

Immunometabolism in Bone Diseases: New Therapeutic

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ABOVE THE STUDY

The intersection of immune regulation and cellular metabolism commonly referred to as immunometabolism has emerged as a compelling framework for understanding the pathogenesis of bone diseases. Traditionally, bone disorders such as osteoporosis, rheumatoid arthritis, and osteolysis have been studied through the lens of hormonal imbalance or structural deterioration. However, it is increasingly evident that immune cell function and metabolic reprogramming play central roles in shaping bone remodeling. In my view, immunometabolism is not only redefining disease mechanisms but also opening a new frontier for therapeutic innovation in skeletal disorders.

Bone is a metabolically active tissue constantly undergoing remodeling through the coordinated actions of osteoblasts and osteoclasts. This process is tightly regulated by immune cells, including macrophages, T cells, and B cells, which produce cytokines that influence bone turnover. What is now becoming clear is that the functional state of these immune cells is deeply linked to their metabolic profiles. For instance, pro-inflammatory macrophages (M1 phenotype) rely on glycolysis to sustain rapid energy demands and produce cytokines such as Tumor Necrosis Factor- α (TNF- α) and interleukin-1 β (IL-1 β), both of which promote osteoclastogenesis and bone resorption. In contrast, anti-inflammatory macrophages (M2 phenotype) depend more on oxidative phosphorylation and are associated with tissue repair and bone formation.

This metabolic dichotomy extends to other immune cells as well. Activated T cells, particularly Th17 cells, exhibit a glycolytic metabolism that supports their pro-inflammatory functions and enhances the production of interleukin-17 (IL-17), a cytokine implicated in bone destruction. Regulatory T cells (Tregs), on the other hand, utilize lipid oxidation and contribute to immune tolerance and suppression of excessive bone resorption. The balance between these immune subsets, shaped by their metabolic states, is a critical determinant of bone health.

One of the most intriguing aspects of immunometabolism is its responsiveness to environmental and systemic factors. Conditions such as obesity, diabetes, and aging are characterized by altered metabolic states that influence immune cell behavior.

For example, excess nutrients and chronic low-grade inflammation in obesity can skew immune cells toward a pro-inflammatory, glycolytic phenotype, thereby accelerating bone loss. Similarly, in diabetes, hyperglycemia and advanced glycation end products disrupt both immune function and bone matrix quality, compounding skeletal fragility.

From a therapeutic standpoint, targeting metabolic pathways in immune cells offers a novel and potentially more precise approach to treating bone diseases. Rather than broadly suppressing the immune system, as is common with current anti-inflammatory therapies, metabolic interventions could selectively modulate harmful immune responses while preserving or even enhancing beneficial ones. For instance, inhibitors of glycolysis or key metabolic enzymes may reduce the activity of pro-inflammatory immune cells and osteoclasts. Conversely, promoting oxidative metabolism could enhance the function of regulatory immune cells and support bone formation.

Several pharmacological agents with metabolic effects are already being explored in this context. Drugs such as metformin, widely used in diabetes, have shown potential in modulating immune responses and improving bone health through activation of AMP-Activated Protein Kinase (AMPK). Similarly, targeting pathways such as mTOR and Hypoxia-Inducible Factor-1 α (HIF-1 α) may influence both immune cell metabolism and bone remodeling. While these approaches are still largely in the experimental stage, they represent a promising shift toward mechanism-based therapies.

In my opinion, one of the key challenges in advancing immunometabolic therapies is achieving specificity. Metabolic pathways are fundamental to many cell types, and systemic modulation may lead to unintended side effects. Therefore, developing targeted delivery systems or identifying cell-specific metabolic regulators will be crucial. Additionally, integrating immunometabolism with other emerging fields, such as microbiome research and single-cell analysis, could provide deeper insights into the complex networks governing bone health.

Another important consideration is the role of lifestyle interventions. Diet, physical activity, and metabolic health have

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profound effects on both immune function and bone integrity. Encouragingly, these factors are modifiable, suggesting that non-pharmacological strategies could complement or even enhance immunometabolic therapies.

In conclusion, immunometabolism offers a powerful and integrative perspective on bone diseases, bridging the gap between immune regulation and metabolic control. By targeting

the metabolic underpinnings of immune cell function, we have the opportunity to develop more precise and effective treatments for skeletal disorders. While challenges remain, the continued exploration of this field holds great promise for transforming the way we understand and manage bone health in the years to come.