

Study helps clarify role of vitamin D in cancer therapy

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A colon cancer cell isn't a lost cause. Vitamin D can tame the rogue cell by adjusting everything from its gene expression to its cytoskeleton. In the Nov. 17 issue of the *Journal of Cell Biology*, Ordóñez-Morán et al. show that one pathway governs the vitamin's diverse effects. The results help clarify the actions of a molecule that is undergoing clinical trials as a cancer therapy.

Vitamin D stymies colon cancer cells in two ways. It switches on genes such as the one that encodes E-cadherin, a component of the adherens junctions that anchor cells in epithelial layers. The vitamin also induces effects on the cytoskeleton that are required for gene regulation and short-circuiting the Wnt/b-catenin pathway, which is overactive in most colon tumors. The net result is to curb division and prod colon cancer cells to differentiate into epithelial cells that settle down instead of spreading.

To delve into the mechanism, the team dosed colon cancer cells with calcitriol, the metabolically active version of vitamin D. Calcitriol triggered a surge of calcium into the cells and the subsequent switching on of RhoA–RhoGTPases, which have been implicated in the cytoskeletal changes induced by vitamin D. The activated RhoA in turn switched on one of its targets, the rho-associated coiled kinase (ROCK), which then roused two other kinases. Each step in this nongenomic pathway was necessary to spur the genomic responses, the researchers showed. The team also nailed down the contribution of the vitamin D receptor (VDR). The receptor was crucial at the beginning of the

pathway, where it permitted the calcium influx, and at the end, where it activated and repressed genes.

The study is the first to show that vitamin D's genomic and nongenomic effects integrate to regulate cell physiology. One question the researchers now want to pursue is whether VDR from different locations—the nucleus, the cytosol, and possibly the cell membrane—has different functions in the pathway.

Source: Rockefeller University

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