

# Metabolic Switching and Regenerative Competence

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*\*Abstract (original summary).\** Repairing tissue requires immune activation, cellular expansion and later specialized function, each with different metabolic requirements. This paper proposes that unsuccessful switching between such states may limit regeneration. It rejects simple good-fuel/bad-fuel accounts and identifies how time-resolved metabolism and function could distinguish cause from adaptive consequence.

## A tissue does not perform the same task at every stage

Following injury, immune cells mobilize, fibroblasts remodel tissue, progenitors may divide and differentiated cells resume specialized function. Each stage imposes different demands on fuel use, redox balance and biosynthesis. The Institute proposes that impaired *metabolic switching* may limit regenerative competence when a tissue cannot transition effectively among these tasks. This is not equivalent to declaring glucose oxidation harmful or fatty acid oxidation beneficial; each pathway serves different purposes in particular cells.

## From substrate to decision

Nutrient sensing through pathways involving AMPK, mTOR and insulin-related signaling influences cellular growth, stress responses and autophagy. Metabolites may also shape epigenetic regulation and inflammatory behavior. But those networks are interconnected and context dependent. An intervention that reduces growth signaling in one phase may preserve cells under stress yet obstruct rebuilding later. A chronically undernourished patient may already be in a state where additional restriction is counterproductive.

## A time-resolved approach

Rather than measuring metabolism at one point, useful research would observe how cell populations transition over the course of repair. Are macrophages adopting an appropriate resolution state? Are progenitors entering growth when adequate substrates exist? Are mature cells re-establishing tissue-specific metabolism? A failure at any transition might prolong inflammation, fibrosis or weakness. The measurements should include actual repair outcomes, not simply pathway markers.

## The counterargument

Metabolic changes may reflect successful adaptation to injury instead of causing failure. In a damaged muscle, reduced oxidation could result from lost mitochondria or inactivity; increasing metabolism would not recreate missing motor neurons. Repair also depends on mechanical and developmental signals outside metabolic pathways. A theory of metabolic switching is strongest when it identifies a precise bottleneck and demonstrates that correcting it improves durable function.

## A clinical thought experiment

After an injury, an early inflammatory cell may benefit from rapid glycolysis, while later tissue reconstruction requires biosynthesis and mature oxidative function. Describing one substrate as 'dirty' and another as 'clean' is a category error. Successful healing depends on context, not allegiance to a dietary or biochemical ideology. The framework is useful when it identifies a transition that can actually be measured and modified.

## What would discriminate among explanations

Time-resolved models should compare cell states against repair outcomes and test whether changing a proposed metabolic bottleneck helps without creating new dysfunction. If every observed metabolic switch is merely secondary to cell differentiation, the intervention logic must be revised. The therapeutic target may be the upstream differentiation signal rather than the fuel itself.

## Different repair phases demand different metabolism

Injury responses involve changes in energy demand, oxygen availability, inflammation and biosynthesis. Early immune activation can rely on metabolic patterns that differ from the demands of proliferating progenitors or mature contractile cells. Later rebuilding requires synthesis of proteins, membranes and extracellular matrix. 'Metabolic switching' is a useful description of these transitions, but there is no single binary switch from sugar-burning pathology to fat-burning health. Cells use multiple substrates simultaneously and organize their metabolism according to local conditions.

The central question is whether inability to change metabolic state constrains repair in some settings. A cell may have adequate fuel at rest but fail to increase ATP production when demand rises. Another may produce energy effectively while lacking amino acids or other materials needed for rebuilding. A third may be limited by oxygen delivery or an inflammatory program that prevents differentiation. All three can produce poor recovery, but they require different interventions.

## A muscle example

After resistance exercise, muscle recovery involves activation of signaling pathways and synthesis of contractile proteins as well as responses in connective tissue and the nervous system. Caloric restriction, inactivity and age-related anabolic resistance can modify the outcome. A diet that promotes weight loss may improve certain cardiometabolic risks while simultaneously making muscle rebuilding more difficult if energy and protein intake are inadequate. Those effects can coexist without invalidating either goal.

A therapeutic program therefore needs to identify the dominant clinical objective. During recovery from major surgery or illness, preservation of lean tissue and energy adequacy may outweigh speculative gains from prolonged catabolic signaling. During stable management of certain metabolic diseases, carefully selected dietary changes may offer benefits. The evidence for one context cannot simply be transported into the other.

## Metabolic flexibility is not a complete diagnosis

The phrase 'metabolic inflexibility' describes several possible phenomena, including impaired adjustment of substrate oxidation in response to feeding or exercise. Yet measuring it is technically demanding, and its clinical significance varies with disease, training status and experimental protocol. Neither a fasting glucose measurement nor the claim that someone 'cannot burn fat' proves a specific defect in tissue regeneration.

The proposed research direction would examine whether particular transitions in fuel use predict subsequent cell differentiation and organ performance. Controlled studies might measure respiratory exchange, tissue metabolites and repair-related gene activity across defined injury phases. They would need to distinguish cause from effect: poor tissue repair may itself reduce activity and alter metabolism.

## A sequencing prediction

The most interesting possibility is that repair benefits from appropriate alternation between conditions favoring clearance, proliferation and mature function. But these processes overlap rather than occurring in universally fixed blocks of time. An athlete recovering from muscle damage, a patient with a chronic wound and a person with inflammatory liver disease may require fundamentally different strategies.

A hypothesis gains force if changing the timing of nutritional or metabolic support improves organ-specific outcomes beyond equal total intake delivered differently. If timing makes no difference once nutrient adequacy and illness severity are controlled, the special-switch model weakens. Regenerative competence is likely to depend on meeting phase-specific demands, not on achieving a fashionable metabolic state.

## **The false binary of burning fat versus burning carbohydrate**

Whole-body fuel-use measurements can describe changing average substrate oxidation, but they do not establish what a particular immune cell or progenitor is doing in a healing tissue. The body can oxidize fat in some compartments while using glucose in others. Hormones, exercise intensity and local oxygen supply modify these patterns simultaneously. An increase in circulating ketones, for example, may reflect fasting physiology without implying that every organ has adopted a regenerative metabolic program.

A meaningful experiment should examine a specific tissue during a defined stage of injury. Researchers could pair metabolic tracing with cell-state markers and functional recovery, then perturb a candidate substrate pathway. If tissue repair improves only when a particular transition occurs, the hypothesis gains support. If whole-body metabolic markers shift while tissue differentiation is unchanged, the clinical interpretation should remain limited.

The more credible research program is therefore tissue-specific metabolic flexibility rather than a universal dietary switch. It asks which substrates and signaling conditions a particular repair process needs, and when those needs change.

## **The meaning of a metabolic transition depends on the endpoint**

A rapid shift toward fat oxidation during fasting may be appropriate for maintaining energy supply, whereas a shift toward biosynthetic activity may support cell proliferation after an injury. Neither transition is intrinsically superior. The outcome depends on whether the cells complete the task required by the tissue. Inflammation, glucose uptake and growth-factor signaling also change together, making it difficult to assign a benefit to fuel preference alone.

A clinical claim should therefore specify whether it concerns insulin sensitivity, physical performance, wound healing or another endpoint. A mechanism shown to improve metabolic biomarkers in obesity may not improve rebuilding after surgery. The temptation to interpret every favorable shift as 'metabolic flexibility' conceals the different physiological priorities in those settings.

The clinically relevant difference between substrate use and repair capacity can be illustrated during infection recovery. As appetite, activity and inflammation change, whole-body fuel oxidation may shift markedly. Some of those shifts are consequences of recovering function rather than causes. A trial of metabolic timing must therefore establish the sequence between the intervention, cellular response and clinical improvement. If tissue recovery begins before the proposed metabolic marker changes, a simple causal interpretation is weakened. Better temporal resolution can help discriminate cause from adaptation, but it does not eliminate all confounding.

## **Selected scientific readings**

- López-Otín C et al. (2023). Hallmarks of aging: An expanding universe. Cell. <https://doi.org/10.1016/j.cell.2022.11.001>
- Vinten KT et al. (2025). NAD+ precursor supplementation in human ageing: clinical evidence and challenges. Nature Metabolism. <https://www.nature.com/articles/s42255-025-01387-7>

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