2 Gene Expression Profiles and Transcription Factors Involved in Parathyroid Hormone Signaling in Osteoblastic Cells

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Abstract

Parathyroid hormone (PTH), a peptide hormone regulating calcium homeostasis in humans, is also one of the most effective treatments for osteoporosis, a metabolic bone disease prevailing in the elderly. Therefore, studying PTH actions and its downstream signaling pathways in osteoblasts has been a focus of the bone research field. The recent advances in microarray technology have identified many novel PTH-regulated genes covering a wide range of biological functions and protein families. In this review, we summarize the implications of DNA microarray data on delineating the mechanism of PTH treatment of osteoporosis. We also describe a computational promoter analysis method to extract useful information about PTH-regulated transcription factors from the microarray dataset. The combination of microarray experiments and bioinformatics analyses will shed light on our final goal to reconstruct the global regulatory network established by PTH.

Key Words: parathyroid hormone, osteoporosis, bone metabolism, osteoblast, computational promoter analysis, transcription factor binding sites.
OSTEOPOROSIS AND PARATHYROID HORMONE TREATMENT

Osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Currently, it is a major public health threat for an estimated 44 million Americans, most of them postmenopausal women or the elderly. Osteoporotic fractures contribute substantially to morbidity and mortality in an aging world population, thus consuming considerable health resources. The cause of osteoporosis is an imbalance of bone remodeling. Bone, a highly mineralized tissue that provides mechanical support and metabolic functions, constantly undergoes remodeling. Bone remodeling occurs at discrete sites within the skeleton and proceeds in an orderly fashion, with bone resorption by osteoclasts always being followed by bone formation by osteoblasts, a phenomenon referred to as coupling. This physiological process is coordinated and tightly regulated by local and endocrine factors to ensure that the bone formation rate matches the bone resorption rate. However, in osteoporosis patients, osteoclast activity exceeds osteoblast activity, leading to irreversible bone loss.

The drugs currently available for osteoporosis treatment fall into two categories. The first, antiresorptives, inhibit osteoclastic bone resorption. This category includes bisphosphonates (alendronate, ibandronate, and risedronate) and oestrogenic compounds (estrogen, tamoxifen, and raloxifene). Although this category of agents dominates osteoporosis therapeutics, there are limitations to their efficacy. Even the most potent antiresorptive drugs only reduce the risk of osteoporotic fractures by about 50% (1) and at best increase bone density by about 10% over ten years’ treatment (2). This is mainly due to the fact that bone remodeling is coupled and therefore the decrease in bone resorption usually correlates with a decrease in bone formation. The other category of therapy, anabolic therapy, promises to overcome this ineffectiveness by primarily targeting the osteoblast and directly promoting bone formation. To date, parathyroid hormone (PTH) 1–34 (teriparatide) is the only FDA-approved anabolic agent for osteoporosis treatment. Several clinical trials demonstrated that PTH is much more effective in stimulating the increase in bone mineral density (BMD) of the skeleton, especially in trabecular bone, than alendronate, the most popular bisphosphonate prescribed for osteoporosis patients (3,4).

Parathyroid hormone is an 84 amino acid peptide secreted by the parathyroid glands and is one of the principal regulators of calcium homeostasis for humans and most likely all terrestrial vertebrates. The amino-terminal region of PTH (the first 34 amino acids) is associated with most of its known biologic actions and shows high homology among the different vertebrate species. PTH’s main targets in the body are bone and kidney, leading to an increase in serum calcium concentrations. Interestingly, administration of either the full length or N-terminal peptide (1–34) of PTH is a double-edged sword for bone metabolism, since continuous infusion of PTH causes bone loss (catabolic action), while intermittent administration induces bone formation (anabolic action). The disparity of these two actions has attracted intensive studies over a long period, and a major effort has been made to investigate the mechanism of its anabolic action because of its use for the osteoporotic patient.

The bone-forming cells, osteoblasts, originate from bone marrow stromal stem cells. These precursors undergo proliferation and differentiation into preosteoblasts and then