**Supplementary Table 1. Modulators in microglia polarization from M1 to M2**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Classification** | **Modulators** | **Related signaling pathways** | **Disease** | **Effects** | **Reference** |
| Transcription factor | **NF-κB** | - | - | Suppressed the inflammatory gene and drove microglia to M2 | (1) |
| **PPAR-γ** | LKB1/AMPK pathway | - | Promoted M1 to M2 through improving autophagy | (2) |
| Receptors | **TREM2** | - | - | Promoted M2 polarization and reduced microglia-mediated inflammation | (3) |
| JAK/STAT/SOCS pathway | AD | Rescued cognitive deficits, decreased Aβ plaques deposition, reduced synaptic and neuronal loss, ameliorated neuroinflammation, promoted M2 polarization, and reduced M1 inflammatory responses | (4) |
| - | PD | Improved the phagocytosis ability of microglia, increased M2 marker Arg-1 and suppressed neuroinflammation | (5) |
| **Acetylcholine**  | JAK2/STAT3 pathway | - | Transformed M1 microglia to M2 through promoting α7 subtype of the nicotinic acetylcholine receptor (α7 nAChR) | (6) |
| **P2X7 (Purinergic P2 receptor for extracellular ATP)** | - | ALS | Reduced neuroinflammation, promoted motor neuron to survive and reduced microgliosis in lumbar spinal cord at late pre-onset with reduced M1 markers and increased M2 markers | (7) |
| Cytokines | **IL-4** | - | - | Shifted microglia from M1 towards M2 | (8) |
| **Insulin-like growth factor-1** | - | - | Shifted microglia from M1 towards M2 | (9) |
| **Glial cell-derived neurotrophic factor** | PI3K/AKT pathway | - | Exerted neuroprotective effects, and modulated microglial polarization to M2 phenotype | (10) |
| **Milk fat globule epidermal growth factor 8** | NF-κB and PI3K/Akt pathways | AD | Reversed the increased M1 markers and the decreased M2 markers | (11) |
| **IL-33** | TLR/MyD88 pathways | AD | Modulated the innate immune response by polarizing microglia toward M2 with enhanced Aβ phagocytic ability | (12) |
| **scAAV9-VEGF-165** | PI3K/Akt pathway | ALS | Improved the motor function, prolonged the survival of SOD1G93A mice, reduced M1 markers, and increased M2 markers | (13) |
| Ion channels | **Kv 1.3 blocker PAP-1** | - | AD | Reduced neuroinflammation, decreased cerebral amyloid load, improved hippocampal neuronal plasticity, and improved behavioral deficits | (14) |
| **Kir6.1/K-ATP channel** | p38 MAPK-NF-κB pathway | PD | Skewed microglia from M1 toward M2, and relieved toxic effects of M1 microglia | (15) |
| Bioactive compounds | **Astaxanthin** | NF-κB and JNK pathways | - | Shifted microglia from M1 to M2 | (16) |
| **Anisalcohol** | NF-κB and JNK pathways | - | Shifted microglia from M1 to M2 | (17) |
| **Naringenin** | MAPK, especially JNK pathway | - | Shifted microglia from M1 to M2 | (18) |
| **Resveratrol** | PGC-1α pathwayNF-κB pathway STAT6 and STAT3 pathways | - | Shifted microglia from M1 to M2 | (19) |
| **Platycodigenin** | NF-κB pathway | - | Shifted microglia from M1 to M2 | (20) |
| **Hydroxytyrosol** | NF-κB and ERK pathway | - | Shifted microglia from M1 to M2 | (21) |
| **Curcumin** | TLR4/NF-κB pathway | - | Shifted microglia from M1 to M2 | (22) |
| CaMKKβ-dependent AMPK pathway | - | Shifted microglia from M1 to M2 | (23) |
| JAK/STAT/SOCS pathway | - | Elicited anti-inflammatory responses | (24) |
| **Isovitexin** | CaMKKβ/AMPK pathway | - | Shifted microglia from M1 to M2 | (25) |
| **Betulinic acid** | CaMKKβ/AMPK pathway | - | Shifted microglia from M1 to M2 | (26) |
| **Rosmarinic acid** | PDPK1/Akt/HIF pathway | - | Shifted microglia from M1 to M2 | (27) |
| **Dihydromyricetin** | - | AD | Ameliorated memory and cognitive deficits, decreased activated microglia, reduced expression and activation of NLRP3 inflammasomes, and promoted clearance of Aβ by increasing levels of proteolytic enzyme neprilysin and shifting microglia to M2 phenotype | (28) |
| **Ginsenoside Rg1** | NF-κB pathway | PD | Skewed microglia from M1 toward M2, and exerted neuroprotective effect against inflammation-induced dopaminergic neuronal degeneration in SN | (29) |
| **Capsaicin** | - | PD | Inhibited pro-inflammatory mediators, shifted the M1 microglia to M2, and reduced oxidative damage and degeneration of nigral dopamine neurons in the LPS-lesioned SN | (30) |
| **Bee venom -derived phospholipase A2** | - | PD | Ameliorated motor dysfunction, down-regulated α-Syn, reduced the activation and numbers of microglia, and influenced microglia polarization to the M2 phenotype | (31) |
| **Camptothecin** | AKT/Nrf2/HO-1 and NF-κB pathways | PD | Improved motor performance, reduced the loss of neurons in the SN, and inhibited M1 polarization and promoted M2 polarization | (32) |
| **Tetramethylpyrazine** | STAT3/SOCS3 and NF-кB pathways | EAE/MS | Protected the BSCB integrity, and alleviates EAE by decreasing microglia activation and modulating microglia polarization from M1 to M2 | (33) |
| Drugs | **Fasudil** | Rho/ROCK pathway  | - | Reduced pro-inflammatory factors NO, IL-1β, IL-6 and TNFα and increased anti-inflammatory factor IL-10 | (34) |
| NF-κB pathway | - | Led to a M2 phenotype | (35) |
| TLR4/Myd88/NF-κB pathway | AD | Improved the cognitive deficits, inhibited microglial activation and promoted M2 phenotype | (36) |
| NF-κB pathway | EAE/MS | Converted microglia from M1 to M2, attenuated demyelination and neuroinflammation, promoted neuroprotection, and reduced the severity of EAE | (37) |
| **Candesartan(angiotensin II type I receptor blocker)** | TLR4/NF-κB pathway | - | Modulated the neuroinflammatory response, reversed neurotoxic effect, and shifted microglia from M1 to M2 | (38) |
|  | AD | Shift microglia toward M2 phenotype, enhanced phagocytosis of Aβ1-42 by microglia, and significantly reduced amyloid burden and microglial activation | (39) |
| **Telmisartan(angiotensin II type I receptor blocker)** | PPAR-γ and CaMKKβ/AMPK pathway | - | Promoted M2 polarization and reduced M1 polarization  | (40) |
| **Dexmedetomidine(alpha2 adrenoceptor agonist)** | ERK1/2 pathway | - | Promoted microglial M2 polarization | (41) |
| **Simvastatin(hydroxymethylglutaryl–coenzyme A reductase inhibitor)** | Notch pathway | - | Regulated microglia polarization from M1 to M2 | (42) |
| **Nicotine** | STAT3 pathway | - | Promoted M2 microglial polarization | (43) |
| **TAK-242(TLR4 antagonist)** | MyD88/NF-κB pathway | AD | Induced microglia switch from M1 to M2, ameliorated learning and memory ability, lowered Aβ deposition, and protected neuronal cells against cytotoxicity | (44) |
| **Rosiglitazone(PPAR-γ agonist)** | - | PD | Switched microglia to M2 | (45) |
| **Edaravone(ROS scavenger)** | - | PD | Mitigated motor dysfunction, inhibited LPS-induced microglial activation, remitted declines of dopaminergic neurons, possibly by inhibiting NLPR3 inflammasome activation and regulating microglia M1/M2 polarization | (46) |
| **Clemastine (histamine H1 receptor antagonist)** |  | ALS | Reduced microgliosis, modulated microglia-related inflammatory genes, improved motor neuron survival, and induced increased P2Y12 and M2 marker Arg-1, and simultaneous inhibited M1 markers | (47) |
| **Fingolimod (modulator of sphingosine 1-phosphate receptor)** | STAT1 pathway | - | Transformed microglia from M1 to M2 through suppressing autophagy | (48) |
| Others | **NADPH oxidase/ROS** | - | - | Inhibiting NADPH oxidase drives microglia phenotype from M1 to M2 | (49) |
| **Mitochondrial fission inhibitor 1 (Mdivi-1)** | TLR2/4-activated GSK3β-NF-κB-p65 pathway | EAE | Decreased antigen presentation capacity of microglia and alleviated inflammation by polarization of microglia from M1 to M2 phenotype | (50) |
| **CDGSH iron-sulfur domain 2** | NF-κB pathway | - | Exerted anti-inflammatory effects and preserved M2 microglia | (51) |
| **Triglyceride-rich lipoprotein (TRL)**  | - | - | Postprandial TRL-monounsaturated fatty acids promote M2 microglia polarization, whereas postprandial TRL-saturated fatty acids improve M1 microglia polarization | (52) |
| **Melatonin** | melatonin receptor 1/JAK2/STAT3/telomerase pathway | - | Ameliorated neurobehavioral disturbances, alleviated axonal hypomyelination in the periventricular white matter of LPS-injected postnatal rats, and reduces neuroinflammation through shifting M1 microglia towards M2 | (53) |
| **TPP-MoS2 QDs** | - | AD | Mitigated Aβ aggregate-mediated neurotoxicity and removed Aβ aggregates by switching microglia phenotype | (54) |
| **Electroacupuncture** | NF-κB & STAT-6 pathway. | AD | Improved learning and memory inhibited the activation of glia and polarized microglia toward the M2 phenotype in hippocampus with decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines | (55)  |
| **Thymosin β4 (Tβ4)** | TLR4/MyD88/NF-κB p65 and p52 pathways | AD | Improved neuronal function and cognitive ability, reduced brain Aβ accumulation, upregulated insulin-degrading enzyme, and alleviated neuroinflammatory response by converting microglia and astrocyte to neuroprotective phenotype | (56) |
| **Jumonji domain containing 3 (Jmjd3)** | - | PD | Suppression of Jmjd3 inhibited M2 polarization and simultaneously exaggerated inflammatory responses. | (57) |
| **HOXA cluster antisense RNA 2 (HOXA-AS2)** | - | PD | HOXA-AS2 knockdown could significantly repress microglial M1 polarization and promote M2 polarization | (58) |
| **TLR2 tolerance** | TLR2 pathway | - | Improved myelin recovery, and shifted microglia from M1 to M2 phenotype | (59) |
| **2-arachidonoylglycerol** | - | EAE | Delayed the onset of EAE, reduced relapse severity, chronic disability and mortality in EAE, increased microglial activation, and shifted microglia to M2 phenotype | (60) |
| **The homeobox gene msh-like homeobox-3** | PPAR-γ & JAK/STAT6 pathways | EAE | Contributed to demyelination and neurodegeneration in EAE, promoted the survival, differentiation and neurite growth of oligodendrocyte progenitor cells through promoting M1 microglia to polarize towards M2 | (61) |
| **17β-estradiol** | - | CPZ | Led to the reduction of M1 phenotype, stimulation of polarized M2 microglia, and repression of NLRP3 inflammasome in the corpus callosum of CPZ demyelination model of MS, improved neurological behavioral deficits, and caused a decrease in demyelination levels and axonal injury | (62) |
| **Bone marrow mesenchymal stem cell-derived exosome** | - | EAE | Reduced inflammation and demyelination in the CNS, attenuated clinical manifestation of EAE, increased M2 markers, and decreased M1 markers | (63) |
| **Exosomes released from mesenchymal stromal cells (MSC-Exo)** | TLR2/IRAK1/NF-κB pathway | EAE&CPZ | Improved neurological outcome, increased the numbers oligodendrocytes and the level of myelin basic protein, decreased amyloid-β precursor protein density, and decreased neuroinflammation by increasing the M2 phenotype and decreasing the M1 phenotype of microglia, as well as their related cytokines and special markers | (64) |

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