Human Microglia

Microglia are important immune cells in the central nervous system. Replacement of mutated microglia by wild-type cells through microglia replacement by bone marrow transplantation can correct gene deficiencies. However, the limited availability of bone marrow cells may restrict its potential to become a widely used clinical treatment. Xu et al. introduced a potentially clinically feasible strategy for achieving efficient microglia replacement by peripheral blood cells in mice, boosting donor cell availability. They named it microglia replacement by peripheral blood (Mr PB). For complete details on the use and execution of this protocol, please refer to Xu et al. (2020). The original abbreviation of this microglia replacement strategy is mrPB [1].

Types

M1 microglia

M2 microglia

Function

As prominent immune cells in the central nervous system, microglia constantly monitor the environment and provide neuronal protection, which are important functions for maintaining brain homeostasis.

Microglia have fundamental roles in health and disease; however, the effects of age, sex, and genetic factors on human microglia have not been fully explored. Patel et al. applied to bulk and single-cell approaches to comprehensively characterize human microglia transcriptomes and their associations with age, sex, and APOE. They identified a novel microglial signature and characterized its expression in bulk tissue and single-cell microglia transcriptomes. They discovered microglial co-expression network modules associated with age, sex, and APOE-ε4 that are enriched for lipid and carbohydrate metabolism genes. Integrated analyses of modules with single-cell transcriptomes revealed significant overlap between age-associated module genes and both pro-inflammatory and disease-associated microglial clusters. These modules and clusters harbor known neurodegenerative disease genes including APOE, PLCG2, and BIN1. Meta-analyses with published bulk and single-cell microglial datasets further supported the findings. Thus, these data represent a well-characterized human microglial transcriptome resource and highlight age, sex, and APOE-related microglial immunometabolism perturbations with potential relevance in neurodegeneration [2].

Microglia, the main innate immune cells in the brain, are among the first responders to brain tissue damage. Recent studies demonstrated that microglia play a critical role in Cortical spreading depolarization initiation and propagation [3].

Microglia are well known to play a critical role in maintaining brain homeostasis.

Microglia are the brain's resident immune cells and function as the main defense against pathogens or injury. However, in the absence of disease, microglia have other functions in the normal brain.

For example, previous studies showed that microglia contribute to circuit refinement and synaptic plasticity in the developing and adult brain, respectively. Thus, microglia actively participate in regulating neuronal excitability and function.

Microglia-related neuroinflammation

Rashad et al., from Sendai, Japan showed the intense activation of immune cells, particularly the microglia, along with the increase in macrophage activity and NLRP3 inflammasome activation that is indicated by NLRP3, Interleukin 1 beta (IL-1β), and Interleukin 18 gene and Caspase-1 upregulation and cleavage as well as pyroptosis.

Leukocytes were observed in the brain parenchyma, indicating a role in cerebral venous thrombosis (CVT)-induced inflammation. In addition, astrocytes were activated, and they induced glial scar leading to parenchymal contraction during the subacute stage and tissue loss. MMP9 was responsible primarily for the BBB breakdown after CVT and it is mainly produced by pericytes. MMP9 activation was observed before inflammatory changes, indicating that BBB breakdown is the initial driver of the pathology of CVT. These results show an inflammation driven pathophysiology of CVT that follows MMP9-mediated BBB breakdown, and identified several targets that can be targeted by pharmaceutical agents to improve the neuroinflammation that follows CVT, such as MMP9, NLRP3, and IL-1β. Some of these pharmaceutical agents are already in clinical practice or under clinical trials indicating a good potential for translating this work into patient care [4].

Findings show that in intervertebral disc degeneration (IVD) microenvironment, Interleukin 8 (IL-8), NGF, Interferon gamma (IFN-γ), Interleukin 17 (IL-17) drive activation of microglia in the spinal cord and increase upregulation of neuroinflammation markers. This, in turn, enhances the inflammatory milieu within intervertebral disc tissues and in the peridiscal space, aggravating the cascade of degenerative events. A study of Navone et al., provides evidence for an important role of microglia in maintaining IVD neuroinflammatory microenvironment and probably inducing low back pain [5].

A subset of microglia extend a single process that specifically associates and overlaps with the axon initial segment (AIS), the site where action potentials are generated. Similar associations were not observed with dendrites or distal axons. Microglia-AIS interactions appear early in development, persist throughout adulthood, and are conserved across species including mice, rats, and primates. However, these interactions are lost after microglial activation following brain injury, suggesting that such interactions may be part of healthy brain function. Loss of microglial CX3CR1 receptors, or the specialized extracellular matrix surrounding the AIS, did not disrupt the interaction. However, loss of AIS proteins by the neuron-specific deletion of the master AIS scaffold AnkyrinG disrupted microglia-AIS interactions. These results reveal a unique population of microglia that specifically interact with the AIS in the adult cortex [6].

Microglial cells share the characteristics of cells of the macrophage lineage [7].

Numerous evidence demonstrate that microglia mediated inflammatory injury plays a critical role in

intracerebral hemorrhage (ICH). Therefore, the way to inhibit the inflammatory response is greatly needed.

Activated microglia and macrophages exert dual beneficial and detrimental roles after central nervous system injury, which are thought to be due to their polarization along a continuum from a classical pro-inflammatory M1-like state to an alternative anti-inflammatory M2-like state.

Kumar et al., performed a detailed phenotypic analysis of M1- and M2-like polarized microglia/macrophages, as well as nicotinamide adenine dinucleotide phosphate oxidase (NOX2) expression, through 7 days post-injury using real-time polymerase chain reaction (qPCR), flow cytometry and image analyses.

They demonstrated that microglia/macrophages express both M1- and M2-like phenotypic markers early after TBI, but the transient up-regulation of the M2-like phenotype was replaced by a predominant M1- or mixed transitional (Mtran) phenotype that expressed high levels of NOX2 at 7 days post-injury. The shift towards the M1-like and Mtran phenotype was associated with increased cortical and hippocampal neurodegeneration. In a follow up study, we administered a selective NOX2 inhibitor, gp91ds-tat, to CCI mice starting at 24 h post-injury to investigate the relationship between NOX2 and M1-like/Mtran phenotypes. Delayed gp91ds-tat treatment altered M1-/M2-like balance in favor of the anti-inflammatory M2-like phenotype, and significantly reduced oxidative damage in neurons at 7 days post-injury.

Therefore, data suggest that despite M1-like and M2-like polarized microglia/macrophages being activated after TBI, the early M2-like response becomes dysfunctional over time, resulting in development of pathological M1-like and Mtran phenotypes driven by increased NOX2 activity [8].

Microglial phagocytosis

Microglial phagocytosis

Microglia polarization

Microglia are polarized to the M2 phenotype following stimulation with Interleukin 4 or Interleukin 13, which are typically released from Th2 cells. M2 microglia secrete anti-inflammatory cytokines and growth factors that promote attenuation of the inflammatory response and repair of damaged tissue.

A systematic review was carried out to identify the microglial cytokine profile against viral infection that has been further evaluated through in vitro studies (pro-inflammatory or anti-inflammatory), along with analysis of its publication frequency over the years. For this review, 531 articles published in the English language were collected from PubMed, Web of Science, EBSCO, and ResearchGate. Only 27 papers met the inclusion criteria for this systematic review. In total, 19 cytokines were evaluated in these studies, most of which are proinflammatory; the most common are IL-6, followed by TNF-α and IL-1β. It should be pointed out that half of the studies were published between 2015 and 2022 (raw data available at https://github.com/dadriba05/SystematicReview.git). In this review, we identified that evaluation of pro-inflammatory cytokines released by microglia against viral infections has been performed more frequently than that of anti-inflammatory cytokines; additionally, a higher frequency of evaluation of the response of microglia cells to viral infection through in vitro studies

from 2015 and beyond was noted [9)]

1)
Xu Z, Rao Y, Peng B. Protocol for microglia replacement by peripheral blood (Mr PB). STAR Protoc. 2021 Jun 11;2(2):100613. doi: 10.1016/j.xpro.2021.100613. PMID: 34179837; PMCID: PMC8209847.
2)
Patel T, Carnwath TP, Wang X, Allen M, Lincoln SJ, Lewis-Tuffin LJ, Quicksall ZS, Lin S, Tutor-New FQ, Ho CCG, Min Y, Malphrus KG, Nguyen TT, Martin E, Garcia CA, Alkharboosh RM, Grewal S, Chaichana K, Wharen R, Guerrero-Cazares H, Quinones-Hinojosa A, Ertekin-Taner N. Transcriptional landscape of human microglia implicates age, sex, and APOE-related immunometabolic pathway perturbations. Aging Cell. 2022 Apr 6:e13606. doi: 10.1111/acel.13606. Epub ahead of print. PMID: 35388616.
3)
Kearns KN, Liu L, Soldozy S, Sharifi KA, Shaffrey ME, Park MS, Tvrdik P. Microglia Modulate Cortical Spreading Depolarizations After Ischemic Stroke: A Narrative Review. Neurocrit Care. 2022 Mar 15. doi: 10.1007/s12028-022-01469-4. Epub ahead of print. PMID: 35288861.
4)
Rashad S, Niizuma K, Sato-Maeda M, Fujimura M, Mansour A, Endo H, Ikawa S, Tominaga T. Early BBB breakdown and subacute inflammasome activation and pyroptosis as a result of cerebral venous thrombosis. Brain Res. 2018 Jul 4. pii: S0006-8993(18)30362-7. doi: 10.1016/j.brainres.2018.06.029. [Epub ahead of print] PubMed PMID: 29981290.
5)
Navone SE, Peroglio M, Guarnaccia L, Beretta M, Grad S, Paroni M, Cordiglieri C, Locatelli M, Pluderi M, Rampini P, Campanella R, Alini M, Marfia G. Mechanical loading of intervertebral disc modulates microglia proliferation, activation, and chemotaxis. Osteoarthritis Cartilage. 2018 Apr 30. pii: S1063-4584(18)31220-2. doi: 10.1016/j.joca.2018.04.013. [Epub ahead of print] PubMed PMID: 29723636.
6)
Baalman K, Marin MA, Ho TS, Godoy M, Cherian L, Robertson C, Rasband MN. Axon initial segment-associated microglia. J Neurosci. 2015 Feb 4;35(5):2283-92. doi: 10.1523/JNEUROSCI.3751-14.2015. PubMed PMID: 25653382.
7)
Frei K, Siepl C, Groscurth P, Bodmer S, Schwerdel C, Fontana A. Antigen presentation and tumor cytotoxicity by interferon-gamma-treated microglial cells. Eur J Immunol. 1987 Sep;17(9):1271-8. PubMed PMID: 3115791.
8)
Kumar A, Alvarez-Croda DM, Stoica BA, Faden AI, Loane DJ. Microglial/Macrophage Polarization Dynamics following Traumatic Brain Injury. J Neurotrauma. 2016 Oct 1;33(19):1732-1750. Epub 2015 Dec 29. PubMed PMID: 26486881.
9)
Barrios-González DA, Philibert-Rosas S, Martínez-Juárez IE, Sotelo-Díaz F, Rivas-Alonso V, Sotelo J, Sebastián-Díaz MA. Frequency and Focus of in Vitro Studies of Microglia-Expressed Cytokines in Response to Viral Infection: A Systematic Review. Cell Mol Neurobiol. 2024 Feb 13;44(1):21. doi: 10.1007/s10571-024-01454-9. PMID: 38349562.