NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | MINI-REVIEW ISSN: 2576-828X

A mini review on genes in stroke recovery: unveiling the genetic blueprint for rehabilitation therapies

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Received: 20 June 2025; **Accepted:** 3 November 2025; **Published:** 29 December 2025
Edited by: Lin Kooi Ong (University of Southern Queensland, Australia)
Reviewed by: Deepak Nainwal (Jayoti Vidyapeeth Women's University, India);
Raghuveer Raghumahanti (Manav Rachna International Institute of Research and Studies, India).
https://doi.org/10.31117/neuroscirn.v8i4.476

Abstract: Stroke remains a significant global cause of death and long-term disability, categorized into hemorrhagic stroke, ischemic stroke, and transient ischemic attack. Recovery outcomes can vary greatly, often influenced by genetic factors. This review highlights key genes involved in stroke recovery, including brain-derived neurotrophic factor (*BDNF*), glial cell-derived neurotrophic factor (*GDNF)*, insulin-like growth factor-1 (*IGF-1*), vascular endothelial growth factor (*VEGF*), C-X-C motif chemokine ligand 12 (*CXCL12*), hypoxia-inducible factor 1-alpha (*HIF1A*), nuclear factor erythroid 2-related factor 2 (*NRF2*), nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (*NLRP3*), sirtuin 1 (*SIRT1*), and tissue inhibitor of metalloproteinase 3 (*TIMP3*). These genes play important roles in neurotrophic support and neuronal survival, angiogenesis, inflammation and immune modulation, and extracellular matrix remodeling after stroke. Insights from both human and animal studies underscore the potential of these genetic markers as prognostic indicators and therapeutic targets for stroke recovery. Understanding these factors may lead to more personalized rehabilitation strategies, and future research is needed to explore gene-environment interactions and translate genetic findings into effective stroke recovery therapies.

Keywords: Stroke recovery; Genetic factors; Prognostic biomarkers; Rehabilitation therapies

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1.0 INTRODUCTION

Stroke remains one of the leading causes of death and long-term disability worldwide, categorized into three primary types: hemorrhagic stroke, ischemic stroke, and transient ischemic attack. Hemorrhagic stroke, which results from the rupture of a cerebral blood vessel, accounts for approximately 34.6% of all stroke cases (Feigin et al., 2024). Ischemic stroke, the most prevalent form, comprises around 65.3% of cases and occurs when a blood clot obstructs a cerebral blood vessel, leading to oxygen deprivation and subsequent neuronal damage (Feigin et al., 2024). Transient ischemic attack, often referred to as mini-stroke, is characterized by temporary blockages of blood flow to the brain, producing stroke-like symptoms but without permanent damage, with an incidence rate of about 2% (Abdul Aziz & Sidek, 2016).

Genome-wide association studies and transcriptomic profiling have highlighted key candidate genes contributing to post-stroke outcomes. Approximately 74 known genetic polymorphisms are distributed across

48 traits related to various post-stroke disability metrics (Carnwath et al., 2024). The identified variants encompass diverse biological systems, including inflammation, vascular homeostasis, growth factors, metabolism, the p53 regulatory pathway, and mitochondrial function. Understanding how these variants influence functional outcomes may help maximize post-stroke recovery. Animal models, particularly rodent studies, have also provided valuable insights into the genetic mechanisms underlying stroke recovery. Numerous studies have reported the involvement of several key genes in stroke recovery in both human and animal research, but a comprehensive review summarizing these findings is lacking.

Therefore, this review explores the current understanding of genetic factors related to stroke recovery, drawing on both human and animal studies. It places particular emphasis on the roles of brain-derived neurotrophic factor (*BDNF*), glial cell-derived neurotrophic factor (*GDNF)*, insulin-like growth factor-1 (*IGF-1*), vascular endothelial growth factor (*VEGF*), C-X-C motif chemokine ligand 12 (*CXCL12*), hypoxia-inducible factor 1-alpha (*HIF1A*), nuclear factor erythroid 2-related factor 2 (*NRF2*), nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (*NLRP3*), Sirtuin 1 (*SIRT1*), and tissue inhibitor of metalloproteinase 3 (*TIMP3*). By integrating findings from human and animal models, this review aims to highlight the genetic factors that influence stroke recovery and outcomes, thereby advancing the development of more effective rehabilitation strategies.

2.0 METHODOLOGY

This work was designed as a narrative mini-review synthesizing current evidence on the genetic mechanisms influencing stroke recovery, with a focus on 10 key genes: *BDNF, GDNF, IGF-1, VEGF, CXCL12, HIF1A, NRF2, NLRP3, SIRT1*, and *TIMP3*. A comprehensive literature search was conducted up to 2024 across major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy combined controlled vocabulary and free-text terms to maximize the retrieval of relevant studies. The primary search string was: ((“stroke” OR “ischemic stroke” OR “cerebral ischemia”) AND (“recovery” OR “rehabilitation”) AND (“gene expression” OR “genetic regulation” OR “transcriptomic profiling”) AND (“BDNF” OR “GDNF” OR “IGF-1” OR “VEGF” OR “CXCL12” OR “HIF1A” OR “NRF2” OR “NLRP3” OR “SIRT1” OR “TIMP3”) AND (“neuroplasticity” OR “angiogenesis” OR “neuroinflammation”) AND (“biomarker” OR “therapeutic target”). Additional relevant articles were identified through manual screening of reference lists from selected articles.

Inclusion criteria encompassed peer-reviewed original research articles, clinical trials, randomized controlled trials, meta-analyses, and systematic reviews published in English within the specified period. Eligible studies examined the role of selected genes in neuroplasticity, angiogenesis, neuroinflammation, synaptic remodeling, neuronal regeneration, or tissue repair during post-stroke recovery, using human or animal models. Exclusion criteria included non-peer-reviewed articles, non-English publications, editorials, letters, commentaries, conference abstracts, and studies not directly related to stroke recovery. Based on the literature screening and evaluation, this mini review focuses on the 10 genes most consistently associated with stroke recovery and their mechanistic relevance.

3.0 GENES INVOLVED IN STROKE RECOVERY

3.1 BDNF

The *BDNF* gene is widely expressed throughout the healthy human brain and plays a crucial role in promoting neuronal survival, synaptic plasticity, and functional recovery. One of its key functions in stroke recovery is its involvement in anti-apoptotic processes, which help protect neurons from programmed cell death and reduce lesion size following a stroke. Research by Chaturvedi et al. (2020) has demonstrated that post-stroke motor learning, as well as the formation and branching of dendritic spines, is closely associated with elevated BDNF protein levels in the cerebral cortex of 208 stroke patients who underwent flexibility training using proprioceptive neuromuscular facilitation. This underscores the gene’s essential contribution to post-stroke neuronal plasticity and functional rehabilitation.

Structurally, the *BDNF* gene spans approximately 70 kilobases and is located on chromosome 11 in the p13-14 region. Its complex genetic structure includes 11 exons (designated I-IX, along with Vh and VIIIh), which are unique to humans and contribute to its diverse regulatory mechanisms and functional roles (Wang et al., 2024). This structural complexity allows for the differential expression of BDNF transcripts, enabling precise regulation of its activity in response to various physiological and pathological conditions. Research suggests that polymorphisms in the *BDNF* gene, particularly the Val66Met polymorphism, may influence post-stroke recovery outcomes (Balkaya & Cho, 2019). Extensive research by Hara indicates that the Val66Met

polymorphism negatively impacts cortical plasticity, with this effect becoming more pronounced with aging (Hara, 2015). Since cortical plasticity is a fundamental mechanism underlying stroke recovery and the effectiveness of rehabilitation, its impairment may hinder post-stroke functional restoration.

Clinical studies further highlight the impact of BDNF on stroke recovery. For instance, a study by Koroleva et al. (2020) found that ischemic stroke patients who engaged in augmented reality-based motor training exhibited a significant increase in serum BDNF levels. In contrast, those who did not undergo active rehabilitation showed comparatively lower levels. This suggests that rehabilitative therapies play a crucial role in upregulating BDNF expression, thereby facilitating neuronal repair and functional improvements. Additionally, a recent meta-analysis by Chen et al. (2023), involving 2,567 stroke patients, confirmed that rehabilitation interventions significantly increased serum BDNF levels, which were strongly correlated with enhanced motor and cognitive recovery.

At the molecular level, BDNF exerts its effects by binding to its high-affinity receptor, tropomyosin receptor kinase B (TrkB), triggering a cascade of intracellular signaling pathways that regulate neuronal survival, plasticity, and repair. Among these, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways play a critical role in promoting neuronal survival, inhibiting apoptosis, and mitigating secondary neuronal damage following ischemic and hemorrhagic brain injuries (Lima Giacobbo et al., 2018).

Additionally, BDNF enhances long-term potentiation by modulating N-methyl-D-aspartate receptor activity, thereby strengthening synaptic connections essential for motor learning and cognitive rehabilitation (Banerjee & Shenoy, 2021). Beyond its neuroprotective effects, BDNF promotes neurogenesis by stimulating the proliferation and differentiation of neural progenitor cells in neurogenic regions such as the hippocampus and subventricular zone, contributing to the brain's capacity for self-repair (Jastrzębski et al., 2024). Thus, the *BDNF* gene serves as a cornerstone of stroke recovery, underscoring its potential as both a biomarker and a therapeutic target to advance rehabilitation strategies and promote brain self-repair after stroke.

3.2 GDNF

GDNF is a prominent member of the transforming growth factor-beta (TGF-β) superfamily. It has emerged as a promising therapeutic agent for stroke recovery due to its neuroprotective, neurogenerative, angiogenic, and anti-inflammatory properties (Palasz et al., 2023). The *GDNF* gene is located on chromosome 5p13.2 and consists of six exons encoding a precursor protein that is proteolytically cleaved into the active GDNF peptide (Luan et al., 2025). This active form plays a crucial role in promoting neuronal survival, facilitating tissue repair, and enhancing functional recovery following cerebral ischemia.

Under normal physiological conditions, *GDNF* is predominantly expressed in neurons, while its expression in astrocytes is relatively low. Once secreted, *GDNF* binds to the glycosylphosphatidylinositol-anchored co-receptor GFRα on the neuronal membrane, forming a GDNF-GFRα complex. This complex subsequently interacts with the rearranged during transfection (RET) receptor, a receptor tyrosine kinase essential for GDNF signal transduction. The binding of the GDNF-GFRα complex to RET promotes the autophosphorylation of specific tyrosine residues within the intracellular domain of RET, thereby facilitating the recruitment of downstream signaling molecules involved in neuronal survival, differentiation, and neurogenesis (Airaksinen & Saarma, 2002).

The activation of RET initiates several intracellular signaling cascades, including the PI3K/Akt and MAPK pathways. These pathways play a crucial role in promoting neuronal survival, enhancing axonal regeneration, and stimulating neurogenesis, processes essential for post-stroke recovery (Zhang et al., 2020). Recent studies emphasize the vital role of *GDNF* in promoting brain repair after focal ischemic stroke. *GDNF* is highly upregulated in reactive astrocytes following stroke, suggesting its involvement in neuroprotection and recovery (Arvidsson et al., 2001). Research using astrocyte-specific GDNF knockout (GLAST-GDNF$^{-/-}$cKO) mice has found that *GDNF* deficiency leads to increased neuronal death, reduced reactive astrogliosis, impaired neurogenesis, elevated oxidative stress due to decreased glucose-6-phosphate dehydrogenase, and worsened motor function (Zhang et al, 2020). These findings underscore the critical role of *GDNF* in neuroprotection, antioxidative defense, and post-stroke recovery, establishing it as a promising therapeutic target for improving long-term stroke outcomes.

3.3 IGF-1

The *IGF-1* gene is instrumental in neuroprotection, neurogenesis, and functional recovery after a stroke. It encodes the IGF-1 protein, a hormone similar in structure to insulin, primarily produced in the liver and brain. *IGF-1* functions both systemically and locally, supporting neuronal survival, synaptic plasticity, and vascular regeneration, which are key processes for post-stroke recovery. Structurally, the *IGF-1* gene is located on chromosome 12 at q23.2, spanning approximately 85 kilobases and comprising six exons with multiple promoters. These promoters generate various *IGF-1* isoforms, each with distinct biological functions (Józefiak et al, 2021). Notably, the IGF-1Ec isoform, also known as mechano-growth factor, is upregulated in the brain following ischemic injury and plays a crucial role in tissue regeneration and repair (Podratz et al., 2020).

At the molecular level, *IGF-1* binds to the IGF-1 receptor, a tyrosine kinase receptor expressed in neurons and glial cells. This binding activates downstream signaling pathways, including the PI3K/Akt and MAPK/ERK pathways, which promote neuronal survival, inhibit apoptosis, and enhance synaptic plasticity (Arjunan et al.,2023). Additionally, *IGF-1* modulates *BDNF* expression, indicating a synergistic relationship between these neurotrophic factors in supporting neuroplasticity and functional recovery post-stroke (Du et al., 2023).

A study by Li et al. (2020) involving 80 patients with acute ischemic stroke and 60 controls revealed lower *IGF-1* expression in stroke patients compared to healthy individuals, with levels decreasing as the condition worsened and showing no significant change after a three-week rehabilitation program. These findings indicated that while *IGF-1* may have value as a baseline prognostic marker, its utility for monitoring rehabilitation progress appears limited. Similarly, Ebinger et al. (2015) concluded that *IGF-1* serum levels are not reliable indicators of stroke recovery. However, findings remain inconsistent. Armbrust et al. (2017) reported that lower *IGF-1* levels during the acute phase (day 8) were associated with a reduced risk of unfavorable outcomes, while higher *IGF-1* levels correlated with cognitive improvements following combined aerobic and cognitive training. These results suggest that *IGF-1* is more relevant as an initial prognostic marker than as a dynamic indicator of recovery progress. However, its potential role in promoting neuroplasticity during rehabilitation highlights the need for further research to clarify its utility.

3.4 VEGF

VEGF is widely expressed in the brain tissue and plays a critical role in neuroinflammation pathophysiology by facilitating the recruitment of inflammatory cells and modulating angiopoietin II secretion. This regulatory function not only promotes vascular remodeling but also influences the permeability of the blood-brain barrier, thereby contributing to the establishment and progression of the inflammatory microenvironment within the central nervous system (Yin et al, 2020). *VEGF* has emerged as a crucial factor in facilitating brain repair and functional recovery after stroke. The *VEGF* gene, located on 6p21.1, comprises eight exons and demonstrates complex alternative splicing, generating multiple isoforms with distinct biological functions. Among these, VEGF-A is the most prominent in stroke recovery, promoting endothelial cell proliferation, migration, and survival under hypoxic conditions (Geiseler & Morland, 2018).

The mechanisms underlying *VEGF* secretion vary depending on the type of stroke. In ischemic stroke, reduced tissue oxygenation leads to an energy deficit, ultimately resulting in neuronal cell death. When blood flow is only partially obstructed, a penumbra zone develops, where cells remain in a necrotic-like state, accompanied by elevated excitotoxicity that damages cytosolic structures. Additionally, ischemia disrupts vascular integrity, further promoting *VEGF* secretion (Mazilina et al., 2022). In hemorrhagic stroke, *VEGF* expression is upregulated in response to intracerebral bleeding, contributing to angiogenesis while also increasing permeability, which may exacerbate edema and secondary injury (Liu et al., 2021). Thus, VEGF's role in stroke recovery is context-dependent, requiring careful modulation to maximize benefits while minimizing potential harm.

VEGF exerts its neuroprotective effects through multiple mechanisms. It stimulates endothelial cell proliferation and migration, facilitating the formation of new capillaries in ischemic tissues. Additionally, *VEGF* promotes neurogenesis by enhancing the proliferation and differentiation of neural stem cells, thereby supporting the repair of damaged neuronal networks. This process is mediated primarily through VEGFR-2, which activates downstream signaling pathways, including the PI3K/Akt and MAPK cascades, known to enhance cell survival and proliferation (Song & Finley, 2020).

While the role of *VEGF* in stroke recovery is well-established, its utility as a biomarker for ischemic stroke

diagnosis remains uncertain. A meta-analysis by Seidkhani-Nahal et al. (2020), involving 769 stroke patients and 621 controls, found no significant correlation between *VEGF* levels and the occurrence of acute ischemic stroke. This suggests that, although *VEGF* plays a crucial role in post-stroke recovery, it may not serve as a reliable indicator of the initial ischemic event. This finding highlights the complexity of VEGF signaling, as its expression appears more closely associated with tissue repair and angiogenesis during the recovery phase than with the acute phase of ischemia.

A study by Geng et al. (2022) demonstrated that initiating treadmill exercise 24 hours after middle cerebral artery occlusion (MCAO) in rats significantly upregulated VEGF and laminin expression on days 1, 3, and 5 compared with the non-exercised MCAO group. This upregulation correlated with increased microvessel density in the ischemic penumbra, suggesting enhanced angiogenesis. The study also observed a reduction in neuronal apoptosis, contributing to improved recovery of neurological function. This finding suggests that rehabilitation strategies incorporating physical activity may enhance endogenous VEGF-mediated repair mechanisms, offering a non-pharmacological approach to stroke recovery. Collectively, *VEGF* has therapeutic potential due to its pro-angiogenic and neuroprotective properties. Precise modulation is crucial to optimizing benefits while minimizing the risks associated with increased blood-brain barrier permeability and inflammation.

3.5 CXCL12

CXCL12, also known as stromal cell-derived factor-1, is a chemokine integral to various physiological processes, including embryogenesis, immune surveillance, and tissue homeostasis. Encoded by the *CXCL12* gene located on chromosome 10 at q11.21, this gene comprises six exons spanning approximately 14.94 kilobases on the reverse strand (Gentile et al., 2017). The CXCL12 protein primarily resides in the extracellular space, where it exerts its function by binding to its receptors, C-X-C chemokine receptor type 4 (CXCR4) and C-X-C chemokine receptor type 7 (CXCR7), on target cells. This gene is primarily localized to the endoplasmic reticulum and Golgi apparatus before being secreted into the extracellular matrix, where it facilitates cell migration, proliferation, and survival (Shi et al., 2020).

The PI3K/Akt pathway acts as a downstream signaling mediator of the CXCL12/CXCR4 axis. Activation of the CXCR4 receptor, a G-protein-coupled receptor, triggers a conformational change in the PI3K protein, which is made up of two subunits called p85 and p110. These changes lead to Akt phosphorylation and pathway activation, which play an important role in regulating cell survival, differentiation, and proliferation (Zuo et al., 2020). A study by Song et al. (2018) reported that the CXCL12/CXCR4 axis plays a crucial role in promoting angiogenesis and regulating cell apoptosis through the activation of the PI3K/Akt signaling pathway. This signaling cascade has been identified as a key downstream component of the CXCL12/CXCR4 axis. These findings highlight the therapeutic potential of targeting the CXCL12/CXCR4/PI3K/Akt pathway to improve stroke outcomes.

A study by Zheng et al. (2024) explored the therapeutic potential of adipose-derived stem cells engineered to express monomeric CXCL12. In their study, mice subjected to MCAO were treated with these modified adipose-derived stem cells, resulting in a significant reduction in infarct size and notable improvements in neurological function compared to the control group. Importantly, the neuroprotective effects were eliminated when the CXCR4 receptor was blocked with the antagonist AMD3100 (a highly specific CXCR4 inhibitor), underscoring the essential role of the CXCL12/CXCR4 axis in stroke recovery. These findings support that *CXCL12* is a multifaceted chemokine that plays a significant role in promoting angiogenesis, neurogenesis, and immune regulation following ischemic stroke. A deeper understanding of its multifaceted functions could pave the way for innovative therapeutic approaches to improve recovery outcomes and minimize long-term neurological impairments in stroke patients.

3.6 HIF-1A

HIF-1A plays a crucial role in regulating cellular responses to hypoxia and has been identified as a significant contributor to neurological outcomes following ischemic stroke. Its downstream target genes support key processes such as glucose metabolism, angiogenesis, erythropoiesis, and cell survival (Shi, 2009). This regulatory function promotes vascular remodeling and adaptive responses within the ischemic microenvironment, particularly in the penumbra. *HIF-1A* supports brain recovery after stroke, with its activity carefully controlled by oxygen levels and cellular stress. The *HIF-1A* gene is located on chromosome 14q23.2 and contains 16 exons in humans (Wang et al., 2018). However, a study by Koh et al. (2008) has identified a unique pVHL-independent mechanism for *HIF-1A* degradation. Despite the global inhibition of protein

translation during hypoxia, constitutive translation of *HIF-1A* still occurs. This indicates that cells can produce and degrade HIF-1A under low-oxygen conditions, even when overall protein production is slowed. This ability helps cells adapt to hypoxia more effectively.

A study by Guo et al. (2021) regarding gene expression revealed significant changes after three days of MCAO in aged and young rats, aligning closely with the role of the PI3K/Akt signaling pathway in regulating HIF-1A activation. Gene ontology analyses identified alterations in genes related to the negative and positive regulation of apoptosis, organ regeneration, responses to hypoxia, and responses to organic cyclic compounds. Among these, *HIF-1A*-regulated genes stood out, with age-related differences in expression patterns. Notably, the expression of pro-angiogenic genes such as angiopoietin-2 and *VEGF-A* differed between aged and young rats, suggesting that age influences *HIF-1A* signaling and its subsequent impact on stroke recovery outcomes.

The PI3K/Akt signaling pathway plays a vital role in regulating key cellular processes, including metabolism, growth, and survival. In terms of *HIF-1A* activation, the PI3K/Akt pathway can stimulate *HIF-1A* under normoxic conditions (normal oxygen concentration). This occurs primarily through the inhibition of prolyl hydroxylases (PHDs), which are responsible for marking *HIF-1A* for degradation. When PI3K/Akt signaling suppresses PHD activity, *HIF-1A* becomes stable, accumulates within the cell, and promotes the transcription of target genes involved in angiogenesis, metabolism, and cell survival (Gómez-Virgilio et al., 2024). These findings indicate that the interplay between *HIF-1A* and the PI3K/Akt signaling pathway plays a crucial role in cellular adaptation to hypoxia and post-stroke recovery. The age-related differences in *HIF-1A* signaling further highlight the need for age-specific therapeutic approaches to optimize stroke rehabilitation outcomes.

3.7 NRF2

NRF2 is a key antioxidant transcription factor that regulates various cytoprotective mechanisms to counteract oxidative stress. This gene is located on human chromosome 2 at q31.2 (Zgorzynska et al., 2021). *NRF2* has emerged as a promising approach for preventing and treating cerebral ischemic injury. During cerebral ischemia, *NRF2* is involved in signaling pathways such as Kelch-like epichlorohydrin-associated protein 1, PI3K/Akt, MAPK, NF-κB, and heme oxygenase 1 (HO-1), thereby mitigating cerebral ischemia-reperfusion injury by reducing oxidative stress (ROS), suppressing inflammation, preserving mitochondrial homeostasis, protecting the blood-brain barrier, and preventing ferroptosis (Wang et al., 2022).

In the brain microvascular system, activation of the *NRF2* defense pathway helps protect against blood-brain barrier disruption and neurological damage during ischemic stroke (Zhao et al., 2021). Conversely, *NRF2* deficiency leads to elevated intracellular ROS levels, highlighting its crucial role in maintaining ROS homeostasis. Activated *NRF2* stimulates the transcription of antioxidant protein-encoding genes, such as superoxide dismutase, catalase, HO-1, and NAD(P)H quinone oxidoreductase 1. Additionally, *NRF2* regulates genes associated with tissue repair, remodeling, and anti-inflammatory responses, indicating that its roles extend beyond antioxidation and detoxification (Sun et al., 2023).

NRF2 activation has emerged as a promising therapeutic target for cerebrovascular accidents, including ischemic stroke. It plays a vital role in controlling excessive oxidative stress following a stroke (Mazur et al., 2021). The primary trigger for *NRF2* activation is hydrogen peroxide, which rises significantly after ischemia-reperfusion (Farina et al., 2021). A study by Michalickova et al. (2020) demonstrated that *NRF2* expression significantly increases during the acute phase of stroke in MCAO models, rising three hours after occlusion and peaking at 24 hours. This indicates that excessive ROS production following cerebral ischemia triggers *NRF2* activation, which subsequently initiates the transcription of various antioxidant genes. Overall, *NRF2* plays a multifaceted neuroprotective role during ischemic stroke by reducing oxidative stress, protecting the blood-brain barrier, and promoting tissue repair, thus making it a promising target for stroke therapy.

3.8 NLRP3

The *NLRP3* inflammasome has emerged as a significant player in the pathophysiology of stroke and the subsequent recovery process. As a key regulator of inflammation, the *NLRP3* inflammasome influences the balance between neuroprotection and neurodegeneration following ischemic or hemorrhagic stroke (Zhang et al., 2024). NLRP3 acts as a sensor of cellular stress, mediating the production of pro-inflammatory cytokines and shaping the post-stroke inflammatory environment. Understanding the dual role of *NLRP3* in injury progression and recovery offers new therapeutic avenues to improve stroke outcomes. The *NLRP3* gene is located on chromosome 1q44 and

encodes a cytoplasmic protein predominantly expressed in immune cells, including microglia, macrophages, and neutrophils (Duez & Pourcet, 2021; Lamkanfi & Kanneganti, 2010).

NLRP3 belongs to the NOD-like receptor family and consists of three major domains: a pyrin domain for protein-protein interactions, a nucleotide-binding domain for oligomerization, and a leucine-rich repeat domain for sensing danger-associated molecular patterns and pathogen-associated molecular patterns. It serves as an intracellular sensor that identifies a wide array of microbial patterns, endogenous danger signals, and environmental irritants, which trigger the formation and activation of the *NLRP3* inflammasome (Shen et al., 2022). This assembly subsequently promotes the caspase-1-dependent release of pro-inflammatory cytokines, including IL-1β and IL-18, as well as gasdermin D-mediated pyroptotic cell death (Swanson et al., 2019).

The activation of the *NLRP3* inflammasome during cell injury typically involves two complementary signals. The first signal is driven by the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and MAPK signaling pathways, which promote the upregulation of *NLRP3* inflammasome complex proteins and the precursors of IL-1β and IL-18. The second signal facilitates the assembly of the *NLRP3* inflammasome complex through the activation of *NLRP3* and the phosphorylation of apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD) (ASC) (Masenga & Kirabo, 2024). This suggests that inhibiting NF-κB/MAPK pathways (first signal) or NLRP3/ASC activation (second signal) can prevent inflammasome activation, making these pathways potential therapeutic targets for inflammatory diseases, including stroke and neurodegenerative conditions.

An animal study by Bellut et al. (2023) revealed that the *NLRP3* inflammasome remains a key driver of neuroinflammation during the subacute phase of stroke. Inhibiting the *NLRP3* inflammasome improved long-term outcomes, even when treatment was delayed by 1 day after stroke onset. This suggests that inflammation-driven infarct progression persists beyond the acute phase, highlighting the potential for delayed therapeutic interventions in ischemic stroke. Similarly, a study by Jia et al. (2022) reported that inhibiting NLRP3 inflammasome expression, through administration of Tranilast (an antiallergy drug) to a mouse model of distal middle cerebral artery occlusion, reduced infarct volumes and improved sensorimotor function. This suggests that post-stroke inflammation extends well into the subacute and chronic phases, making NLRP3 inhibition a viable target for therapeutic strategies beyond the acute window. Its targeted modulation holds significant potential for enhancing stroke recovery.

3.9 SIRT1

SIRT1 is a NAD^+-dependent deacetylase known for its role in cellular metabolism, stress resistance, and longevity (Thapa et al., 2024). It belongs to the sirtuin family, which consists of seven members (*SIRT1*-*SIRT7*), each located in different cellular compartments. Among them, *SIRT1* is the most extensively studied, particularly in the context of neuroprotection and stroke. This gene is highly expressed in neurons, especially in the hippocampus, cortex, and cerebellum. Its expression increases following ischemic stroke, suggesting a protective role in response to cerebral ischemia.

SIRT1 plays a crucial role in various physiological and pathological processes, making its regulation vital for health outcomes, particularly in stroke recovery. Both clinical and animal studies have demonstrated the potential of *SIRT1* as a therapeutic target and biomarker. A case-control study by Esmayel et al. (2021) found that *SIRT1* activity in the serum of acute ischemic stroke patients was significantly lower than that in healthy controls. Additionally, *SIRT1* levels showed a strong negative correlation with stroke severity, suggesting its potential as a biomarker for predicting acute ischemic stroke risk. Findings from animal models further support the protective role of *SIRT1* in stroke recovery. A study by Zhang et al. (2018) demonstrated that *SIRT1* activation reduces infarct size and neurological deficits following ischemic stroke. For instance, mice overexpressing *SIRT1* exhibited increased resistance to global ischemia while maintaining cerebral perfusion at 45%-50% of baseline levels, underscoring its potential to improve post-stroke outcomes.

Beyond neuroprotection, *SIRT1* modulates key signaling pathways involved in stroke recovery, particularly the MAPK pathway. An animal model study by Teertam and Prakash (2021) showed that *SIRT1* activation regulates Jun N-terminal kinase and ERK phosphorylation, promoting neuronal survival through an AKT-dependent mechanism. Interestingly, the protective effects varied with age: younger rats experienced greater benefits, suggesting age-dependent differences in SIRT1 efficacy during stroke recovery. Therefore, these findings underscore the dual potential of *SIRT1* as both a

predictive marker for stroke risk and severity and as a therapeutic target for stroke recovery.

3.10 TIMP3

TIMP3 is a protein encoded by the *TIMP3* gene, which belongs to the TIMP family. This family of proteins inhibits matrix metalloproteinases (MMPs), enzymes responsible for degrading the extracellular matrix (ECM). *TIMP3* is unique among TIMPs due to its strong binding affinity to the ECM, allowing it to effectively regulate ECM composition and inhibit a broad range of metalloproteinases, including MMPs, a disintegrin and metalloproteinases, and a disintegrin and metalloproteinases with thrombospondin motifs (Fan & Kassiri, 2020). This gene is located in2 human chromosome 22 and mouse chromosome 10.

The balance between *MMPs* and *TIMP* is crucial in stroke, particularly ischemic stroke. *MMPs* contribute to the breakdown of the blood-brain barrier and ECM degradation, leading to neuronal damage. Inhibiting *MMPs* helps *TIMP3* maintain the integrity of the ECM and the blood-brain barrier, potentially reducing tissue damage and promoting recovery. However, excessive *MMP* activity can increase brain damage in animal models of cerebral ischemia, suggesting that balanced *MMP* activity is necessary for optimal recovery (Montaner et al., 2019). Another animal study by Meng et al. (2021) reported that TIMP3 overexpression can attenuate oxidative stress and apoptosis in models of cerebral ischemia or reperfusion injury. For instance, *TIMP3* overexpression in PC12 cells exposed to oxygen-glucose deprivation or reoxygenation minimized cell damage by activating the Akt signaling pathway. This indicates that *TIMP3* plays a protective role; its overexpression activates the Akt signaling pathway, which promotes cell survival, reduces oxidative stress, and prevents apoptosis, thereby helping to minimize brain injury after ischemic stroke.

While meta-analyses specifically examining the role of *TIMP3* in stroke recovery are limited, broader investigations have explored the impact of *MMPs* and their inhibitors on stroke outcomes. Beyond its role as an *MMP* inhibitor, TIMP3 also exhibits a high affinity for low-density lipoprotein receptor-related protein-1 (LRP-1). This interaction facilitates LRP-1-mediated endocytosis by enhancing the binding of target metalloproteinases to LRP-1, thereby exacerbating cerebral vascular injury (Xiao et al., 2022). Therefore, achieving a finely tuned balance between MMP activity and *TIMP3* expression appears crucial for protecting the brain from ischemic injury while promoting tissue repair and functional recovery. The findings suggest that *TIMP3* plays a dual role in stroke recovery. It protects brain tissue by inhibiting MMPs, reducing oxidative stress, and preventing apoptosis through the Akt signaling pathway. This maintains blood-brain barrier integrity and promotes cell survival during ischemia. Therefore, while *TIMP3* has therapeutic potential for stroke recovery, its effects depend on achieving a balanced level of expression to avoid adverse outcomes.

4.0 SUMMARY AND FUTURE PERSPECTIVES

Figure 1 illustrates key genes involved in stroke recovery, categorized into four main functions: neurotrophic support and neuronal survival, angiogenesis, inflammation and immune modulation, and extracellular matrix remodeling. Genes such as *BDNF*, *GDNF*, and *IGF-1* support neuron protection and growth. *VEGF*, *CXCL12*, and *HIF1A* facilitate angiogenesis, particularly under low oxygen conditions. *NRF2* reduces oxidative stress, while *NLRP3* triggers inflammation, exacerbating damage. Additionally, *SIRT1* and *TIMP3* aid in tissue repair and prevent excessive cell death. Overall, *BDNF* emerges as an essential player in multiple recovery pathways. Future research should focus on the interplay between these genes and their interactions with the environment in stroke recovery. Future treatments may emphasize boosting *BDNF* activity and managing inflammation through gene therapy, precision medicine, pharmacological interventions, and rehabilitation to optimize stroke recovery and improve patient outcomes.

5.0 CONCLUSIONS

In conclusion, this review highlights the crucial role of genetic factors in stroke recovery, emphasizing how key genes such as *BDNF*, *GDNF, IGF-1, VEGF*, *CXCL12*, *HIF1A*, *NRF2*, *NLRP3*, *SIRT1*, and *TIMP3* influence neuroprotection, inflammation regulation, angiogenesis, and neuronal regeneration. It suggests that genetic markers hold promise as both predictors of stroke outcomes and targets for therapeutic strategies in stroke recovery. This understanding paves the way for personalized rehabilitation approaches based on an individual's genetic makeup.

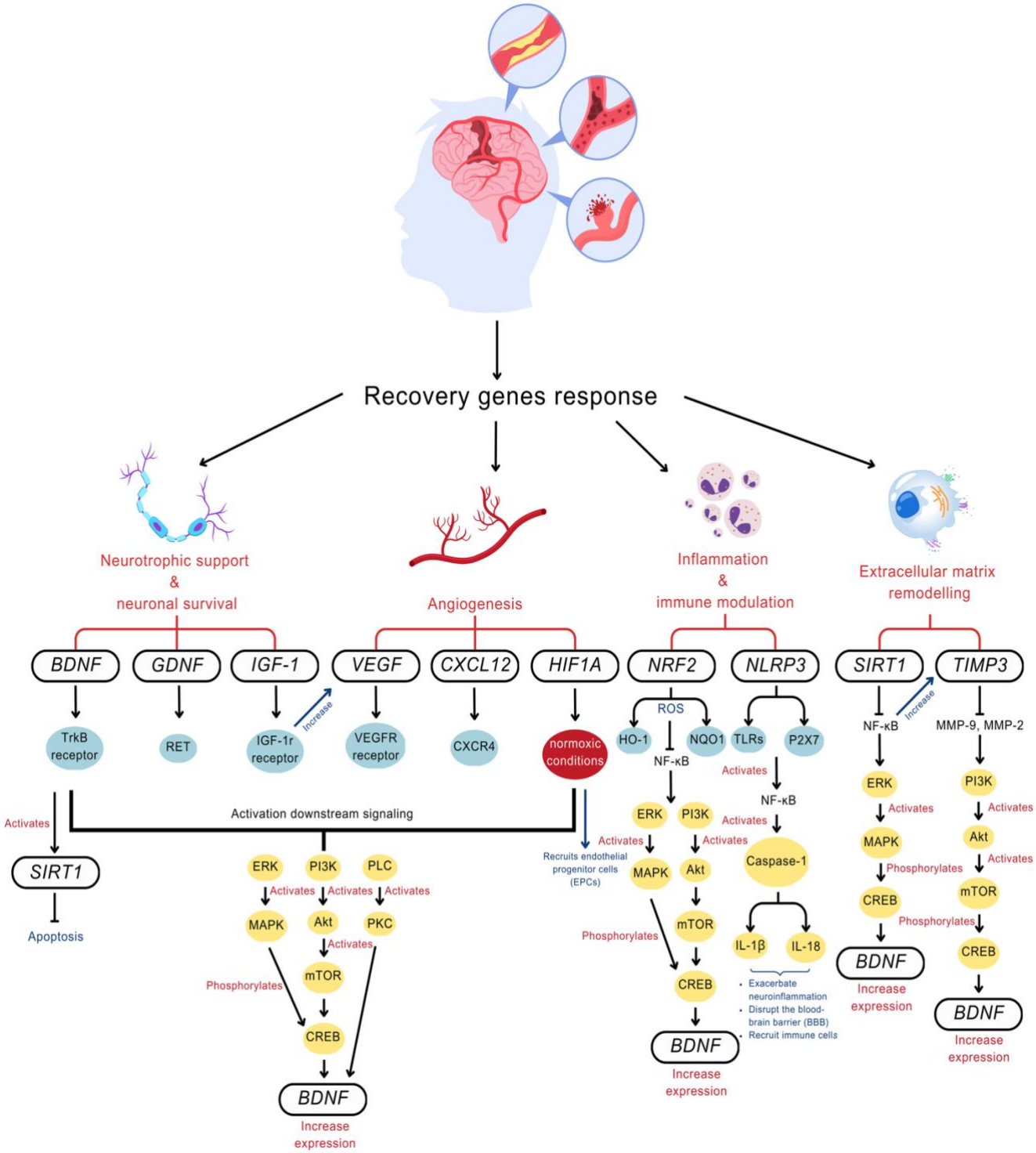

Figure 1: The molecular pathways of genes involved in stroke recovery.

Acknowledgements: This work is supported by the Malaysian Ministry of Higher Education under the Fundamental Research Grant Scheme (FRGS/1/2024/STG01/UMS/02/2).

Author Contributions: Conceptualization: E.T.J.C.; data curation: N.R.; funding acquisition: E.T.J.C.; supervision: E.T.J.C.; visualization: N.R.; writing - original draft: N.R.; writing - review & editing: N.R., E.T.J.C. All authors approved the final version of the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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