Vitamin D3 (cholecalciferol) acts as a negative regulator of breast cancer cell invasiveness in the absence of activation of classical VDR signalling

M.M. Hossain, R. Afroz, C.R. Dunstan
Biomedical Engineering, The University of Sydney, Sydney, Australia

Aim/Background: Vitamin D deficiency is a risk factor for breast cancer and is associated with worse breast cancer outcomes. However, the mechanisms by which vitamin D3, also known as cholecalciferol and its bioactive metabolite 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3) act to influence breast cancer is not fully resolved. Cholecalciferol is thought to be a biologically inert precursor for bioactive 1,25(OH)2D3 and can be converted into the active form by 25-hydroxylase and 1α-hydroxylase enzymes in the liver and kidney respectively. It has been shown that 1,25(OH)2D3 inhibits cancer cell proliferation and migration but a role for cholecalciferol itself in breast cancer has not been defined.

Methods: We investigated the in vitro effects of cholecalciferol and 1,25(OH)2D3 on the growth (MTT assay), and invasiveness (Matrigel droplet escape) for the human breast cancer cell lines MDA-MB-231 and MCF-7.

Results: As expected, we showed that 1,25(OH)2D3 inhibits both cancer cell growth and invasiveness. Interestingly, for both cell lines, we also found that cholecalciferol reduces cancer cell invasiveness at a concentration of 10^{-7} M while having no effects on cell growth. CYP24, encoding the enzyme that degrades 1,25(OH)2D3, is an early response gene for vitamin D receptor (VDR) activation. 1,25(OH)2D3 at 10^{-7} M profoundly increased CYP24 expression by 37 fold on day 1 (p < 0.001) and 9 fold on day 3 (p < 0.001) in MDA-MB-231 cells and 243 fold on day 3 (p < 0.001) in MCF-7 cells indicating activation of the VDR in MDA-MB-231 and MCF-7 cells. In contrast, CYP24 levels were not changed by cholecalciferol treatment.

Conclusions: Cholecalciferol had no effect on CYP24 gene expression indicating its actions were not initiated via classical activation of the VDR. These results suggest that cholecalciferol has a biological effect on the migration of breast cancer cells that may be independent of the VDR.

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