pharmacol. 2020, 50, 67–73.
23. Jinno, S. Aging affects new cell production in the adult hippocampus: A quantitative anatomic review. J. Chem. Neuroanat. 2016, 76, 64–72.
24. Vasic, V.; Barth, K.; Schmidt, M.H.H. Neurodegeneration and Neuro-Regeneration-Alzheimer's Disease and Stem Cell Therapy. Int. J. Mol. Sci. 2019, 20, 4272.
25. Yang, Q.-Q.; Zhou, J.-W. Neuroinflammation in the central nervous system: Symphony of glial cells. Glia 2019, 67, 1017–1035.
26. Verkerke, M.; Hol, E.M.; Middeldorp, J. Physiological and Pathological Ageing of Astrocytes in the Human Brain. Neurochem. Res. 2021.
27. Rivera, A.D.; Chacon-De-La-Rocha, I.; Pieropan, F.; Papanikolau, M.; Azim, K.; Butt, A.M. Keeping the ageing brain wired: A role for purine signalling in regulating cellular metabolism in oligodendrocyte progenitors. Pflug. Arch. 2021.
28. Rodríguez-Gómez, J.A.; Kavanagh, E.; Engskog-Vlachos, P.; Engskog, M.K.R.; Herrera, A.J.; Espinosa-Oliva, A.M.; Joseph, B.; Hajji, N.; Venero, J.L.; Burguillos, M.A. Microglia: Agents of the CNS Pro-Inflammatory Response. Cells 2020, 9, 1717.
29. Webers, A.; Heneka, M.T.; Gleeson, P.A. The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease. Immunol. Cell Biol. 2020, 98, 28–41.
30. Marosova, L.; Neradil, P.; Zilka, N. How can viruses influence the neuroinflammation and neurodegeneration in the aged human brain. Acta Virol. 2013, 2013, 273–281.
31. Abdullahi, A.M.; Sarmast, S.T.; Jahan, N. Viral Infections of the Central Nervous System in Children: A Systematic Review. Cureus 2020, 12, e11174.
32. Rezaei, S.J.; Mateen, F.J. Encephalitis and meningitis in Western Africa: A scoping review of pathogens. Trop. Med. Int. Health 2021, 26, 388–396.

33. Yuan, J.; Yang, S.; Wang, S.; Qin, W.; Yang, L.; Hu, W. Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) in adults-a case report and literature review. BMC Neurol. 2017, 17, 103.
34. Khandaker, G.; Jung, J.; Britton, P.N.; King, C.; Yin, J.K.; Jones, C.A. Long-term outcomes of infective encephalitis in children: A systematic review and meta-analysis. Dev. Med. Child Neurol. 2016, 58, 1108–1115.
35. Chhatbar, C.; Prinz, M. The roles of microglia in viral encephalitis: From sensome to therapeutic targeting. Cell. Mol. Immunol. 2021, 18, 250–258.
36. Shemer, A.; Jung, S. Differential roles of resident microglia and infiltrating monocytes in murine CNS autoimmunity. Semin. Immunopathol. 2015, 37, 613–623.
37. Batterman, K.V.; Cabrera, P.E.; Moore, T.L.; Rosene, D.L. T Cells Actively Infiltrate the White Matter of the Aging Monkey Brain in Relation to Increased Microglial Reactivity and Cognitive Decline. Front. Immunol. 2021, 12, 607691.
38. Gagnon, M.-M.; Savard, M. Limbic Encephalitis Associated with GAD65 Antibodies: Brief Review of the Relevant literature. Can. J. Neurol. Sci. 2016, 43, 486–493.
39. Sonar, S.; Lal, G. Role of Tumor Necrosis Factor Superfamily in Neuroinflammation and Autoimmunity. Front. Immunol. 2015, 6, 364.
40. Viviani, B.; Boraso, M. Cytokines and neuronal channels: A molecular basis for age-related decline of neuronal function? Exp. Gerontol. 2011, 46, 199–206.
41. Zuena, A.R.; Casolini, P.; Lattanzi, R.; Maftei, D. Chemokines in Alzheimer’s Disease: New Insights into Prokineticins, Chemokine-Like Proteins. Front. Pharmacol. 2019, 10, 622.
42. Singh, H.; Koury, J.; Kaul, M. Innate Immune Sensing of Viruses and Its Consequences for the Central Nervous System. Viruses 2021, 13, 170.
43. Keogh, C.E.; Rude, K.M.; Gareau, M.G. Role of pattern recognition receptors and the microbiota in neurological disorders. J. Physiol. 2021, 599, 1379–1389.
44. Guan, Y.; Han, F. Key Mechanisms and Potential Targets of the NLRP3 Inflammasome in Neurodegenerative Diseases. Front. Integr. Neurosci. 2020, 14, 37.
45. Chiarini, A.; Armato, U.; Hu, P.; Dal Prà, I. Danger-Sensing/Patten Recognition Receptors and Neuroinflammation in Alzheimer’s Disease. Int. J. Mol. Sci. 2020, 21, 9036.
46. Balança, B.; Desmurs, L.; Grelier, J.; Perret-Liaudet, A.; Lukaszewicz, A.-C. DAMPs and RAGE Pathophysiology at the Acute Phase of Brain Injury: An Overview. Int. J. Mol. Sci. 2021, 22, 2439.
47. Aiello, A.; Farzaneh, F.; Candore, G.; Caruso, C.; Davinelli, S.; Gambino, C.M.; Ligotti, M.E.; Zareian, N.; Accardi, G. Immunosenescence and Its Hallmarks: How to Oppose Aging

Strategically? A Review of Potential Options for Therapeutic Intervention. Front. Immunol. 2019, 10, 2247.

48. Bruce, M.; Streifel, K.M.; Boosalis, C.A.; Heuer, L.; González, E.A.; Li, S.; Harvey, D.J.; Lein, P.J.; van de Water, J. Acute peripheral immune activation alters cytokine expression and glial activation in the early postnatal rat brain. J. Neuroinflamm. 2019, 16, 200.
49. De Maeyer, R.P.H.; Chambers, E.S. The impact of ageing on monocytes and macrophages. Immunol. Lett. 2021, 230, 1–10.
50. Azhari, H.; Swain, M.G. Role of Peripheral Inflammation in Hepatic Encephalopathy. J. Clin. Exp. Hepatol. 2018, 8, 281–285.
51. Badal, V.D.; Vaccariello, E.D.; Murray, E.R.; Yu, K.E.; Knight, R.; Jeste, D.V.; Nguyen, T.T. The Gut Microbiome, Aging, and Longevity: A Systematic Review. Nutrients 2020, 12, 3759.
52. Costello, H.; Gould, R.L.; Abrol, E.; Howard, R. Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. BMJ Open 2019, 9, e027925.
53. Li, L.; Acioglu, C.; Heary, R.F.; Elkabes, S. Role of astroglial toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. Brain Behav. Immun. 2021, 91, 740–755.
54. Mishra, R.; Banerjea, A.C. Neurological Damage by Coronaviruses: A Catastrophe in the Queue! Front. Immunol. 2020, 11, 565521.
55. Pajares, M.; Rojo, A.I.; Manda, G.; Boscá, L.; Cuadrado, A. Inflammation in Parkinson’s Disease: Mechanisms and Therapeutic Implications. Cells 2020, 9, 1687.
56. Sánchez-Sarasúa, S.; Fernández-Pérez, I.; Espinosa-Fernández, V.; Sánchez-Pérez, A.M.; Ledesma, J.C. Can We Treat Neuroinflammation in Alzheimer’s Disease? Int. J. Mol. Sci. 2020, 21, 8751.
57. Liao, X.; Liu, Y.; Fu, X.; Li, Y. Postmortem Studies of Neuroinflammation in Autism Spectrum Disorder: A Systematic Review. Mol. Neurobiol. 2020, 57, 3424–3438.
58. Nagy, E.E.; Frigy, A.; Szász, J.A.; Horváth, E. Neuroinflammation and microglia/macrophage phenotype modulate the molecular background of post-stroke depression: A literature review. Exp. Ther. Med. 2020, 20, 2510–2523.
59. De Picker, L.J.; Morrens, M.; Chance, S.A.; Boche, D. Microglia and Brain Plasticity in Acute Psychosis and Schizophrenia Illness Course: A Meta-Review. Front. Psychiatry 2017, 8, 238.
60. Troubat, R.; Barone, P.; Leman, S.; Desmidt, T.; Cressant, A.; Atanasova, B.; Brizard, B.; El Hage, W.; Surget, A.; Belzung, C.; et al. Neuroinflammation and depression: A review. Eur. J. Neurosci. 2021, 53, 151–171.

61. van Mierlo, H.C.; Schot, A.; Boks, M.P.M.; de Witte, L.D. The association between schizophrenia and the immune system: Review of the evidence from unbiased ‘omic-studies’. Schizophr. Res. 2020, 217, 114–123.
62. Bobbo, V.C.D.; Jara, C.P.; Mendes, N.F.; Morari, J.; Velloso, L.A.; Araújo, E.P. Interleukin-6 Expression by Hypothalamic Microglia in Multiple Inflammatory Contexts: A Systematic Review. Biomed. Res. Int. 2019, 2019, 1365210.
63. Chen, J.; Liu, X.; Zhong, Y. Interleukin-17A: The Key Cytokine in Neurodegenerative Diseases. Front. Aging Neurosci. 2020, 12, 566922.
64. He, J.-J.; Sun, F.-J.; Wang, Y.; Luo, X.-Q.; Lei, P.; Zhou, J.; Zhu, D.; Li, Z.-Y.; Yang, H. Increased expression of interleukin 17 in the cortex and hippocampus from patients with mesial temporal lobe epilepsy. J. Neuroimmunol. 2016, 298, 153–159.
65. Katayama, H. Anti-interleukin-17A and anti-interleukin-23 antibodies may be effective against Alzheimer′s disease: Role of neutrophils in the pathogenesis. Brain Behav. 2020, 10, e01504.
66. Liu, G.; Guo, J.; Liu, J.; Wang, Z.; Liang, D. Toll-like receptor signaling directly increases functional IL-17RA expression in neuroglial cells. Clin. Immunol. 2014, 154, 127–140.
67. Sommer, A.; Marxreiter, F.; Krach, F.; Fadler, T.; Grosch, J.; Maroni, M.; Graef, D.; Eberhardt, E.; Riemenschneider, M.J.; Yeo, G.W.; et al. Th17 Lymphocytes Induce Neuronal Cell Death in a Human iPSC-Based Model of Parkinson’s Disease. Cell Stem Cell 2018, 23, 123–131.e6.
68. Soytürk, H.; Yılmaz, M. A comparison of IL-17 and IL-34 concentrations in the cerebrospinal fluid of patients with acute inflammatory demyelinating neuropathy and chronic inflammatory demyelinating polyneuropathy. Rev. Assoc. Med. Bras. 2020, 66, 1583–1588.
69. Waisman, A.; Hauptmann, J.; Regen, T. The role of IL-17 in CNS diseases. Acta Neuropathol. 2015, 129, 625–637.
70. Su, F.; Bai, F.; Zhang, Z. Inflammatory Cytokines and Alzheimer′s Disease: A Review from the Perspective of Genetic Polymorphisms. Neurosci. Bull. 2016, 32, 469–480.
71. Borsini, A.; Cattaneo, A.; Malpighi, C.; Thuret, S.; Harrison, N.A.; Zunszain, P.A.; Pariante, C.M. Interferon-Alpha Reduces Human Hippocampal Neurogenesis and Increases Apoptosis via Activation of Distinct STAT1-Dependent Mechanisms. Int. J. Neuropsychopharmacol. 2018, 21, 187–200.
72. Stampanoni Bassi, M.; Iezzi, E.; Mori, F.; Simonelli, I.; Gilio, L.; Buttari, F.; Sica, F.; de Paolis, N.; Mandolesi, G.; Musella, A.; et al. Interleukin-6 Disrupts Synaptic Plasticity and Impairs Tissue Damage Compensation in Multiple Sclerosis. Neurorehabil. Neural Repair 2019, 33, 825–835.
73. Cyr, B.; de Rivero Vaccari, J.P. Age-Dependent Microglial Response to Systemic Infection. Cells 2021, 10, 1037.

74. Borrajo, A.; Spuch, C.; Penedo, M.A.; Olivares, J.M.; Agís-Balboa, R.C. Important role of microglia in HIV-1 associated neurocognitive disorders and the molecular pathways implicated in its pathogenesis. Ann. Med. 2021, 53, 43–69.
75. Goulding, D.R.; Kraft, A.; Mouton, P.R.; McPherson, C.A.; Avdoshina, V.; Mocchetti, I.; Harry, G.J. Age-Related Decrease in Tyrosine Hydroxylase Immunoreactivity in the Substantia Nigra and Region-Specific Changes in Microglia Morphology in HIV-1 Tg Rats. Neurotox. Res. 2019, 36, 563–582.
76. Chen, N.C.; Partridge, A.T.; Sell, C.; Torres, C.; Martín-García, J. Fate of microglia during HIV-1 infection: From activation to senescence? Glia 2017, 65, 431–446.
77. Rai, M.A.; Hammonds, J.; Pujato, M.; Mayhew, C.; Roskin, K.; Spearman, P. Comparative analysis of human microglial models for studies of HIV replication and pathogenesis. Retrovirology 2020, 17, 35.