Review

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Stress Induced Transcriptional and Epigenetic Plasticity of Astrocytes, Microglia and Oligodendrocytes in the Pathophysiology of Depression

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Abstract

Major Depressive Disorder (MDD) remains a leading cause of disability worldwide, perpetuated by an incomplete understanding of its pathophysiology and the limited efficacy of conventional antidepressants. For decades, research has been dominated by neuron-centric models, particularly the monoamine hypothesis. However, a paradigm shift is underway, placing glial cells such as astrocytes, microglia, and oligodendrocytes at the centre of depression-related pathology. These cells are not merely supportive but are active participants in neuroinflammation, synaptic plasticity, neurotransmitter homeostasis, and metabolic regulation, processes profoundly disrupted in MDD. We discuss how stress-induced epigenetic modifications such as histone acetylation, methylation, and DNA methylation alter astrocytic glutamate transport, microglial inflammatory states, and oligodendrocyte-mediated myelination. Special emphasis is placed on the concept of glial transcriptional plasticity, whereby environmental adversity induces durable and cell type specific gene expression changes that underlie neuroinflammation, excitatory–inhibitory imbalance, and white matter deficits observed in MDD. By integrating findings from postmortem human tissue, single-cell omics, and stress-based animal models, this review highlights converging molecular mechanisms linking stress to glial dysfunction. We further outline how targeting glial transcriptional regulators may provide new therapeutic avenues beyond conventional monoaminergic approaches.

Keywords: astrocyte dysfunction; microglial priming; epigenetic regulation; myelin plasticity; susceptibility and resilience; neuroinflammation; histone modifications

1. Introduction

The neurobiological understanding of Major Depressive Disorder (MDD) has long been connected to the neuronal dysregulation. The monoamine hypothesis, which propounds that depression arises from deficiency in synaptic serotonin, norepinephrine, or dopamine, has long guided antidepressant development for over half a century [1]. While transformative, the delayed therapeutic onset of monoaminergic drugs, their limited efficacy in a substantial subset of patients, and the complex, multifactorial nature of MDD all point to pathological mechanisms that extend beyond the synapse. A fundamental shift in perspective is imperative, moving from neuron-centric to viewing the nervous system (CNS) as a complex ecosystem of interacting cell types. Glial cells such as astrocytes, microglia, and oligodendrocytes emerge as passive critical drivers of brain health and

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disease [2]. Glial cells collectively outnumber neurons in many brain regions and are indispensable for nearly every aspect of CNS function, including synaptic transmission, metabolic support, immune surveillance, and the formation of myelin insulation [3]. Crucially, dysfunction in glia mediated processes is now recognized as one of the core features of MDD [4]. Post-mortem and neuroimaging studies consistently reveal changes in glial cell numbers and density, particularly astrocytes and oligodendrocytes, in key mood-regulating brain regions of individuals with MDD, such as the prefrontal cortex (PFC), hippocampus, and amygdala [5–7]. Concurrently, microglial activation and the ensuing neuroinflammatory cascade are increasingly understood as both a cause and a consequence of depressive states [8]. The marked interindividual variability in antidepressant response [9] may, in part, stem from stress-induced transcriptional and epigenetic reprogramming of glial cells, which shapes neuroinflammation, synaptic support, and myelin integrity in depression.

A critical question is: what mechanisms translate environmental risk factors, most notably chronic psychosocial stress, into these profound and lasting states of glial dysfunction? The answer appears to lie within the domain of epigenetic regulation. Epigenetic modifications, such as histone post-translational modifications, are heritable changes in gene expression that occur without altering the underlying DNA sequence. These mechanisms provide a molecular interface between the environment and the genome, allowing experiences like early-life adversity or chronic stress to induce stable changes in cellular function [10]. Histone modifications, catalyzed by a diverse enzymatic network of "writers" (acetyltransferases, methyltransferases) and "erasers" (deacetylases, demethylases), alter chromatin architecture to control the accessibility of genes to the transcriptional machinery. Epigenetic changes in microglia can prime them for a chronic, pro-inflammatory state that perpetuates a pathological milieu throughout the brain [11–13]. This review propounds that stress induced alterations in glial transcriptional plasticity serves as one of the key mechanisms, driving the pathophysiology of depression. The various hypotheses of depression such as neuroinflammatory, neurotrophic, and glutamatergic are not disparate entities but rather interconnected consequences of transcriptional reprogramming within glial cells. Understanding histone-dependent transcriptional control in glia is not just an incremental advance; it provides a foundational approach for linking stress to the diverse cellular and synaptic dysfunctions of MDD and offers a new frontier for the rational design of novel antidepressant strategies. Given that depression is among the leading causes of global disability with marked gender-specific manifestations [14], understanding stress-induced glial transcriptional remodeling provides a critical bridge between molecular mechanisms and clinical disability outcomes.

2. Epigenetic Codes of Glial Identity and CNS Homeostasis

The foundation of CNS stability rests heavily on the coordinated functions of astrocytes and microglia. Astrocytes are the principal homeostatic cells of the CNS. They regulate the extracellular environment by controlling ion concentrations clearing neurotransmitters like glutamate, providing metabolic substrates to neuron via the astrocyte-neuron lactate shuttle, and maintaining the integrity of the blood-brain barrier. Complementing this role, microglia function as the resident immune cells of the brain. In the healthy state, they are not merely quiescent but are highly active, continuously surveying their local microenvironment with motile processes. This surveillance is critical for normal brain development, where microglia mediate neurogenesis and synaptic pruning by phagocytosing apoptotic neural progenitors and eliminating redundant or weak synaptic connections, thereby shaping the architecture of nascent neural circuits [15].

The functional identity of an astrocyte is not merely a product of its genetic code but is actively established and maintained by a specific epigenetic landscape. During neurodevelopment, the promoter of the canonical astrocyte marker gene, glial fibrillary acidic protein (GFAP), is demethylated, a crucial step that permits its expression and solidifies the astrocytic fate. This process is governed by the activity of DNA methyltransferases (DNMTs) such as DNMT1 and DNMT3a, which ensure that astrocyte-specific genes are transcriptionally accessible while genes associated with other neural lineages remain silenced. Recent single-cell multi-omics analyses have reinforced

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this principle, demonstrating that distinct DNA methylation profiles, dependent on DNMT3A, separate functional astrocytes from neural stem cells by selectively methylating stemness-related genes and demethylating astrocyte-specific genes [16,17]. While DNA methylation provides a stable foundation for cell identity, histone modifications offer a dynamic functional regulation. The differentiation of astrocytes from neural stem cells is guided by the crosstalk of histone methyltransferases (HMTs) like Ezh2 and demethylases such as Jmjd2c [17,18].

Microglia, too, are defined by a unique epigenetic signature that distinguishes them from peripheral macrophages and other CNS cells. The establishment of microglial identity is driven by lineage-determining transcription factors, most notably PU.1, which binds to specific enhancer regions across the genome. The accessibility of the PU.1 gene locus itself is epigenetically controlled; histone H4 acetylation at its promoter is required for its transcription, and this can be modulated by HDAC inhibitors [19]. In the homeostatic state, the functional poise of microglia is maintained by a delicate balance of repressive and activating histone marks. The histone methyltransferase EZH2 deposits the repressive mark H3K27me3 at the promoters of pro-inflammatory genes, keeping them silenced. This is counteracted by the demethylase JMJD3, which removes this mark to permit gene expression. In the healthy brain, this balance is tightly regulated to maintain a state of quiescent readiness [20].

The stable homeostasis of the CNS is not simply the sum of independent astrocyte and microglial functions but arises from their continuous, bidirectional communication, which is itself governed by epigenetic mechanisms. This forms a reciprocal feedback loop that maintains the quiescent, supportive state of both cell types. The process begins with the astrocyte's epigenetically controlled secretome. In a healthy state, a specific pattern of histone acetylation and DNA methylation in astrocytes ensures the baseline expression of factors that promote microglial quiescence and suppresses those that would provoke activation. These astrocytic signals are received by microglia, whose response is predetermined by their own epigenetic landscape. For instance, the methylated, repressed state of pro-inflammatory gene promoters in homeostatic microglia ensures that they do not overreact to minor fluctuations in their environment [17,20]. The molecular mechanism maintaining this homeostatic loop is complex and involves multiple signaling systems that are themselves subject to epigenetic control. Purinergic signaling is the primary mode of rapid communication. Astrocytes can release adenosine triphosphate (ATP), which acts as a crucial signaling molecule. In the extracellular space, ATP can directly stimulate ionotropic (P2X) and metabotropic (P2Y) purinergic receptors on microglia. The microglial P2Y12 receptor is critical for sensing ATP and guiding microglial process motility toward sites of release. The signal is tightly regulated by ecto-nucleotidases like CD39 and CD73 on the cell surface, which sequentially hydrolyze ATP to adenosine. Adenosine then acts on P1 receptors to exert distinct, often opposing, modulatory effects, creating a finely tuned system for reciprocal communication [21,22].

The generation of mature, myelinating oligodendrocytes from their progenitors (OPCs, also known as NG2-glia) is a process governed by a precise and exquisitely timed epigenetic cascade. This sequence ensures that differentiation occurs at the correct developmental window. The process is initiated by histone deacetylation. Class I HDACs, specifically HDAC1 and HDAC2, are recruited to the promoters of genes that actively inhibit oligodendrocyte differentiation (*Hes5*, *Id2*) and genes that promote alternative neuronal or astrocytic fates. The removal of acetyl groups by these HDACs silences the inhibitors, effectively mediates oligodendrocyte lineage program to commence [23,24]. Chronic and social stressors reprogram glial epigenomes perturbing inter-glial communication and redirect lineage programs, producing functionally immature or maladaptive astrocytes, primed microglia and lead to dysregulation in oligodendrocyte maturation.

3. Astrocytic Gene Expression Landscape and Remodeling in Depressive Disorders

Astrocytes are the most abundant glial cell type in the CNS, where they perform a vast array of homeostatic functions critical for neuronal health and circuit function. They are integral components

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of the "tripartite synapse," regulating neurotransmitter levels, particularly glutamate; providing metabolic substrates to neurons; maintaining ion and water balance; and contribute to the structural and functional integrity of the blood-brain barrier (BBB) [25–27]. In MDD, this homeostatic network is significantly disrupted, with post-mortem studies revealing altered expression of genes encoding astrocyte-specific transporters and enzymes such as GLT1 (SLC1A2) and glutamine synthetase (GLUL), impairing glutamate clearance and turnover [28]. In response to CNS insults or pathological stimuli, astrocytes undergo a process known as reactive astrogliosis, adopting distinct phenotypes that can be either neuroprotective or neurotoxic. This include s the pro-inflammatory "A1" state, which is induced by signals from activated microglia and can promote neuronal death, and the neuroprotective "A2" state, which supports tissue repair and neuronal survival [29]. Astrocytic transcriptional plasticity under chronic stress is marked by a shift toward the neurotoxic A1 phenotype, prominently in the medial prefrontal cortex (mPFC) and hippocampus [30]. In an investigation, chronic social defeat stress (CSDS) induced upregulation of A1-specific transcripts such as *C3*, *Serping1*, and *Amigo2*, accompanied by microglial release of IL-1α, TNF-α, C1q, and fragmented mitochondria, which together drove astrocytic hypertrophic reactivation. This astrocytic state was associated with reduced frequency and amplitude of sEPSCs and sIPSCs, reflecting impaired excitatory–inhibitory balance. Importantly, chemogenetic inhibition of astrocytic calcium signaling (via hM4Di DREADDs) suppressed A1-specific responses, restored synaptic activity, and reversed depressive-like behaviors, whereas selective astrocytic activation exacerbated neuronal inhibition. Furthermore, microglial depletion abrogated stress-induced A1 astrocytic responses and rescued behavioral deficits, suggesting of a microglia-astrocyte axis in stress-driven transcriptional remodeling [30].

The implication of astrocytes in the pathophysiology of MDD is supported by a robust and converging line of evidence from both human and animal studies. Seminal postmortem analyses of brain tissue from individuals with MDD have consistently revealed a significant reduction in the density, size, and number of astrocytes and their molecular markers, such as glial fibrillary acidic protein (GFAP), in key brain regions implicated in mood regulation, including the prefrontal cortex (PFC), hippocampus, and amygdala [31]. Most critically, recent studies have provided causal evidence for the primary role of astroglial dysfunction in driving depressive phenotypes. Pharmacological or genetic manipulation of astrocytes specifically within the PFC is sufficient to induce anhedonia and other depressive-like behaviors in rodents [32,33].

3.1. Histone Acetylation and Deacetylation

The balance between histone acetylation, which generally promotes gene transcription by creating a more open chromatin structure, and deacetylation, which represses it, is a critical determinant of astrocyte function. This dynamic is controlled by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Class I and II HDACs have emerged as powerful repressors of astrocytic gene expression, with significant implications for synaptic function. A paradigmatic example is the epigenetic regulation of the primary astrocytic glutamate transporter, GLT-1 (encoded by the *SLC1A2* gene), which is responsible for clearing the majority of synaptic glutamate [34]. Impaired GLT-1 function leads to glutamate accumulation, excitotoxicity, and depressive-like behaviors. Research in a mouse model of subarachnoid haemorrhage, which induces delayed depression and memory impairment, demonstrated a significant upregulation of astrocytic HDAC2 [34]. This increase in HDAC2 activity led to histone hypoacetylation at the *Slc1a2* promoter, resulting in transcriptional repression of the gene and a subsequent reduction in GLT-1 protein levels. Critically, pharmacological inhibition of HDAC2 rescued GLT-1 expression and ameliorated the depressive-like behaviors, establishing a direct causal link between astrocytic histone deacetylation, impaired glutamate homeostasis, and depression. These preclinical findings are consistent with human post-mortem studies showing reduced expression of both EAAT1 and EAAT2 (the human homologs of GLAST and GLT-1) in individuals with MDD [35].

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Another study focussing on astrocyte-mediated inflammation demonstrated that HDAC7 is a key regulator of the pro-inflammatory NF-κB pathway. In response to an inflammatory stimulus, HDAC7 levels were selectively elevated in astrocytes. Mechanistically, HDAC7 was found to physically bind to and activate the IKK complex via deacetylation, leading to NF-κB activation, pro-inflammatory gene expression, and the induction of anxiety-like behaviors in mice [36]. Targeted interventions have revealed that pharmacological modulation of astrocytic HDAC regulators may counteract stress-induced pathology. In a chronic social defeat stress model characterized by astrocyte dysfunction, the antidepressant effects of the compound edaravone were found to be mediated by activating a signaling cascade initiated by Sirtuin 1 (Sirt1), a class III HDAC. This activation of the Sirt1/Nrf2/HO-1/Gpx4 pathway in the hippocampus and medial prefrontal cortex served to mitigate oxidative stress and ferroptosis [37]. The impact of substance abuse on astrocytic epigenetics was explored in a separate investigation. In cultured astrocytes, exposure to psychostimulants like cocaine and methamphetamine, as well as opioids like morphine, led to significant, drug-specific alterations in the expression and cellular localization of the sirtuin family of class III HDACs (SIRT1-7) [38].

While HDACs often repress homeostatic functions, HATs, such as CREB-binding protein (CBP) and p300, are essential for activating gene expression programs that provide trophic and metabolic support to neurons. Astrocytes are a significant source of neurotrophic factors, including BDNF and glial cell line-derived neurotrophic factor (GDNF) [39]. Pharmacological interventions that promote histone acetylation, such as treatment with HDAC inhibitors, robustly increase the expression of both BDNF and GDNF in cultured astrocytes, an effect that confers protection to co-cultured dopaminergic neurons [40]. Emerging evidence shows that disruptions in the same HAT/HDAC balance under pathophysiological conditions, such as hormonal decline, can reprogram astrocytic chromatin states toward maladaptive outcomes.A recent study in a model of perimenopausal depression, revealed that hormonal changes directly impact the astrocytic epigenome [41]. In hypothalamic astrocytes, reduced estrogen levels disrupt the critical balance between histone acetyltransferases (HATs) and HDACs, leading to a significant decrease in histone 3 lysine 9 acetylation (acetyl-H3K9). The loss of this key activating mark on the histone tail initiates a cascade of pathological events, beginning with the activation of the endoplasmic reticulum stress pathway mediated by IRE1α and its downstream target, XBP1. This activation, in turn, triggers ferroptosis, a form of iron-dependent cell death. The molecular hallmarks of this process in astrocytes include mitochondrial damage, evidenced by pyknosis and cristae reduction, and the collapse of the cell's antioxidant defenses, marked by the downregulation of glutathione peroxidase 4 (GPX4) and the cystine/glutamate antiporter SLC7A11[41].

3.2. Histone Methylation

Histone methylation is a more complex modification than acetylation, as its effect on transcription depends on the specific lysine residue methylated and the degree of methylation (mono, di, or tri-methylation). In astrocytes, specific methylation patterns are emerging as key drivers of a pro-inflammatory, reactive state that contributes to stress susceptibility. A pivotal recent discovery from single-cell analysis of human post-mortem OFC tissue from MDD patients has identified the transcription factor ZBTB7A as a master regulator of astrocyte-mediated stress susceptibility [42]. This work revealed that genetic risk variants for MDD are significantly enriched in the open chromatin regions of non-neuronal cells, particularly astrocytes. Translating this to a mouse model, it was demonstrated that astrocyte-specific overexpression of ZBTB7A in the PFC was sufficient to induce behavioral and molecular signatures of stress susceptibility, driven by widespread changes in chromatin accessibility at ZBTB7A target genes [42].

Another study demonstrated that only astrocytic deletion of ALKBH5, and not its deletion in neurons or endothelial cells, was sufficient to evoke antidepressant-like behaviors suggesting that astrocytic m6A dynamics (ALKBH5) control stress-induced depressive-like behavior and modify the astrocytic transcriptome, while DNMT and TET-dependent CpG remodeling reconfigures astrocyte

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methylomes during injury and by analogy after stress to permit dedifferentiation or loss of mature astrocyte identity [16,43]. In human primary astrocytes, exposure to psychostimulants and opioids induces distinct and specific epigenetic remodeling. The Histone Acetyltransferases (HATs) PCAF and GCN5 are significantly downregulated at the protein level by psychostimulants cocaine and METH. All three stressors-cocaine, METH, and morphine lead to a significant upregulation of acetylation at H3K27 and H3K56 [44]. While direct causal links between specific methylation marks and core astrocyte functions like glutamate transport are still being forged, genome-wide association studies integrated with methylation data are identifying novel candidate genes. One such study identified elevated DNA methylation of *Bicaudal D Cargo Adaptor 2 (BICD2)* in the blood of MDD patients. Functional follow-up in rodent models showed that altering *Bicd2* expression in the hippocampus had antidepressant-like effects, potentially mediated by changes in BDNF expression [45].

3.3. The Non-Coding Transcriptome and Regulation of Astroglial Responses

Studies have begun to identify specific miRNAs that are dysregulated in MDD and stress. For instance, one study found a significant elevation of miR-182-5p in plasma-derived small extracellular vesicles (sEVs) from MDD patients, a finding that was validated in animal models of chronic stress [46]. Astrocytes, with their specialized "end-feet" processes enwrapping cerebral blood vessels, are perfectly positioned to interact with and internalize the contents of these circulating vesicles. Several lncRNAs have been implicated in stress-related behaviors. An integrated analysis of lncRNA and mRNA expression in the hippocampus of rats susceptible to depression identified thousands of differentially expressed molecules, including the lncRNAs *Uc. 354+* and *MRAK035806* [47]. The identification of lncRNAs that are specifically or highly expressed in astrocytes, such as PRDM16-DT, is an active area of research, with the potential to uncover novel regulators of astrocyte function in health and disease [48]. A compelling case study highlights the critical role of a specific circRNA in mediating the antidepressant effects of esketamine. Research has shown that chronic stress leads to an upregulation of an astrocyte-specific circRNA, *circKat6b*, in the hippocampus [49].

Table 1. Summary of Astroglia related Epigenetic Alterations in Depression.

Stress Paradigm / Model	Epigenetic Mechanism	Target Genes / Pathways	Observed Astrocyte Response	Behavioral/Functional Outcome	Therapeutic Implications / Interventions	Study Reference
Subarachnoid Haemorrhage (SAH) Mouse Model	Upregulation of astrocytic HDAC2 leads to histone hypoacetylation at the gene promoter.	Slc1a2 (encodes glutamate transporter GLT-1).	Transcriptional repression of Slc1a2, resulting in reduced GLT-1 protein levels and impaired glutamate homeostasis.	Delayed depression and memory impairment.	Pharmacological inhibition of HDAC2 rescued GLT-1 expression and ameliorated depressive-like behaviors.	[34]
Inflammatory Stimulus in Mice	Histone Deacetylation: HDAC7 physically binds to and deacetylates the IKK complex, leading to its activation.	NF-κB signaling pathway.	Activation of NF-κB and subsequent expression of pro-inflammatory genes specifically in astrocytes.	Induction of anxiety-like behaviors.	Implies that targeting HDAC7 could be a potential therapeutic strategy for astrocyte-mediated inflammation.	[36]

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Chronic Social Defeat Stress (CSDS) Model	Histone Deacetylation (Class III): Activation of Sirtuin 1 (Sirt1), a class III HDAC.	Sirt1/Nrf2/HO-1/Gpx4 signaling cascade.	Mitigation of oxidative stress and ferroptosis in astrocytes within the hippocampus and medial prefrontal cortex.	Stress-induced astrocyte dysfunction and depressive behaviors.	The compound edaravone was found to mediate antidepressant effects by activating this pathway.	[37]
Perimenopausal Depression Rat Model	Histone Acetylation: Reduced estrogen levels disrupt the HAT/HDAC balance, decreasing histone 3 lysine 9 acetylation (acetyl-H3K9).	IRE1α/XBP1 endoplasmic reticulum stress pathway; Downregulation of GPX4 and SLC7A11.	Activation of ER stress in hypothalamic astrocytes, triggering ferroptosis, mitochondrial damage, and collapse of antioxidant defenses.	Depressive-like behaviors associated with perimenopause.	Quercetin was shown to alleviate depressive-like behavior by modulating the acetyl-H3K9 mediated ferroptosis pathway.	[41]
Human Post-Mortem MDD Tissue & Mouse Overexpression Model	Chromatin Remodeling: MDD risk variants are enriched in astrocyte open chromatin regions. ZBTB7A acts as a master regulator altering chromatin accessibility.	ZBTB7A and its downstream target genes.	Astrocyte-specific overexpression of ZBTB7A drives widespread changes in chromatin accessibility, promoting a state of stress susceptibility.	Induction of behavioral and molecular signatures of stress susceptibility.	Identifies the transcription factor ZBTB7A as a potential therapeutic target for modulating astrocyte-mediated stress responses.	[42]
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Human Post-Mortem MDD Tissue & Mouse Overexpression Model	Chromatin Remodeling: MDD risk variants are enriched in astrocyte open chromatin regions. ZBTB7A acts as a master regulator altering chromatin accessibility.	ZBTB7A and its downstream target genes.	Astrocyte-specific overexpression of ZBTB7A drives widespread changes in chromatin accessibility, promoting a state of stress susceptibility.	Induction of behavioral and molecular signatures of stress susceptibility.	Identifies the transcription factor ZBTB7A as a potential therapeutic target for modulating astrocyte-mediated stress responses.	[42]

4. The Microglial Response to Stress

Accounting for approximately 10% of all brain cells, microglia are the resident immune cells of the CNS, acting as sentinels that constantly survey the brain microenvironment for signs of injury, infection, or homeostatic disturbance [50]. In response to such challenges, they undergo a rapid transformation from a resting, ramified state to an activated, amoeboid phenotype, capable of phagocytosis, antigen presentation, and the release of a vast array of signaling molecules, including cytokines, chemokines, and reactive oxygen species. While this response is essential for CNS protection, its chronic and uncontrolled activation is a key pathological feature of MDD [51]. Growing evidence from both preclinical models and human studies demonstrates that chronic stress triggers a shift in microglial state, often towards a pro-inflammatory and neurotoxic phenotype that contributes to the synaptic and neuronal deficits underlying depressive behaviors [52].

Definitive evidence establishing a causal role for these altered microglial states in driving depressive behaviors comes from depletion and repopulation experiments. Using a colony-stimulating factor 1 receptor (CSF1R) inhibitor (PLX5622) to selectively eliminate microglia, researchers have demonstrated that microglia are necessary for the development of stress-induced behavioral deficits [53]. One study showed that depleting microglia before repeated social defeat stress prevented the development of social withdrawal and cognitive impairment [54]. Early-life stress (ELS) induces enduring transcriptional reprogramming in hippocampal microglia that persists into adulthood and contributes to depressive vulnerability. While minimal changes are observed

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immediately after ELS (P9), adult mice (P200) exhibit 186 differentially expressed genes under basal conditions. Upregulated transcripts included inflammatory mediators such as *Ripk* and *Gas6*, *Akirin1* and *C1qbp*, and genes linked to Akt signaling. Conversely, transcripts associated with cytoskeletal plasticity (*Map*, *Stmn2*, *Stmn3*) and gliogenesis (*Cdh2*, *Metrn*) were downregulated. Weighted gene co-expression network analysis identified an ELS-linked module enriched for protein polyubiquitination and proteasome-mediated degradation, indicating a lasting pro-inflammatory and catabolic microglial phenotype. Importantly, *Gas6* upregulation was validated in post-mortem hippocampal tissue of depressed individuals with childhood abuse, where TMEM119+ microglia displayed elevated GAS6 [55].

Stress engages the High Mobility Group Box 1 (HMGB1) pathway to drive transcriptional plasticity in microglia during depression. In a CSDS model, stress-susceptible mice showed elevated HMGB1 expression in medial prefrontal cortex (mPFC) microglia. This triggered signaling via the HMGB1/STAT3/p65 axis, with RAGE and TLR4 receptors promoting STAT3 and p65 phosphorylation, alongside reduced expression of SOCS3, a negative STAT3 regulator. Functionally, this reprogramming induced a pro-inflammatory microglial phenotype, reflected by hyper-ramified morphology, increased Iba1 expression, and upregulation of cytokines IL-1β and IL-6. In parallel, the pathway enhanced autophagy, marked by elevated Atg5, Beclin-1, and LC3B-II levels. Viral-mediated knockdown of HMGB1 in the mPFC abolished these molecular and cellular changes, rescuing depressive-like behaviors [56].

In response to acute traumatic stress, such as electric foot-shocks, microglia exhibit a distinct pro-inflammatory transcriptional profile. Studies on mouse models of post-traumatic stress disorder (PTSD) have revealed that these cells increase in number and undergo morphological activation in the hippocampus. This is accompanied by a significant transcriptional upregulation of pro-inflammatory cytokines, including Interleukin-1β (IL-1β), IL-6, and Tumor Necrosis Factor-α (TNF-α). Mass cytometry has further shown increased expression of functional markers like iNOS and CD38. Pharmacological inhibition of this activation state alleviates the associated anxiety and fear behaviors [57]. Delving into the upstream molecular machinery, CSDS study revealed profound intracellular stress response centered on the interface between the endoplasmic reticulum (ER) and mitochondria. Stress signals, mediated by extracellular ATP, promote the formation of a tripartite tethering complex consisting of IP3R3-GRP75-VDAC1 at mitochondria-associated membranes (MAMs). This structural change facilitates excessive calcium (Ca2+) transfer from the ER into mitochondria. The resulting mitochondrial damage and reactive oxygen species (ROS) production serves as a direct trigger for the assembly and activation of the NLRP3 inflammasome, a key driver of microglial-mediated neuroinflammation in depression [58].

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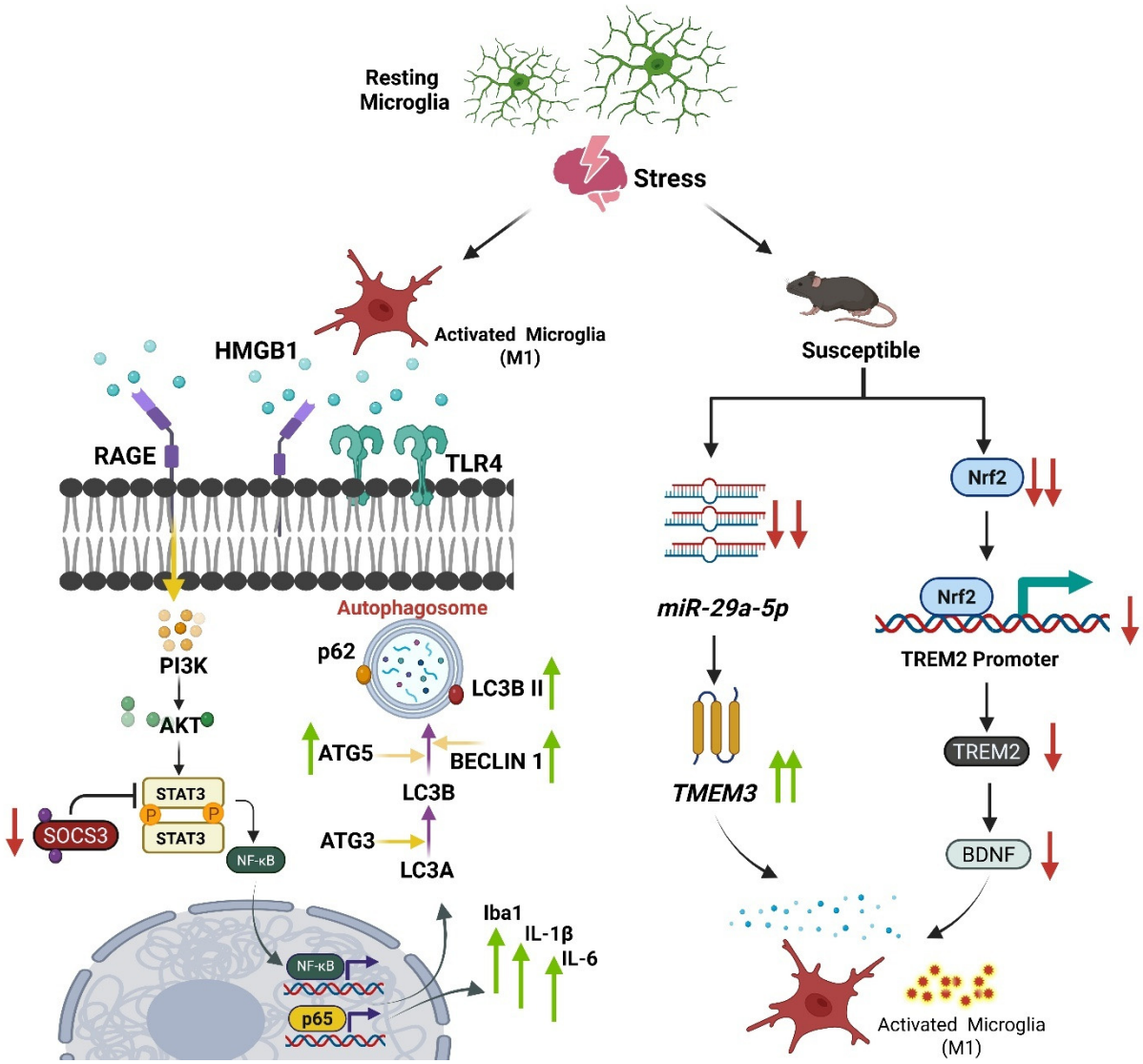

Figure 1. Key transcriptional pathways in mPFC microglia that regulate stress susceptibility and resilience. Stress induces pro-inflammatory, pro-depressive signaling through two distinct pathways: (1) The elevation of HMGB1, which signals via RAGE/TLR4 to activate the STAT3/p65 axis, and (2) the downregulation of miR-29a-5p, which increases its target TMEM33 to promote M1 polarization. In contrast, the Nrf2-TREM2 axis promotes a resilient, anti-inflammatory phenotype. The activation of Nrf2 drives TREM2 transcription, leading to an anti-inflammatory state and antidepressant-like effects.

4.1. Stress-Induced Changes in Microglial Density, Morphology, and State

Chronic stress does not simply cause a transient activation of microglia; it is a potent remodeling agent that induces durable phenotypic shifts, a process known as "priming". A primed microglia is one that has been altered by a prior stimulus (stress) such that its response to a subsequent challenge is exaggerated or otherwise modified. A recent study using the chronic unpredictable mild stress (CUMS) paradigm in mice found a non-linear pattern of microglial activation in the hippocampal dentate gyrus. Microglial density decreased after two weeks, increased at four weeks, and declined again at six weeks, suggesting an initial adaptation, followed by reactive proliferation and eventual exhaustion under prolonged stress [59]. Similarly, the repeated social defeat stress (RSDS) model, which recapitulates aspects of psychosocial stress in humans, induces a rapid and sustained increase in microglial density and proliferation in the mPFC of mice that are susceptible to the stressor [53]. Morphologically, these microglia transition from their normal, highly ramified "surveying" state to a more amoeboid phenotype characterized by a larger cell body, shorter processes, and reduced

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process complexity [53]. In a rat model of CUMS, this activation was confirmed using multimodal approaches; in vivo positron emission tomography (PET) imaging with the translocator protein (TSPO) ligand [18F] DPA-714 showed significantly increased signal in the hippocampus of stressed rats, which was corroborated by post-mortem immunohistochemistry showing elevated protein levels of the microglial markers Iba-1 and CD11b. Together, these studies establish that chronic stress is a powerful driver of microglial proliferation and morphological transformation in key mood-regulating circuits [60].

4.2. Divergent Microglial Phenotypes in Stress Susceptibility vs. Resilience

A pivotal advance in depression research is the recognition that not all individuals exposed to stress develop the disorder, and this difference is reflected in microglial responses. The response of microglia to stress is not uniform; instead, these cells exhibit remarkable plasticity, adopting distinct phenotypes that can either confer vulnerability or promote resilience. Morphological analysis in a social defeat stress model reveals that this phenotypic divergence is structurally evident within the CA1 region of the hippocampus. In this model, mice resilient to stress are characterized by the predominance of a "hyper-ramified" microglial morphology, distinguished by longer and more complex processes. Functionally, these hyper-ramified microglia in resilient animals show significantly increased physical contact with both GABAergic and glutamatergic synaptic puncta compared to vulnerable counterparts. Conversely, vulnerable mice exhibit a shift toward a "de-ramified" phenotype with shorter, less complex processes and increased microglial density, indicating that distinct morphological states of microglia are tightly correlated with behavioral outcomes of stress [61].

Beyond morphology, specific microRNA-mediated transcriptional regulation plays a crucial role in directing microglial polarization and determining stress outcomes. Research using a chronic unpredictable mild stress (CUMS) model in mice demonstrates that the expression of *miR-29a-5p* is significantly downregulated in the medial prefrontal cortex (mPFC) of susceptible animals. This downregulation leads to an increase in its target gene, transmembrane protein 33 (*TMEM33*). The resulting elevation in TMEM33 promotes the polarization of microglia toward a pro-inflammatory M1 state, characterized by increased levels of cytokines like IL-1β and TNF-α, while suppressing the anti-inflammatory M2 phenotype. Crucially, restoring *miR-29a-5p* levels in the mPFC rescues these effects; it suppresses TMEM33, facilitates M2 polarization, alleviates neuroinflammation, and ameliorates depressive-like behaviors, highlighting the miR-29a-5p/TMEM33 axis as a key transcriptional switch in microglial-mediated stress responses [62]. Another critical transcriptional axis governing the microglial phenotype in depression involves the transcription factor Nrf2 and its target TREM2. Nrf2 directly regulates *TREM2* transcription by binding to its promoter region. In response to stress, susceptible mice show reduced Nrf2 expression and TREM2 transcription in the mPFC. The activation of Nrf2 via the administration of sulforaphane (SFN) initiates *TREM2* transcription, which in turn promotes an anti-inflammatory, arginase 1+ microglial phenotype. This Nrf2-TREM2 pathway is associated with increased BDNF, and is essential for the antidepressant-like effects observed, implicating its importance in promoting a resilient microglial state [63].

Microglial transcriptional plasticity not only alters their own inflammatory state but also directs the production of secreted factors that directly impact neuronal health and contribute to depressive phenotypes. For instance, in CUMS-susceptible mice, microglia in the prelimbic cortex (PrL) exhibit significantly increased transcription and expression of Vitamin D Binding Protein (*VDBP*). This microglia-derived VDBP acts on the neuronal receptor megalin, triggering the downstream SRC signaling pathway. The activation of this pathway precipitates neuronal apoptosis and synaptic damage, including reduced dendritic spine density and impaired synaptic transmission. Targeted overexpression of microglial *VDBP* is sufficient to induce depression-like behaviors and aggravate CUMS-induced synaptic pathology, identifying it as a key pathogenic mediator in microglia-neuron communication during stress [64]. In stark contrast to pathogenic signaling, microglial transcriptional activity can also be harnessed to promote resilience, particularly through pathways shaped by early-

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life experiences. Maternal care, for example, stimulates the release of insulin-like growth factor-1 (IGF-1) from microglia in the mPFC of pups. This microglial IGF-1 acts on neuronal IGF-1 receptors, activating mTORC1 signaling, which in turn alters the translational ratio of the transcription factor C/EBPβ toward its inhibitory isoform, LIP. This reduction in C/EBPβ transcriptional activity leads to the downregulation of its target gene *Dnm1l* (encoding DRP1), a key mediator of mitochondrial fission. By preventing stress-induced mitochondrial dysfunction, this microglia-neuron axis established by positive early-life experience confers lasting resilience to stress in adolescence [65].

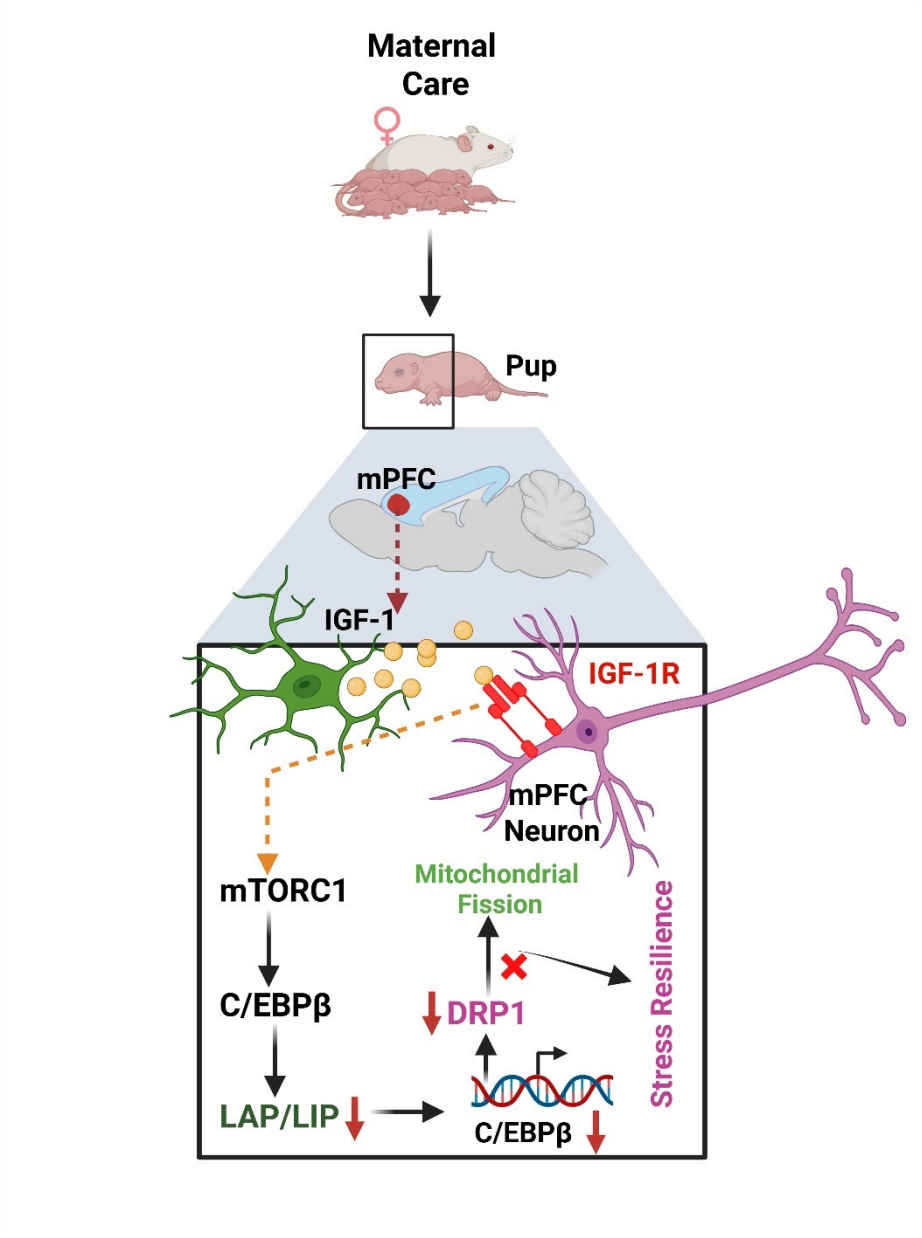

Figure 2. The microglia-to-neuron signaling axis mediating stress resilience. High maternal care stimulates microglia in the medial prefrontal cortex (mPFC) to release insulin-like growth factor-1 (IGF-1). This growth factor acts on neuronal receptors to activate mTORC1 signaling, which in turn increases the ratio of the inhibitory C/EBPβ-LIP isoform. The subsequent reduction in C/EBPβ transcriptional activity downregulates its target DRP1, preventing mitochondrial dysfunction and promoting resilience to stress.

Social factors, such as social hierarchy, can also powerfully modulate microglial transcriptional programs to influence susceptibility to stress-induced disorders like PTSD. In CSDS model, social rank was found to predict PTSD vulnerability, with dominant mice exhibiting greater susceptibility

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and more severe initial symptoms. At the molecular level, susceptible individuals show overactivation of microglia in the mPFC, which is associated with a specific transcriptional signature involving the activation of NF-κB p65 and STAT1 pathways. This activation drives increased expression of the ubiquitin-like modifier activating enzyme 7 (*Uba7*) gene and subsequent production of the pro-inflammatory cytokine TNF-α, linking a defined social context to a distinct, pathogenic transcriptional state in microglia [66]. In a study using RSDS model, in the mPFC, stress-susceptible mice displayed a pro-inflammatory microglial profile, with elevated CD86 expression and upregulation of TNF-α, CXCL10, and IL-1β. By contrast, resilient mice, despite undergoing the same stress, showed a pro-resolution phenotype with increased CD206 and IL-10 expression [53].

4.3. The Concept of Microglial "Priming" as an Epigenetic Memory

After the primary stressor is removed, microglia can return to a seemingly quiescent state, but they retain epigenetic marks on their histone tails that constitute a long-lasting memory of the event. Direct evidence for this epigenetic memory comes from studies of specific molecular modulators. In one primary study, priming microglia with an inflammatory trigger was shown to establish an "immune memory" that augmented the response to a second environmental stressor. The molecular underpinnings of this memory were identified as the enhanced deposition of active histone marks, specifically H3K27ac, H3K4me3, and H3K4me1 at gene regulatory regions [67]. Pharmacologically inhibiting the deposition of the key enhancer mark H3K27ac successfully prevented the formation of this immune memory and blocked the exaggerated secondary inflammatory response. At a molecular level, priming involves the binding of transcription factors to enhancer regions of the genome, leading to the acquisition of these activating histone modifications [68]. DNA methylation provides another mechanism for this long-term cellular memory. A study investigating the lasting impact of early-life stress (ELS) found that mice subjected to early social isolation displayed a drastic decrease in global DNA methylation levels specifically within their microglial cells. This stable alteration to the microglial methylome is one of the key mechanisms through which microglia "hold memories" of the early adverse experience, programming them to be more reactive to challenges later in life [69].

A study examining a model of post-stroke anxiety found that the epigenetic regulator HDAC3 was specifically upregulated in microglia, not astrocytes. In this model, which combined photothrombotic stroke with restraint stress, it was microglial HDAC3 that drove anxiety-like behavior. The molecular mechanism involved HDAC3 deacetylating the p65 subunit of NF-κB. This post-translational modification altered the transcription of genes involved in prostaglandin synthesis, such as cox*1*, leading to an overproduction of prostaglandin E2 (PGE2) in the damaged cortex. This PGE2 then diffused to the amygdala, where it acted on neuronal EP2 receptors to elicit anxiety susceptibility, highlighting a distinct, microglia-specific epigenetic response to this particular combined stressor [70].

4.4. DNA Methylation as a Molecular Imprint of Stress in Microglia

Among epigenetic mechanisms, DNA methylation- the covalent addition of a methyl group to cytosine residues, most commonly within CpG dinucleotides represents a particularly stable modification that can induce persistent alterations in gene expression potential. Owing to its stability, DNA methylation is considered a key mechanism through which early-life or chronic stress may imprint enduring molecular signatures within the microglial genome, thereby establishing a long-lasting predisposition to depressive pathology [71]. Progress in understanding the human microglial epigenome has been hampered by the difficulty of isolating these cells from the complex milieu of the brain. Genome-scale methylation analysis on pure microglia acutely isolated from post-mortem human brain tissue from 22 donors, including individuals with mood disorders and non-psychiatric controls revealed that microglia possess a DNA methylation profile that is distinct from other CNS cells. A key finding was that interindividual variation, rather than brain region, was the dominant source of methylation differences, suggesting that genetic background and life experiences including stress, profoundly shape the microglial epigenome [72].

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4.5. Microglial Regulation via Histone Modifications and Non-Coding RNAs in Stress

A recent study uncovered a novel and highly specific mechanism of communication between microglia and neurons in depression that is mediated by miRNAs. Using the CUMS rat model, tit was shown that stressed microglia significantly increase their secretion of extracellular vesicles known as exosomes. Critically, these exosomes were found to be enriched with a specific microRNA, miR-146a-5p [73]. These exosomes are taken up by neurons in the hippocampal dentate gyrus, a key site for adult neurogenesis that is implicated in depression. Once inside the neurons, miR-146a-5p exerts its regulatory function by directly suppressing the mRNA of Krüppel-like factor 4 (KLF4), a transcription factor essential for the differentiation and survival of new neurons.

A peripheral immune challenge with Bacille Calmette-Guerin (BCG) has been shown to induce persistent depression-like behaviors, providing a model to investigate lasting molecular changes in microglia. Proteomic profiling of isolated microglia after symptom onset revealed broad alterations in protein abundance and post-translational modifications, including histone acetylation. This was accompanied by reduced abundance of histone clusters 1-3 and increased H2A variants, suggesting disrupted chromatin architecture [74].

4.5.1. The H3K27me3 Axis: EZH2 vs. Jmjd3

The trimethylation of histone H3 at lysine 27 (H3K27me3) is a canonical repressive mark that silences gene expression. The dynamic regulation of this mark is a central for the control of microglial activation. The “writers” of this mark are the histone methyltransferases of the Polycomb Repressive Complex 2 (PRC2), whose catalytic subunit is EZH2. Under homeostatic conditions, EZH2 deposits H3K27me3 at the promoters of inflammatory genes, keeping them silenced. However, in a mouse model of adolescent depression, the expression of Polycomb group factor 1 (PCGF1), a component of the related PRC1 complex that helps recruit PRC2 to its targets, was found to be significantly decreased in microglia. This reduction in PCGF1 function led to diminished deposition of both H2AK119ub (a mark placed by PRC1) and H3K27me3 at the promoter of the pro-inflammatory gene *Matrix Metalloproteinase 10* (*MMP10*). The resulting transcriptional de-repression of *MMP10* unleashed a neuroinflammatory cascade that drove neuronal damage and depressive-like behaviors [13].

In direct opposition to EZH2 are the “erasers” of this mark, the H3K27 demethylases. The most prominent of these in microglia is Jumonji domain-containing protein 3 (Jmjd3), also known as KDM6B [75]. Jmjd3 expression is induced by inflammatory stimuli, such as lipopolysaccharide (LPS) or chronic stress, via activation of the NF-κB signaling pathway. Once expressed, Jmjd3 is recruited to the promoters of pro-inflammatory cytokines, where it actively removes the repressive H3K27me3 mark. This epigenetic switch from a repressed to an active chromatin state allows for robust transcription of genes like *Il-6* and *Tnf-α*, driving the inflammatory response [75].

4.5.2. The H3K9me2 Axis: The G9a/GLP Complex

Another critical repressive mark is the dimethylation of histone H3 at lysine 9 (H3K9me2), deposited by a complex of the methyltransferases G9a and GLP. Inhibition of this complex in adult mice produces anxiolytic effects, suggesting that reducing H3K9me2-mediated repression is beneficial. However, the same inhibition during embryonic development increases anxiety-like behaviors in adult offspring, highlighting a critical developmental window for this epigenetic mechanism [76].

4.6. The Heterogeneous Microglial Transcriptome in Depression

While preclinical models often point towards a pro-inflammatory microglial state, research in human post-mortem tissue has presented a more complex perspective. A key study performing RNA-sequencing on pure microglia isolated from the occipital cortex grey matter of MDD donors found a predominantly immune-suppressed profile. Strikingly, transcriptional alterations were restricted to

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GM microglia, defining a phenotype termed Depressive Disease-Associated Microglia (DepDAM), characterized by immune suppression rather than classical activation. A total of 81 genes were significantly downregulated, including key players in immune activation and phagocytosis such as the scavenger receptor. *CD163*, the opsonin *SPP1* (osteopontin), and critical components of the classical complement pathway (*C1QA*, *C1QB*, *C1QC*). This signature suggests a state of functional inhibition. Interestingly, the upregulation of neuronal regulatory genes *CD200* and *CD47* was also observed in the microglia of MDD patients, suggesting this immunosuppressive phenotype may be actively maintained by signals from neurons [77]. However, few studies point to different molecular signatures, highlighting the heterogeneity of the microglial response. For instance, by combining spatial and single-cell transcriptomics, one study identified a specific microglial subgroup, designated Mic03, that was strongly correlated with depression. This subgroup was characterized by elevated expression of genes involved in controlling microglial activation and neuroinflammation, including *IQGAP2*, *FYN*, *PDE7A*, and *ARHGEF3*. These divergent findings may reflect differences in brain region, disease chronicity, or patient-specific factors [78].

In models of prolonged, chronic mild stress, microglia can adopt an entirely different state characterized by widespread transcriptional repression. This response involves the significant downregulation of numerous interferon-regulated genes (IRGs), which correlates with decreased chromatin accessibility at Interferon-Stimulated Response Element (ISRE) motifs. This immunosuppressive phenotype appears to be actively mediated, driven not by a change in interferon levels but by the upregulation of the transcriptional repressor Activating Transcription Factor 3 (ATF3), demonstrating the remarkable and context-dependent plasticity of the microglial transcriptome in stress-related disorders [79].

4.7. Therapeutic Implications of Microglial Epigenetic Regulation in Stress

The convergence of findings from diverse preclinical models and human studies strongly indicates that the microglial epigenome is a druggable target for novel antidepressant development. The studies summarized in Table 2 reveal that pharmacological interventions aimed at specific epigenetic regulators can successfully reverse stress-induced microglial activation and ameliorate depressive-like behaviors. A particularly robust strategy involves targeting the H3K27me3 demethylase JMJD3, as both the selective inhibitor GSK-J4 and the natural compound Ginsenoside Rd have been shown to be effective in distinct stress paradigms by restoring this repressive histone mark at inflammatory gene loci [80,81]. Furthermore, the field is advancing toward greater therapeutic precision, exemplified by the efficacy of a selective HDAC11 inhibitor, which suppresses microglial activation in an LPS-induced depression model [82]. The natural compound Nerolidol has been shown to exert antidepressant effects by downregulating DNA methyltransferase 1 (DNMT1) [83]. Finally, emerging evidence points to the therapeutic potential of modulating non-coding RNA networks, such as targeting the circular RNA circ-UBE2K, to rescue depressive phenotypes [84]. These studies establish that precision epigenetic modulators, designed to reprogram rather than simply suppress microglial function, represent a promising future class of therapeutics for stress-related disorders.

Table 2. Epigenetic Mechanisms and Therapeutic Targeting of Microglia in Stress-Related Depression.

Stress	Epigenetic Mechanism	Target Genes/ Pathways	Observed Microglial Response	Behavioral/Functional Outcome	Therapeutic Implications / Interventions	Study Reference
Chronic Unpredictable Mild Stress (CUMS) in adolescent rats	Histone Demethylation (via KDM6B/JMJD3)	Increased Jmjd3 expression, decreased H3K27me3 levels. Upregulation of pro-inflammatory	Microglial activation in the prefrontal cortex (PFC) and	Depressive-like behaviors (anhedonia, despair). Increased susceptibility to	Minocycline (microglial inhibitor) reversed microglial activation, normalized Jmjd3/H3K27me3 levels, and alleviated	[85]

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		cytokines (IL-1β, TNF-α).	hippocampus (HIP).	stress in adulthood.	depressive-like behaviors.	
Chronic Unpredictable Mild Stress (CUMS) in C57BL/6 and obese (ob/ob) mice	Histone Demethylation (via JMJD3)	Increased JMJD3 and NF-κB expression; decreased H3K27me3 levels. Increased pro-inflammatory cytokines. Downregulation of adiponectin (APN).	Microglial activation in PFC and HIP; excessive activation in ob/ob mice.	Depressive-like behaviors and memory impairment. Obese mice showed worse behavioral outcomes, suggesting increased susceptibility.	GSK-J4 (selective JMJD3 inhibitor) relieved depressive-like behaviors, memory impairment, microglial activation, and normalized epigenetic/inflammatory markers.	[81]
Chronic Unpredictable Mild Stress (CUMS) in mice	DNA Methylation (via DNMT1)	Downregulation of DNA methyltransferase 1 (DNMT1).	Suppression of CUMS-induced microglial activation and inflammatory response.	Reduction in depressive-like behavior (assessed by OFT, SPT, TST).	Nerolidol (a natural sesquiterpene) reduced DNMT1 levels and suppressed microglial activation.	[83]
Lipopolysaccharide (LPS)-induced depression model in mice	Histone Deacetylation (via HDAC11)	Inhibition of HDAC11 deacetylase function.	Suppression of LPS-induced microglial activation. Initiation of autophagy and inhibition of nitric oxide (NO) production.	Alleviation of depression-like behavior (reduced immobility, increased sucrose preference).	Novel selective HDAC11 inhibitor (Compound 5) alleviated depressive-like behavior by inhibiting microglial activation.	[82]
Human Post-Mortem Brain Tissue (Dorsolateral Prefrontal Cortex) from individuals with Major Depressive Disorder (MDD)	Chromatin Remodeling (Single-nucleus Assay for Transposase-Accessible Chromatin sequencing - snATAC-seq)	Decreased accessibility at binding sites for TFs known to regulate immune homeostasis. Disruption of TF binding sites linked to genes affecting synaptic communication. Key TF mentioned: NR4A2 (activity-dependent, stress-reactive).	A specific gray matter microglia cluster (termed Mic2) exhibited significantly decreased chromatin accessibility at key regulatory regions.	The study directly links these cell type specific epigenetic alterations to the clinical diagnosis of MDD in humans, providing strong evidence for real, measurable brain changes underlying the disorder.	Identification of a specific microglial subtype and regulatory mechanism opens pathways for developing highly targeted therapies	[86]
Gut microbiota-dysbiosis mouse model (germ-free mice colonized with microbiota from MDD patients vs. healthy controls).	Non-coding RNAs (lncRNA-miRNA-mRNA networks)	ceRNA networks involving lncRNAs (*4930417H01Rik*), miRNAs (*mmu-miR-883b-3p*), and mRNAs (*Adcy1*, *Nr4a2*). Axonal guidance and	Dysregulation of microglial function via altered inflammatory signaling (IFNG	Dysregulated inflammatory response and neurodevelopment in the hippocampus	Identifies specific ncRNA networks in the gut-brain-epigenome axis as potential biomarkers and therapeutic targets for microbiota-based antidepressant strategies.	[87]

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		synaptogenesis pathways.	pathway), contributing to decreased neuronal activity (*Fos* downregulation)			
Chronic unpredictable mild stress (CUMS)	circRNA-mediated regulation	UBE2K (ubiquitin conjugating enzyme) downstream enrichment of TNF, IL-17, cytokine signaling.	Microglia show morphological activation (shorter branches, increased soma size, elevated Iba1 intensity), increased iNOS/CD68 and pro-inflammatory cytokines	Worsened depression-like behaviours; increased neuroinflammation and neuronal/synaptic damage.	Targeting circ-UBE2K (knockdown) or disrupting circ-UBE2K/HNRNPU axis reduced microglial activation and rescued depressive-like phenotypes suggests circRNA or HNRNPU as therapeutic targets/biomarkers	[84]
Lipopolysaccharide (LPS) systemic inflammation model in mice.	Histone demethylation: activation of JMJD3 (H3K27me3 demethylase).	TLR4, PI3K, AKT, NF-κB signaling; JMJD3-regulated pro-inflammatory gene transcription.	Microglial overactivation with elevated IL-1β, IL-6, TNF-α; reduced by Rd treatment.	LPS-induced depressive-like behavior with decreased sucrose preference and increased immobility; Rd rescues behavior and synaptic protein expression (PSD-95, SYP).	Ginsenoside Rd reduces JMJD3 expression and suppresses TLR4-PI3K-AKT-NF-κB signaling, leading to decreased microglial activation and behavioral improvement.	[80]
Postmortem brain tissue (4 regions) from donors with mood disorders (n=13) vs. control (n=8) donors.	DNA Methylation (Genome-wide methylation array)	Differentially Methylated Regions (DMRs) associated with mood disorder status, linked to genes involved in myeloid cell function and neuropsychiatric disorders.	Altered DNA methylation profiles in isolated microglia. Interindividual factors	Findings suggest the microglial methylome is highly responsive to individual-specific factors, contributing to cellular heterogeneity.	Identifies mood disorder-associated DMRs in microglia that could serve as biomarkers or targets for epigenetic drugs.	[72]

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		and age showed a larger effect on the methylome than brain regions.

5. The Oligodendrocytes: Myelin Plasticity and Vulnerability in Depression

Oligodendrocytes are the myelinating cells of the CNS, responsible for ensheathing axons with lipid-rich myelin, which is essential for rapid saltatory nerve conduction and provides vital metabolic support to axons. For a long time, myelin was considered a static structural element, but this view is being rapidly overturned. There is now a wealth of evidence indicating that myelination is a dynamic and plastic process that continues throughout life and is crucial for learning, memory, and cognitive function [88,89]. Correspondingly, disruptions in oligodendrocyte function and myelin integrity have been increasingly identified as a core pathological feature of MDD. The lifelong process of generating new oligodendrocytes from a resident pool of oligodendrocyte precursor cells (OPCs), known as oligodendrogenesis, is critical for brain plasticity, learning, and repair. Chronic stress appears to directly affect this fundamental process. A study utilizing the repeated social defeat stress (RSDS) mouse model, demonstrated that chronic psychosocial stress inflicts profound damage on the OPC population in the medial prefrontal cortex (mPFC) [90].

The timing of stress exposure is also a critical variable. Adolescence is a period of dynamic white matter development and circuit refinement, rendering the brain particularly vulnerable to environmental insults. A recent work on adolescent mice uncovered a significant, region-specific impairment of oligodendrogenesis. In the mPFC and the lateral habenula (LHb); two brain regions heavily implicated in mood regulation and depression, stress caused a marked decrease in the number of proliferative cells and, consequently, a reduction in newly formed OPCs and mature oligodendrocytes. Notably, this effect was not observed in the amygdala, highlighting a circuit-specific vulnerability [91].

5.1. Transcriptional Control of Myelination and its Disruption by Stress

Numerous studies using animal models of chronic stress and depression have documented significant myelin deficits, demyelination, and reductions in the number and function of oligodendrocytes and their precursor cells (OPCs) in mood-related brain circuits. This pathology is mirrored in humans. Post-mortem studies of individuals with MDD have revealed altered expression of a suite of key myelin and oligodendrocyte related genes, including *Proteolipid Protein 1* (*PLP1*), *2',3'-Cyclic-Nucleotide 3'-Phosphodiesterase* (*CNP*), *Myelin Oligodendrocyte Glycoprotein* (*MOG*), and the transcription factor *OLIG1*[92]. Furthermore, a recent study using cell-type-specific nuclear isolation from the post-mortem basolateral amygdala found that expression of *Myelin-Associated Oligodendrocyte Basic Protein* (*MOBP*) was significantly decreased specifically in the oligodendrocytes of depressed individuals who had a history of childhood abuse, directly linking early life trauma to specific molecular deficits in this cell type [93].

These myelin deficits are not simply a passive consequence of neuronal damage but represent an active, pathological process driven by the epigenetic suppression of the myelinogenic program within oligodendrocytes. This concept of "epigenetic silencing" is well-established in demyelinating diseases like multiple sclerosis, where mature oligodendrocytes present in lesions fail to produce myelin [94]. A clear molecular mechanism for this process was recently elucidated in a model of Parkinson's disease, another disorder with myelin pathology [95]. In this model, the DNA methyltransferase DNMT3A was upregulated, leading to hypermethylation and silencing of the promoter for the transcription factor *STAT5B*. This reframes myelin integrity as a form of

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epigenetically regulated structural plasticity that is highly vulnerable to stress. Antidepressant treatments appear to counteract this pathological silencing. For instance, the immunomodulatory drug teriflunomide protects oligodendrocytes from stress-induced apoptosis and damage [96], while the SSRI paroxetine promotes the proliferation and differentiation of OPCs, restoring myelin integrity in a corticosterone-induced depression model [97]. Furthermore, perinatal exposure to fluoxetine has been shown to directly alter the expression of myelin genes like *Mag* and *Mbp* through changes in DNA methylation, underscoring the sensitivity of the oligodendrocyte epigenome to pharmacological intervention during critical developmental windows [98].

In models such as chronic unpredictable mild stress (CUMS) and repeated social defeat stress (RSDS), animals exhibit depressive-like behaviors that are accompanied by significant pathology in the prefrontal cortex (PFC), a key region for mood regulation. Single-nucleus RNA sequencing of the PFC in these models reveals that chronic stress induces profound structural and transcriptional alterations in oligodendrocytes, with particularly strong effects observed in male mice, leading to disrupted neuro-glial interactions [99]. Pathway analyses of the widespread transcriptomic changes in the PFC of chronically stressed mice consistently point to a core set of upstream regulators that directly link the stress response to the fundamental machinery of myelination and its epigenetic control. Among the top predicted regulators are Myelin Regulatory Factor (Myrf), a master transcription factor essential for oligodendrocyte differentiation, and Methyl-CpG binding protein 2 (Mecp2), a key epigenetic "reader" protein that translates DNA methylation patterns into changes in gene expression [100].

Stress induces a profound dysregulation of the oligodendrocyte transcriptome, shifting the cell's genetic program away from myelination and maintenance toward a state of dysfunction. A comprehensive 2018 study using a chronic social stress (CSS) model in mice found a general downregulation of oligodendrocyte gene expression, including genes essential for myelin formation and axonal support. By using mice genetically engineered to be heterozygous for the oligodendrocyte gene *Cnp1* (encoding 2′,3′-cyclic-nucleotide 3′-phosphodiesterase), thereby having constitutively reduced expression of a key myelin-related protein, the researchers demonstrated that these mice were more vulnerable to the behavioral effects of stress. This provides translational evidence that a reduction in oligodendrocyte gene expression is not merely a correlate of stress but is a causal contributor to the development of stress-induced aversion and anxiety phenotypes [101]. The robustness of this finding has been solidified by a large-scale congruent analysis performed in 2023. This work moved beyond a single stress paradigm by integrating and re-analyzing publicly available transcriptomic datasets from multiple, distinct mouse models of adversity, including social defeat, chronic unpredictable stress, early life stress, and adolescent social isolation. The analysis revealed a conserved transcriptional signature of oligodendrocyte dysregulation across all these models. Critically, the study extended this finding to humans, identifying a similar oligodendrocyte transcriptome change in post-mortem prefrontal cortex tissue from both male and female patients with MDD, establishing a clear translational bridge between preclinical models and the human condition [102].

5.2. Early-Life Stress impairs Oligodendrocyte Developmental Trajectories

The impact of early-life stress (ELS) is particularly insidious because it occurs during a critical period of oligodendrogenesis and myelination, creating a developmental vulnerability that can last a lifetime. Studies using the maternal separation model in rodents, a well-established paradigm for ELS, have uncovered a paradoxical mechanism of damage [103]. Unbiased mRNA profiling in the medial PFC (mPFC) of maternally separated pups revealed that ELS induces a precocious differentiation of oligodendrocytes. While this leads to a transient increase in the expression of myelin-related genes during the postnatal period, it comes at a steep long-term cost: the premature exhaustion and subsequent depletion of the renewable OPC pool in the adult brain [104]. This ELS-induced disruption does not occur in isolation. The initial insult to the OPC population radiates outward, affecting the development and function of the entire glial network. A 2021 study by Wang

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and colleagues demonstrated that the ELS-induced reduction in the OPC population secondarily hinders the development of astrocytes in the hippocampus. This occurs because OPCs provide essential paracrine signals, specifically Wnt ligands, that are required for the proper formation of astrocytic networks. The loss of these signals due to OPC depletion leads to a secondary astrocytopathy, compounding the damage to the brain's supportive cellular architecture [105]. The integrity of white matter tracts, which is critical for the rapid communication and synchronization of distributed neural networks, is highly dependent on the health and function of oligodendrocytes. Clinical studies have shown that prenatal maternal depression, a human correlate of ELS, is associated with significant alterations in the white matter microstructure of infants, a link that appears to be mediated by epigenetic modifications detectable at birth in umbilical cord blood [106].

5.3. Linking Stress to Oligodendrocyte Transcriptional Dysfunction

The balance between histone acetylation and deacetylation is fundamental to oligodendrocyte lineage progression. This balance is maintained by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). A substantial body of work on affective disorders have established that HDAC activity is essential for OPCs to differentiate into mature, myelinating oligodendrocytes [107]. Histone Deacetylase 11 (HDAC11), the sole member of the Class IV HDAC family, plays a complex and essential role. Its expression increases as oligodendrocytes mature, and it is required for the proper expression of the major myelin genes *MBP* and *PLP*. Disrupting HDAC11 function impairs both gene expression and the morphological development of oligodendrocytes [108]. Exposure to stress, particularly early-life adversity, induces widespread and persistent changes in DNA methylation patterns across the genome [109]. Methyl-CpG binding protein 2 (MeCP2) is the canonical reader of the DNA methylome in the brain, and its function is indispensable for normal oligodendrocyte development and myelination. MeCP2 deficiency in oligodendrocytes leads to profound dysregulation of myelin gene expression and impaired myelin formation. Intriguingly, studies in cultured rat oligodendrocytes have revealed that MeCP2 normally functions as a negative regulator, or a brake, on the expression of key myelin genes, including myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG), as well as the neurotrophin BDNF [110].

The diverse epigenetic insults triggered by stress likely converge on a select few master regulatory genes that orchestrate the complex process of oligodendrocyte differentiation. Myelin Regulatory Factor (*Myrf*) is one such master transcription factor; its timely activation is an absolute requirement for OPCs to differentiate and begin producing myelin [111]. The expression of *Myrf* is itself under tight control by upstream factors and is associated with specific promoter and enhancer elements [112]. The finding that Myrf is a top predicted upstream regulator of the entire transcriptomic response to chronic stress in the PFC strongly suggests that its regulatory regions are a key target of stress-induced epigenetic changes [100]. A plausible mechanism is that chronic stress, through the activation of DNA methyltransferases (DNMTs) induces repressive hypermethylation at a critical enhancer element of the *Myrf* gene.

5.4. MicroRNAs and Long Non-Coding RNAs in Oligodendrocyte Function

MicroRNAs are small (~22 nucleotide) RNA molecules that typically function by binding to messenger RNA (mRNA) targets, leading to their degradation or translational repression. A single miRNA can regulate hundreds of different mRNA targets, allowing it to act as a master regulator of entire cellular pathways. Specific miRNAs are known to be essential for normal oligodendrocyte development. For example, miR-219 is a critical factor for promoting the transition of OPCs into mature, myelinating oligodendrocytes; its absence can halt this developmental progression [113]. Recent research has directly implicated miRNA dysregulation in the pathophysiology of MDD. A 2024 study analyzing postmortem brain tissue from individuals with MDD identified a significant decrease in the expression of two specific miRNAs, miR-92a-3p and miR-129-5p [114]. This decrease was found specifically within extracellular vesicles (EVs), which are small membrane-bound particles

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released by cells for intercellular communication. Oligodendrocytes are a major source of brain-derived EVs, suggesting they may be the origin of this pathological signal.

Using a mouse model of chronic unpredictable mild stress (CUMS), high-throughput sequencing of both miRNA and mRNA from the mPFC revealed a clear inverse relationship: the expression of mRNAs encoding proteins crucial for myelination, GABAergic and dopaminergic synapses, and neuronal growth was significantly downregulated in the stressed mice. Concurrently, the expression of a set of miRNAs predicted to target these very mRNAs was significantly upregulated. This finding demonstrates that stress activates a miRNA-driven program that actively dismantles the transcriptional machinery required for maintaining white matter integrity [115]. Complementing this work, a 2025 study analyzed human brain tissue from patients with a range of psychiatric and neurodegenerative disorders and identified 49 unique miRNAs whose expression levels were associated with conditions including MDD and PTSD, suggesting that specific miRNA candidates may represent points of convergent pathology, contributing to shared disease mechanisms across different stress-related disorders and providing potential targets for future therapeutic intervention [116].

Long non-coding RNAs are a large and diverse class of RNA molecules greater than 200 nucleotides in length that do not code for proteins. Recent studies have identified lncRNAs that are specifically and critically involved in oligodendrocyte biology. One such example is *MYRACL* (*MYelination RegulAting oligodendroCyte associated LncRNA*), which is highly enriched in mature oligodendrocytes relative to their progenitor cells. Experimental manipulation in human cell culture models demonstrated that knocking down *MYRACL* expression disrupts oligodendrocyte maturation, whereas overexpressing it promotes differentiation and enhances myelin formation in vitro [117]. This identifies *MYRACL* as a potent pro-myelinating lncRNA whose expression could be a key target for disruption by chronic stress. Indeed, transcriptomic analyses from both human MDD brains and animal stress models reveal widespread dysregulation of the lncRNA landscape. A single-nucleus transcriptomic study of postmortem MDD brain tissue identified the lncRNA *MALAT1* as one of the top-ranked genes whose expression within the oligodendrocyte lineage could distinguish MDD cases from healthy controls [118]. In parallel, studies in mice have shown that another lncRNA, *NEAT1*, is highly expressed in glial cells and is essential for regulating the adaptive behavioral response to stress. Loss of *NEAT1* function results in neuronal hyperexcitability and panic-like behaviors, demonstrating its crucial role in maintaining emotional homeostasis [119]. The complex patterns of ncRNA dysregulation suggest they play two key roles in the oligodendrocyte response to stress. First, they act as "signal integrators." A single environmental stressor triggers a coordinated change in the expression of hundreds of genes related to cell survival, metabolism, and differentiation.

Table 3. Summary of studies on Modulation of Oligodendrocytes in Stress-Induced Depression.

Stress Paradigm / Model	Key Genes / Pathways Affected	Observed Oligodendrocyte Response	Behavioral/Functional Outcome	Study Reference
Repeated Social Defeat Stress (RSDS) Mouse Model	Oligodendrocyte Precursor Cells (OPCs)	Profound damage and reduction of the OPC population in the medial prefrontal cortex (mPFC).	Disruption of oligodendrogenesis, which is critical for brain plasticity, learning, and repair.	[91]
Major Depressive Disorder (MDD) (Post-mortem human	Altered expression of long non-coding RNA MALAT1	Greatest transcriptional dysregulation found in immature OPCs; MALAT1 expression in early OPCs (OPC2 stage) has high	Associated with the clinical diagnosis of MDD.	[118]

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prefrontal cortex)		predictive power for distinguishing MDD cases.		
Human Post-Mortem MDD Tissue	*PLP1*, *CNP*, *MOG*, *OLIG1*, *MOBP*	Decreased expression of key genes related to myelin and oligodendrocyte function. *MOBP* decrease linked to childhood abuse.	Myelin deficits and impaired integrity of white matter tracts are considered core pathological features of MDD.	[92,93]
Early-Life Stress (ELS) / Maternal Separation Model	Wnt signaling pathway	An initial, premature differentiation of oligodendrocytes leads to the long-term depletion and exhaustion of the renewable OPC pool in the adult brain.	Impairs secondary development of astrocytes and leads to lasting white matter vulnerability.	[104,105]
Chronic Unpredictable Mild Stress (CUMS) / RSDS Models	Myelin Regulatory Factor (Myrf), Methyl-CpG binding protein 2 (Mecp2)	Widespread transcriptomic changes, with Myrf and Mecp2 identified as top upstream regulators linking the stress response to myelination machinery.	Shifts the genetic program away from myelination, contributing to stress-induced aversion and anxiety.	[101]
Chronic Unpredictable Mild Stress (CUMS) Mouse Model	Upregulation of miRNAs that target myelination-related mRNAs	A significant downregulation of mRNAs for myelination, GABAergic/dopaminergic synapses, and neuronal growth, inversely correlated with an upregulation of their targeting miRNAs.	Active dismantling of the transcriptional machinery required to maintain white matter integrity in the mPFC.	[115]

6. Conclusions

The paradigm for understanding major depression is shifting from a purely neuron-centric model to one that recognizes glial cells as critical drivers of its pathophysiology. The evidence reviewed here establishes that chronic stress induces profound, cell-type-specific transcriptional and epigenetic reprogramming in astrocytes, microglia, and oligodendrocytes, which collectively orchestrate the neuroinflammation, synaptic deficits, and white matter abnormalities seen in depression. Stress compromises astrocytic control over glutamate homeostasis through histone modifications, epigenetically "primes" microglia for a chronic pro-inflammatory state, and impairs oligodendrocyte maturation and myelin integrity by silencing essential genes. These are not independent pathologies but interconnected consequences of maladaptive glial plasticity. This glial-centric framework unveils a new frontier for therapeutic development that moves beyond monoamine-based approaches. Future strategies should prioritize the development of precision epigenetic modulators capable of reversing these pathological changes. Targeting specific histone-modifying enzymes like HDACs or demethylases such as JMJD3, modulating DNA methylation, and harnessing non-coding RNAs offer tangible pathways to reprogram glia back to a homeostatic state. By directly addressing the molecular mechanisms through which stress becomes embedded in the brain's cellular architecture, such interventions hold the promise of creating more effective and enduring treatments for depressive disorders.

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