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Source
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Abstract
High homocysteine (HCY) levels are a risk factor for osteoporotic fracture. Furthermore, bone quality and strength are compromised by elevated HCY owing to its negative impact on collagen maturation. HCY is cleared by cystathionine β-synthase (CBS), the first enzyme in the transsulfuration pathway. CBS converts HCY to cystathionine, thereby committing it to cysteine synthesis. A microarray experiment on MC3T3-E1 murine preosteoblasts treated with 1,25-dihydroxyvitamin D(3) [1,25(OH)(2) D(3)] revealed a cluster of genes including the cbs gene, of which the transcription was rapidly and strongly induced by 1,25(OH)(2) D(3) .

Quantitative real-time PCR and Western blot analysis confirmed higher levels of cbs mRNA and protein after 1,25(OH)(2) D(3) treatment in murine and human cells. Moreover, measurement of CBS enzyme activity and quantitative measurements of HCY, cystathionine, and cysteine concentrations were consistent with elevated transsulfuration activity in 1,25(OH)(2) D(3) -treated cells. The importance of a functional vitamin D receptor (VDR) for transcriptional regulation of cbs was shown in primary murine VDR knockout osteoblasts, in which upregulation of cbs in response to 1,25(OH)(2) D(3) was abolished. Chromatin immunoprecipitation on chip and transfection studies revealed a functional vitamin D response element in the second intron of cbs. To further explore the potential clinical relevance of our ex vivo findings, human data from the Longitudinal Aging Study Amsterdam suggested a correlation between vitamin D status [25(OH)D(3) levels] and HCY levels. In conclusion, this study showed that cbs is a primary 1,25(OH)(2) D(3) target gene which renders HCY metabolism responsive to 1,25(OH)(2) D(3).

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