Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(8): 54110
https://doi.org/10.31083/FBL54110

Review

From Neuroinflammation to Precision Stroke Recovery: A Phase-Specific Immune–Metabolic Framework

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Academic Editors: Moo-Ho Won and Xudong Huang
Submitted: 21 May 2026 Revised: 13 June 2026 Accepted: 2 July 2026 Published: 14 August 2026

Abstract

Stroke recovery varies markedly among patients and cannot be fully predicted by infarct size, lesion location, or acute treatment success. This variability suggests that recovery is shaped by evolving interactions among neural injury, immune activation, neurovascular integrity, metabolic reserve, and repair-related plasticity. This review proposes a phase-specific immune–metabolic framework for precision stroke recovery. Rather than treating neuroinflammation as a uniformly detrimental process, this review conceptualizes neuroinflammation as a time-dependent biological gate that may either amplify injury or support repair, depending on the phase, cellular context, blood–brain barrier integrity, and systemic metabolic state. In the acute phase, regulated cell death, oxidative stress, inflammasome activation, blood–brain barrier disruption, and proteolytic remodeling contribute to secondary injury and neurovascular instability. During the subacute phase, controlled immune responses may facilitate debris clearance, angiogenesis, synaptic remodeling, and rehabilitation-induced neuroplasticity. In contrast, persistent low-grade inflammation in the chronic phase may impair network reorganization, promote glial reactivity, and contribute to delayed neurodegeneration or poor functional recovery. The available evidence suggests that metabolic and microbiome-related factors are not secondary modifiers but integral components of recovery biology. Nutritional status, sarcopenia, metabolic imbalance, and post-stroke gut dysbiosis may influence immune tone, blood-brain barrier function, microbial metabolite signaling, and neuroplastic potential. These interactions provide a rationale for defining biological recovery endotypes that integrate inflammatory, neurovascular, metabolic, microbiome-related, and plasticity-related signatures. By linking neuroinflammation with immune-metabolic regulation and repair biology, this review reframes stroke recovery as a phase-dependent and biologically stratified process. The framework may support the development of multimodal biomarkers, phase-matched interventions, and patient-stratification strategies for precision stroke recovery trials.

Keywords: stroke; recovery of function; inflammation; biomarkers; precision medicine; frailty; rehabilitation

1. Introduction

Stroke is a major cause of long-term disability and mortality worldwide, despite major advances in acute reperfusion therapies, including intravenous thrombolysis and endovascular thrombectomy [1,2]. These treatments have improved early recanalization and reduced the infarct burden for selected patients, but successful reperfusion does not guarantee meaningful functional recovery. Many survivors continue to experience persistent neurological deficits, reduced independence, and impaired quality of life, which indicates that there is a gap between acute neurovascular rescue and long-term recovery [3,4].

Stroke outcome has traditionally been interpreted through an injury-centered model in which infarct size, lesion location, and initial neurological severity are viewed as the main determinants of recovery. These variables are important, but do not fully explain why patients with apparently comparable lesions often recover differently. This mismatch suggests that recovery is shaped not only by the initial ischemic insult but also by later biological processes that influence repair, adaptation, and functional reorganization [5,6].

Current preclinical and translational evidence points to several processes that are especially relevant to recovery: regulated cell death, neuroinflammation, neurovascular dysfunction, neuroplasticity, and systemic metabolic regulation [7,8]. These processes are closely interconnected. Early ischemia triggers excitotoxicity, mitochondrial dysfunction, oxidative stress, and regulated cell death, which activate innate immune responses and disrupt the integrity of the blood–brain barrier. Recent work has emphasized that the dysfunction of the blood–brain barrier is closely coupled with neuroinflammation and may influence both tissue injury but also the biology of recovery [9,10]. Whether subsequent recovery proceeds effectively depends in part on whether the local and systemic environment supports, or restricts, synaptic remodeling, angiogenesis, remyelination, and rehabilitation-induced plasticity. The interconnected inflammatory, immune, metabolic, gut–brain, and neuroplasticity-related processes that influence ischemic injury and recovery, together with their potential integration into biomarker-defined recovery endotypes, are summarized in Fig. 1.

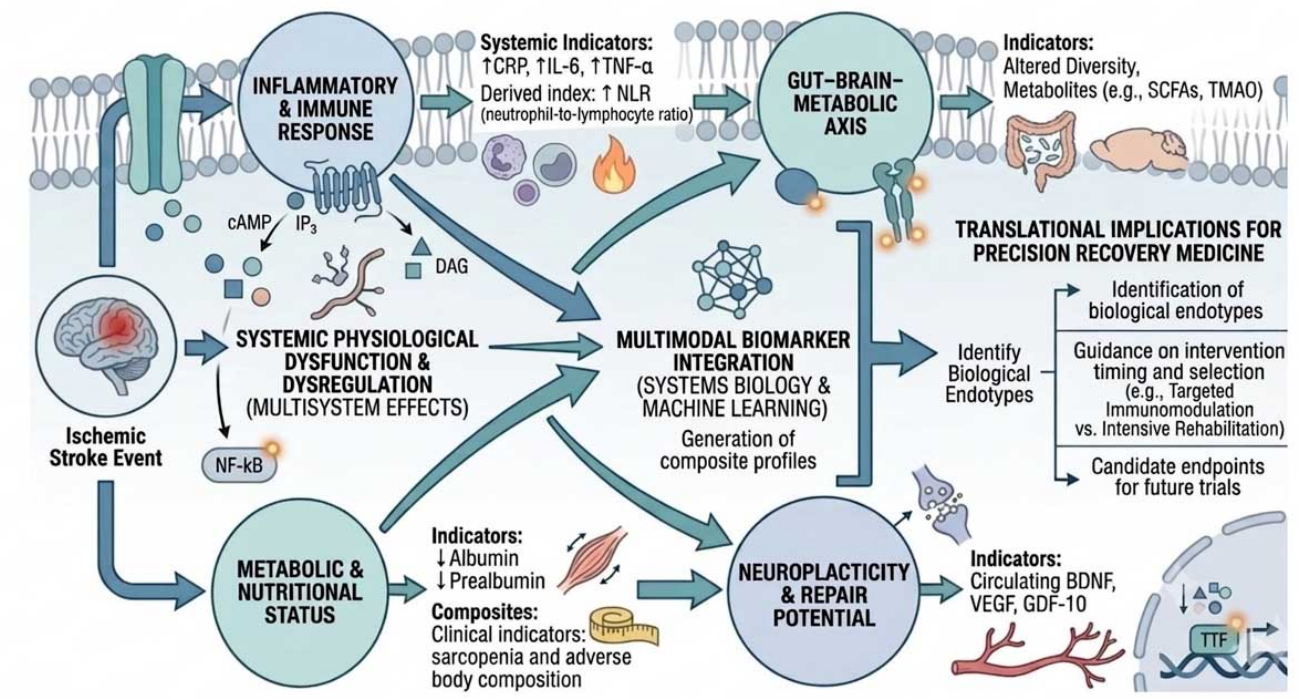

Fig. 1. Proposed systems-level framework for multimodal biomarker integration in precision stroke recovery medicine. The schematic illustrates a conceptual framework linking ischemic stroke with inflammatory and immune responses, systemic physiological dysfunction, metabolic and nutritional status, the gut–brain–metabolic axis, and neuroplasticity and repair potential. Representative inflammatory indicators include C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and the neutrophil-to-lymphocyte ratio (NLR). Metabolic and nutritional indicators include serum albumin, prealbumin, sarcopenia, and adverse body composition. The gut–brain–metabolic axis is represented by altered microbial diversity and microbiome-derived metabolites, including short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO). Candidate markers related to neuroplasticity and repair include circulating brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and growth differentiation factor 10 (GDF-10). The framework proposes that integration of these multidimensional data through systems-biology approaches and computational modeling may support the generation of composite recovery profiles. Such profiles may help identify biologically relevant recovery endotypes, guide the timing and selection of future interventions, and inform the development of candidate endpoints for clinical trials. The arrows represent proposed interactions among biological domains rather than established causal relationships. The framework is intended as a hypothesis-generating model that requires prospective validation before clinical implementation. TTF, Transcription Termination Factor; cAMP, Cyclic Adenosine Monophosphate; IP_3, Inositol trisphosphate; DAG, Diacylglycerol; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; ↑ indicates increased expression; ↓ indicates decreased expression. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

Neuroinflammation is central to this transition, but it should not be treated as simply harmful or beneficial. In the acute phase, excessive inflammatory activation can worsen neuronal injury, promote blood–brain barrier disruption, and extend secondary damage. In the subacute phase, more regulated immune responses may contribute to debris clearance, vascular remodeling, and synaptic reorganization. During the chronic phase, ongoing low-grade inflammation may maintain glial reactivity, hinder network remodeling, and facilitate delayed neurodegeneration [11]. The effect of neuroinflammation therefore depends on timing, cellular source, neurovascular integrity, and the state of ongoing repair.

Neuroplasticity provides the biological basis for functional recovery, but it does not occur in isolation. Neurotrophic and growth-related pathways regulate axonal sprouting, synaptogenesis, angiogenesis, and remyelination, which are essential for functional improvement [12]. Systemic conditions such as nutritional status, metabolic reserve, inflammation, and frailty can either support or limit these processes. Blood-based biomarker studies and recent rehabilitation-focused reviews indicate that molecular signals related to neuroplasticity, including brain-derived neurotrophic factor (BDNF) and other repair-associated markers, may help explain variability in rehabilitation responsiveness, although standardization and validation remain necessary [13,14]. Recovery is therefore better understood

as the result of both brain repair capacity and whole-body physiological state, rather than as a purely brain-intrinsic process.

The microbiota–gut–brain axis is increasingly relevant in this context. Stroke-induced dysbiosis may influence systemic inflammation, immune-cell activity, blood–brain barrier integrity, and neuroplasticity through microbial metabolites and gut–brain signaling pathways [15,16]. Clinical evidence suggests that gut dysbiosis may persist across subacute and convalescent phases of stroke, supporting the need to interpret microbiome changes as part of recovery biology rather than as a static post-stroke complication [17]. At the same time, autonomic and neuroendocrine disturbances after stroke may alter gut permeability, microbial composition, and host metabolism. These observations place metabolic and microbiome-related factors within the biology of recovery, rather than at its margins.

This article is a critical conceptual narrative review. Relevant literature was identified through targeted searches of PubMed, Scopus, and Web of Science, focusing on ischemic stroke, neuroinflammation, blood-brain barrier dysfunction, regulated cell death, neuroplasticity, the gut-brain axis, metabolism, biomarkers, and rehabilitation. Foundational mechanistic studies were retained when they established key concepts or widely accepted biological mechanisms, whereas recent evidence, particularly studies published between 2021 and 2026, was prioritized to capture current developments in immune-metabolic regulation, biomarker-guided stratification, rehabilitation responsiveness, and precision stroke recovery. This review was not designed as a systematic review or meta-analysis; rather, it aimed to synthesize converging evidence into a phase-specific immune-metabolic framework for precision stroke recovery. Greater interpretive weight was assigned to human studies, longitudinal investigations, systematic reviews, meta-analyses, and findings replicated across independent research groups. Where evidence remained inconsistent, the uncertainty was stated explicitly, and mechanistic interpretations were presented as provisional rather than definitive. Multimodal biomarker integration, phase-matched interventions, and biologically informed patient stratification have been proposed previously in the context of precision stroke recovery. The present framework is intended to provide an integrative, phase-sensitive synthesis of these concepts and to outline priorities for future validation rather than to represent an established clinical algorithm.

2. Ischemic Cascade and Regulated Cell Death

2.1 Classical Ischemic Cascade: From Acute Injury to Recovery Constraint

Cerebral ischemia initiates a rapid sequence of metabolic and molecular disturbances that determines not only the extent of acute tissue injury and the biological conditions under which recovery must occur. An abrupt reduction in cerebral blood flow deprives brain tissue of oxygen and glucose, leading to impaired oxidative phosphorylation and rapid depletion of adenosine triphosphate (ATP) [18,19]. Energy failure disrupts ATP-dependent ion pumps, causes membrane depolarization, and promotes excessive glutamate release.

Glutamate-mediated excitotoxicity remains a central mechanism of early ischemic injury. Overactivation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors drives pathological calcium influx, which activates proteases, lipases, and endonucleases and accelerates cellular dysfunction [20]. Mitochondria are both targets and amplifiers of this process. Calcium overload and oxidative stress impair mitochondrial membrane integrity, disrupt electron transport, and increase reactive oxygen species (ROS) generation [21]. In parallel, ischemia-induced nitric oxide production contributes to reactive nitrogen species formation, further compounding oxidative injury [22].

The distinction between the infarct core and ischemic penumbra remains clinically important, but it should be interpreted beyond the traditional concept of tissue salvage. The core is dominated by rapid and largely irreversible necrotic injury, whereas the penumbra contains metabolically compromised but potentially recoverable tissue in which delayed and regulated forms of cell death predominate [23,24]. Recent reviews of programmed cell death in ischemic stroke reinforce this view, showing that multiple death pathways may coexist and interact across ischemic regions and reperfusion phases rather than occurring as isolated events [25,26]. The penumbra, therefore, represents not only a target for acute neuroprotection but also a biologically unstable zone in which inflammatory signaling, neurovascular integrity, and metabolic reserve may influence subsequent repair potential.

2.2 Regulated Cell Death as an Upstream Driver of Immune–Metabolic Recovery States

Classical accounts of ischemic injury often separate cell death from recovery biology. This separation is increasingly difficult to maintain. Regulated cell death pathways generate inflammatory mediators, damage-associated molecular patterns, oxidative products, and lipid signals that shape the post-stroke immune environment. In this sense, cell death is not merely an endpoint of ischemic injury; it is an upstream determinant of the inflammatory and metabolic conditions that influence recovery.

Beyond necrosis and apoptosis, ischemic brain injury involves several regulated cell death pathways with overlapping and context-dependent roles [27]. Recent literature has placed increasing emphasis on the coexistence and crosstalk of apoptosis, necroptosis, pyroptosis, and ferroptosis in ischemic brain injury, including the possibility of PANoptosis-like coordination among inflammatory cell death pathways [25,26]. Their coexistence may help ex-

plain why therapies directed at a single injury mechanism have shown limited translational success. More importantly for precision recovery, the dominant mode of cell death may influence the timing, intensity, and quality of neuroinflammatory activation, thereby affecting whether the local environment becomes injury-amplifying or repair-permissive.

2.2.1 Apoptosis

Apoptosis is prominent in the ischemic penumbra, where tissue is injured but not immediately lost. It is mediated through intrinsic mitochondrial and extrinsic death receptor pathways. Mitochondrial outer membrane permeabilization promotes cytochrome c release, caspase-9 activation, and downstream caspase-3 signaling [28]. The balance between pro-apoptotic and anti-apoptotic Bcl-2 family proteins remains an important determinant of cell fate after ischemic injury [29].

For a recovery-oriented framework, apoptosis is important because it reflects delayed cellular vulnerability in potentially salvageable tissue. Its temporal profile overlaps with the period in which neurovascular stabilization, inflammation control, and early rehabilitation may begin to influence outcome. Recent discussions of PANoptosis in cerebral ischemia further suggest that apoptosis should not be interpreted in isolation, because apoptotic, pyroptotic, and necroptotic signals may coexist in ischemic models and may collectively shape inflammatory injury [25]. Thus, apoptosis should be considered not only as a target for neuroprotection but also as part of the biological window that links acute injury to later repair.

2.2.2 Necroptosis

Necroptosis is a programmed form of necrotic death mediated primarily by receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and mixed lineage kinase domain-like pseudokinase (MLKL) signaling [30]. Unlike apoptosis, necroptosis is strongly pro-inflammatory because membrane rupture promotes the release of damage-associated molecular patterns. Recent reviews support the role of necroptosis in cerebral ischemic injury and neuroinflammation, and necroptosis inhibitors have been discussed as potential strategies for reducing ischemic damage [31]. In ischemic stroke, necroptosis may contribute to neuronal and glial injury, particularly when apoptotic pathways are inhibited or overwhelmed.

The relevance of necroptosis to the present framework lies in its capacity to convert cell death into immune amplification. By releasing intracellular danger signals, necroptosis can strengthen microglial activation, leukocyte recruitment, and blood–brain barrier dysfunction. It therefore represents a plausible link between early ischemic injury and the acute inflammatory state that may restrict subsequent neuroplasticity.

2.2.3 Pyroptosis

Pyroptosis provides a direct mechanistic bridge between regulated cell death and inflammation. It is driven by inflammasome activation, particularly the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, followed by caspase-1 activation, gasdermin D cleavage, membrane pore formation, and release of interleukin-1 beta (IL-1β) and IL-18 [32]. Recent reviews identify the NLRP3 inflammasome as a key inflammatory platform in ischemic stroke that links sterile inflammation, pyroptotic signaling, and blood–brain barrier disruption [33,34]. In ischemic stroke, pyroptosis has been implicated in neuronal and microglial injury and is closely related to innate immune activation. Within a phase-specific model, pyroptosis is especially relevant during the acute and early subacute phases, when inflammasome signaling may worsen neurovascular injury and intensify cytokine-mediated damage. At the same time, its timing and cellular source may determine whether inflammatory signaling remains pathological or begins to resolve. This makes pyroptosis a candidate mechanism for identifying patients with an inflammation-dominant recovery endotype.

2.2.4 Ferroptosis

Ferroptosis is an iron-dependent form of regulated cell death that is characterized by lipid peroxide accumulation and failure of antioxidant defense, particularly glutathione peroxidase 4 (GPX4) activity [35]. During the delayed phase of ischemic injury, iron overload, lipid peroxidation, impaired GPX4-dependent antioxidant defense, and ferroptosis contribute to secondary neuronal and neurovascular injury [36,37,38,39]. Ferroptosis is particularly important for an immune–metabolic framework because it links cell death to redox balance, lipid metabolism, and delayed neurodegeneration. Unlike purely excitotoxic models of ischemic injury, ferroptosis points to metabolic vulnerability as a determinant of tissue fate. It may also help explain why patients with systemic metabolic dysfunction, poor nutritional reserve, or chronic oxidative stress show limited recovery despite comparable initial injury.

2.3 Temporal and Spatial Integration of Cell Death Pathways

Regulated cell death pathways do not occur in a fixed sequence or isolated anatomical region. The core of the infarct is dominated by rapid necrotic injury, whereas the penumbra shows overlapping apoptosis, necroptosis, pyroptosis, and ferroptosis, which evolve over hours to days after the onset of stroke [40]. Recent transcriptomic and experimental evidence also suggests that iron-related mechanisms may promote both ferroptotic and necroptotic signaling during early ischemic injury, which reinforces the concept that cell-death pathways can interact rather than functioning as isolated modules [41]. Oxidative stress can ac-

tivate both apoptosis and ferroptosis, while inflammasome signaling connects pyroptosis to broader inflammatory cascades. Necroptosis, in turn, promotes the release of danger signals and immune activation.

This overlap has two implications. First, it limits the likelihood that a single neuroprotective target will be sufficient across heterogeneous patients and recovery phases. Second, it supports the need to identify dominant biological states rather than isolated molecular events. A patient whose early response is dominated by inflammasome activation, blood–brain barrier disruption, and leukocyte recruitment may require a different therapeutic strategy from one in whom delayed oxidative and metabolic injury predominates. The major cellular and molecular components contributing to phase-specific immune responses after stroke are illustrated in Fig. 2.

2.4 Translational Implications for Precision Stroke Recovery

Regulated cell death should be viewed as the upstream entry point into phase-specific immune–metabolic recovery states. These pathways generate the danger signals, cytokine responses, lipid mediators, and redox disturbances that shape neuroinflammation, blood–brain barrier integrity, and later plasticity. Their clinical importance therefore extends beyond acute neuroprotection.

For precision recovery medicine, the key question is not simply which cell death pathway occurs after a stroke, but which pathway dominates in a given patient, at a given phase, and under which metabolic conditions. Mapping these patterns may help define biological recovery endotypes and guide phase-matched interventions. Acute strategies may aim to reduce inflammatory amplification and neurovascular breakdown, whereas subacute and chronic strategies may focus on supporting plasticity, metabolic resilience, and recovery-permissive immune remodeling.

3. Neuroinflammation and Immune Response

Neuroinflammation is not a uniform pathological response after stroke but a phase-dependent process that can either amplify injury, permit repair, or sustain maladaptive remodeling. After ischemic injury, inflammatory signaling results from the interaction among resident glial cells, the neurovascular unit, circulating immune cells, and systemic immune–metabolic status. The clinical relevance of this response depends less on the presence of inflammation per se than on its timing, cellular composition, vascular context, and resolution pattern [7,8,11]. The interactions among innate immune activation, metabolic dysfunction, and secondary neuronal injury are presented in Fig. 3.

In a precision recovery framework, neuroinflammation should be viewed as a biological state that changes across the acute, subacute, and chronic phases of recovery. In the acute phase, excessive innate immune activation may worsen neuronal injury and disruption of the blood–brain barrier. In the subacute phase, regulated inflammatory responses can support the clearance of debris, vascular remodeling, and synaptic reorganization. In the chronic phase, unresolved inflammation may limit plasticity, sustain glial reactivity, and contribute to delayed neurodegeneration. This phase-specific interpretation is essential because broad suppression of inflammation may be beneficial in one window but counterproductive in another.

3.1 Activation of Resident Glial Cells

Microglia are among the earliest cellular responders to ischemic injury. Within minutes to hours after stroke onset, they change morphology, migrate toward the injured region, proliferate, and produce inflammatory mediators [42]. The traditional M1/M2 classification has been useful as a simplified teaching model, but it is increasingly inadequate for explaining post-stroke immune biology. Microglial states are heterogeneous, temporally unstable, and strongly shaped by local signals such as cell-death products, cytokines, blood-derived proteins, and metabolic stress. Their function cannot be reduced to a fixed pro-inflammatory or anti-inflammatory identity [43].

In the acute phase, activated microglia release cytokines, chemokines, and reactive oxygen species that can intensify neuronal injury and promote blood–brain barrier disruption. IL-1β, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are particularly relevant because they link innate immune activation with excitotoxicity, endothelial dysfunction, and leukocyte recruitment. However, microglia are not only injury amplifiers. At later stages, selected microglial programs contribute to debris clearance, angiogenesis, synaptic remodeling, and tissue repair [44]. The key issue is therefore not whether microglia are “good” or “bad”, but whether their activation state is matched to the biological needs of the recovery phase.

Astrocytes also shape the inflammatory and repair environment after stroke. Reactive astrogliosis involves cellular hypertrophy, proliferation, and increased glial fibrillary acidic protein expression. Astrocytes regulate extracellular glutamate, support blood–brain barrier integrity, modulate cytokine signaling, and contribute to scar formation [45]. These functions may be protective when they limit excitotoxicity and stabilize the neurovascular unit, but restrictive when persistent astrogliosis forms a non-permissive environment for axonal growth and synaptic reorganization. Like microglia, astrocytes should therefore be interpreted through a phase-specific lens rather than as a single reactive phenotype.

3.2 Peripheral Immune Cell Infiltration

Ischemic stroke recruits peripheral immune cells into the injured brain in a process that is facilitated by blood–brain barrier disruption, endothelial activation, chemokine signaling, and matrix metalloproteinase-related vascular re-

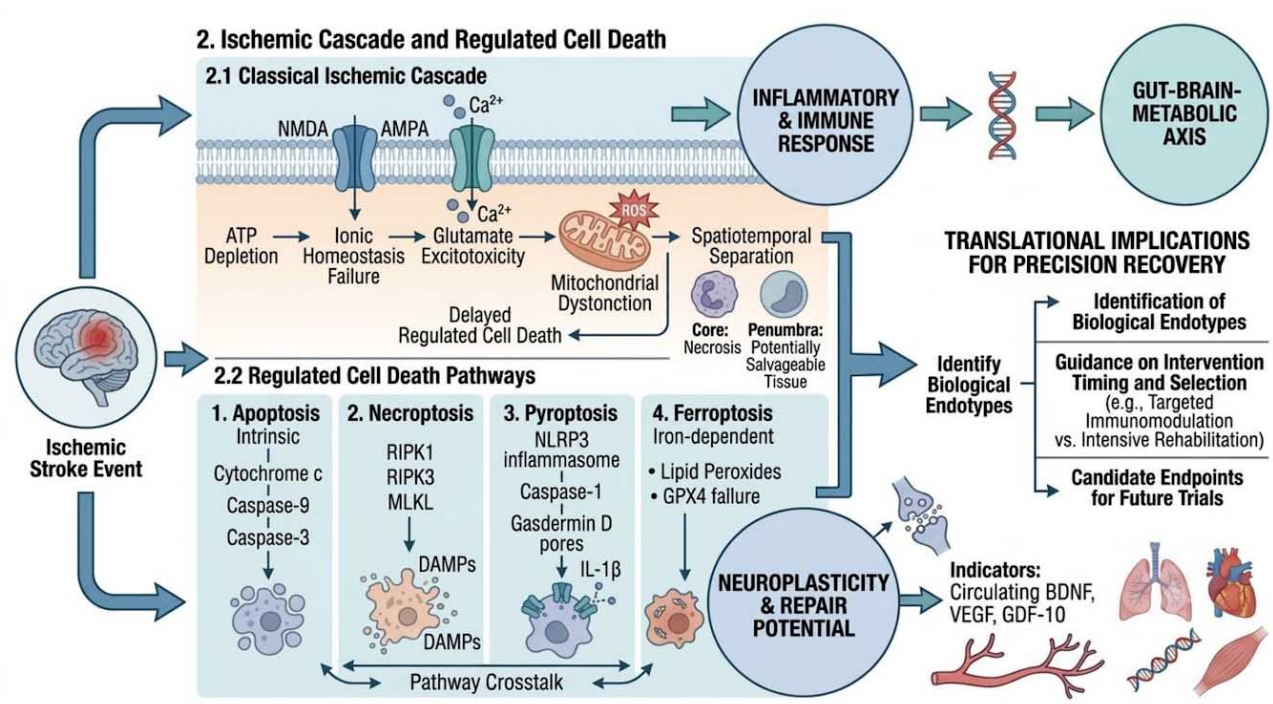

Fig. 2. Ischemic cascade, regulated cell-death pathways, and their potential implications for precision stroke recovery. The schematic summarizes the progression from the initial ischemic event to acute cellular injury, delayed regulated cell death, inflammatory activation, and recovery-related biological responses. Energy failure after ischemia disrupts ionic homeostasis and promotes excessive glutamatergic signaling through N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The resulting calcium overload, mitochondrial dysfunction, and generation of reactive oxygen species (ROS) contribute to the spatiotemporal evolution of tissue injury. This process encompasses the necrotic infarct core and the potentially salvageable penumbra, in which delayed regulated cell-death mechanisms may remain biologically relevant. Four representative regulated cell-death pathways are illustrated. Intrinsic apoptosis involves mitochondrial cytochrome *c* release and sequential activation of caspase-9 and caspase-3. Necroptosis is represented by receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and mixed lineage kinase domain-like pseudokinase (MLKL), with downstream release of damage-associated molecular patterns (DAMPs). Pyroptosis is linked to nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation, caspase-1 activity, gasdermin D pore formation, and interleukin-1 beta (IL-1β) release. Ferroptosis is characterized by iron-dependent lipid peroxidation and failure of glutathione peroxidase 4 (GPX4)-mediated antioxidant defense. Bidirectional arrows indicate pathway crosstalk rather than mutually exclusive mechanisms. The figure further illustrates the proposed relationship of these injury pathways with inflammatory and immune responses, the gut–brain–metabolic axis, and neuroplasticity and repair potential. Candidate indicators related to repair include circulating brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and growth differentiation factor 10 (GDF-10). Integration of these biological domains may support the identification of recovery endotypes, inform the timing and selection of future interventions, and contribute to the development of candidate endpoints for prospective trials. The arrows represent proposed biological relationships and translational hypotheses rather than established causal or clinically validated pathways. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

modeling [46]. Peripheral immune infiltration is often described as a marker of injury severity, but it has greater relevance for recovery in how it reshapes the neurovascular and inflammatory environment. Neutrophils are among the earliest infiltrating leukocytes, and through proteolytic enzymes, reactive oxygen species, and neutrophil extracellular traps, they can aggravate vascular injury, thrombosis, and blood–brain barrier dysfunction. This makes neutrophil-dominant inflammation a plausible marker of an acute injury-amplifying state. Monocytes and macrophages enter later and have more diverse roles. Depending on the timing and tissue signals, they may sustain inflammation or participate in debris clearance, matrix remodeling, and repair [47]. Adaptive immune responses add another layer of complexity. Pro-inflammatory Th1 and Th17 responses have been associated with greater tissue injury, whereas regulatory T cells may suppress excessive inflammation and support repair-oriented signaling [19]. The balance

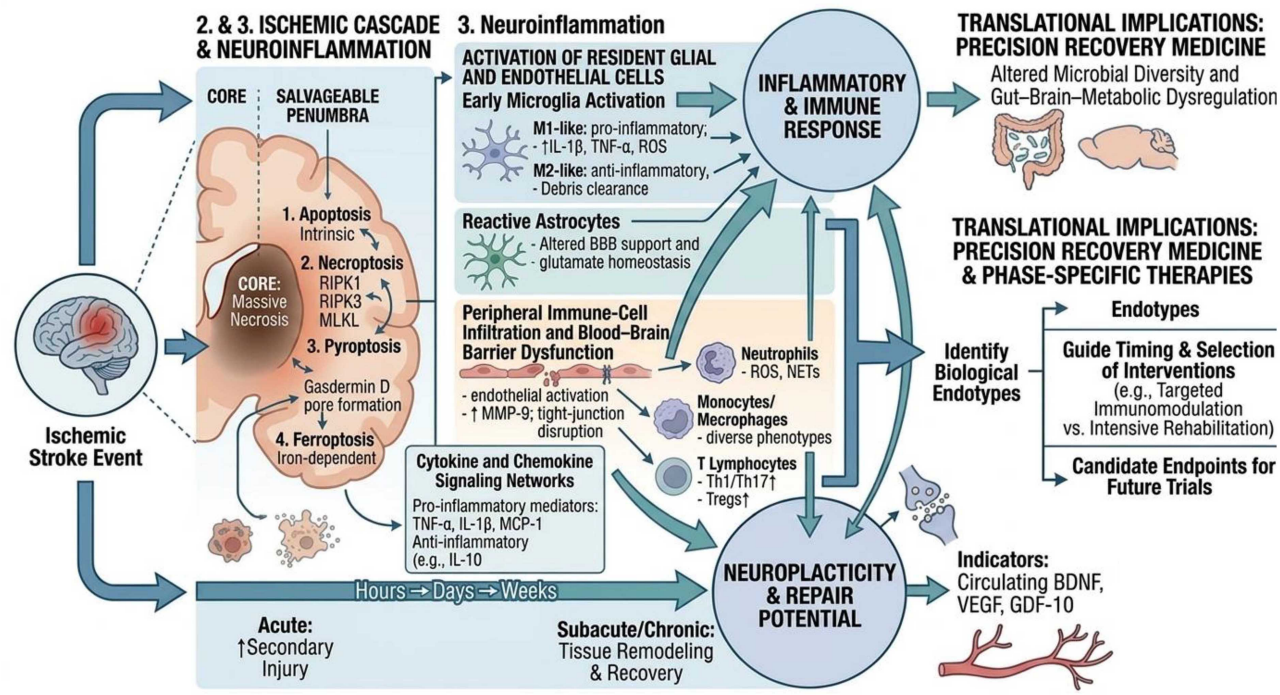

Fig. 3. Integrated overview of the ischemic cascade, neuroinflammation, and recovery-related biological transitions after stroke. The schematic illustrates the progression from ischemic injury to acute tissue damage, neuroinflammatory activation, blood–brain barrier dysfunction, peripheral immune-cell infiltration, and subsequent repair-related responses. The infarct core is characterized by extensive necrotic injury, whereas the surrounding penumbra represents potentially salvageable tissue in which delayed regulated cell-death pathways, including apoptosis, necroptosis, pyroptosis, and ferroptosis, may remain biologically relevant. Neuroinflammation involves resident glial and endothelial cells, reactive astrocytes, increased matrix metalloproteinase-9 activity, tight-junction disruption, and recruitment of neutrophils, monocytes/macrophages, and T lymphocytes. Neutrophil-associated reactive oxygen species and neutrophil extracellular traps may further amplify secondary injury. The lower timeline depicts the transition from acute secondary injury over hours to days toward subacute and chronic tissue remodeling and recovery over days to weeks. Neuroplasticity and repair potential are represented by circulating brain-derived neurotrophic factor, vascular endothelial growth factor, and growth differentiation factor 10. Altered microbial diversity and gut–brain–metabolic dysregulation are also included as potential contributors to recovery heterogeneity. Integration of inflammatory, neurovascular, metabolic, and repair-related information may support the identification of biological recovery endotypes and inform the timing and selection of future interventions. The arrows indicate proposed phase-dependent relationships rather than established causal pathways. The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

among these populations may help define distinct immune recovery endotypes. A patient with persistent neutrophil-driven vascular injury may require a different therapeutic approach from one whose recovery is limited by chronic adaptive immune activation or impaired resolution.

3.3 Cytokine and Chemokine Signaling Networks

Cytokines and chemokines coordinate the transition from ischemic injury to immune activation. IL-1β, TNF-α, and IL-6 are rapidly increased after ischemia and can worsen neuronal injury by increasing excitotoxicity, oxidative stress, endothelial activation, and permeability of the blood–brain barrier [48]. Chemokines such as MCP-1/CCL2 promote recruitment of monocytes and other peripheral immune cells into the injured tissue.

These mediators, however, should not be interpreted only as isolated markers of inflammation. Their meaning depends on timing and tissue context. An early rise in pro-inflammatory cytokines may reflect acute danger signaling and secondary injury, whereas failure to resolve inflammatory signaling may indicate transition toward chronic maladaptive inflammation. Conversely, IL-10 and TGF-β may support resolution and repair in later phases, but their effects are likely to depend on the surrounding cellular and metabolic environment. For precision recovery, cytokine profiles may be most useful when interpreted longitudinally rather than as single time-point measurements.

3.4 Blood–Brain Barrier Dysfunction

The blood–brain barrier is not merely a passive structure disrupted by ischemia; it is an active neurovascular in-

terface that regulates immune-cell entry, endothelial signaling, plasma protein leakage, and communication between the circulation and the injured brain. Structurally, it is embedded in the neurovascular unit, which includes brain microvascular endothelial cells, pericytes, astrocytic end-feet, basement membrane, and associated immune and glial elements. Its function depends on coordinated paracellular and transcellular transport mechanisms that maintain homeostasis of the central nervous system.

After ischemic stroke, blood–brain barrier dysfunction occurs early and can actively shape the inflammatory trajectory rather than simply reflect tissue damage. Endothelial activation, oxidative stress, tight-junction disruption, matrix degradation, and altered vesicular transport increase vascular permeability and permit entry of circulating immune cells and plasma-derived mediators. This process links the vascular compartment to innate immune activation and glial reactivity. Contemporary evidence therefore supports viewing blood–brain barrier dysfunction as an early driver of ischemic stroke pathology and a central component of immune–metabolic recovery states, rather than as a secondary consequence alone [49,50].

Within a phase-specific framework, blood–brain barrier status may help distinguish patients whose recovery is limited by ongoing neurovascular instability from those in whom inflammation has transitioned toward repair. Persistent barrier leakage may expose the brain to fibrinogen, albumin, complement factors, and peripheral cytokines, thereby sustaining microglial activation and astrocytic reactivity. In contrast, restoration of barrier integrity may create a more permissive environment for synaptic remodeling, angiogenesis, and rehabilitation-induced plasticity. Blood-brain barrier (BBB)-related biomarkers and imaging measures may therefore have value not only for assessing acute injury severity, but also for stratifying recovery biology. The mechanisms underlying blood–brain barrier dysfunction after ischemic stroke including tight-junction degradation, MMP-9–mediated proteolysis, oxidative endothelial injury, increased paracellular permeability and transcytosis, and subsequent vasogenic edema are illustrated in Fig. 4.

3.4.1 Molecular and Cellular Mechanisms of BBB Breakdown

Following cerebral ischemia, BBB disruption is initiated within minutes to hours through endothelial activation, oxidative stress, and inflammatory signaling cascades. Reactive oxygen species (ROS), largely derived from NADPH oxidase and mitochondrial dysfunction, directly injure endothelial cells and destabilize junctional complexes, thereby increasing vascular permeability. Simultaneously, degradation of the endothelial glycocalyx, a critical luminal structure regulating shear stress and immune interactions, further amplifies permeability and leukocyte adhesion.

At the structural level, ischemia induces profound alterations in tight junction (TJ) and adherens junction proteins, including claudin-5, occludin, zonula occludens-1 (ZO-1), and VE-cadherin. These proteins normally maintain the restrictive phenotype of brain microvascular endothelial cells (BMECs); however, their phosphorylation, internalization, and proteolytic degradation lead to paracellular leakage and loss of barrier integrity. In parallel, transcellular permeability is increasingly recognized as a major contributor, driven by enhanced caveolae-mediated transcytosis and suppression of regulatory proteins such as MFSD2A [37,38].

3.4.2 MMP-9 as an Immuno-Vascular Amplifier: Integration with Inflammasome Signaling, NETosis, and Endothelial Transport

Beyond its canonical role in extracellular matrix degradation, matrix metalloproteinase-9 (MMP-9) is increasingly conceptualized as a central immuno-vascular amplifier that integrates proteolytic remodeling with innate immune activation and endothelial dysfunction. In the context of ischemic stroke, MMP-9 operates within a tightly coupled network involving inflammasome signaling, neutrophil extracellular trap (NET) formation, and dysregulated endothelial transport, thereby transforming localized vascular injury into a self-propagating neuroinflammatory cascade.

At the molecular level, MMP-9 intersects functionally with the NLRP3 inflammasome axis, a key regulator of sterile inflammation in ischemic brain injury. Ischemia-induced oxidative stress activates nuclear factor kappa B (NF-κB)–dependent priming and subsequent assembly of the NLRP3 inflammasome, leading to the maturation of IL-1β and IL-18 and amplification of inflammatory signaling. Recent mechanistic studies further demonstrate that inflammasome activation in both microglia and infiltrating neutrophils directly contributes to blood–brain barrier (BBB) disruption and vascular permeability, positioning inflammasome signaling upstream of structural barrier failure. Within this framework, MMP-9 acts synergistically by proteolytically remodeling the extracellular matrix and facilitating cytokine bioavailability, thereby reinforcing inflammasome-driven inflammatory amplification. Emerging data also suggest bidirectional crosstalk, whereby MMP-9 activity may modulate inflammasome signaling dynamics, further intensifying neuroinflammation.

Concurrently, MMP-9 is mechanistically linked to neutrophil extracellular trap (NET) formation (NETosis), a process now recognized as a critical driver of thromboinflammation and BBB injury. NET accumulation exacerbates endothelial damage, increases vascular permeability, and worsens neurological outcomes following ischemic stroke. Notably, recent evidence indicates that NLRP3 activation enhances NET formation through ROS-dependent pathways, while NET-associated proteases—including MMP-9—contribute to matrix degradation and

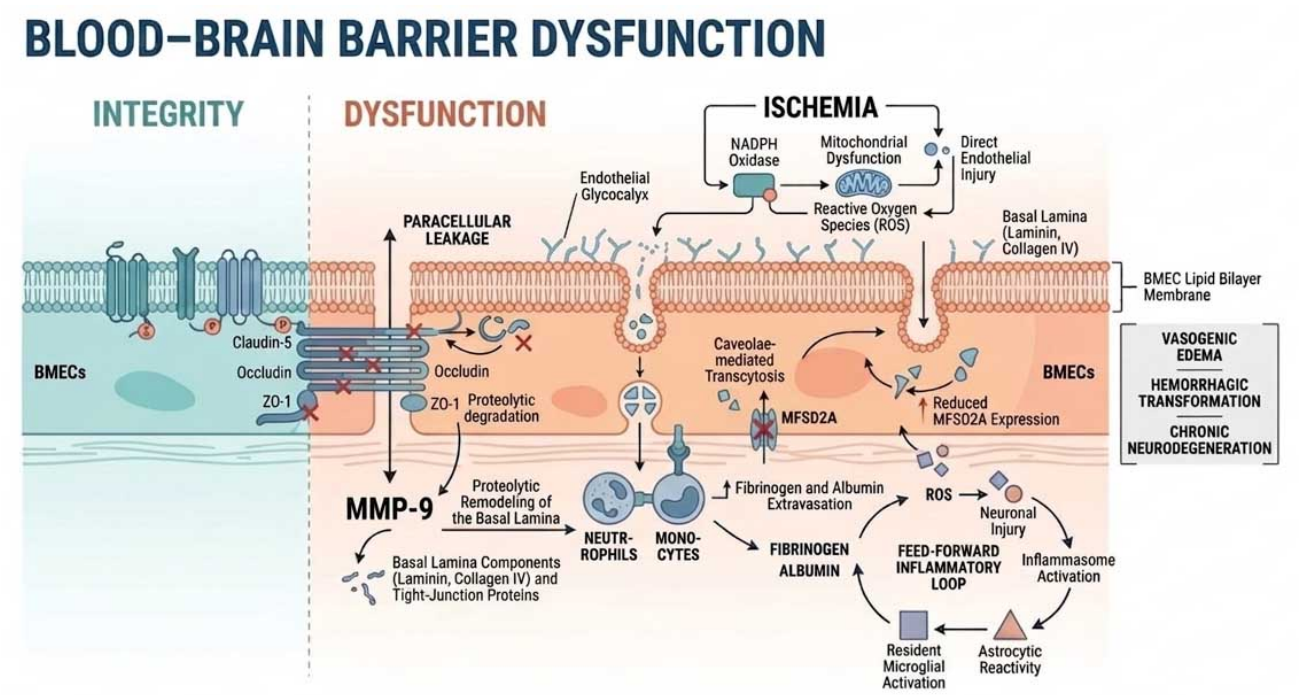

Fig. 4. Mechanisms of blood–brain barrier dysfunction after cerebral ischemia. The schematic contrasts blood–brain barrier integrity with ischemia-induced endothelial dysfunction. Under physiological conditions, brain microvascular endothelial cells (BMECs) maintain barrier integrity through tight-junction proteins, including claudin-5, occludin, and zonula occludens-1 (ZO-1). Following ischemia, oxidative stress, mitochondrial dysfunction, and direct endothelial injury promote paracellular leakage, proteolytic degradation of tight-junction proteins, and matrix metalloproteinase-9 (MMP-9)-mediated remodeling of the basal lamina. Reduced major facilitator superfamily domain-containing protein 2A (MFSD2A) expression may further increase caveolae-mediated transcytosis. Barrier disruption facilitates the extravasation of fibrinogen and albumin, recruitment of neutrophils and monocytes, and amplification of reactive oxygen species (ROS), inflammasome activation, microglial activation, and astrocytic reactivity. These interacting processes may establish a feed-forward inflammatory loop and contribute to vasogenic edema, hemorrhagic transformation, and chronic neurodegenerative changes. The arrows indicate proposed mechanistic relationships rather than a strictly linear sequence of events. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

barrier destabilization. This establishes a pathogenic axis in which neutrophils not only infiltrate the injured brain but actively remodel the neurovascular environment, promoting both structural disruption and sustained immune activation. The molecular and cellular mechanisms contributing to blood-brain barrier dysfunction after stroke including NLRP3 inflammasome activation, NF-κB signaling, neutrophil extracellular trap formation, MMP-9-mediated tight-junction degradation, and increased transcytosis are summarized in Fig. 5.

3.4.3 BBB Dysfunction as an Immuno-Vascular Interface Linking Acute Injury to Long-Term Recovery

BBB breakdown changes the immune status of the injured brain. Once barrier integrity is compromised, neutrophils, monocytes, lymphocytes, plasma proteins, complement factors, and peripheral cytokines can enter or influence the brain parenchyma. This process is promoted by endothelial adhesion molecules, including ICAM-1 and VCAM-1, as well as chemokine gradients that direct leukocyte trafficking. Importantly, BBB dysfunction is not merely permissive; it actively reshapes the neuroimmune microenvironment. Leakage of fibrinogen and albumin can trigger microglial activation, astrocytic reactivity, and inflammasome signaling, thereby linking vascular leakage to innate immune amplification [9,10]. This supports the view of stroke as a neurovascular–immune disorder rather than a purely ischemic event [7,8,51].

The consequences of BBB dysfunction extend beyond immune-cell entry. In the acute phase, loss of barrier integrity contributes to vasogenic edema by allowing plasma proteins and water to enter the interstitial space, thereby increasing brain swelling and intracranial pressure. Structural compromise of the vascular wall also increases the risk of hemorrhagic transformation, particularly after reperfusion therapy. These events can intensify neurovascular instability and secondary injury.

For recovery biology, BBB status is relevant because it influences the transition from acute injury to repair. Continued leakage may sustain immune-cell trafficking, cy-

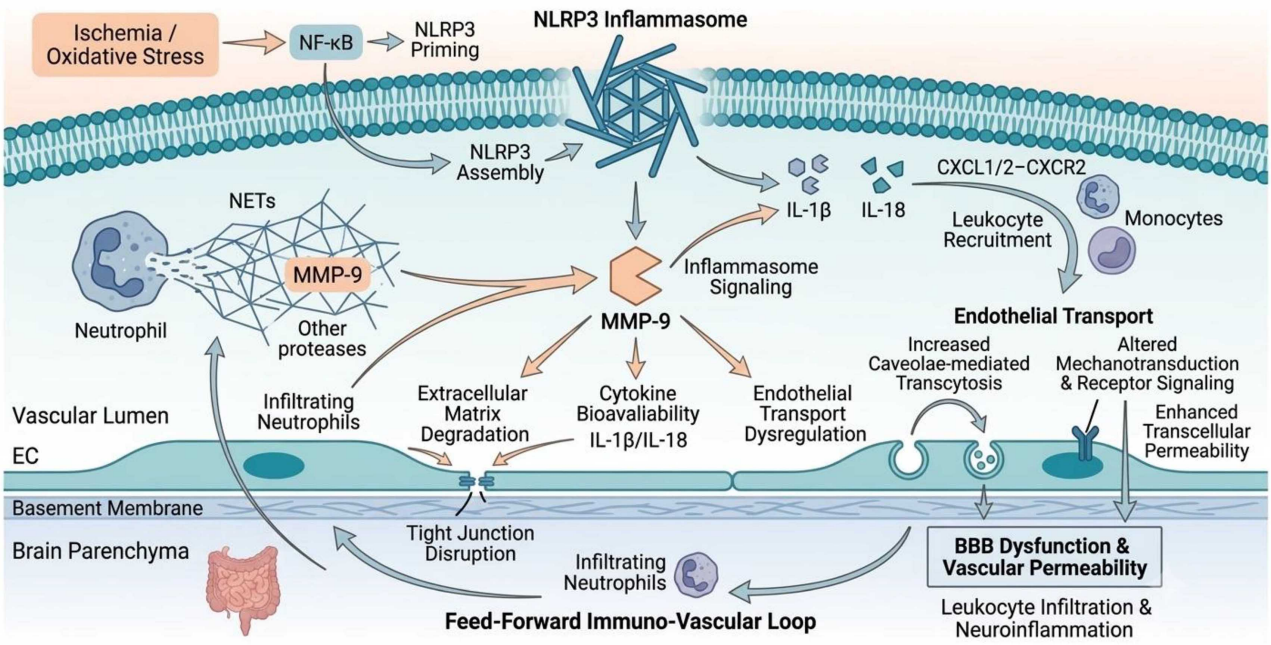

Fig. 5. MMP-9 as a mediator of proteolytic remodeling, innate immune activation, and endothelial dysfunction after cerebral ischemia. The schematic illustrates how ischemia and oxidative stress may promote nuclear factor kappa B (NF-κB)-dependent priming and assembly of the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. Inflammasome signaling and neutrophil extracellular trap formation contribute to matrix metalloproteinase-9 (MMP-9) release, extracellular matrix degradation, tight-junction disruption, and altered cytokine bioavailability. MMP-9-related endothelial dysfunction may further increase caveolae-mediated transcytosis, transcellular permeability, and leukocyte recruitment through the CXCL1/2–CXCR2 axis. These interacting processes may establish a feed-forward immune–vascular loop that amplifies blood–brain barrier dysfunction, vascular permeability, leukocyte infiltration, and neuroinflammation. The arrows indicate proposed mechanistic relationships rather than a strictly linear sequence of events. The intestinal icon in the lower-left corner denotes the potential contribution of the gut–brain axis and gut-derived systemic inflammatory signaling to neutrophil activation, blood–brain barrier dysfunction, and the feed-forward immuno-vascular loop. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

tokine exposure, microglial activation, astrocytic reactivity, and inflammasome signaling long after the initial ischemic event. Such persistent barrier dysfunction may delay the formation of a plasticity-permissive environment and has been linked to delayed neurodegeneration, post-stroke cognitive decline, and vascular dementia. By contrast, restoration of vascular integrity may limit peripheral immune exposure and create conditions more favorable for synaptic remodeling, circuit reorganization, and rehabilitation-induced plasticity. BBB integrity should therefore be considered a candidate marker of recovery phase, not only of acute injury severity.

3.5 Temporal Dynamics: From Injury Amplification to Repair-Permissive Inflammation

A central problem in stroke immunology is that inflammation is often discussed as though it were a single therapeutic target. This view is too broad for recovery medicine. The same inflammatory pathway may be harmful in the acute phase, useful during tissue clearance and remodeling, and maladaptive if it persists chronically. In the acute phase, inflammatory responses can expand tissue injury, worsen BBB disruption, and increase infarct progression. In the subacute phase, selected immune functions are needed for debris clearance, angiogenesis, extracellular matrix remodeling, and synaptic reorganization. In the chronic phase, unresolved inflammation may sustain glial reactivity, impair plasticity, and contribute to delayed neurological decline [11]. This temporal pattern has direct therapeutic implications. Broad anti-inflammatory treatment may reduce early injury but could interfere with later repair if given at the wrong time. A phase-specific approach is therefore needed. The goal should be to identify when inflammation is injury-amplifying, when it is repair-permissive, and when it has become chronically maladaptive.

3.6 Translational Implications and Link to Systemic Processes

Post-stroke inflammation is not confined to the brain. Stroke can induce systemic immune changes, includ-

ing lymphopenia and increased susceptibility to infection, which influence clinical outcome [52]. At the same time, peripheral metabolic status, nutritional reserve, frailty, and gut microbiota composition may alter immune tone and recovery potential. This systemic dimension is central to the immune–metabolic framework proposed in this review. A patient with BBB disruption, neutrophil-dominant inflammation, malnutrition, and dysbiosis may have a different recovery biology from a patient with preserved metabolic reserve and resolving inflammation. These differences may help define biological recovery endotypes and guide intervention selection.

For precision stroke recovery, neuroinflammation should therefore be assessed together with neurovascular status and systemic metabolic context. Biomarkers of inflammation, BBB integrity, nutritional reserve, microbiome-related metabolites, and plasticity potential may be more informative when combined than when interpreted separately. Fig. 6 summarizes the temporal and multiscale mechanisms of post-stroke neuroplasticity and repair across the acute, subacute, and chronic phases, including network reorganization, axonal remodeling, synaptic plasticity, angiogenesis, neurogenesis, and associated growth-regulatory signaling pathways.

4. Neuroplasticity and Repair Biology

Neuroplasticity is the biological basis of functional recovery after stroke, but it should not be viewed as an autonomous brain repair program. The capacity for circuit reorganization depends on the state of the injured tissue, the inflammatory environment, neurovascular stability, metabolic reserve, and the timing of rehabilitation. In this sense, plasticity is not simply "present" or "absent"; it is permitted, constrained, or misdirected by the biological conditions created after ischemic injury. Recent reviews similarly emphasize that post-stroke plasticity depends on interactions among neural repair, glial regulation, vascular remodeling, and rehabilitation-driven activity rather than on a single intrinsic repair mechanism [53,54].

A phase-specific view is therefore necessary. In the acute phase, excitotoxicity, oxidative stress, ionic imbalance, and blood–brain barrier disruption dominate the local environment. Early synaptic changes and unmasking of latent connections may occur, but this period is still largely defined by tissue vulnerability. During the subacute phase, the brain enters a more plasticity-permissive window. Growth-associated signaling, neurotrophic factors, synaptic remodeling, axonal sprouting, dendritic restructuring, and vascular repair become more prominent. This is the period in which rehabilitation is most likely to shape recovery biology rather than merely support compensation. In the chronic phase, plasticity persists but becomes less flexible. Network reorganization may support functional gains, but it may also reinforce inefficient compensatory patterns, abnormal synergies, or spasticity. This phase-dependent view is consistent with recent biomarker and rehabilitation studies showing that recovery-related molecular signals may change over time and may relate to functional response during therapy [14,55].

At the cellular level, repair depends on coordinated but non-identical roles of neurons, glia, oligodendrocyte lineage cells, and vascular elements. Neurons mediate activity-dependent synaptic modification and circuit remapping. Astrocytes regulate extracellular glutamate, provide metabolic support, modulate synaptic signaling, and contribute to scar formation. Microglia can either restrict plasticity through persistent inflammatory signaling or support repair through debris clearance and synaptic remodeling. Recent work highlights that microglial regulation is closely coupled with neuroplasticity after stroke and may influence network rewiring in a spatiotemporal manner [56]. Oligodendrocyte precursor cells contribute to remyelination, which is essential for restoring conduction efficiency. The neurovascular unit supports angiogenesis and perfusion recovery, processes that are closely linked to synaptic and structural repair.

At the molecular level, recovery reflects the balance between growth-promoting and growth-inhibitory signals. Neurotrophins, CREB activation, PI3K/Akt signaling, and MAPK/ERK pathways support neuronal survival and synaptic remodeling. In contrast, Nogo-A, myelin-associated glycoprotein, RhoA/ROCK signaling, and extracellular matrix components such as chondroitin sulfate proteoglycans restrict axonal regeneration and may contribute to a non-permissive repair environment. This balance is not fixed. It is influenced by inflammation, metabolic state, age, comorbidity, and rehabilitation intensity. Recent studies of angiogenesis and neuroplasticity biomarkers further support the relevance of BDNF, vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and MMP-9 as candidate indicators of repair potential and rehabilitation responsiveness [57,58].

At the systems level, recovery involves reorganization within and between motor, sensory, and cognitive networks. Functional MRI and diffusion tensor imaging studies show that recovery is associated with changing patterns of ipsilesional and contralesional connectivity. Early re-engagement of ipsilesional networks is often associated with better outcomes, whereas persistent reliance on contralesional recruitment may indicate compensation that is less efficient or potentially maladaptive. These patterns suggest that recovery quality depends not only on the amount of neural activity, but on whether activity is organized through biologically and functionally efficient networks. Recent precision rehabilitation proposals argue that imaging, molecular, electrophysiological, and computational markers should be integrated to better predict functional outcomes and guide individualized rehabilitation planning [4].

Rehabilitation is central to this process because plasticity is experience-dependent. Task-specific training,

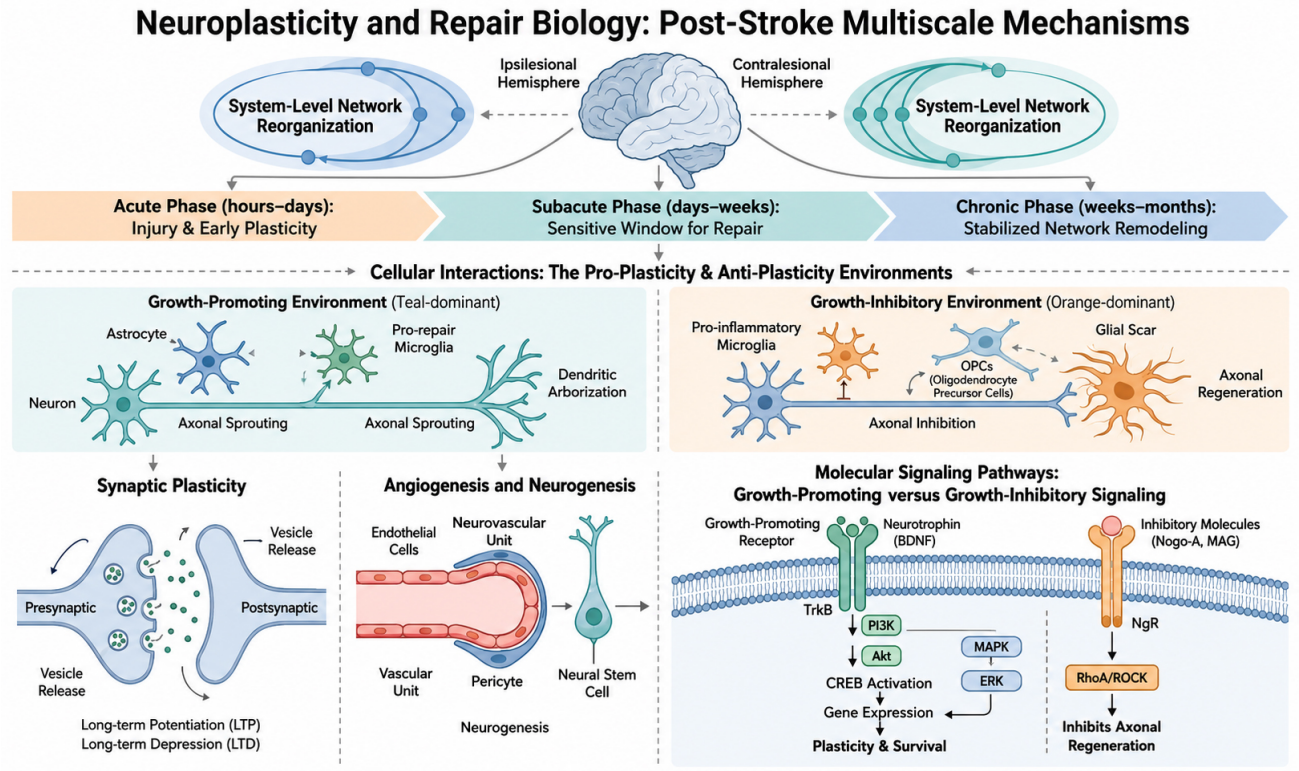

Fig. 6. Multiscale mechanisms of neuroplasticity and repair after stroke. The schematic summarizes recovery-related processes across acute, subacute, and chronic phases after stroke. Early injury is followed by a subacute window of enhanced repair sensitivity and subsequent stabilization of network remodeling. At the systems level, recovery involves reorganization of ipsilesional and contralesional neural networks. At the cellular level, the balance between growth-promoting and growth-inhibitory environments influences axonal sprouting, dendritic arborization, glial responses, and axonal regeneration. Synaptic plasticity is represented by presynaptic and postsynaptic remodeling, vesicle release, long-term potentiation, and long-term depression. Angiogenesis and neurogenesis are illustrated through interactions among endothelial cells, pericytes, the neurovascular unit, and neural stem cells. Molecular regulation includes brain-derived neurotrophic factor (BDNF)–TrkB signaling through PI3K/Akt and MAPK/ERK pathways, which supports CREB-related gene expression and neuronal survival, whereas inhibitory molecules, including Nogo-A and MAG, may activate NgR–RhoA/ROCK signaling and restrict axonal regeneration. The arrows indicate proposed biological interactions rather than a strictly linear sequence of events. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

enriched environments, and neuromodulatory approaches such as transcranial magnetic stimulation and transcranial direct current stimulation can influence synaptic strength and network organization through Hebbian and homeostatic mechanisms. However, the same rehabilitation input may not produce the same biological effect in all patients. Its impact is likely to depend on inflammatory status, blood–brain barrier integrity, metabolic reserve, fatigue, nutrition, and the stage of recovery. Systematic review evidence indicates that blood and cerebrospinal fluid biomarkers may be associated with functional improvement after stroke rehabilitation, although the field still requires stronger longitudinal validation and harmonized measurement protocols [14].

For precision stroke recovery, the key question is not only how to enhance plasticity, but how to identify when the brain is biologically prepared to respond to plasticity-oriented intervention. Patients with persistent inflammation, neurovascular instability, sarcopenia, or metabolic dysfunction may have reduced responsiveness to rehabilitation despite similar lesion characteristics. Conversely, patients with resolving inflammation and preserved metabolic reserve may be better positioned to benefit from intensive, task-specific training. Neuroplasticity should therefore be interpreted as a phase-dependent and immune–metabolically conditioned process, rather than as a generic mechanism of spontaneous repair.

4.1 Structural Plasticity: Axonal Sprouting and Synaptogenesis

Structural plasticity is a major substrate of post-stroke recovery, but its contribution depends on whether new connections are functionally useful and biologically supported. After ischemic injury, surviving neurons in peri-infarct re-

gions undergo axonal sprouting, dendritic remodeling, and synaptogenesis. Sprouting from intact cortical areas, including ipsilesional and contralesional regions, contributes to the reorganization of functional networks [59].

Dendritic spine turnover increases in the peri-infarct cortex, reflecting a period of heightened synaptic remodeling. These new synapses may compensate for lost connections and support functional improvement. However, plasticity is not inherently adaptive. Excessive or poorly directed rewiring may contribute to inefficient network activity, abnormal movement patterns, or other maladaptive outcomes. Rehabilitation is therefore important not only because it stimulates plasticity, but because it helps shape which connections are strengthened and retained [60]. Recent discussions of post-stroke plasticity similarly emphasize that rehabilitation must guide adaptive network reorganization rather than simply increase neural activity [53,54].

Within a precision recovery framework, structural plasticity should be interpreted as a conditional process. It is more likely to support meaningful recovery when inflammation is resolving, the neurovascular environment is stable, metabolic reserve is adequate, and task-specific training provides appropriate activity-dependent input.

4.2 Angiogenesis and Neurovascular Remodeling

Neuronal repair after stroke depends closely on vascular repair. Ischemia induces pro-angiogenic mediators such as vascular endothelial growth factor (VEGF), which promote new vessel formation in peri-infarct regions [61]. These microvessels improve oxygen and nutrient delivery and may support neuronal survival, synaptic remodeling, and functional recovery. Recent biomarker literature also supports the relevance of angiogenesis-related pathways, including VEGF and related vascular remodeling markers, as potential indicators of recovery biology after stroke [57,58].

Angiogenesis should not be viewed as a separate vascular event. It is part of a broader neurovascular remodeling process involving endothelial cells, pericytes, astrocytes, and extracellular matrix components. Re-establishment of neurovascular coupling allows neuronal activity and cerebral blood flow to become better matched during recovery. This is particularly relevant during rehabilitation, when increased neural activity requires adequate perfusion and metabolic support.

The quality of angiogenesis may matter as much as its magnitude. Vascular remodeling that restores stable perfusion and barrier integrity can support plasticity, whereas immature or leaky vessels may sustain inflammation and edema. Thus, neurovascular remodeling represents one of the key interfaces between inflammation control, metabolic support, and rehabilitation responsiveness.

4.3 Oligodendrocyte Function and Remyelination

White matter injury is a major contributor to post-stroke disability because efficient communication between neural networks depends on intact myelinated pathways. After ischemia, oligodendrocyte precursor cells are activated, migrate toward injured regions, and may differentiate into mature oligodendrocytes that contribute to remyelination [62]. Recent reviews of remyelination after cerebral ischemia emphasize that oligodendrocyte precursor cell differentiation and myelin repair are regulated by coordinated signaling pathways, including Sonic Hedgehog, receptor tyrosine kinase, and Wnt/β-catenin-related mechanisms [63].

Remyelination can restore conduction efficiency and improve network coordination. In practice, however, this process is often incomplete, especially in older patients or those with comorbidities. Persistent inflammation, oxidative stress, and metabolic dysfunction can impair oligodendrocyte survival and differentiation. Experimental evidence also suggests that targeting white matter repair and remyelination pathways may support recovery after ischemic stroke, including mechanisms involving EphA4/RhoA/ROCK signaling and activity-related oligodendroglial repair [64,65]. This makes remyelination an important example of how repair capacity depends on the immune–metabolic environment.

For precision recovery, white matter repair should be considered alongside gray matter plasticity. Patients with poor metabolic reserve, chronic inflammation, or extensive white matter vulnerability may require different rehabilitation timing, intensity, or adjunctive strategies than patients with preserved oligodendrocyte and vascular support.

4.4 Neurotrophic and Molecular Mediators of Recovery

Post-stroke plasticity is regulated by competing molecular signals that either support or restrict repair. Brain-derived neurotrophic factor (BDNF) is among the most studied mediators. It promotes neuronal survival, dendritic growth, synaptic plasticity, and activity-dependent remodeling, linking rehabilitation and environmental stimulation to molecular repair programs [66].

Other mediators add complementary repair functions. VEGF supports angiogenesis and neurogenesis, while growth differentiation factor-10 has been implicated in axonal sprouting and circuit reorganization [67]. Insulin-like growth factor-1 may contribute to neuronal survival and repair, particularly in relation to metabolic regulation. These molecules should not be interpreted simply as isolated biomarkers. Their meaning depends on recovery phase, tissue context, inflammatory status, and rehabilitation exposure.

Extracellular matrix remodeling is also central to recovery. Matrix metalloproteinases and their inhibitors can either permit structural reorganization or destabilize the neurovascular environment, depending on timing and mag-

nitude. This duality illustrates a recurring theme in stroke recovery: the same biological pathway may support repair in one phase but worsen injury in another.

4.5 Functional Reorganization and Network-Level Recovery

Functional recovery requires reorganization of distributed neural networks. Imaging studies show that both ipsilesional and contralesional regions contribute to recovery, with activation patterns changing over time [68]. Early contralesional recruitment may compensate for loss of function, whereas later recovery is often associated with re-engagement of ipsilesional networks. The distinction between compensation and recovery is important. Increased activation does not always indicate efficient repair. Persistent reliance on contralesional networks or excessive interhemispheric inhibition may reflect maladaptive plasticity rather than true restoration of function. Cortical map reorganization in motor and sensory systems can support improvement, but only when it is functionally organized and reinforced by appropriate behavioral training. Neuromodulation and task-specific rehabilitation may help guide network reorganization. However, their effects are likely to vary across patients depending on lesion characteristics, inflammatory status, neurovascular stability, metabolic reserve, and time since stroke. Network-level recovery should therefore be interpreted as a biologically conditioned process rather than a uniform response to rehabilitation.

4.6 Interaction with Inflammation and Metabolic State

Neuroplasticity does not occur in a neutral biological environment. Persistent neuroinflammation can impair synaptic remodeling, inhibit neurogenesis, disrupt oligodendrocyte function, and reduce responsiveness to rehabilitation [5]. In contrast, resolution of inflammation and the presence of repair-oriented immune signals may create conditions that support axonal sprouting, angiogenesis, remyelination, and synaptic reorganization.

Metabolic state is equally important. Energy availability, oxidative balance, protein reserve, and nutritional status influence the cellular work required for repair. Protein-energy malnutrition and sarcopenia have been associated with poorer functional gains during rehabilitation, possibly because they limit muscle function, immune regulation, and neuroplastic responses. These factors may partly explain why patients with similar lesion burden can differ substantially in recovery. This interaction between inflammation, metabolism, and plasticity is central to precision stroke recovery. A patient with persistent inflammation, BBB dysfunction, sarcopenia, and low metabolic reserve may have limited capacity to respond to intensive rehabilitation. Another patient with resolving inflammation and adequate metabolic support may be more biologically prepared for high-intensity, task-specific therapy. Identifying these differences is essential for moving from standardized rehabilitation schedules toward recovery strategies matched to biological endotypes.

4.7 Translational Implications

The translational challenge is not simply to enhance neuroplasticity, but to identify when and in whom plasticity-oriented interventions are likely to work. Post-stroke repair is time-sensitive and biologically conditioned. Rehabilitation, neuromodulation, and pharmacological strategies may be most effective during a subacute plasticity-permissive window, whereas persistent inflammation, BBB dysfunction, sarcopenia, or poor metabolic reserve may reduce treatment responsiveness. This supports a shift from standardized rehabilitation schedules toward phase-matched recovery strategies. Acute interventions may prioritize secondary injury control and neurovascular stabilization; subacute interventions may aim to reinforce adaptive plasticity; and chronic interventions may need to address maladaptive network organization, persistent inflammation, fatigue, and metabolic constraints. Neuroplasticity-related biomarkers, including neurotrophic factors, inflammatory markers, metabolic indicators, and imaging-based connectivity measures, may help define whether a patient is biologically prepared for intensive recovery-oriented therapy.

Within a precision recovery framework, neuroplasticity is both a therapeutic target and a marker of recovery readiness. Aligning rehabilitation with immune status, neurovascular integrity, metabolic reserve, and biomarker trajectories may improve the selection, timing, and intensity of interventions after stroke.

5. The Gut–Brain–Metabolic Axis in Stroke Recovery

The gut–brain–metabolic axis provides a systemic layer to post-stroke recovery biology. Stroke does not only injure the brain; it also alters autonomic regulation, gut barrier function, microbial ecology, immune tone, and host metabolism. These changes may influence whether the post-stroke environment becomes injury-amplifying, repair-permissive, or chronically maladaptive. Within a phase-specific immune–metabolic framework, the gut microbiota and metabolic state should therefore be viewed as active determinants of recovery potential rather than peripheral modifiers of brain injury [15,69].

5.1 Post-Stroke Gut Dysbiosis

Clinical studies have reported post-stroke alterations in gut microbiota composition and diversity. Recent evidence further indicates that gut dysbiosis and altered microbial metabolic pathways are associated with unfavorable functional outcomes after ischemic stroke [70]. These changes may arise from autonomic dysfunction, impaired gut motility, reduced oral intake, dysphagia, infection, med-

ication exposure, and systemic inflammation. The relevance of dysbiosis for recovery lies not only in microbial composition, but in its functional consequences. Dysbiosis may alter immune-cell activity, gut barrier integrity, microbial metabolite production, and systemic inflammatory tone. It has been linked to worse neurological outcomes and increased mortality, although causality in human stroke remains difficult to establish. For precision recovery, the key question is whether specific dysbiotic patterns identify patients with an immune–metabolic state that limits repair or increases vulnerability to complications.

5.2 Microbial Metabolites and Immune–Metabolic Signaling

Microbial metabolites are one of the main routes through which the gut microbiota can influence stroke recovery. Short-chain fatty acids, including acetate, propionate, and butyrate, help maintain intestinal barrier integrity, regulate immune responses, and modulate neuroinflammatory signaling [71]. Their potential relevance after stroke is that they may support immune resolution and microglial homeostasis, creating conditions more favorable for repair. Not all microbial metabolites are beneficial. Trimethylamine N-oxide has been associated with vascular dysfunction, thrombosis, and adverse cardiovascular outcomes [72]. In the post-stroke setting, elevated trimethylamine N-oxide (TMAO) may reflect a metabolic profile that favors vascular injury, inflammation, and impaired recovery. Lipopolysaccharide (LPS) is another important mediator. When gut permeability increases, LPS can enter the circulation, activate innate immune pathways, and amplify neuroinflammation [15]. These metabolites should not be interpreted as isolated biochemical markers. They may help define immune–metabolic recovery states. A profile characterized by reduced SCFA signaling, increased LPS exposure, and elevated TMAO may indicate a systemic environment that is less supportive of neurovascular repair and rehabilitation-induced plasticity.

5.3 Gut Barrier Dysfunction and Systemic Inflammation

Gut barrier dysfunction provides a mechanistic link between intestinal changes and systemic inflammation after stroke. Increased intestinal permeability allows microbial products, including LPS and other pathogen-associated molecular patterns, to enter the circulation. This can activate innate immune signaling and contribute to secondary neuroinflammatory responses [73]. The clinical significance of this process extends beyond inflammation alone. Gut barrier failure may interact with post-stroke immunosuppression, infection risk, malnutrition, and metabolic instability. Pneumonia and other infections are not simply complications occurring outside the brain; they may alter systemic immune tone and worsen recovery conditions. In this context, intestinal homeostasis becomes part of the biological infrastructure required for recovery.

5.4 Bidirectional Communication in the Microbiota–Gut–Brain Axis

The microbiota–gut–brain axis is bidirectional. Neural pathways, particularly the vagus nerve, provide rapid communication between the gut and the central nervous system, while immune and endocrine pathways provide slower but sustained routes of signaling [74]. After stroke, disruption of autonomic and neuroendocrine regulation can alter gut motility, secretion, permeability, and microbial composition. Signals from the gut may in turn influence the injured brain by modulating systemic inflammation, microbial metabolite availability, endothelial function, and blood–brain barrier integrity. These pathways may also affect cognitive and emotional outcomes, including post-stroke depression and cognitive impairment. This bidirectional relationship is important because it suggests that gut dysfunction may be both a consequence of stroke and a contributor to poor recovery.

5.5 Nutritional and Metabolic Modulation of the Gut–Brain Axis

Nutrition is one of the most clinically accessible ways to influence the gut–brain–metabolic axis. Dietary intake affects microbial diversity, metabolite production, inflammatory tone, and systemic metabolic reserve. After stroke, dysphagia, reduced oral intake, immobilization, and catabolic stress can worsen malnutrition and dysbiosis, thereby reducing the biological resources available for repair. Protein-energy malnutrition and sarcopenia are particularly relevant because they may impair immune regulation, muscle function, rehabilitation tolerance, and neuroplastic responses. In this sense, nutritional status is not merely a supportive-care issue. It may determine whether a patient can respond to intensive rehabilitation and sustain the metabolic demands of recovery. Microbiome-targeted strategies, including dietary fiber, prebiotics, probiotics, and fecal microbiota transplantation, remain promising but not yet established for clinical stroke recovery. Their preclinical rationale is strong, but human evidence remains limited. Future studies should therefore avoid treating microbiome modulation as a generic intervention and instead test whether it benefits defined immune–metabolic recovery endotypes.

5.6 Integration with Neuroinflammation and Neuroplasticity

The gut–brain–metabolic axis connects directly with the inflammatory and plasticity mechanisms discussed earlier. Gut-derived inflammatory signals can amplify microglial activation, cytokine production, blood–brain barrier dysfunction, and oxidative stress. In contrast, beneficial microbial metabolites such as short-chain fatty acids (SCFAs) may support immune resolution and a repair-permissive environment. Metabolic state also shapes neuroplasticity. Energy availability, glucose metabolism, protein reserve, and oxidative balance influence synaptic re-

modeling, angiogenesis, remyelination, and rehabilitation responsiveness. Disruption of these processes may help explain why some patients show limited recovery despite similar lesion burden or comparable rehabilitation exposure. Within a precision recovery framework, the gut–brain–metabolic axis may help identify patients whose recovery is limited by systemic constraints rather than by brain injury alone. A patient with dysbiosis, gut barrier dysfunction, malnutrition, sarcopenia, and persistent inflammation may require a different intervention strategy from a patient with preserved nutritional reserve and resolving immune activation.

5.7 Translational Implications and Future Directions

The translational value of the gut–brain–metabolic axis lies in its potential to identify recovery constraints that are clinically modifiable. Unlike lesion location or infarct size, nutritional status, metabolic reserve, gut barrier function, and microbiome-related signaling may be partly adjustable through targeted care. This makes them attractive components of precision recovery medicine. However, the field should move cautiously. Most microbiome-related findings in stroke remain associative, and clinical evidence for microbiome-targeted interventions is still limited. Future studies need longitudinal designs that combine microbiome profiling, microbial metabolites, inflammatory biomarkers, nutritional assessment, body composition, rehabilitation exposure, and functional outcomes. Fig. 7 illustrates the bidirectional communication of the gut–brain–metabolic axis, highlighting how stroke-induced gut dysbiosis leads to the translocation of metabolites and bacterial products (e.g., LPS, TMAO, and PAMPs) into the systemic circulation. These signals, along with reduced short-chain fatty acids (SCFAs), activate microglia and trigger systemic inflammation. Within the brain, this neuroinflammatory cascade drives neuroplasticity changes and may lead to secondary brain injury. Nutrient modulation is presented as a potential intervention to influence this pathway.

A phase-specific approach is also needed. Acute studies should examine whether gut barrier dysfunction and microbial products contribute to systemic inflammation, infection risk, and BBB injury. Subacute studies should test whether nutritional and microbiome-related interventions improve rehabilitation responsiveness and plasticity-related biomarkers. Chronic studies should assess whether persistent dysbiosis and metabolic dysfunction contribute to fatigue, cognitive decline, depression, and delayed neurodegeneration. For precision stroke recovery, the gut-brain-metabolic axis should not be treated as an isolated therapeutic target. Its value lies in helping define immune-metabolic recovery endotypes and in guiding combined interventions that include rehabilitation, nutritional optimization, metabolic support, infection prevention, and biomarker monitoring.

6. Integration Model: A Phase-Specific Immune–Metabolic Framework for Stroke Recovery

The preceding sections suggest that stroke recovery cannot be explained by a single dominant mechanism. Ischemic injury, regulated cell death, neuroinflammation, blood–brain barrier dysfunction, neuroplasticity, and the gut–brain–metabolic axis do not act as parallel processes. They influence one another across time and help determine whether the post-stroke biological environment becomes injury-amplifying, repair-permissive, or chronically maladaptive [5,7,8]. Recent evidence further supports this integrated view: blood–brain barrier dysfunction is closely linked to neuroinflammation and imaging-defined vascular injury, rehabilitation outcomes are increasingly associated with molecular and blood-based biomarkers, and precision rehabilitation frameworks now emphasize the need to combine molecular, imaging, and computational markers rather than relying on lesion burden alone [4,9,10,14]. Key translational priorities for precision stroke recovery are summarized in Fig. 8.

At the center of this model is the transition from acute injury to repair. Cerebral ischemia initiates bioenergetic failure, excitotoxicity, oxidative stress, and regulated cell death. These early events generate danger signals that activate resident glial cells, recruit peripheral immune cells, and disrupt neurovascular integrity. Cell death therefore does more than mark tissue loss; it helps shape the inflammatory state into which repair mechanisms must emerge.

Neuroinflammation is the main biological gate in this transition. In the acute phase, excessive inflammatory activation can expand injury through cytokine release, leukocyte recruitment, oxidative stress, and blood–brain barrier breakdown. In the subacute phase, controlled immune activity is needed for debris clearance, angiogenesis, matrix remodeling, and synaptic reorganization. In the chronic phase, unresolved inflammation may sustain glial reactivity, impair network remodeling, and contribute to delayed neurodegeneration. This phase-dependent interpretation is consistent with recent reviews describing neuroinflammation as a double-edged process, with early injury-amplifying effects but potential roles in repair and plasticity depending on timing and cellular context [11,75].

Neuroplasticity provides the functional substrate of recovery, but it is conditioned by the immune and metabolic environment. Axonal sprouting, synaptogenesis, angiogenesis, remyelination, and network reorganization require a repair-permissive milieu. Persistent inflammation, oxidative stress, blood–brain barrier leakage, poor nutritional reserve, and metabolic dysfunction can restrict these processes. Recent rehabilitation literature emphasizes that neuroplasticity after stroke is influenced by individual variability, intervention timing, clinical context, and biological readiness, while blood-based markers such as BDNF, VEGF, IGF-1, and MMP-9 are being investigated as indi-

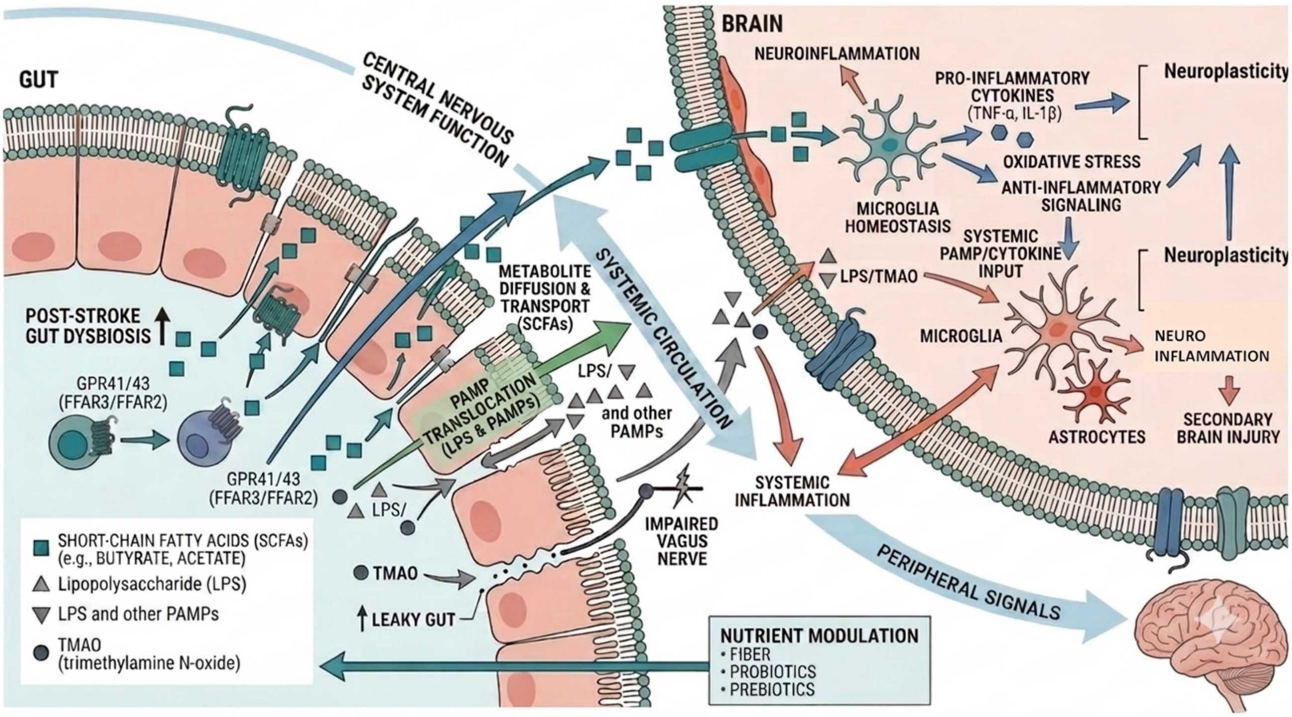

Fig. 7. Proposed gut–brain–metabolic pathways influencing neuroinflammation and recovery after stroke. The schematic illustrates how post-stroke gut dysbiosis and impaired intestinal barrier integrity may alter communication between the gut and brain. Microbial metabolites, including short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO), together with lipopolysaccharide (LPS) and other pathogen-associated molecular patterns (PAMPs), may enter the systemic circulation and influence central nervous system function through peripheral inflammatory signaling, blood–brain barrier (BBB) dysfunction, and altered vagal signaling. Within the brain, these signals may affect microglial homeostasis, astrocytic reactivity, oxidative stress, and the balance between pro-inflammatory and anti-inflammatory pathways. Depending on the biological context and recovery phase, gut-derived signals may contribute either to neuroplasticity-related processes, including dendritic arborization, neurogenesis, and angiogenesis, or to exacerbated neuroinflammation and secondary brain injury. Nutritional strategies, including dietary fiber, probiotics, and prebiotics, are presented as investigational approaches that require further clinical validation. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

cators of recovery potential and rehabilitation responsiveness [54,58]. This helps explain why lesion burden alone is an incomplete predictor of recovery and why patients with similar infarcts may respond differently to rehabilitation.

The gut–brain–metabolic axis adds a systemic dimension to this model. Stroke-induced dysbiosis, gut barrier dysfunction, altered microbial metabolites, malnutrition, and sarcopenia can modify systemic immune tone and influence central repair biology. Conversely, autonomic and neuroendocrine changes after stroke may worsen gut dysfunction and metabolic instability. Clinical studies have shown that gut dysbiosis may persist across subacute and convalescent phases of stroke, and recent reviews have linked gut microbiota to post-stroke complications through immune, metabolic, and inflammatory pathways [17,76]. Nutritional impairment also appears clinically relevant: neuronutrition literature highlights the contribution of poor nutritional status to unsatisfactory rehabilitation outcomes, while stroke-related sarcopenia has been linked to nutritional deficiency, disuse atrophy, denervation, and metabolic disturbance [77,78]. These bidirectional effects mean that recovery depends not only on the injured brain, but also on the physiological state of the whole patient.

This framework supports a move from mechanism listing to biological stratification. Patients may differ according to dominant recovery-limiting states, such as acute neurovascular inflammation, persistent BBB disruption, low plasticity potential, metabolic frailty, or microbiome-related immune activation. These states are not mutually exclusive, but identifying the dominant pattern may help guide treatment timing and selection. From a translational perspective, precision stroke recovery should not rely on a single biomarker or intervention. It requires multimodal assessment of inflammatory activity, neurovascular integrity, metabolic reserve, microbiome-related signals, plasticity potential, and rehabilitation responsiveness. Interventions should then be matched to the recovery phase and biological state: acute strategies to limit injury amplification, subacute

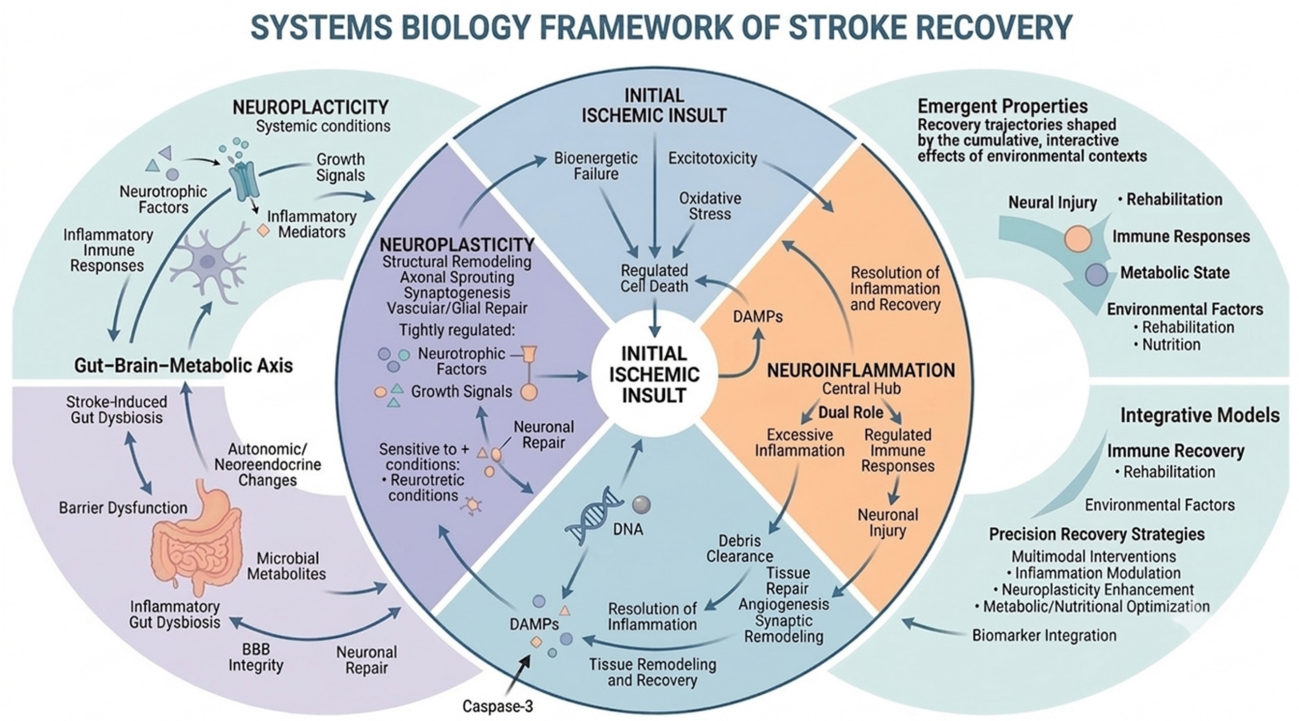

Fig. 8. Systems-biology framework of stroke recovery. The schematic conceptualizes stroke recovery as an emergent and phase-dependent process arising from interactions among the initial ischemic insult, regulated cell-death pathways, neuroinflammation, neuroplasticity, and the gut–brain–metabolic axis. The initial ischemic event induces bioenergetic failure, excitotoxicity, oxidative stress, and regulated cell-death signaling. The release of damage-associated molecular patterns (DAMPs) may amplify neuroinflammatory responses and contribute to secondary tissue injury. Neuroinflammation is represented as a central regulatory hub with context-dependent effects. Excessive or persistent inflammatory activation may exacerbate neuronal injury, whereas appropriately regulated immune responses may support debris clearance, resolution of inflammation, angiogenesis, synaptic remodeling, and tissue repair. Neuroplasticity is depicted as a dynamic process influenced by neurotrophic factors, growth signals, axonal sprouting, synaptogenesis, and vascular and glial repair. These repair-related responses are not autonomous, but remain sensitive to systemic metabolic and nutritional conditions. The gut–brain–metabolic axis may further modify recovery through stroke-associated gut dysbiosis, impaired intestinal barrier integrity, microbial metabolites, and autonomic or neuroendocrine signaling. These peripheral influences may interact with blood–brain barrier integrity, inflammatory tone, and neuronal repair capacity. The figure further emphasizes that recovery trajectories are shaped by the cumulative and interactive effects of biological state, rehabilitation exposure, nutrition, and other environmental or care-related factors. Integrative recovery models may therefore require the combination of immune, metabolic, neurovascular, and neuroplasticity-related information rather than reliance on a single biomarker or pathway. Multimodal biomarker integration may support the identification of biologically meaningful recovery profiles and inform future precision-recovery strategies, including inflammation modulation, neuroplasticity enhancement, and metabolic or nutritional optimization. The arrows indicate proposed interactions and feedback relationships rather than a strictly linear sequence or a clinically validated algorithm. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

strategies to enhance adaptive plasticity, and chronic strategies to address maladaptive inflammation, fatigue, sarcopenia, and network inefficiency. This direction is supported by recent biomarker and precision rehabilitation literature, which argues for integrating molecular, imaging, computational, nutritional, and rehabilitation-response data to guide individualized recovery care and trial stratification [4,14].

7. Biomarkers and Translational Implications

Biomarkers are often discussed in stroke as tools for prognosis, but their value for recovery medicine should be broader than outcome prediction. If stroke recovery is shaped by phase-specific interactions among inflammation, neurovascular integrity, metabolism, microbiome-related signaling, and plasticity, then biomarkers should help identify the dominant biological state of each patient. The clinical question is not simply whether a biomarker predicts poor

outcome, but whether it can guide the timing, selection, and intensity of recovery-oriented interventions. Traditional predictors such as infarct volume and baseline neurological severity remain useful, but they provide limited information about the biological conditions that shape recovery after the acute event. Patients with similar infarct burden may differ in inflammatory activity, blood–brain barrier stability, nutritional reserve, microbiome-related signaling, and capacity for activity-dependent plasticity. Biomarkers that capture these differences may help move stroke recovery research from population-level prediction toward biologically stratified care [5,7,8].

7.1 Inflammatory and Immune Biomarkers

Inflammatory biomarkers are among the most studied markers in stroke, but they should be interpreted with attention to timing and biological context. Elevated C-reactive protein, interleukin-6, and tumor necrosis factor-α have been associated with worse functional outcomes and increased mortality [7,8,79,80]. Composite indices such as the neutrophil-to-lymphocyte ratio provide accessible measures of systemic immune imbalance and have shown prognostic value in acute and subacute phases [81,82].

For precision recovery, these markers should not be viewed only as indicators of inflammation severity. Their main value may lie in distinguishing inflammatory states. A high early inflammatory profile may indicate acute injury amplification, whereas persistent elevation across the subacute or chronic phase may suggest failure of immune resolution and reduced plasticity potential. This distinction matters because inflammation-targeted treatment may be useful in one phase but harmful or ineffective in another [5,7,8,51,83].

7.2 Biomarkers of Neuroplasticity and Repair

Biomarkers of neuroplasticity shift attention from injury burden to recovery capacity. Brain-derived neurotrophic factor (BDNF) is a key candidate because it is involved in synaptic plasticity, neuronal survival, and activity-dependent remodeling. A recent systematic review and meta-analysis reported that circulating BDNF is reduced after stroke and may have value as a biomarker across motor, cognitive, and affective domains, although heterogeneity across studies remains substantial [13]. Biomarkers associated with functional improvement after stroke rehabilitation have also been examined in randomized controlled trials, supporting the relevance of blood-based markers for monitoring rehabilitation-related recovery, but also highlighting the need for better standardization of timing, assay methods, and clinical endpoints [14].

Other repair-related biomarkers include vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), matrix metalloproteinase-9 (MMP-9), and growth differentiation factor-10 (GDF-10). A prospective post-stroke rehabilitation study reported changes in VEGF, IGF-1, and MMP-9 expression during rehabilitation and suggested that molecular profiles related to neuroplasticity and angiogenesis may help estimate recovery potential [58]. More recent multicenter evidence suggests that endostatin, GDF-10, and uPAR may serve as blood biomarkers associated with recovery trajectories during post-stroke rehabilitation, although their clinical utility requires external validation [55]. These markers should therefore be interpreted as part of a broader recovery profile rather than as standalone predictors. A patient with preserved neurotrophic signaling but persistent inflammation or metabolic frailty may not respond to rehabilitation in the same way as a patient with both high plasticity potential and a repair-permissive immune–metabolic environment.

7.3 Metabolic and Nutritional Biomarkers

Metabolic and nutritional biomarkers are central to an immune–metabolic model of recovery. Serum albumin, prealbumin, nutritional risk indices, body composition measures, and muscle function assessments provide information about systemic reserve. These markers are clinically important because recovery is metabolically demanding. Synaptic remodeling, angiogenesis, remyelination, immune regulation, and participation in rehabilitation all require adequate energy and protein availability.

Recent clinical literature supports the view that nutritional status influences rehabilitation outcomes after stroke. A scoping review concluded that post-stroke nutritional status is a critical determinant of rehabilitation efficacy and that nutritional interventions may improve activities of daily living and functional recovery when integrated with rehabilitation care [84]. Sarcopenia is also increasingly recognized as a recovery-limiting condition. In subacute post-stroke patients undergoing rehabilitation, sarcopenia has been associated with poorer recovery of independence and ambulation [85]. These findings support the idea that malnutrition and sarcopenia should not be reduced to general frailty or supportive-care issues. They may identify a metabolic-frail recovery endotype in which the biological capacity to respond to intensive rehabilitation is limited. In such patients, nutritional optimization and resistance-oriented rehabilitation may be necessary components of precision recovery rather than optional adjuncts.

7.4 Microbiome-Related Biomarkers

Microbiome-related biomarkers may help capture systemic immune–metabolic regulation after stroke. Microbial diversity, bacterial composition, short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and other metabolite signatures have been associated with stroke severity, vascular risk, inflammatory responses, and functional outcomes. Recent reviews describe gut dysbiosis as a biologically plausible contributor to ischemic stroke pathogenesis and prognosis through bacterial metabolites, immune signaling, endothelial dysfunction, and metabolic regulation [76,86].

However, the field remains immature. Microbiome findings are sensitive to diet, medication exposure, infection, geography, stroke phase, sequencing methods, and analytic pipelines. Before clinical implementation, microbiome-related biomarkers require standardization and validation in large, longitudinal stroke cohorts. Their most realistic near-term role may be to support endotype discovery rather than to guide individual treatment decisions immediately. In this context, microbiome-related markers should be interpreted alongside inflammatory, neurovascular, nutritional, and rehabilitation-response biomarkers rather than as isolated predictors.

Despite increasing mechanistic interest, the gut–brain–metabolic axis should be interpreted with appropriate caution. Comparability across stroke microbiome studies remains limited by substantial variation in study design and analytical workflow. Sources of heterogeneity include the timing of specimen collection, stool handling and storage procedures, sequencing platform, taxonomic resolution, bioinformatic pipeline, dietary assessment, medication exposure, and adjustment for comorbidities [87,88]. These methodological differences may contribute to the inconsistent replication of microbial signatures across cohorts. Interpretation is further complicated by marked interindividual variation in gut microbial composition, which may reflect age, geographic setting, habitual diet, antibiotic exposure, metabolic status, frailty, stroke severity, and stage of recovery [76,89]. A single cross-sectional microbial profile is therefore unlikely to provide a sufficiently robust basis for patient stratification.

Longitudinal and functionally oriented designs are required to clarify the translational relevance of microbiome-related findings. Future studies should evaluate temporal changes in microbial composition across acute, subacute, and chronic recovery phases and integrate taxonomic profiles with microbial metabolites, nutritional status, inflammatory markers, and clinical outcomes. Short-chain fatty acids, trimethylamine N-oxide, and other metabolite-related pathways merit particular attention; however, neither individual taxa nor isolated metabolites should be regarded as validated stand-alone biomarkers [89,90,91]. Experimental and observational evidence supports biologically plausible associations between dysbiosis, intestinal barrier dysfunction, systemic inflammation, and post-stroke complications [76,89]. Nevertheless, clinical intervention data remain limited, and microbiome-directed approaches, including dietary modification, prebiotic or probiotic supplementation, and other microbiota-modulating strategies, should be considered investigational rather than established components of post-stroke recovery care. At present, microbiome-associated signatures are more appropriately viewed as exploratory components of multimodal recovery profiling that require prospective validation across diverse populations.

7.5 Toward Integrated and Multimodal Biomarker Profiles

Single biomarkers are unlikely to capture the biology of stroke recovery. A high C-reactive protein (CRP) level, low albumin, reduced BDNF, altered VEGF/MMP-9 signaling, or dysbiotic microbiome profile may each provide useful information, but none is sufficient alone. Recovery depends on the interaction among inflammatory activity, neurovascular stability, metabolic reserve, repair signaling, microbiome-related metabolites, and rehabilitation exposure. A multimodal biomarker profile may therefore be more informative than any single marker.

Such a profile could integrate circulating inflammatory markers, BBB-related measures, neurotrophic factors, metabolic and nutritional indicators, microbiome-related metabolites, neuroimaging, body composition, and clinical rehabilitation data. Recent work on precision post-stroke rehabilitation argues that molecular, imaging, and computational biomarkers should be integrated to support individualized rehabilitation planning rather than used only for outcome prediction [4]. The aim should be to define recovery endotypes such as inflammation-dominant, neurovascular-instability, plasticity-limited, metabolic-frail, or microbiome-disrupted states.

Machine learning and systems biology approaches may help identify such patterns, but they should be used cautiously. Predictive models must be biologically interpretable, externally validated, and linked to actionable treatment decisions. A statistically accurate model has limited clinical value if it cannot inform what should be done differently for the patient.

7.6 Translational Implications: Toward Precision Recovery Medicine

The translational goal is to use biomarkers not only to predict recovery, but to guide intervention matching. Patients with persistent inflammatory activation may require closer monitoring for unresolved immune responses and may be candidates for phase-specific immunomodulatory strategies. Patients with preserved plasticity markers may be better suited for intensive task-specific rehabilitation or neuromodulation. Patients with low nutritional reserve, sarcopenia, or metabolic dysfunction may first require metabolic and nutritional optimization to improve responsiveness to rehabilitation.

Biomarkers may also improve clinical trial design. Instead of enrolling heterogeneous stroke populations and testing a uniform intervention, future trials could stratify patients by biological recovery state. This approach is consistent with recent precision rehabilitation proposals emphasizing multimodal biomarker integration for individualized post-stroke rehabilitation and functional outcome prediction [4]. Biomarkers could also serve as intermediate endpoints, helping determine whether an intervention modifies the intended mechanism before functional outcomes become apparent. In this framework, precision recovery

Table 1. Candidate biomarkers and mechanistic domains across stroke recovery phases: potential clinical utility, evidence strength, and clinical readiness.

Domain / candidate marker	Phase	Biological relevance	Potential clinical utility	Evidence and human validation	Readiness / refs.
Systemic inflammation CRP, IL-6, NLR	Acute-early subacute	Systemic inflammatory burden and immune activation.	Prognostic enrichment; identification of persistent inflammatory burden when interpreted with stroke severity and imaging.	Moderate-high. Multiple human cohorts and reviews support prognostic associations; specificity for brain injury remains limited.	Adjunct use; not standalone. [92]
BBB / neurovascular injury MMP-9	Acute; early repair	BBB degradation, extracellular-matrix remodeling, hemorrhagic-transformation risk.	Adjunct risk stratification after reperfusion; exploratory monitoring of BBB injury.	Moderate-high. Human observational evidence and recent reviews; timing and thresholds remain unresolved.	Investigational adjunct. [92,93]
BBB / astrocytic injury S100B	Acute-subacute	Astrocytic injury and BBB leakage; extracerebral sources may contribute.	Adjunct assessment of injury burden and recovery risk; interpretation should remain phase-sensitive.	Moderate. Human literature is substantial, but assay variability and extracerebral release limit specificity.	Multimodal panels only. [92,94]
Glial injury GFAP	Acute-subacute	Astroglial injury and tissue impact.	Adjunct differentiation of intracerebral hemorrhage from ischemic stroke; prognostic enrichment.	Moderate. Human validation is increasing; kinetics vary by stroke type and sampling window.	Investigational adjunct. [94,95]
Neuroaxonal injury NfL	Subacute-chronic	Axonal injury burden and secondary neurodegeneration.	Longitudinal monitoring; refinement of long-term prognosis and cognitive-risk assessment.	Moderate. Human observational evidence is growing; age, renal function, and timing affect interpretation.	Research panels. [92,104]
Neuroplasticity BDNF	Subacute-chronic	Plasticity potential, neurotrophic signaling, rehabilitation responsiveness.	Monitoring of rehabilitation-associated biological change; exploratory assessment of plasticity potential.	Moderate. Reviews and meta-analyses support associations, but assay, timing, and intervention heterogeneity remain substantial.	Longitudinal research. [13,14]
Angiogenesis / plasticity VEGF-related measures	Subacute-chronic	Angiogenesis, vascular remodeling, repair-permissive biology.	Exploratory assessment of recovery potential with imaging and functional measures.	Low-moderate. Mechanistic rationale is strong, but clinical standardization is limited.	Investigational only. [57]
Metabolic / nutritional reserve Serum albumin	Acute-subacute	Nutritional status, systemic reserve, vulnerability to complications.	Identification of reduced reserve; enrichment of nutrition- and frailty-adapted rehabilitation studies.	Moderate-high. Registry data, systematic review, and meta-analysis support outcome associations; marker remains nonspecific.	Contextual marker. [96]
Metabolic stress Stress hyperglycemia ratio	Acute	Relative stress-related dysglycemia and metabolic vulnerability.	Exploratory identification of a metabolic-frail recovery profile; prognostic enrichment in older adults.	Moderate. Human observational evidence is emerging; thresholds and generalizability require further study.	Exploratory stratifier. [97]
Microbiome signatures Diversity and dysbiosis profiles	Acute-chronic	Altered microbial composition and interindividual microbial heterogeneity.	Exploratory longitudinal phenotyping; selection of subgroups for microbiome-focused studies.	Low-moderate. Human and animal evidence exists, but reproducibility is limited by methods, diet, medication, geography, and comorbidity.	Research only. [98,99]
Microbiome metabolites SCFAs	Subacute-chronic	Microbiota-derived immunometabolic signaling.	Exploratory monitoring of gut-brain-metabolic status; hypothesis generation for selected interventions.	Low-moderate. Strong preclinical rationale; human intervention evidence remains limited.	Investigational only. [98,99,100]
Microbiome metabolites TMAO and related metabolites	Acute-chronic	Microbial metabolite-related vascular and metabolic risk.	Exploratory characterization of vascular-metabolic risk and dysbiosis-associated profiles.	Low-moderate. Observational evidence exists; recovery-specific validation remains limited.	Not ready for selection. [99]

Table 1. Continued.

Domain / candidate marker	Phase	Biological relevance	Potential clinical utility	Evidence and human validation	Readiness / refs.
Regulated cell death Ferroptosis-related signatures	Acute; early subacute	Iron-dependent lipid peroxidation and oxidative cell injury.	Mechanism-informed enrichment of preclinical studies; potential future target-engagement markers.	Low for clinical use. Evidence remains predominantly experimental, with minimal human validation for recovery stratification.	Research only. [101,102]
Regulated cell death Necroptosis pathways	Acute	Regulated necrotic signaling and inflammatory amplification.	Mechanism-oriented preclinical stratification; future target-engagement assessment.	Low for clinical use. Evidence remains predominantly experimental, with minimal human validation.	Research only. [31,101]
Regulated cell death Pyroptosis pathways	Acute-early subacute	Inflammasome-linked inflammatory cell death.	Mechanistic profiling in experimental studies; potential future target-engagement assessment.	Low for clinical use. Evidence remains predominantly preclinical, with minimal human validation.	Research only. [101]
Clinical reserve modifier Frailty assessment	All phases	Reduced multisystem reserve and vulnerability to physiological stress.	Contextual stratification for rehabilitation tolerance, nutritional support, and trial eligibility.	Moderate-high. Recent systematic reviews and meta-analyses support outcome associations; consistent instrument selection is needed.	Clinical stratifier. [97,103]

Table notes. Evidence strength was assigned conservatively: moderate-high indicates convergent human evidence; low-moderate indicates partial human validation with important methodological limitations; low indicates predominantly preclinical or exploratory evidence. BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; GFAP, glial fibrillary acidic protein; IL, interleukin; MMP-9, matrix metalloproteinase-9; NfL, neurofilament light chain; NLR, neutrophil-to-lymphocyte ratio; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; VEGF, vascular endothelial growth factor.

medicine requires phase-matched and mechanism-matched care. The key question is not simply "which biomarker predicts outcome", but "which biomarker profile identifies the dominant recovery constraint and the most appropriate intervention window".

7.7 Future Directions for Biomarker Translation

Future biomarker research should move beyond single time-point prediction. Longitudinal measurement is essential because the biological meaning of a marker changes across recovery phases. A high inflammatory signal in the acute phase may reflect expected danger signaling, whereas persistence into the subacute or chronic phase may indicate unresolved inflammation and reduced plasticity potential. Recent longitudinal rehabilitation biomarker work supports this direction by showing that neuroplasticity-related blood markers may change during therapy and may relate to functional outcomes over time [55].

Several priorities follow from this view. First, biomarker assays need standardization across laboratories and populations. Second, studies should combine molecular markers with imaging, body composition, microbiome profiling, rehabilitation dose, and functional outcomes. Third, biomarker models should be tested prospectively to determine whether they improve treatment selection, not merely outcome prediction. Finally, trials should evaluate whether interventions matched to biological endotypes produce better recovery than standardized care.

The future of biomarker research in stroke recovery is therefore not a search for a single ideal marker. It is the development of interpretable, longitudinal, multimodal profiles that can identify recovery constraints and guide precision recovery medicine. Table 1 (Ref. [13,14,31,57,92,93,94,95,96,97,98,99,100,101,102,103,104]) summarizes representative candidate biomarkers and mechanistic domains that may support phase-sensitive assessment after stroke. No single marker should be interpreted as a stand-alone clinical decision tool; potential value is greatest when biomarkers are integrated with clinical severity, imaging, rehabilitation exposure, frailty, and longitudinal outcomes.

8. Future Directions and Translational Challenges

The central translational challenge in stroke recovery research is no longer the identification of additional isolated mechanisms. A more pressing task is to determine how established biological processes interact across recovery phases and whether these interactions define clinically meaningful subgroups. Neuroinflammation, blood–brain barrier dysfunction, regulated cell death, neuroplasticity, metabolic reserve, and gut–brain signaling have each been studied extensively. However, these domains are frequently examined in isolation, assessed at single time points, and interpreted in clinically heterogeneous populations. As a result, mechanistic knowledge has accumulated more rapidly than clinically actionable recovery models. Precision post-stroke rehabilitation therefore requires the integration of molecular, imaging, functional, and computational markers if prediction is to inform intervention planning rather than remain primarily prognostic [4].

The temporal dimension is particularly important. The biological significance of inflammation, glial activation, metabolic adaptation, and neuroplasticity is not constant throughout recovery. A pathway associated with injury amplification during the acute phase may acquire a permissive or reparative role during the subacute phase, whereas persistent activation may become maladaptive during chronic recovery. Single measurements cannot adequately represent these transitions. Longitudinal studies are needed to distinguish injury-dominant, repair-permissive, and chronically maladaptive states and to determine whether changes in biomarker trajectories are more informative than absolute values measured at a single time point. Rehabilitation-related changes in serum BDNF and other blood-based markers support the need to interpret candidate biomarkers in relation to treatment exposure and recovery phase [14].

A similar caution applies to the gut–brain–metabolic axis. Stroke-associated dysbiosis, impaired gut barrier integrity, microbial metabolites, malnutrition, and sarcopenia may influence systemic inflammation and recovery biology. However, causal interpretation in humans remains limited. Microbiome findings may vary according to sampling procedures, sequencing platforms, bioinformatic pipelines, diet, medication exposure, geography, age, comorbidities, and stroke severity. Interindividual microbial heterogeneity further limits reproducibility and external validity. Longitudinal profiling remains preferable to cross-sectional sampling because microbial signatures may change across recovery phases [17]. At present, microbiome-associated markers should be regarded as exploratory components of multimodal profiling rather than clinically validated tools for treatment selection.

The value of an endotype-guided framework does not lie in presenting multimodal biomarkers or phase-matched interventions as entirely new concepts. Rather, its value lies in specifying how these concepts might be evaluated in biologically heterogeneous stroke populations. Recent evidence continues to emphasize that age, comorbidities, and biological vulnerability substantially affect recovery and may limit the generalizability of findings derived from younger and otherwise healthy experimental models [105]. Future studies should therefore prioritize longitudinal, multimodal designs capable of integrating inflammatory markers, blood-brain barrier-related measures, neurotrophic factors, metabolic and nutritional indicators, microbiome-related signatures, imaging findings, rehabilitation exposure, and functional outcomes. Biomarkers of neuroplasticity and angiogenesis, including BDNF- and VEGF-related pathways, may be useful components of such models, but their interpretation is likely to be more informa-

tive when combined with immune, vascular, metabolic, and imaging measures rather than considered in isolation [57].

Computational tools and multi-omics platforms may facilitate data integration, but predictive performance alone is insufficient. A clinically relevant model should clarify why recovery is limited, identify which biological constraints may be modifiable, and indicate whether an intervention window remains open. The purpose of precision recovery research is therefore not to generate increasingly complex biomarker panels, but to develop parsimonious, interpretable, and prospectively testable models that improve clinical decision-making.

8.1 Ageing, Frailty, and Biological Reserve as Determinants of Recovery Heterogeneity

Ageing should not be treated solely as a demographic covariate in stroke recovery research. Older stroke survivors frequently present with hypertension, diabetes, vascular disease, sarcopenia, malnutrition, and reduced physiological reserve. These factors may alter immune regulation, vascular stability, metabolic flexibility, neuroplastic potential, and tolerance of rehabilitation. Experimental studies conducted predominantly in young and otherwise healthy animals may therefore incompletely represent the biological context in which stroke recovery occurs in clinical practice [105].

Chronological age and biological vulnerability are related but not interchangeable. Individuals of similar age may differ substantially in frailty, premorbid independence, nutritional status, comorbidity burden, and capacity to withstand physiological stress. Frailty is particularly relevant because it captures diminished reserve across multiple systems and may provide information that is not adequately represented by age alone. Recent systematic reviews and meta-analyses have identified an association between pre-stroke frailty and poorer outcomes after stroke, while a recent World Stroke Organization scientific statement has emphasized the need for more consistent frailty assessment in both clinical care and stroke research [103,106,107].

Biological reserve also has implications for rehabilitation design. A patient with preserved nutritional status, stable metabolic function, and low frailty burden may tolerate a different rehabilitation intensity from a patient with sarcopenia, malnutrition, or metabolic instability. Integrated rehabilitation and nutritional support may therefore be more appropriate than isolated supportive measures in selected patients [108,109]. These observations do not justify a fixed frailty-based treatment algorithm. Rather, they support the inclusion of ageing, frailty, nutritional status, and metabolic reserve as prespecified variables in future recovery trials.

8.2 A Hypothetical Biomarker-Guided Precision Recovery Trial

A practical test of the proposed framework could be conducted as an exploratory, biomarker-guided precision recovery trial after acute clinical stabilization. Patients with ischemic stroke could undergo multidimensional assessment on day 3 after stroke, when immediate reperfusion decisions have already been made but recovery-oriented planning is beginning to assume greater importance. The assessment could incorporate stroke severity, lesion characteristics, premorbid functional independence, pre-stroke frailty, comorbidity burden, nutritional status, renal function, and selected inflammatory and metabolic indicators.

A prespecified exploratory profile could be used to identify a metabolic-frail recovery endotype. Candidate features might include clinically relevant frailty, reduced premorbid reserve, low serum albumin or other evidence of nutritional vulnerability, impaired renal function, stress-related glucose dysregulation, and a persistent inflammatory profile. Premorbid frailty and the stress hyperglycemia ratio have already been examined in relation to functional outcome after acute ischemic stroke, supporting their consideration as candidate stratification variables rather than as validated components of a clinical decision rule [97]. Where feasible, additional biomarkers reflecting glial injury, neuroaxonal injury, blood–brain barrier dysfunction, and neuroplastic potential could be incorporated as exploratory measures, guided by the evidence summarized in Table 1.

Within the metabolic-frail stratum, a trial could compare standard-of-care rehabilitation with standard-of-care rehabilitation supplemented by a frailty-adapted supportive strategy. Such a strategy could include individualized rehabilitation dosing, nutritional optimization, closer metabolic monitoring, and repeated assessment of functional tolerance. The objective would not be to presume that a single supportive package is universally effective, but to determine whether a biologically informed approach improves recovery planning in a subgroup with reduced systemic reserve.

Outcomes should be assessed longitudinally at discharge and during follow-up, for example at 30 and 90 days. Relevant endpoints could include functional independence, cognitive performance, rehabilitation tolerance, quality of life, and biomarker trajectories. The incremental value of the endotype should be evaluated against established clinical predictors rather than considered in isolation. Fig. 9 summarizes this workflow, from day-3 multidimensional profiling to exploratory endotype classification, stratified trial allocation, and longitudinal reassessment.

This hypothetical design is intended as a testable research model, not as an established clinical algorithm. Substantial barriers remain, including assay standardization, optimal sampling windows, external validation, cost-effectiveness, and the risk of overstratification. Progress will depend on whether multimodal profiling can be reduced to clinically feasible decision models that remain biologically interpretable and sufficiently robust for prospective validation.

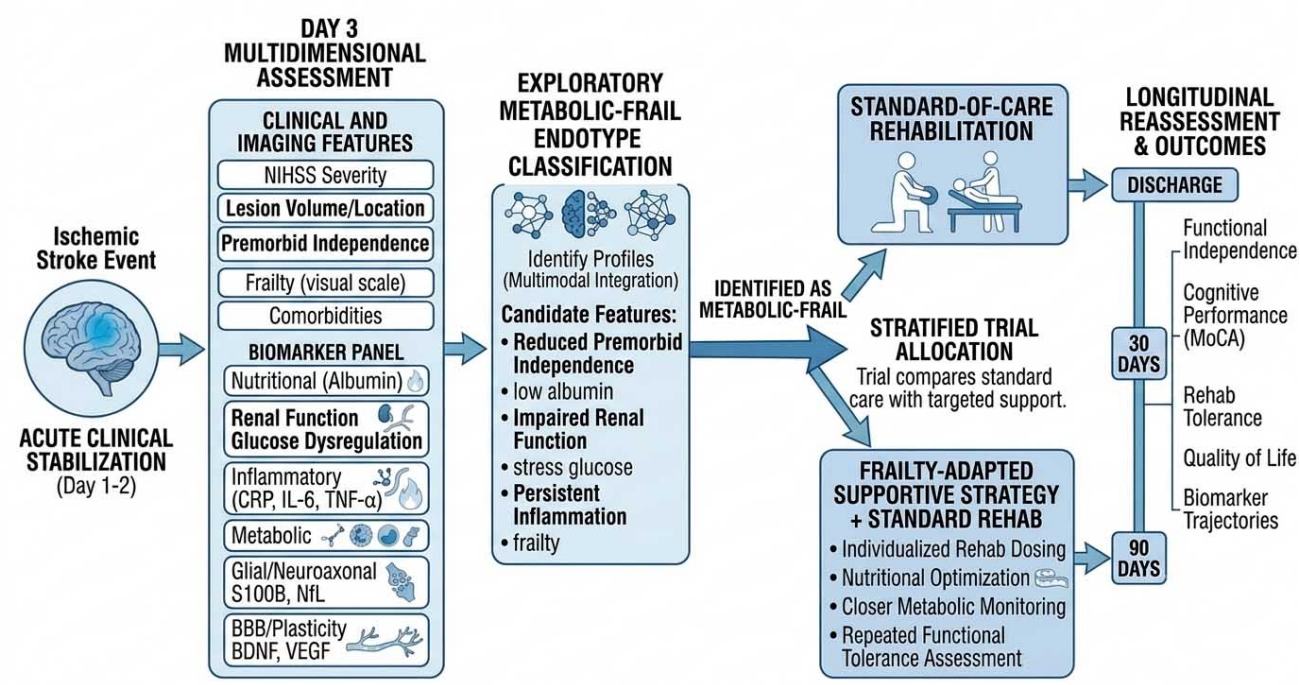

Fig. 9. Proposed design of a biomarker-guided precision recovery trial for patients with a metabolic-frail profile. The schematic presents a hypothetical trial design for evaluating whether early multidimensional assessment can improve the stratification of patients after ischemic stroke. Following acute clinical stabilization, patients are assessed on day 3 using clinical and imaging variables, including stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS), lesion volume and location, premorbid functional status, pre-stroke frailty, and comorbidity burden. These measures are considered alongside candidate biomarkers reflecting nutritional reserve, renal function, glucose regulation, systemic inflammation, metabolic vulnerability, glial and neuroaxonal injury, blood–brain barrier integrity, and neuroplasticity-related processes. The integrated profile is used to identify patients with a metabolic-frail pattern characterized by reduced premorbid reserve, nutritional vulnerability, impaired renal function, stress-related hyperglycemia, persistent inflammation, and frailty. Patients meeting these exploratory criteria are then randomized to receive either standard-of-care rehabilitation or standard-of-care rehabilitation supplemented by a frailty-adapted supportive strategy. The latter includes individualized rehabilitation dosing, nutritional optimization, closer metabolic monitoring, and repeated assessment of treatment tolerance. Clinical outcomes are evaluated at discharge and at 30 and 90 days after stroke. The proposed endpoints include functional independence assessed by the modified Rankin Scale (mRS), cognitive performance assessed by the Montreal Cognitive Assessment (MoCA), rehabilitation tolerance, quality of life, and longitudinal biomarker changes. This model is intended to provide a practical framework for future prospective studies rather than a validated clinical decision tool. **Note**: The figure was prepared and manually revised by the author using Microsoft PowerPoint, with schematic rendering provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions.

9. Conclusion

Stroke recovery should no longer be viewed as a passive consequence of tissue survival after ischemic injury. It is shaped by time-dependent interactions among neuroinflammation, neurovascular integrity, systemic metabolism, microbiome-related signaling, and repair-related plasticity. Thus, the central issue is not whether neuroinflammation should be suppressed, but when, in whom, and through which pathway it should be modulated.

The phase-specific immune–metabolic framework proposed in this review reframes neuroinflammation as a biological gate between injury and repair. Acute inflammatory activation may amplify tissue damage and blood–brain barrier disruption, whereas regulated subacute immune responses may support debris clearance, vascular remodeling, and rehabilitation-induced plasticity. In the chronic phase, unresolved inflammation, metabolic dysfunction, and maladaptive network remodeling may restrict further recovery.

This framework supports a shift toward precision stroke recovery. Patients with similar infarct burden may differ in inflammatory status, neurovascular stability, metabolic reserve, microbiome-related signaling, and plasticity potential. Defining these biological recovery endotypes may help match rehabilitation, immunomodulation, nutritional optimization, metabolic support, microbiome-targeted strategies, and biomarker monitoring to the dominant constraints operating in each patient. Future research should therefore move beyond descriptive mechanism mapping toward phase-matched and biologically stratified recovery care.

Author Contributions

PK conceived the review, performed the literature search, developed the conceptual framework, prepared the figures, wrote, and revised the manuscript, and approved the final version. The sole author agrees to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable. This manuscript is a narrative review and does not involve original research with human participants, animals, or identifiable personal data conducted by the author.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The author declares no conflicts of interest.

Declaration of AI and AI-Assisted Technologies

The AI was not involved in the generation of textual content, data analysis, or the formulation of scientific conclusions. The author maintains full accountability for the integrity and originality of the entire work. All figures are original conceptual figures developed by the author. Some schematic rendering assistance was provided by Gemini 3 Flash based solely on the author's original scientific concepts and instructions. The AI tool was not used to generate scientific conclusions, analyze data, or write the manuscript text.

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