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Review

Mechanism of inhibitory action of Eldecalcitol, an active vitamin D analog, on bone resorption in vivo

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ABSTRACT

Bone-resorbing osteoclasts differentiate from hematopoietic precursors under the strict regulation of bone-forming osteoblasts. Osteoblasts express two cytokines essentially required for osteoclastogenesis; macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor κB ligand (RANKL). Osteoblasts express constitutively M-CSF, and inducibly RANKL in response to bone resorption-stimulating factors. The active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$], is known to be a hormone which enhances RANKL expression in vitro. Nevertheless, Calcitoriol [1α,25$(OH)_2D_3$] and its prodrug, Alfacalcidol (1α-hydroxyvitamin D_3) have been taken as therapeutic drugs in osteoporotic patients in Japan. In addition, Eldecalcitol [2β-(3-hydroxypropoxy)-1α,25$(OH)_2D_3$], a new analog of 1α,25$(OH)_2D_3$, was approved as a therapeutic agent for osteoporosis in Japan in 2011. Interestingly, those vitamin D compounds increased bone mineral density due to the suppression of bone resorption in vivo. We previously showed that cycle-arrested quiescent osteoclast precursors (QOPs) were the direct osteoclasts precursors in vivo. We then investigated effects of daily administration of Eldecalcitol on bone resorption in mice. Bone mineral density was increased through the suppression of RANKL expression in osteoblasts in mice treated with Eldecalcito. The number of QOPs remained unchanged in bone. These results suggest that a long-term exposure of osteoblasts to vitamin D compounds down-regulate RANKL expression.

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Contents

1. Introduction

The active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$], is a steroid hormone that enhances intestinal calcium absorption through the vitamin D receptor (VDR) [1,2]. In vivo and in vitro experiments showed that 1α,25$(OH)_2D_3$ stimulates osteoclastic bone resorption [3,4]. Nevertheless, 1α,25$(OH)_2D_3$ (Calcitriol) and its pro-drug, 1α-hydroxyvitamin D_3 [1α$(OH)D_3$, Alfacalcidol], are used as therapeutic drugs for the treatment of osteoporosis in Japan, for the reason that both compounds improve bone mineral density (BMD) and decrease the risk of osteoporotic fractures. Interestingly, the beneficial in vivo effect of vitamin D compounds was caused by the inhibition of osteoclastogenesis [5]. Eldecalcitol is a new 1α,25$(OH)_2D_3$ derivative approved as a therapeutic drug for osteoporosis in Japan [6–8]. We have examined how Eldecalcitol suppressed bone resorption

Abbreviations: 1α,25$(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; VDR, vitamin D receptor; M-CSF, macrophage-colony stimulating factor; RANKL, receptor activator of nuclear factor κB ligand; BMD, bone mineral density; QOP, cell cycle-arrested quiescent osteoclast precursors; DBP, vitamin D binding protein; PTH, parathyroid hormone; PGE_2, prostaglandin E_2; IL-11, interleukin 11; OPG, osteoprotegerin.

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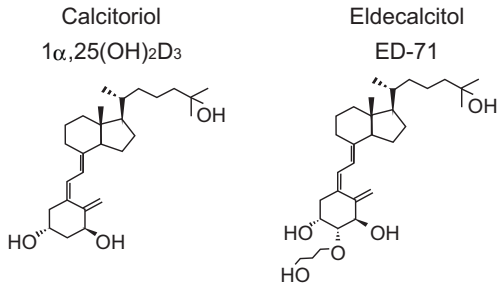

	Calcitoriol	Eldecalcitol
Binding to VDR	100	45
Binding to DBP	100	422
PTH suppression	100	3.5
Half life in serum	Short	Long

Fig. 1. Comparison of Calcitoriol and Eldecalcitol. (A) Structures of Calcitoriol [1α,25(OH)$_2$D$_3$] and Eldecalcitol [ED-71, 1α,25-dihydroxy-2β-(3-hydroxypropoxy) vitamin D$_3$] are shown. (B) Some characteristics of Eldecalcitol are compared with those of Calcitoriol [16,17].

in vivo [9]. We found that in vivo administration of Eldecalcitol to mice suppressed RANKL expression in osteoblasts and increased BMD. This review article summarizes the background and results of this study. The mechanism of the reverse actions of vitamin D compounds on in vitro and in vivo osteoclastogenesis has been discussed in more detail in the other article [10].

2. Eldecalcitol

Eldecalcitol [ED-71, 1α,25-dihydroxy-2β-(3-hydroxypropoxy) vitamin D$_3$] was isolated from more than 900 vitamin D analogs based on the activity that stimulated BMD in vivo (Fig. 1) [11]. Eldecalcitol administration suppressed bone turnover and increased BMD in osteoporosis patients [6,7]. The efficacy of Eldecalcitol was compared with that of Alfacalcidol [1α(OH)$_2$D$_3$] in a phase III study for osteoporosis patients [8]. Eldecalcitol administration increased BMD and decreased the frequency of bone fractures more effectively than Alfacalcidol administration. The beneficial effect of Eldecalcitol on bone was caused by the suppression of bone resorption in osteoporotic patients [6,8]. Previous studies using various animal models also showed that the daily administration of Eldecalcitol increased BMD by suppressing bone resorption [12–14,7,15]. On the basis of these results, Eldecalcitol was approved as a new drug used for the treatment of osteoporosis in Japan in 2011. Eldecalcitol binds more weakly to VDR [one-eighth of 1α,25(OH)$_2$D$_3$], but more strongly to serum vitamin D binding protein (DBP) (2-fold) than 1α,25(OH)$_2$D$_3$ (Fig. 1) [16,17]. The longer half life of Eldecalcitol than 1α,25(OH)$_2$D$_3$ in serum may be related to the higher affinity of Eldecalcitol for DBP. Eldecalcitol more weakly suppresses parathyroid hormone (PTH) production than 1α,25(OH)$_2$D$_3$ [18,19]. Alfacalcidol [1α(OH)$_2$D$_3$] is converted to 1α,25(OH)$_2$D$_3$ in hepatic 25-hydroxylase (CYP27A1). In contrast, Eldecalcitol is not metabolized to 1α,25(OH)$_2$D$_3$ [20]. Such differences may be related to the higher efficacy of Eldecalcitol than 1α,25(OH)$_2$D$_3$.

3. Regulation of osteoclast formation by osteoblasts

Osteoblasts and osteoclasts are involved in bone formation and bone resorption, respectively. Osteoclasts differentiate from precursor cells of the monocyte/macrophage lineage. The differentiation of osteoclasts was strictly controlled by osteoblasts, osteocytes, and bone marrow-derived stromal cells (referred to as "osteoblasts" in this review) (Fig. 2) [4]. Osteoblasts express two cytokines, macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL), which induce osteoclast differentiation [21,22]. Osteoblasts constitutively express M-CSF and inducibly express RANKL. Bone resorption-stimulating factors including 1α,25(OH)$_2$D$_3$, PTH, prostaglandin E$_2$ (PGE$_2$) and interleukin 11 (IL-11) enhance RANKL expression in osteoblasts [21]. Osteoclast precursors possess c-Fms (M-CSF receptor) and RANK (RANKL receptor), and their differentiation into osteoclasts is induced by osteoblast-derived M-CSF and RANKL. Osteoblasts also secrete osteoprotegerin (OPG), a decoy receptor of RANKL, which suppresses osteoclast formation by inhibiting the binding of RANKL to RANK [21,22]. Thus, 1α,25(OH)$_2$D$_3$ up-regulates RANKL expression in osteoblasts, which in turn induces osteoclastogenesis.

4. In vivo characteristics of osteoclast precursors

We previously reported that cell cycle progression and subsequent cell cycle arrest in osteoclast progenitors are required for their differentiation into direct osteoclast precursors [23]. We identified these direct osteoclast precursors and named them "cell cycle-arrested quiescent osteoclast precursors" (QOPs) (Fig. 3). In vivo experiments showed that QOPs survived for several weeks, and differentiated into osteoclasts without cell cycle progression

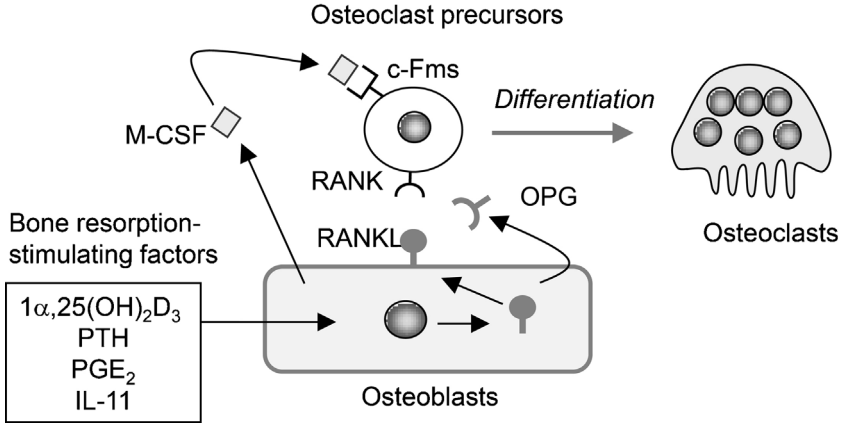

Fig. 2. Regulation of osteoclast formation by osteoblasts. Osteoblasts express two cytokines essential for osteoclast differentiation, M-CSF and RANKL. Osteoblasts constitutively express M-CSF, while osteoblasts express RANKL as a membrane-associated form in response to bone resorption-stimulating factors [21]. Osteoclast precursors express c-Fms (M-CSF receptor) and RANK (RANKL receptor) and differentiate into osteoclasts in the presence of M-CSF and RANKL [21]. Osteoblasts also produce OPG, which inhibits osteoclastogenesis by blocking the RANKL–RANK interaction.

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