Both ligand and VDR expression levels critically determine the effect of 1α,25-dihydroxyvitamin-D3 on osteoblast differentiation

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Abstract

Previous studies have shown that 1α,25-dihydroxyvitamin D3 (1,25D) through vitamin D receptor (VDR) signalling has both catabolic and anabolic effects on osteoblast differentiation. However, the mechanism of these differential effects by 1,25D is not fully understood. In this study, mice with three different genetic backgrounds, representing a normal VDR level (wild-type, WT), VDR over-expression specifically in mature osteoblasts (ObVDR-B6) and global VDR knockout (VDRKO), were utilised to generate primary osteoblast-like cultures to further elucidate the effects of 1,25D on osteoblast differentiation. Our data confirm the importance of VDR in the late stage of osteogenic differentiation and also for the expression of factors critical for osteoblastic support of osteoclast formation. This study also demonstrates the differential effects of a pharmacological level of 1,25D (1 nM) on the expression of osteogenic differentiation markers, including Ocn and Sost, depending on the relative level of VDR. Our findings suggest that 1,25D plays an inhibitory role in matrix mineralisation, possibly through the modulation of the tissue non-specific alkaline phosphatase to ectonucleotide pyrophosphatase/phosphodiesterase 1 axis, in a VDR level-dependent manner. We conclude that the relative VDR level and the 1,25D availability to cells, are important co-determinants for whether 1,25D plays a promoting or suppressive role in osteoblast-mediated osteogenic activity.

Keywords: Vitamin D, Osteoblast, VDR, Mineralisation, VDR knockout, Differentiation.