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Opinion Article

# Metabolic Reprogramming of Bone Cells in Health and Disease

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## ABOVE THE STUDY

The concept of metabolic reprogramming cells adapting their energy production and biosynthetic pathways to meet functional demands has gained significant attention across biomedical research. In bone biology, this paradigm is reshaping how we understand the behavior of osteoblasts, osteoclasts, and osteocytes in both physiological and pathological contexts. In my view, metabolic reprogramming is not merely a supportive process but a central regulator of bone remodeling, linking cellular energetics with skeletal integrity and disease progression.

Bone remodeling is a dynamic process requiring substantial energy and biosynthetic activity. Osteoblasts, responsible for bone formation, must produce large amounts of extracellular matrix proteins and facilitate mineralization. To meet these demands, osteoblasts undergo metabolic shifts during differentiation. Early-stage osteoprogenitors rely more on glycolysis, which provides rapid ATP and metabolic intermediates for biosynthesis. As differentiation progresses, there is a transition toward oxidative phosphorylation in mitochondria, supporting sustained energy production and matrix maturation. Disruption of this metabolic transition can impair osteoblast function and reduce bone formation.

Osteoclasts, in contrast, exhibit a distinct metabolic profile tailored to their resorptive function. These multinucleated cells require significant energy to acidify the resorption lacuna and degrade bone matrix. Both glycolysis and oxidative phosphorylation contribute to osteoclast activity, but recent studies suggest that enhanced mitochondrial biogenesis and oxidative metabolism are particularly important for mature osteoclasts. Metabolic reprogramming in osteoclasts is closely linked to signaling pathways such as RANKL, which not only drives differentiation but also influences cellular metabolism. In pathological conditions, excessive metabolic activation of osteoclasts can lead to increased bone resorption and skeletal fragility.

Osteocytes, the most abundant bone cells, also exhibit metabolic adaptations that support their unique role as mechanosensors and regulators of bone remodeling. Embedded within the mineralized matrix, osteocytes exist in a relatively low-oxygen environment and rely on a combination of glycolytic and oxidative pathways. Their metabolic flexibility allows them to respond to mechanical and biochemical signals, coordinating the activity of osteoblasts and osteoclasts. In my opinion, the metabolic resilience of osteocytes is essential for maintaining long-term skeletal homeostasis.

Metabolic reprogramming in bone cells is tightly regulated by signaling pathways that integrate environmental and systemic cues. Key regulators include AMP-activated protein kinase (AMPK), Mammalian Target of Rapamycin (mTOR), and Hypoxia-Inducible Factors (HIFs). AMPK acts as an energy sensor, promoting catabolic pathways and enhancing mitochondrial function under low-energy conditions. In osteoblasts, AMPK activation has been associated with increased bone formation. Conversely, mTOR promotes anabolic processes and cell growth, playing a critical role in osteoblast differentiation but also requiring careful regulation to prevent dysregulated bone formation.

Systemic factors such as hormones, nutrients, and inflammatory mediators further influence metabolic programming in bone cells. For example, insulin and insulin-like growth factors enhance osteoblast activity, while glucocorticoids can disrupt cellular metabolism and impair bone formation. Chronic inflammation, a hallmark of many metabolic disorders, can shift bone cell metabolism toward a pro-resorptive state, contributing to bone loss. These interactions highlight the close between systemic metabolism and skeletal health.

In disease states, metabolic reprogramming often becomes maladaptive. In osteoporosis, impaired osteoblast metabolism and enhanced osteoclast activity lead to an imbalance in bone remodeling. In diabetes, altered glucose metabolism and increased oxidative stress negatively affect bone quality and repair. Similarly, aging is associated with mitochondrial dysfunction and reduced metabolic flexibility in bone cells, contributing to decreased regenerative capacity.

From a therapeutic perspective, targeting metabolic pathways offers promising opportunities for improving bone health. Pharmacological agents that modulate AMPK, mTOR, or mitochondrial function are being explored for their potential to

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enhance osteogenesis or inhibit excessive resorption. In addition, lifestyle interventions such as exercise and nutritional optimization can positively influence bone cell metabolism and support skeletal integrity.

Emerging technologies, including metabolomics and single-cell analysis, are providing deeper insights into the metabolic heterogeneity of bone cells. These approaches enable the identification of distinct metabolic states and their association with specific cellular functions or disease conditions. In my view, integrating these technologies with systems biology will be essential for developing precision therapies that target metabolic pathways in bone.

In conclusion, metabolic reprogramming is a fundamental aspect of bone cell biology, influencing the balance between formation and resorption. By linking cellular energetics with function, it provides a unifying framework for understanding skeletal health and disease. Continued research in this area holds great promise for uncovering novel therapeutic targets and advancing the treatment of bone disorders.