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Review

Metabolic Transition Windows in Tissue Repair: Timing, Boundary Conditions and Resolution

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ABSTRACT: Regenerative repair is accompanied by extensive cellular remodeling, with metabolic reprogramming frequently observed across injury models. Glycolytic upregulation is commonly reported early after tissue damage, yet similar metabolic shifts have also been described in settings that progress toward functional regeneration or fibrotic remodeling. These observations indicate that pathway enrichment alone provides an incomplete explanation for divergent repair trajectories. Accumulating studies are consistent with a time-resolved perspective in which outcomes may depend on the onset, magnitude, and reversibility of metabolic remodeling, together with spatial and niche-derived boundary conditions. This review synthesizes recent work linking metabolic flux to chromatin regulation and cell-state plasticity. Metabolites such as acetyl-CoA, α-ketoglutarate, and lactate have been associated with chromatin remodeling and changes in epigenetic constraints in multiple contexts, although their necessity and directionality remain model dependent. We discuss evidence that immune microenvironments can shape metabolic boundary conditions by modulating oxygenation, inflammatory cues, and debris clearance, thereby influencing when reparative programs are engaged and whether tissues transition toward maturation and oxidative recovery. Comparative analysis across the heart, nervous system, lung, and liver supports the concept of organ-specific bottlenecks that may limit repair at distinct stages, including constrained entry into reparative states, impaired maintenance of rebuilding programs, or delayed resolution that coincides with persistent inflammation and scarring. We highlight methodological challenges that complicate causal interpretation, including reliance on transcript-level proxies and incomplete temporal sampling. We propose that advancing the field will require longitudinal and stage-resolved analyses coupled with functional repair endpoints, with explicit consideration of tissue microenvironmental context.

Keywords: metabolic reprogramming, glycolysis, tissue repair, regeneration, epigenetic regulation

1. Introduction

Regenerative medicine aims to restore damaged tissues by activating endogenous repair programs or engineering functional replacements [1]. Yet a fundamental biological constraint persists: highly regenerative species such as zebrafish (Danio rerio) and axolotl (Ambystoma mexicanum) can rebuild tissue architecture and function, whereas adult mammals more often resolve comparable injuries through fibrotic repair, culminating in scar formation and lasting functional compromise [2]. Overcoming the limits imposed by scar-based healing therefore remains a major challenge in the field.

A growing body of evidence suggests that metabolic reprogramming constitutes a pivotal yet complex layer of the injury response, alongside classical signaling and

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transcriptional programs, frequently manifesting as stage- and cell type-specific rebalancing between glycolysis and mitochondrial oxidative metabolism (OXPHOS) [3]. This notion is supported by observations across regenerative and repair contexts, including zebrafish heart and fin regeneration, nerve injury, and cutaneous wound healing, where injury-associated metabolic remodeling has been repeatedly reported [4–6]. However, the direction, duration, and cellular localization of these metabolic changes vary across tissues and injury stages and remain incompletely characterized. This highlights the need for a spatiotemporal framework to interpret when metabolic switching is adaptive, when it supports regenerative amplification, and when it must be resolved to enable functional maturation.

In regenerative states, cells often display a metabolic signature reminiscent of aerobic glycolysis (a "Warburg-like" metabolism), preferentially converting glucose to lactate even under normoxic conditions [7, 8]. This glycolytic shift is orchestrated by regulators such as Hypoxia-Inducible Factor 1α (HIF-1α) and the pyruvate kinase isoenzyme PKM2, which increase glucose transporters and divert glycolytic flux into biosynthetic shunts [9–12]. Importantly, this metabolic plasticity has two functions beyond ATP supply. First, it acts as a biosynthetic hub: the diversion of glycolytic intermediates into collateral pathways—such as the pentose phosphate pathway (PPP) and serine synthesis—provides essential building blocks (nucleotides, amino acids, and NADPH) for rapid cellular reconstruction [13, 14]. Second, as an epigenetic regulator, glycolysis-derived metabolites can act as bioactive signaling moieties [15]. For instance, acetyl-CoA and α-ketoglutarate (α-KG) serve as cofactors for histone acetyltransferases and for α-KG-dependent demethylases, respectively, thereby linking metabolic flux to chromatin remodeling required for cell dedifferentiation and fate transitions [16, 17].

Despite these advances, a key conceptual gap remains. Glycolysis activation per se is not sufficient to explain successful regeneration, because similar glycolytic shifts can precede divergent outcomes across tissues and injury contexts. This review proposes the Metabolic Transition Window (MTW) as a framework that treats metabolic remodeling not as a static switch, but as a stage-resolved and time-bounded process in which entry, maintenance, and closure may each become limiting. Although the MTW concept extends beyond glycolysis, glycolytic remodeling provides a representative and tractable entry point for this review because it is among the most broadly documented metabolic features of tissue repair and links metabolic support with cell-state plasticity and metabolite-associated signaling. In this view, metabolic programs must be initiated with appropriate timing to permit entry into reparative states, maintained long enough to support regenerative amplification, and terminated in a coordinated and reversible manner to enable redifferentiation and restoration of homeostasis; deviations in timing, duration, or reversibility may instead bias repair toward pathological remodeling. In this review, repair is used as the broader term for post-injury tissue response, within which regeneration and fibrotic remodeling are considered divergent trajectories rather than interchangeable outcomes. We therefore focus on how glycolytic flux supports plasticity and metabolite–chromatin coupling, how immune and microenvironmental factors shape the timing and reversibility of the MTW, how different tissues may be limited at distinct phases of this process, and how stage-resolved strategies may help strengthen causal inference and guide translation.

2. Mechanisms of Glycolysis in Regeneration and Cell Fate Regulation

The cellular decision to proliferate, differentiate, or remain quiescent is tightly coupled to cellular metabolic state. During regeneration, cells must transiently relax homeostatic constraints to survive injury-associated stress, re-enter the cell cycle, and expand progenitor-like populations, before re-establishing specialized functions during tissue maturation. These transitions are accompanied by coordinated metabolic remodeling, with glycolysis frequently emerging as a central and adaptable metabolic module rather than a passive consequence of increased energy demand.

2.1 Glycolysis supports plasticity and regenerative amplification

Rather than a mere bioenergetic preference, the shift toward a glycolysis-dominant state represents a central functional reconfiguration that supports cellular plasticity and regenerative amplification under injury-associated constraints. Across diverse stem and progenitor systems, high glycolytic flux is frequently observed during early activation and proliferative expansion [18, 19], consistent with the paradigm that regenerating cells prioritize carbon throughput and resource allocation over maximal ATP yield. Notably, this "glycolysis-forward" configuration, used here to denote a glycolysis-dominant, anabolic, and proliferative state in reparative contexts, is often most prominent during early activation or amplification, and becomes progressively rebalanced as cells transition toward lineage commitment and functional maturation, consistent with a stage-dependent metabolic trajectory rather than a fixed preference [20].

A key advantage of this metabolic configuration is its capacity to divert carbon into biosynthetic and redox-supporting routes essential for rapid tissue rebuilding. A central hub in this network is the diversion of glucose-6-phosphate into PPP, which supplies ribose-5-phosphate for nucleotide synthesis and generates NADPH to maintain redox homeostasis in inflammatory or hypoxic microenvironments [21, 22]. Furthermore, glycolysis-linked intermediates support broader anabolic demands; for instance, the serine synthesis pathway provides one-carbon units for methylation, while pyruvate-derived acetyl-CoA fuels the lipid biogenesis required for membrane expansion. Collectively, these pathways help ensure that the metabolic infrastructure matches the biosynthetic requirements of progenitor expansion. Consistent with this logic, restricting glycolytic throughput or its branching capacity can blunt early progenitor expansion, whereas sustaining glycolytic carbon availability during the early response tends to preserve proliferative competence—an emerging general principle across stem/progenitor biology [20].

Concurrently, reliance on glycolysis can restrain excessive mitochondrial electron transport, thereby limiting the accumulation of reactive oxygen species (ROS). This reduction in oxidative stress is important for preventing DNA damage and avoiding premature differentiation [23]. In hematopoietic stem cells (HSCs), for example, hypoxia-driven HIF-1α signaling promotes glycolysis and induces pyruvate dehydrogenase kinase (PDK) activity to suppress mitochondrial pyruvate oxidation. This mechanism can act as a metabolic checkpoint, contributing to the preservation of a quiescent, undifferentiated state within the niche [24].

Crucially, regenerative success also requires a timely progression toward functional maturation, which often necessitates a metabolic switch back to OXPHOS [25]. Thus, the central challenge is not a unidirectional glycolysis-to-OXPHOS transition, but the temporal coordination between a transient, glycolysis-supported phase for plasticity and amplification and a subsequent restoration of oxidative metabolism to sustain specialized functions [26, 27]. This dynamic is exemplified in adult zebrafish heart regeneration, where injury-border tissues exhibit a transient upregulation of glucose transporters and glycolytic enzymes (e.g., PKM2, LDHA) to support cardiomyocyte proliferation before reverting to homeostasis [28]. Similarly, following peripheral nerve injury, Schwann cells undergo a marked glycolytic upregulation that supports axonal survival and regeneration, consistent with a damage-adaptive metabolic program that is eventually resolved upon functional recovery [29].

2.2 Glycolysis-derived metabolites as state-to-fate signals

Glycolysis can become instructive for regeneration because its metabolites can help cells execute two fate-critical steps: opening chromatin to rapidly write injury-responsive programs (Writing), and relaxing pre-existing identity constraints to enable fate transitions (Erasing).

Writing. Early after injury, cells must rapidly activate repair-related transcription. Glycolysis-linked carbon can support cytosolic acetyl-CoA pools that fuel histone acetylation and enhancer activity (for example, H3K27ac), thereby increasing transcriptional readiness for cell-cycle entry and plasticity. In pluripotent stem cells, glycolysis-dependent acetyl-CoA has been shown to regulate histone acetylation and influence early fate decisions, providing a mechanistic template for injury-induced reprogramming [30]. In cardiac settings, moderate hypoxia engages metabolic remodeling that alters acetyl-CoA–linked histone acetylation with measurable consequences for cardiomyocyte cell-cycle activity, supporting a connection between acetyl-CoA–enabled chromatin opening and proliferative competence in vivo [31].

Lactate provides an additional route by which a glycolytic microenvironment can be transduced into chromatin-level priming. Injury sites frequently accumulate lactate, and histone lactylation has been established as a lactate-derived histone modification that can stimulate transcription from chromatin [32]. In vivo, histone lactylation dynamics in macrophages have been linked to gene-expression programs in tissue regeneration contexts, supporting a role for lactate-associated chromatin writing during the inflammation-to-repair transition [33]. Rather than acting as a universal switch, lactate is best viewed as a context-dependent epigenetic cue that can bias repair-associated transcriptional competence [32, 34]. Importantly, current evidence supports lactylation as a dynamic and context-shaped modification (cell type, lactate availability, microenvironmental parameters), rather than a uniform "master regulator" across regenerative tissues [32, 34].

Erasing. Writing a repair program is often insufficient if mature identity programs remain rigid. Here, α-ketoglutarate (α-KG) offers a concrete biochemical route for demethylation-based remodeling because it serves as a cofactor for multiple dioxygenases involved in histone and DNA demethylation [35]. In adult mouse heart, inhibition of fatty acid oxidation via cardiomyocyte Cpt1b disruption promoted regeneration after ischemia–reperfusion injury and was associated with α-KG accumulation and activation of the α-KG–dependent demethylase KDM5, linking metabolic rewiring to chromatin remodeling and proliferative re-

entry [36]. Complementing this genetic evidence, α-KG administration has been reported to extend the window of cardiomyocyte proliferation during development and to promote heart regeneration after myocardial infarction in association with cardiomyocyte proliferation [37]. Together, these observations support a working principle: metabolite availability can modulate epigenetic barriers, enabling transient relaxation of mature programs to permit re-entry into regenerative trajectories [38]. Mechanistically, this axis is also constrained by competing TCA-derived metabolites (e.g., succinate and fumarate) and oncometabolites (e.g., 2-HG), which can inhibit α-KG–dependent dioxygenases and thereby bias the "erasing" capacity in a context-dependent manner [38, 39].

2.3 Metabolic Transition Window: time–space–resolution

In regenerative paradigms, metabolic reprogramming is not a static binary switch but instead follows a dynamic, phased trajectory. A recurring theme across diverse tissues is that glycolytic features are enriched during early activation and proliferative expansion, whereas mitochondrial maturation and oxidative metabolism are often observed in association with redifferentiation and functional restoration [40]. This pattern motivates a conceptual shift: rather than simply turning glycolysis on, it becomes important to understand how metabolic programs are temporally coordinated, spatially patterned, and ultimately resolved in order to re-establish tissue homeostasis. In this context, the concept of the "Metabolic Transition Window" (MTW) provides a unifying framework to summarize how dynamic metabolic programs are temporally organized and resolved during tissue repair (Fig. 1). The schematic is intended to visualize the phased structure of the MTW together with representative boundary conditions, molecular transitions, and divergent closure-linked outcomes.

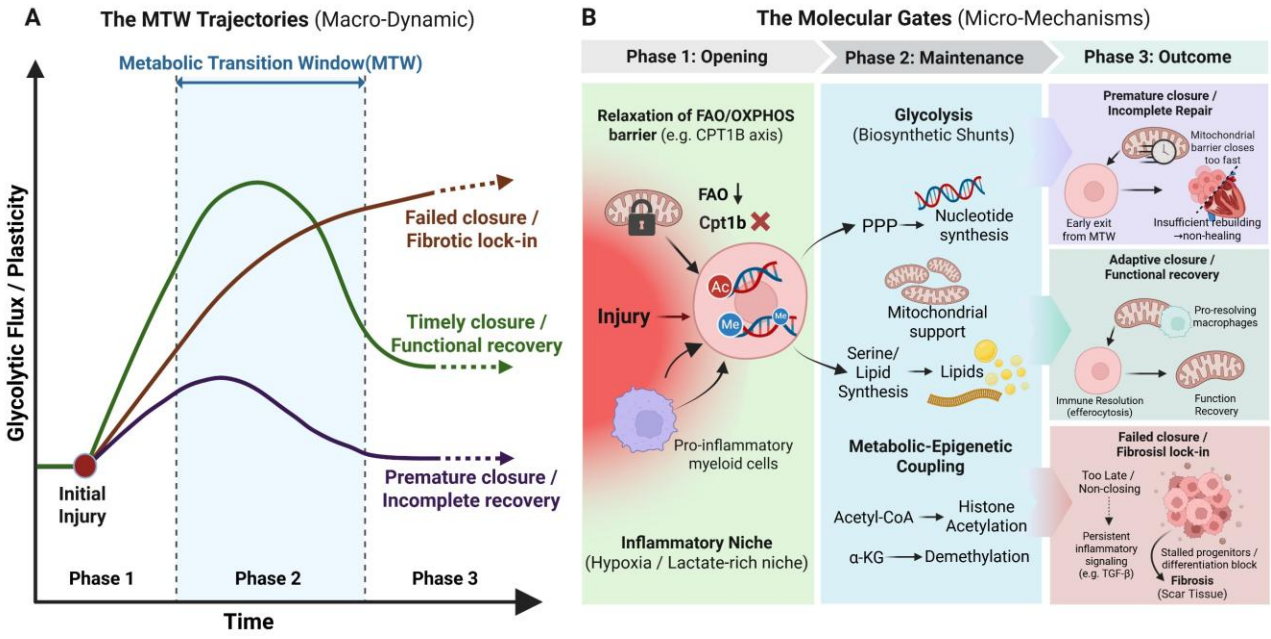

Figure 1. The Metabolic Transition Window (MTW): stage-resolved metabolic gating of tissue repair. Phase 3 represents closure-linked outcomes rather than a purely metabolic state, emphasizing that successful, delayed, or failed closure may lead to divergent repair trajectories. FAO, fatty acid oxidation; Cpt1b, carnitine palmitoyltransferase 1b; PPP, pentose phosphate pathway; α-KG, α-ketoglutarate; TGF-β, transforming growth factor beta. (Created in BioRender. Zhu, F. (2026) https://BioRender.com/3pt76fu).

We do not present the MTW as a wholly separate alternative to established concepts such as metabolic plasticity or staged injury responses. Rather, its value lies in bringing these observations into a common framework that emphasizes three features: a phase-resolved trajectory, boundary conditions that shape progression through the window, and outcome-relevant closure. In this sense, the MTW is intended less as a single mechanistic model than as a unifying and operational framework that may help organize evidence and generate testable predictions across tissues.

2.3.1 The temporal switch: from glycolytic expansion to oxidative maturation

Across stem cell differentiation and tissue repair contexts, prolonged glycolytic signatures generally co-occur with immature or proliferative states, whereas increased respiratory capacity accompanies late-stage maturation [41]. Importantly, this association does not imply that glycolysis is universally incompatible with differentiation; rather, evidence from multiple systems suggests that failure to exit a high-flux glycolytic state is often linked to delayed acquisition of stable differentiated functions [42].

This stage-dependent remodeling is well illustrated in cardiac regeneration. Single-cell analyses and mechanistic studies in zebrafish show that border-zone cardiomyocytes undergo metabolic reprogramming toward glycolysis with reduced mitochondrial oxidative activity during the proliferative window, and genetic or pharmacologic perturbations support glycolysis as an important contributor for efficient cardiomyocyte proliferation in this model [28, 43]. Conversely, later regenerative progression involves reacquisition of differentiated structure and function [44]; consistent with this, recent work indicates that upregulation of oxidative phosphorylation is associated with cardiomyocyte redifferentiation and long-term regenerative outcome in heart regeneration [40]. Together, these studies are consistent with a phase-linked metabolic transition, in which a glycolysis-dominant state aligns with the proliferative window, whereas restoration of oxidative metabolism accompanies cardiomyocyte redifferentiation and functional recovery. Whether maintaining glycolytic dominance beyond the expansion phase is sufficient to delay maturation remains unclear and will require temporally controlled perturbations applied at defined stages.

2.3.2 Spatial heterogeneity: metabolic microenvironments as positional cues

Injured tissues are not metabolically uniform. Gradients of oxygen tension, perfusion, and metabolite accumulation create heterogeneous microenvironments across the injury field. Classical wound-healing literature emphasizes that early wound beds are relatively hypoxic and that hypoxia-linked programs (e.g., HIF signaling) influence multiple stages of repair, with prolonged hypoxia generally being associated with impaired healing [45]. In parallel, single-cell and imaging-informed studies of skin repair have revealed regionally distinct epithelial states; for example, basal cell populations with distinct transcriptional programs and metabolic preferences can become spatially segregated during re-epithelialization [46]. Human wound single-cell atlases further support the notion that the wound margin contains anatomically organized cell states across healing stages [47].

Within such landscapes, it is plausible that hypoxic, lactate-enriched niches may sustain early activation and plasticity programs, whereas better-perfused regions may facilitate oxidative metabolism and maturation. At present, much of the evidence supports spatial association rather than strict causality; therefore, the idea of "metabolic zoning" is best treated as a working hypothesis. Combining spatial metabolic readouts (e.g., lactate or oxygen proxies or metabolic imaging) with lineage tracing and fate markers should help clarify whether local metabolic gradients merely correlate with, or contribute to shaping, the spatial segregation of proliferative versus differentiated states in vivo [48]. Importantly, these gradients are not always passive consequences of disrupted perfusion. Evidence from immunometabolism suggests that early infiltrating myeloid cells can rapidly amplify local oxygen depletion and metabolite accumulation, thereby helping to define where glycolysis-favoring niches emerge across the wound field [49].

2.3.3 The Goldilocks principle: unresolved glycolysis and maladaptive lock-in

A balance-and-resolution perspective clarifies why glycolysis can be a double-edged sword. If a glycolytic program becomes persistent and fails to transition back toward a homeostatic baseline, tissues may remain locked in activated remodeling states, increasing the likelihood of maladaptive outcomes. This concept aligns with fibrosis literature, where enhanced glycolytic flux and lactate accumulation are frequently coupled to inflammatory and profibrotic transcriptional programs. In kidney injury models, for instance, PFKFB3-driven glycolysis has been shown to promote lactate accumulation and histone lactylation–linked NF-κB activation, amplifying inflammatory responses and fibrosis [50]; genetic or pharmacologic attenuation of PFKFB3 mitigated these pathological features.

Collectively, these findings support a broader principle for regeneration: metabolic reprogramming is more likely to be beneficial when it is transient, staged, and reversible, but potentially deleterious when it stabilizes into chronic activation. For translation, this suggests that "always-on" metabolic interventions may produce mixed or even counterproductive effects. Instead, approaches that are timed to the repair sequence—supporting early plasticity and later promoting mitochondrial recovery—may better reflect how tissues naturally progress from activation to resolution [40].

Together, the Goldilocks principle argues that the key question is not whether glycolysis is induced, but how its

initiation, amplitude, and resolution are bounded in vivo. A growing body of work in immunometabolism indicates that immune cells are major "boundary setters" of this process, because they remodel oxygen tension and metabolite availability at the lesion site. This motivates an "extrinsically bounded" view of the MTW, in which immune-driven niche construction helps determine when the window opens and whether it can close on time. [10, 51, 52].

2.3.4 Operationalizing the Metabolic Transition Window: a glycolysis-centred minimal framework

To improve the testability of the MTW concept while maintaining the glycolysis-centred focus of this review, we propose a simplified operational framework that can guide future experimental and translational studies. This reduction is intended as a practical entry point rather than a full representation of metabolic control, because the dominant constraint may shift across tissues and phases to include mitochondrial fitness, fatty acid oxidation, redox balance, or other context-dependent pathways.

First, MTW phases can be provisionally defined using time-resolved metabolic signatures. The opening phase refers to the early injury-response period in which glycolytic activity rapidly increases relative to baseline, typically accompanied by elevated glucose uptake and lactate production. The maintenance phase corresponds to a transient period in which glycolysis remains dominant and supports biosynthetic and proliferative programs required for tissue rebuilding. The closure phase is characterized by a reconfiguration of metabolic patterns in which the dominant role of glycolysis diminishes and oxidative metabolism recovers, in parallel with cellular maturation and functional restoration.

Second, a glycolysis-centred minimal measurement panel may facilitate the empirical characterization of MTW dynamics. Key candidate readouts include glycolytic flux indicators such as extracellular acidification rate (ECAR) [53], tissue or circulating lactate levels and the lactate/pyruvate ratio [54], phosphorylation status of pyruvate dehydrogenase (p-PDH) or expression of PDK isoforms reflecting pyruvate entry into oxidative metabolism [55], and representative glycolysis-associated regulators such as PFKFB3 or GLUT1 [56]. Several of these parameters are readily measurable in experimental systems, whereas selected markers such as lactate, lactate/pyruvate ratio, and expression-based readouts may also be applicable to clinical samples. To capture the broader metabolic state more rigorously, complementary parameters should also be considered, including mitochondrial reserve capacity **a**ssessed by measuring OCR before and after treatment with an uncoupler [57], redox balance measured via the NAD+/NADH ratio or GSH/GSSG ratio [58], and mitochondrial membrane potential together with reactive oxygen species (ROS) levels to monitor mitochondrial health during the transition from maintenance to closure [59].

Third, MTW generates a series of experimentally testable predictions. For example, transient enhancement of glycolysis during the opening phase may support early reparative responses [60], whereas prolonged maintenance of glycolytic dominance beyond the physiological window may impair tissue maturation and favor persistence of maladaptive repair states, including fibrosis-prone remodeling [61]. Conversely, inadequate early glycolytic engagement may limit or delay regenerative initiation in some injury settings. Testing such predictions across injury models will help determine whether MTW represents a generalizable regulatory principle in tissue repair. However, such predictions should not be judged by phase-associated markers alone, but by whether phase-restricted perturbations alter subsequent state progression and repair outcomes in a temporally coherent manner.

This minimal framework is not intended to capture the full complexity of metabolic regulation. Additional dimensions, including mitochondrial reserve capacity, redox balance, metabolite-epigenetic coupling, and in some contexts fatty acid or lipid metabolic programs, are likely to refine MTW boundaries and may be incorporated in future studies. To facilitate practical reference, the main components of this operational framework are summarized in Table 1.

2.4 Immune–metabolic niche construction sets the boundary conditions of the MTW

Although tissue repair is often presented as a linear sequence (hemostasis → inflammation → proliferation → remodeling), in vivo these phases frequently overlap. In many injury settings, immune cells do not merely accompany repair; they actively shape the local conditions in which metabolic transitions occur. By altering oxygen availability, competing for nutrients, and releasing metabolites, they influence when glycolysis-favoring states emerge, how long they persist, and whether tissues can later shift toward oxidative maturation and resolution. In this sense, immune–metabolic niche construction may be understood in three linked functions: helping open the MTW through local oxygen depletion and hypoxia-coupled signaling, helping maintain it through metabolite-rich inflammatory microenvironments, and helping close it through pro-resolving metabolic rewiring. Figure 1 summarizes this phased view of how immune microenvironments shape MTW dynamics.

Table 1. Representative approaches and readouts for operationalizing the MTW framework.

MTW phase	Representative readouts	Representative approaches (when feasible)	Interpretation
Opening	Early lactate accumulation or lactate-related shift; ECAR increase; glucose uptake/glycolytic regulators; PDH/PDK-associated pyruvate routing; early repair-state markers	Targeted metabolite assays; Seahorse analysis; qPCR/ protein assays; immunostaining; tissue-contextual state-marker assessment	Supports entry into an early injury-responsive, glycolysis-forward reparative state
Maintenance	Coordinated ECAR/OCR pattern; biosynthetic support markers; mitochondrial support or redox-related signals; selected metabolite–chromatin coupling indicators; sustained reparative-state markers	Seahorse analysis; targeted metabolite profiling; redox assays; gene/protein expression assays; selected chromatin-related assays where appropriate	Suggests active maintenance of reparative metabolism and stabilization of the transitional cell state
Closure	Recovery of oxidative balance; improved mitochondrial reserve/function; reduced lactate dependence; decline in persistent inflammatory or fibrotic signaling; emergence of maturation-associated markers	Seahorse analysis; redox/mitochondrial assays; qPCR/protein assays; immunostaining; histology	Indicates successful exit from prolonged plasticity and progression toward resolution or maturation
Outcome validation	Concordance between metabolic transition, cell-state progression, and tissue outcome; tissue-specific functional readouts; fibrosis/scarring or incomplete rebuilding where relevant	Functional assays; histology; imaging; molecular assays; organ-specific phenotyping	Distinguishes adaptive repair from delayed closure, premature closure, or fibrotic/incomplete recovery

Note: The listed readouts are representative rather than mandatory. Their applicability depends on tissue context, injury model, spatial accessibility, and whether measurements are made in tissue, isolated cells, or circulating biofluids. Whenever possible, MTW phase assignment should rely on coordinated trajectories of metabolic, cell-state, and functional readouts rather than any single marker alone.

2.4.1 Opening the window: inflammatory oxygen sinks and hypoxia-coupled programs

At the opening stage of the MTW, early immune influx can favor glycolytic engagement by altering local oxygen conditions. Immediately after injury, lesions are often enriched in innate immune cells, and hypoxia within inflammatory sites arises not only from disrupted perfusion but also from high oxygen demand of recruited neutrophils and macrophages. This form of inflammation-associated hypoxia is increasingly recognized as an active feature of the immune microenvironment rather than a simple byproduct of injury [49, 51].

Hypoxia-linked transcriptional responses, most prominently HIF-1 signaling, provide a mechanistic route through which immune-driven oxygen depletion can promote glycolytic programs across cell types. Hypoxia/HIF pathways participate broadly in wound repair and remodeling [10, 62], but their consequences are strongly stage- and context-dependent: transient hypoxia may support early activation, whereas prolonged or unresolved hypoxia is more often associated with delayed healing and fibrotic remodeling. Accordingly, immune-dominated hypoxia may help lower the threshold for glycolytic adoption in nearby stromal and progenitor cells, but productive regeneration still requires timely restoration of oxygenation and resolution programs to prevent pathological persistence [63].

Immune oxygen consumption is also spatially heterogeneous, often producing leukocyte-dense hypoxic cores alongside more perfused margins. Such patterning may help explain how MTW opening can occur locally without fully precluding the later emergence of regions permissive for oxidative recovery.

2.4.2 Maintaining the window: metabolite fields generated by inflammatory niches

Beyond oxygen tension, inflammatory lesions are also shaped by metabolite-rich microenvironments generated through leukocyte metabolic rewiring and immune–stromal crosstalk. During the maintenance phase of the MTW, the key contribution of these niches is not simply continued hypoxia, but the accumulation of metabolites that can help sustain activation-permissive conditions across the lesion.

Succinate provides one representative example. In activated myeloid cells, inflammatory stimulation can rewire the TCA cycle and drive succinate accumulation; classic work showed that succinate stabilizes HIF-1α and promotes IL-1β production, reinforcing a link between metabolic state and inflammatory signaling [64]. Extracellular succinate can also function as a stress signal

through SUCNR1/GPR91, potentially propagating inflammatory tone across the lesion [65]. Its effects are not uniformly pro-inflammatory, and available evidence indicates strong dependence on cell phenotype, tissue context, and stimulus conditions [66]. Still, in the present framework, succinate is most relevant as an example of how inflammatory metabolism can help sustain the niche conditions associated with MTW maintenance [67].

Lactate provides a second example. It accumulates readily in inflamed, hypoxic, and glucose-competitive environments where immune cells exhibit high glycolytic flux. At the niche level, lactate-rich microdomains may help sustain an environment compatible with ongoing proliferation and remodeling. Several studies also suggest that lactate can influence immune-state transitions, including macrophage transcriptional programs, and in some settings this has been linked to histone lactylation as a possible route of later-phase gene regulation [32] [70]. At the same time, its effects are strongly concentration- and context-dependent [68, 69]. In this sense, lactate may support repair-associated remodeling when properly timed, but persistent lactate accumulation may also contribute to maladaptive lock-in if immune-state transition toward resolution fails [71].

Together, succinate- and lactate-centered metabolite fields illustrate how immune metabolism can help maintain the MTW long enough to support activation and remodeling, highlighting immune-state transition as a major determinant of whether this phase remains adaptive or becomes pathological.

2.4.3 Closing the window: resolution requires immune–metabolic synchrony

Resolution does not simply begin after regeneration is completed; rather, immune-state switching often overlaps with ongoing proliferative remodeling. For this reason, successful MTW closure depends not only on parenchymal maturation, but also on whether immune programs shift in a timely way from supporting early activation to supporting resolution.

A central node in this transition is macrophage efferocytosis, the clearance of apoptotic inflammatory cells, which is widely viewed as necessary for resolving inflammation and restoring tissue homeostasis. Efferocytosis imposes distinct bioenergetic demands and is supported by increased reliance on mitochondrial metabolism, including fatty acid oxidation (FAO) and OXPHOS [72–74]. Pro-resolving mediators can actively reinforce this shift; for example, Resolvin D1 enhances necroptotic cell clearance by promoting macrophage FAO and OXPHOS, supporting the idea that resolution signals can directly instruct metabolic switching [75].

As these resolving programs engage, the niche constraints that sustained the MTW also begin to relax. Reduced inflammatory oxygen consumption, together with vascular and tissue remodeling, supports restoration of oxygenation and attenuation of hypoxia-linked dominance. Consistent with wound-healing literature, early hypoxic responses may be permissive or instructive, whereas prolonged hypoxia is more often associated with delayed healing and pathological repair [76, 77]. Additional brakes on inflammatory persistence are provided by metabolite-linked negative-feedback circuits. Itaconate, for example, is an anti-inflammatory metabolite that activates Nrf2 via KEAP1 alkylation, providing a concrete mechanism by which inflammatory metabolism can shift toward a resolution-supportive state [78, 79].

Taken together, these findings support a closure model in which MTW termination depends on coordinated immune metabolic rewiring toward an oxidative, pro-resolving state. When this synchrony is achieved, oxygen and metabolite landscapes normalize and parenchymal cells are more likely to proceed toward oxidative maturation [80]; when it fails, persistent inflammation and fibrotic lock-in become more likely.

3. Metabolic Reprogramming Across Species: Timing, Reversibility, and Regenerative Capacity

3.1 Highly Regenerative Species: Metabolic Flexibility with Rapid Onset and Reversible Resolution

Animal models with robust regenerative capacity, such as zebrafish and salamanders, often display a shared metabolic motif during regeneration. Injured tissues transiently shift toward a glycolysis-dominant metabolic state to meet acute energetic and biosynthetic demands while enabling cell-state plasticity. In light of the MTW concept introduced above, these systems are informative not because they simply exhibit elevated glycolysis, but because metabolic programs are deployed with discernible temporal structure, encompassing early activation during rebuilding and later rebalancing as tissues mature.

A clear example comes from zebrafish heart regeneration, where proliferative repair is concentrated in cardiomyocytes near the injury border. Multi-omics analyses across post-injury stages suggest that metabolic remodeling follows a phase-dependent trajectory rather than a uniformly glycolytic state. Early time points can exhibit enrichment of oxidative programs, whereas later stages show a more prominent glycolytic signature together with remodeling of membrane glycan biology [4]. Consistent with a proliferative border-zone state, stimulating glycolysis and pyruvate routing through nodes such as PKM and the PDK family promotes

cardiomyocyte proliferation after injury [28]. Single-cell analyses further indicate that Nrg1/ErbB2 signaling coordinates a proliferative cardiomyocyte program with an embryo-like metabolic signature, characterized by reduced mitochondrial gene expression and increased glycolysis-related programs and glucose utilization [43]. Complementing these findings, injury-induced Klf1 has been linked to cardiomyogenic triggering with mitochondrial metabolism remodeled away from oxidative respiration toward anabolic pathways, supporting the broader view that regenerative competence is coupled to coordinated rewiring of energy production and biosynthetic flux [81]. Together, these studies support a coherent interpretation in which glycolysis-dominant and anabolic programs accompany, and may reinforce, a transient return to cardiomyocyte plasticity and proliferation, while later-stage remodeling enables progression toward structural and functional restoration.

In zebrafish tail regeneration, the metabolic response is notably rapid. Tail truncation triggers a rapid rise in lactate within minutes, together with increased glucose uptake and upregulation of core glycolytic enzymes (HK1, PFKP, PKMA, LDHA) in the regeneration zone [82]. Perturbation experiments support functional relevance, since inhibiting glycolysis, for example with 2-DG, markedly compromises wound closure dynamics and regenerative outgrowth, including blastema-associated processes [82]. Beyond ATP supply, injury-triggered metabolic adaptation can also channel carbon into biosynthetic and signaling-supportive routes. One example is metabolic rewiring linked to identity transitions and cell-cycle re-entry during blastema formation and bone regeneration, which includes engagement of glycosylation-linked programs that help sustain pro-regenerative signaling [83].

Metabolic remodeling is also implicated in other regenerative contexts, although the most direct evidence for rapid glycolytic shifts is currently strongest in the injury models above. Transcriptomic and systems-level analyses in zebrafish retinal degeneration and remodeling provide a framework in which metabolic pathways participate in chronic tissue restructuring [84]. In muscle, disruption of the sialic-acid salvage axis through N-acetylneuraminate pyruvate lyase perturbs glycoprotein sialylation and compromises muscle regeneration and function, with associated changes in cellular metabolism [85]. These studies highlight that regeneration-associated metabolic programs extend beyond fuel choice and intersect with glycan biology and protein modification.

In salamanders, developmental regulators may help sustain the regenerative state. Limb regeneration has been linked to the Lin28/let-7 circuit, and functional perturbation of this axis affects regenerative outcomes together with changes in central carbon metabolism, including TCA-related intermediates, supporting a role for developmental control in shaping regeneration-associated metabolic reprogramming during the blastema stage [86]. Such regulation offers a plausible mechanism by which pro-growth metabolic settings are maintained long enough to generate sufficient progenitor mass.

Overall, high-regeneration systems repeatedly show that metabolic remodeling is timed and task-specific. In zebrafish, injury can trigger a rapid glycolysis-associated response that is functionally required for regenerative outgrowth, whereas regenerating cardiomyocytes in the heart adopt a proliferation-linked glycolytic program under defined signaling control and within specific post-injury phases. Together, these observations support the practical view that regenerative success depends less on "high glycolysis" as a static trait and more on the capacity to deploy, sustain, and later re-balance metabolic programs in a stage-appropriate manner, consistent with the MTW logic introduced above.

3.2 Regeneration Versus Repair in Mammals: Stage-Dependent Metabolic Remodeling Across Organs

Mammalian injury responses frequently include glycolysis-linked activation, yet full regenerative rebuilding remains uncommon in many adult organs. This apparent paradox suggests that the main limitation is often not whether glycolysis can be triggered, but whether metabolic states are deployed with the right timing, in the right cells, and with proper progression across repair phases. Reviews of developmental and regenerative metabolism emphasize that metabolic switches can shape proliferation and maturation, and that repair outcome depends on whether these states are activated, maintained, and resolved in a context-appropriate manner [87, 88]. In skin repair, for example, PKM2 is induced in wound keratinocytes within hyperproliferative epithelia and is coupled to angiogenic programs, illustrating that glycolysis can be productively engaged early while remaining insufficient, by itself, to guarantee regenerative rebuilding [60]. Together, these observations support the view that the main MTW constraint may differ across organs, with some tissues limited mainly at entry, others by the coordination required to sustain and translate rebuilding programs, and others by the balance or resolution needed to restore function.

To facilitate comparison across organs, Table 2 summarizes the major MTW features discussed in the sections below.

Table 2. Tissue-specific MTW profiles highlight distinct stage-limiting constraints in regenerative repair.

Organ	MTW-Opening (entry requirement)	MTW-Maintenance (supporting program)	MTW-Closing (resolution requirement)	Actionable molecular gates	Predominant MTW constraint / translational challenge	References
Heart	Transient relaxation of the mature FAO/OXPHOS program to permit cardiomyocyte plasticity and cell-cycle entry	Glycolysis-linked growth support and metabolite–chromatin coupling to sustain a permissive, less mature state	Timely return to **OXPHOS-supported redifferentiation** and contractile function	CPT1B/FAO brake; SDH–succinate/ROS; glycolysis-linked growth modules; OXPHOS restoration	**Entry-limited:** the permissive window is narrow, and excessive or prolonged de-maturation risks dysfunction and arrhythmia	Li et al., 2023[113] Bae et al., 2021[92] Honkoop et al., 2019[43] Fukuda et al., 2020[28] Lekkos et al., 2025[40]
Nervous (CNS / PNS)	Distributed metabolic opening through **glial glycolytic support and local axonal glycolytic responses**	Intercellular metabolite support and metabolic–gene regulatory coupling in glia and neurons sustain regrowth programs	Resolution of **local energy stress** and restoration of functional support without persistent injury activation	Lactate/MCT shuttle; Schwann-cell glycolytic competence; axonal glycolysis; pyruvate-to-acetyl-CoA routing / regeneration-linked gene activation	**Coordination-limited:** the dominant bottleneck may shift across cells and compartments, from early regrowth support to later maturation and functional recovery	Babetto et al., 2020[29] Masin et al., 2024[95] Li et al., 2020[94] Zhang et al., 2024[96]
Lung (alveolus/airway)	**Inflammation-associated HIF1α–glycolysis** supports entry into transient progenitor states	Metabolic support is required for progression through intermediate states and AT2-to-AT1 differentiation	**Inflammation damping and metabolic maturation** are required to permit epithelial differentiation and avoid lock-in	HIF1α entry gate; AMPK–PFKFB2 (aging rescue); FAO rewiring; MPC as metabolic checkpoint	**Resolution-limited:** entry can be robust, but timely closure is vulnerable, with persistence predisposing to stalled repair and fibrosis	Choi et al., 2020[61] Wang et al., 2023[101] Crotta et al., 2023[114] Li et al., 2025[115]
Liver	Context-dependent glycolytic support enables rapid regenerative entry	Expansion must remain coupled to biosynthesis, mitochondrial competence, lipid coordination, and multicellular metabolic support	Return toward hepatic homeostasis and controlled termination of regenerative growth	JAK2/STAT3/HK2 axis; Nrf2-linked metabolic rewiring; hepatocyte ETC/acetyl-CoA availability; PFKFB3-related stromal support; termination pathways	**Balance-limited:** regeneration must support rapid expansion without uncoupling proliferation from mitochondrial function, lipid handling, and organ-level metabolic stability	Tan et al., 2024[116] Cao et al., 2024[112] Mejias et al., 2020[117] de Haan et al. 2024[118] Haridoss et al., 2017[119]

3.2.1 Heart

In the heart, the main MTW limitation appears to lie in the very narrow window during which mature cardiomyocytes can temporarily loosen their highly oxidative metabolic program without compromising their ability to regain stable function. In mammals, cardiomyocyte regenerative capacity declines rapidly after birth, in parallel with the shift from a more glycolytic fetal state to OXPHOS- and FAO-dominant maturation [89–91]. This close association suggests that, in the adult heart, metabolic manipulation is more likely to be effective when it briefly relaxes the mature oxidative program, rather than when it attempts to maintain a sustained pro-proliferative state [87].

In adult mouse hearts, cardiomyocyte-specific Cpt1b inactivation reduced FAO and promoted proliferation and scar-sparing repair after ischemia–reperfusion injury [36], accompanied by α-KG accumulation and chromatin changes associated with a less mature, more cell-cycle-permissive state [92]. Likewise, modulation of mitochondrial metabolism, for example through malonate-mediated inhibition of succinate dehydrogenase, has also been reported to enhance adult cardiomyocyte proliferation and repair. By contrast, improved glucose utilization after injury, such as derepression of glucokinase in ischemia–reperfusion

settings, seems to contribute mainly to early survival and metabolic support rather than to sustained regenerative expansion [93]. Taken together, these findings suggest that the cardiac MTW is chiefly limited at the entry stage: interventions may need to transiently increase early plasticity, but they must still permit timely metabolic re-stabilization so that redifferentiation, electrophysiological integrity, and contractile recovery can proceed.

3.2.2 Nervous System

In the nervous system, the MTW is defined less by a uniform metabolic switch within a single cell type than by coordinated, stage-dependent interactions across neurons, glia, and different injury compartments. Compared with other organs, neural repair depends more strongly on intercellular metabolic support and is further constrained by neuronal polarity and long-distance transport. This means that successful repair requires early metabolic permissiveness for axon regrowth, followed by stabilization of repair programs in support cells and neurons, and ultimately restoration of tissue function without remaining trapped in a prolonged injury-activated state.

Several lines of evidence support this view. Early after injury, glial glycolytic reprogramming can promote axon regrowth and functional recovery through metabolite-mediated signaling to neurons [94]. In parallel, injured retinal axons can rapidly increase local glycolytic dependence, accompanied by higher expression of glycolytic genes and increased lactate efflux during the early regenerative phase [95]. These findings suggest that permissiveness for regrowth is not purely neuron-intrinsic, but depends on spatially localized energy support and metabolite exchange between cells. At later stages, durable repair appears to depend more on the metabolic competence of support cells and on coupling metabolism to gene regulation. In the PNS, TREM2 deficiency disrupts glycolysis and anabolic programs in Schwann cells, impairs mitochondrial function, and worsens repair outcomes [96], while Runx2 promotes the Schwann-cell repair phenotype through chromatin remodeling and Sox2 activation [97]. On the neuronal side, enhanced pyruvate-to-acetyl-CoA conversion supports regeneration and is accompanied by activation of regeneration-related genes [98]. Together, these studies suggest that the nervous-system MTW is chiefly coordination-limited, because successful repair depends on stage-dependent metabolic interactions across neurons, glia, and distinct injury compartments rather than on a single dominant pathway. Effective intervention is therefore likely to require phase-specific support for early regrowth together with later stabilization of maturation-related programs.

3.2.3 Lung

The lung appears to have an MTW that is defined less by failure of activation than by failure of resolution. The adult lung contains regionally organized epithelial progenitor pools, and in the alveolus AT2 cells serve as resident stem cells that regenerate AT1 cells through intermediate states shaped by the injury niche [61, 99, 100].

In this regenerative trajectory, metabolism is best viewed as a constraint that gates progression rather than a generic signature. Inflammatory cues engage HIF1α-dependent glycolytic programs that support entry into transient progenitor states, whereas persistent inflammation is associated with impaired completion of differentiation and accumulation of these intermediate states [61]. Consistently, AT2-to-AT1 differentiation is energetically demanding and requires enhanced glycolysis-mediated energy production; aging compromises this axis, and activation of AMPK–PFKFB2 can restore defective alveolar regeneration in aged mice [101]. Disease settings such as idiopathic pulmonary fibrosis further suggest that effective repair must ultimately restore lineage-specific lipid metabolic programs rather than remain in an injury-like metabolic state [102]. A parallel constraint is evident in the airway, where regeneration depends on autophagy and glucose metabolism, and mitochondrial pyruvate carriers connect substrate routing to acetyl-CoA availability and histone acetylation programs that shape basal-cell fate and epithelial integrity [103, 104].

Taken together, these findings suggest that the lung MTW is mainly limited at the resolution stage: transient metabolic activation is needed for repair entry, but successful recovery requires timely metabolic re-stabilization to support epithelial maturation and avoid persistence of a fibrotic-like regenerative state.

3.2.4 Liver

In the liver, the MTW appears to be limited less by failure to initiate regeneration than by the need to support rapid expansion without compromising organ-level metabolic competence. Although the liver can efficiently restore tissue mass after injury, regenerative outcome is strongly shaped by disease context and by coordinated metabolic support across multiple cell types [105, 106]. From an MTW perspective, the key issue is therefore not simply whether metabolism is activated, but whether metabolic remodeling is matched to the changing demands of proliferation while still permitting return toward hepatic homeostasis.

Several studies support this view. Early regenerative expansion can require increased glycolytic throughput: in partial hepatectomy models, activation of the JAK2/STAT3/HK2 axis promotes regeneration, whereas suppression of glycolysis weakens this response [107]. At the same time, proliferative metabolism in hepatocytes is not uniform across regenerative settings. In some models, regeneration is accompanied by a strongly glycolytic, growth-oriented program, whereas in others the metabolic profile is more mixed, indicating that the form of rewiring depends on the surrounding injury context [108]. A more consistent constraint emerges at the level of mitochondrial and biosynthetic competence. Regenerative proliferation is curtailed when hepatocyte electron transport chain function is impaired, in part because reduced acetyl-CoA availability creates a bottleneck for expansion [109]. In parallel, lipid metabolism is dynamically coordinated across regenerative phases [106, 110, 111], and metabolic outputs from non-parenchymal cells can also contribute to orchestration [112]. Overall, these findings suggest that the liver MTW is chiefly balance-limited: metabolic activation must support proliferation and biosynthesis, but still remain compatible with mitochondrial function, lipid handling, and timely return toward functional hepatic homeostasis.

3.3 Aging as a Higher-Order Constraint on MTW Dynamics

Beyond organ-specific differences, aging imposes an additional constraint on MTW dynamics across tissues. Aging reduces metabolic elasticity and weakens the ability of tissues to adjust energy programs in response to changing demands [120]. Mechanistically, aging alters AMPK complex composition and persistently lowers expression of the refeeding-associated γ1 subunit, thereby blunting nutrient sensing and raising the threshold for exit from catabolic metabolism into an anabolic state [121]. At the same time, mitochondrial decline [122] and reduced immune clearance capacity [123] make timely closure of the window more difficult, favoring persistence of inflammatory and metabolically dysregulated states [124]. This may partly explain why aged tissues, including the lung and heart, are more likely to undergo fibrotic repair than functional recovery after injury [125, 126].

Aging also influences MTW through changes in stem and progenitor cell timing. Evidence from several systems suggests that the problem is not simply reduced regenerative output, but altered entry into, progression through, and exit from reparative state transitions. In skeletal muscle, aged MuSCs largely retain a youthful activation trajectory but move through it more slowly, indicating delayed transition kinetics rather than a fundamentally different fate path [127]. In the lung, aged AT2 progenitors show reduced AMPK–PFKFB2 signaling and ATP production during alveolar regeneration, consistent with insufficient metabolic support at a critical transitional stage [101]. In the intestine, aging disrupts mitochondrial Ca^{2+}-coupled metabolic adaptation in intestinal stem cells (ISCs), promoting a Warburg-like shift associated with maladaptive persistence rather than productive regeneration [128]. Related findings in neural and hematopoietic stem-cell systems likewise suggest greater barriers to quiescence exit, increased mitochondrial stress, or prolonged maintenance of low-quality states under maladaptive metabolism [129, 130]. Together, these findings suggest that aged stem/progenitor cells often operate within a narrower, mistimed, and less reversible metabolic window, providing a plausible cellular basis for MTW dysregulation in aging tissues.

4. Operational and Translational Challenges of the MTW Framework

The MTW framework is most useful when treated as a way to organize recurring patterns in regeneration studies, rather than as a single metabolic recipe. Its contribution is not simply to restate that metabolism changes over time, but to frame these changes as a bounded and stage-sensitive process in which entry, maintenance, and closure may each become limiting under different tissue contexts. This framing may be particularly useful when asking not only whether metabolic remodeling occurs, but when it becomes permissive, when it supports rebuilding, and when its persistence becomes maladaptive. Across organs, metabolic programs appear to influence whether cells can enter a reparative state, progress through rebuilding, and ultimately return to mature physiology. Table 2 highlights that the limiting step is not uniform everywhere: adult myocardium is often constrained at entry, neural repair depends strongly on intercellular metabolic support, lung repair is vulnerable during resolution, and liver regeneration is constrained mainly by metabolic balance and controlled termination. These differences suggest that progress will depend on making MTW experimentally operational in each tissue and aligning interventions with the dominant constraint in that setting.

A persistent barrier lies in measurement. MTW dynamics cannot be inferred reliably from transcript abundance or single time-point measurements alone, because a true transition window is defined not only by pathway activity, but also by timing, duration, and reversibility. A practical way forward is to design regeneration studies as time series by default, with sampling that spans initiation, active rebuilding, and

resolution. These analyses should be paired with representative measures of mitochondrial function, redox balance, metabolite signals linked to cell-state change, and tissue-contextual state markers. When spatial heterogeneity is pronounced, temporally resolved data will also need to be interpreted together with information on where these transitions occur. Ultimately, the goal is not to reproduce every mechanistic readout in clinical settings, but to identify combinations of indicators that remain informative about phase transition, closure, and repair quality. At present, many observations in this field remain hypothesis-generating rather than causal, particularly when they are based on transcript abundance, metabolic signatures, or single time-point associations. Stronger causal support will usually require temporally restricted perturbations, aligned to defined MTW phases, together with downstream assessment of cell-state progression, tissue rebuilding, and functional recovery.

Establishing causality is the next challenge. Metabolic remodeling is nearly universal after injury, but only a subset of changes are likely to be permissive constraints that determine whether repair advances or stalls. This argues for stage-aware perturbation designs aligned with the repair sequence. Nodes proposed to facilitate entry should be perturbed transiently around the initiation phase and evaluated by whether more cells commit to repair programs, not simply by changes in glycolytic markers. Nodes proposed to support differentiation or resolution should be assessed by whether they accelerate the completion of lineage transitions and restore function, rather than whether they prolong a proliferative phenotype. Brief, reversible perturbations aligned to defined phases would render mechanistic claims more testable and reduce the risk that associations are misinterpreted as drivers.

A related challenge is that metabolic control is not always cell-autonomous. In some tissues, phase transitions depend on coordinated exchanges between parenchymal cells and their supporting microenvironment. The nervous system provides a particularly clear example, because regenerative metabolism is distributed across neurons, glia, and different injury compartments. In such settings, manipulating neuron-intrinsic metabolism alone may have limited impact if the surrounding metabolic niche remains restrictive. Future studies should therefore quantify and perturb metabolic coupling more explicitly, including substrate availability, transport capacity, and compartment-specific demand, while using cell-type–specific strategies to distinguish intrinsic incapacity from support failure. Similar logic may apply in other organs when immune, vascular, and stromal programs set the boundary conditions for repair.

Resolution and return to function are common bottlenecks in regenerative repair, but the nature of the bottleneck differs by organ. In the lung, entry into transitional progenitor states can be robust, while persistent inflammatory signaling may impede completion of differentiation and bias remodeling toward fibrosis. In the adult heart, the challenge is different: loosening mature metabolic programs may facilitate cell-cycle competence, but prolonged de-maturation risks compromising electrical and contractile stability. In the liver, initiation is typically strong, and the more decisive issue becomes how regenerative proliferation is terminated while metabolic homeostasis is restored. These contrasts argue against uniform or chronic metabolic modulation across tissues and instead favor interventions matched to the dominant constraint in each organ.

Clinically, monitoring MTW phase transitions will likely remain indirect and multimodal rather than relying on any single metabolic marker. In practice, a layered strategy may be needed, integrating imaging-compatible metabolic readouts, circulating biomarker patterns, and organ-specific functional assessment. Such measures may help capture broader shifts in metabolic activity or resolution status, but they are unlikely to define MTW phases on their own and will require tissue-specific validation. For this reason, translational monitoring should focus less on any one marker and more on coordinated temporal changes across metabolic, inflammatory, and functional domains.

A further translational issue is safety. The main risk is not metabolic activation itself, but prolonged or mistimed repair-associated plasticity. Delayed closure of early reparative metabolic programs may favor incomplete maturation, chronic inflammation, fibrotic remodeling, or other maladaptive outcomes, whereas premature restriction may blunt regenerative entry before repair is adequately established. This reinforces the central MTW principle that successful intervention depends not only on opening the window, but also on maintaining it within an appropriate range and allowing timely closure.

Overall, the next phase of MTW-oriented work should focus on making the framework experimentally testable while preserving its translational relevance. This will require time-resolved measurements, phase-aware perturbation strategies, and closer integration of metabolic readouts with cell-state progression, tissue function, and safety outcomes. Across organs, the value of the MTW framework will depend less on identifying a single universal metabolic program than on defining when, where, and for how long metabolic plasticity remains beneficial during repair.

5. Conclusion

Metabolic remodeling is widely observed during tissue repair, yet similar metabolic shifts can accompany very different outcomes. The literature reviewed here suggests that early glycolytic activation is best interpreted as part of a dynamic response rather than a standalone marker of regenerative success. Whether tissues progress toward recovery or toward chronic inflammation and scarring may depend on how metabolic programs change over time, how long early repair states are maintained, and how efficiently tissues transition back toward oxidative homeostasis.

Across organs, the main limitation does not appear to be the same. In some tissues, mature metabolic programs may restrict entry into reparative states. In others, rebuilding stalls, or the exit from repair is delayed, coinciding with impaired maturation and fibrotic remodeling. These transitions are shaped not only by cell-intrinsic programs but also by local immune and stromal cues that set oxygenation, inflammatory tone, and clearance capacity. This view helps explain why metabolic interventions can produce mixed results across models and highlights a central trade-off: extending early plasticity may aid rebuilding, but prolonged activation can carry costs. Future progress will require time-resolved evidence linked to functional endpoints, with careful attention to tissue context and safety.

Author Contributions

Fangyuan Zhu: conceptualization; visualization, writing – original draft preparation; writing – review and editing (supporting). Feixin Liang: funding acquisition; supervision; writing – review and editing (supporting). Sijia Song: Conceptualization; writing – original draft preparation; writing – review and editing. All the authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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