# Novel Therapeutic Strategies in Combating Musculoskeletal Diseases by Targeting CaMKK2

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Musculoskeletal diseases are a leading cause of disability worldwide, and place a tremendous economic burden on the society. Globally, one in three women and one in five men will experience osteoporotic fractures in their lifetime. Treatment costs aside, a hip fracture is associated with tremendous individual suffering and increased morbidity. Despite its utmost clinical significance, therapies that stimulate bone formation and promote efficient bone healing are lacking.

Imbalances in bone remodeling, a process characterized by osteoblast-mediated anabolic synthesis and osteoclast-mediated catabolic resorption, result in pathological conditions such as osteoporosis. $Ca^{2+}$/calmodulin (CaM)-dependent protein kinase kinase 2 (CaMKK2) plays key roles in both the anabolic and catabolic pathways of bone remodeling. Its global deletion or pharmacological inhibition stimulates osteoblasts and inhibits osteoclasts, resulting in the prevention of hormone loss-induced osteoporosis and age-associated osteopenia. Mechanistic studies reveal that CaMKK2 inhibits normal osteoblast differentiation by inhibiting cyclic adenosine mono phosphate-protein kinase signaling in osteoprogenitors, whereas it stimulates normal osteoclast differentiation by positively modulating nuclear factor of activated T cells c1. Recent studies reveal cell-intrinsic roles for CaMKK2 in osteocytes, the most abundant bone cells, to regulate bone remodeling in a sex-dependent manner. Further, pharmacological inhibition of CaMKK2 accelerates the early cellular and molecular events associated with endochondral ossification such as Indian hedgehog signaling, resulting in a more rapid and efficient healing of bone fractures. These studies highlight the potential for CaMKK2 as a therapeutic target in the treatment of osteoporosis and accelerating bone healing.

Over 250 million people worldwide suffer from osteoarthritis (OA), another major orthopaedic disease that causes debilitating pain, deformity and functional impairment. To-date, there are no effective disease-modifying therapies against OA, mainly due to a lack of understanding of the molecular mechanisms involved. Our recent studies reveal a major role for CaMKK2 in OA. Articular chondrocytes express CaMKK2 and its levels increase in OA. Absence of CaMKK2 or its inhibition protects against cartilage degradation, synovial inflammation, and subchondral bone alterations in a murine model of surgically induced OA. When challenged with interleukin (IL)-1β, articular chondrocytes from Camkk2-/- mice display attenuated catabolic and inflammatory responses, in part through the downregulation of adenosine mono-phosphate dependent protein kinase (AMPK) signaling. Thus, CaMKK2 coordinates chondrocyte-responses to injury and inflammatory cytokines, and its inhibition is a novel therapeutic approach to treat OA, a disease with no effective cure.

The long-term goal of our studies is to understand the cell-intrinsic and mechanistic roles of CaMKK2 in bone cells and chondrocytes, identify its downstream targets and develop its inhibition in the treatment of osteoporosis and OA.