The inhibition of Wnt/β-catenin signalling by 1α,25-dihydroxyvitamin D3 is abrogated by Snail1 in human colon cancer cells.

Abstract:

The Wnt/β-catenin signalling pathway is activated in 90% of human colon cancers by nuclear accumulation of β-catenin protein due to its own mutation or to that of adenomatous polyposis coli. In the nucleus, β-catenin regulates gene expression promoting cell proliferation, migration and invasiveness. 1α,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3)) inhibits β-catenin signalling by inducing its binding to vitamin D receptor (VDR) and by promoting β-catenin nuclear export. The transcription factor Snail1 represses VDR expression and we demonstrate here that Snail1 also abolishes the nuclear export of β-catenin induced by 1,25(OH)(2)D(3) in SW480-ADH cells. Accordingly, Snail1 relieves the inhibition exerted by 1,25(OH)(2)D(3) on genes whose expression is driven by β-catenin, such as c-MYC, ectodermal-neural cortex-1 (ENC-1) or ephrin receptor B2 (EPHB2). In addition, Snail1 abrogates the inhibitory effect of 1,25(OH)(2)D(3) on cell proliferation and migration. In xenografted mice, Snail1 impedes the nuclear export of β-catenin and the inhibition of ENC-1 expression induced by EB1089, a 1,25(OH)(2)D(3) analogue. The elevation of endogenous SNAIL1 protein levels reproduces the effect of an ectopic Snail1 gene. Remarkably,
the expression of exogenous VDR in cells with high levels of Snail1 normalizes the transcriptional responses to 1,25(OH)2D3. However, this exogenous VDR failed to fully restore the blockage of the Wnt/beta-catenin pathway by 1,25(OH)2D3. This suggests that the effects of Snail1 on this pathway are not merely due to the repression of VDR gene. We conclude that Snail1 is a positive regulator of the Wnt/beta-catenin signalling pathway in part through the abrogation of the inhibitory action of 1,25(OH)2D3.

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