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Novel approaches to the treatment of osteoporosis

Natasha M. Appelman-Dijkstra, MD,
Socrates E. Papapoulos, MD, PhD, Professor *

Center for Bone Quality, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

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Despite the availability of efficacious treatments for fracture reduction in patients with osteoporosis, there are still unmet needs requiring a broader range of therapeutics. In particular, agents that are capable of replacing already lost bone and that also drastically reduce the risk of non-vertebral fractures are needed. Studies of rare bone diseases in humans and animal genetics have identified targets in bone cells for the development of therapies for osteoporosis with novel mechanisms of action. Here, we review these new developments, with emphasis on inhibitors of cathepsin K in osteoclasts and sclerostin in osteocytes, which are currently studied in phase 3 clinical trials.

Introduction

Over the past 20 years there have been significant developments in the pharmacotherapy of osteoporosis and efficacious treatments to reduce the risk of fractures, the main clinical consequence of the disease, are available. These treatments have improved substantially the management of patients with osteoporosis but the risk of fragility fractures is by far not eliminated and there are still unmet needs requiring a broader range of therapeutics. In particular, there is a need of agents capable to replace already lost bone and to drastically reduce the risk of nonvertebral fractures, the most frequent fragility fractures.

* Corresponding author. Tel.: +31 71 526 2490; Fax: +31 71 524 8136.
E-mail address: m.v.iken@lumc.nl (S.E. Papapoulos).

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The pathophysiological basis of osteoporosis lies in the imbalance between bone resorption and bone formation which leads to loss of bone and deterioration of its structural and material properties resulting in decreased bone strength and increased bone fragility [1–4]. An increased rate of bone remodelling, as it occurs after the menopause, will amplify these changes [5,6]. This background provides the rationale for developing therapies for osteoporosis which are distinguished into inhibitors of bone resorption and turnover and stimulators of bone formation. The majority of available agents reduce bone resorption while only PTH peptides have been shown to stimulate bone formation. Particularly relevant for new approaches have been studies of rare human bone diseases and animal genetics which led to identification of targets in bone cells for the development of therapies for osteoporosis which are discussed in this article.

Inhibitors of bone resorption

Antiresorptive agents reduce the rate of bone resorption followed by a decrease in the rate of bone formation leading to a new balance between resorption and formation at a lower rate of bone turnover. These changes are associated with increases in BMD and maintenance or improvement of structural and material properties of bone, increase in bone strength and reduction of the risk of fractures. Of these agents, bisphosphonates are currently the most frequently used antiosteoporotic treatments. With the approval of the RANKL inhibitor denosumab, the most potent antiresorptive agent, novel approaches in this class of therapeutics were exhausted. Studies of animal models and humans with osteopetrosis indicated, however, that reduction of bone resorption may not necessarily be followed by decreases of bone formation if the osteoclasts are intact [7], and led to search for targets in osteoclasts for the development of treatments for osteoporosis with a mechanism of action different from that of existing antiresorptives. One such target is cathepsin K, a protease abundantly expressed in osteoclasts responsible for the degradation of the organic matrix of bone.

Cathepsin K inhibitors

Cathepsin K is a member of a family of cysteine proteases with shared sequence and structural homology [8–10]. It is synthesized as a pro-enzyme before being transported to lysosomes where it is cleaved to produce the active enzyme. Cathepsin K is unique among cysteine proteases in that it can cleave the triple helix of type I collagen, in addition to cleaving collagen telopeptides at the N- and C-termini [11].

The importance of cathepsin K in osteoclast biology was demonstrated in human and animal studies. Congenital absence of cathepsin K in patients with pycnodysostosis, a rare, autosomal recessive osteochondrodysplasia, is characterized by increased bone density, bone deformities and increased bone fragility [12]. Mice deficient in cathepsin K had osteopetrosis in the presence of fully differentiated osteoclasts and no extraskeletal abnormalities [13]. Conversely, mice over-expressing cathepsin K had decreased trabecular bone volume and increased bone turnover [14]. Subsequent studies of bone biopsies from cathepsin K-deficient mice confirmed the decreased bone resorption and revealed the presence of increased osteoclast numbers, with maintenance, however, or increase in bone formation [15] (Fig. 1). Recently, targeted ablation of cathepsin K in haematopoietic cells or specifically in osteoclasts and cells of the monocyte-osteoclast lineage resulted in increased bone volume and bone formation rates as well as in osteoclast and osteoblast numbers [16]. In contrast, targeted deletion of cathepsin K in osteoblasts had no effect on bone turnover or bone formation rates demonstrating that the increased bone formation in these animals is osteoclast-dependent. The discovery that cathepsin K decreases bone resorption with increased osteoclast numbers and the surprising finding of preservation or even increase in bone formation in cathepsin K-deficient animal models supported the development of a new class of antiresorptive agents targeting the enzyme [17,18]. A number of cathepsin K inhibitors have been tested in animal models and humans. There have been, however, problems in this development. Firstly, there are differences in the amino acid sequence of cathepsin K between humans and rodents, which are typically used in preclinical research. This led to development of a new rabbit model of oestrogen deficiency as well as to the extensive use of nonhuman primates in preclinical studies. Secondly, the development of two cathepsin K inhibitors, relacatib and balicatib,