The vitamin D receptor is a target for p53-mediated transcriptional activation.

Abstract #4032

The vitamin D receptor is a target for p53-mediated transcriptional activation

Reo Maruyama, Minoru Toyota, Yasushi Sasaki, Hirofumi Akashi, Fumio Aoki, Hiroaki Mita, Hiromu Suzuki, Hirofumi Tatsumi, Kohzoh Imai and Takashi Tokino

Sapporo Medical University, Sapporo, Japan

The Vitamin D Receptor (VDR) is a nuclear receptor that mediates the effects of 1,25-dihydroxyvitamin D3. The actions of 1,25-dihydroxyvitamin D3 include the maintenance of calcium homeostasis and effects on numerous other cell systems, including effects on the immune system and on the growth and differentiation of cancer cells. Although the mechanism of various vitamin D actions and VDR functions is fairly well defined, the mechanism of the regulation of VDR expression is poorly understood. Here we report that the human VDR gene is transcriptionally regulated by the tumor suppressor protein p53. The quantitative Realtime PCR and Western blot analysis show that HCT116 human colorectal cancer cells transfected with Ad-p53, exhibited elevated endogenous VDR levels compared with control cells transfected with Ad-LacZ. In addition, the induction of endogenous p53 by DNA-damaging agent, adriamycin in RKO cells that express wild-type p53 increased the level of the endogenous VDR gene product. We also reveal that the human VDR gene contains several putative p53-binding sites in its regulatory region by the computational search. And only a single site which is located in the first intronic region has the sequence conservation between the murine and human VDR genes, and others are not. This candidate p53-binding site can directly interact with the p53 protein in vivo, as assessed by a chromatin immunoprecipitation assay. And a heterologous reporter assay also reveals that this p53-binding site is a functional response element. Furthermore, to determine the effect of p53-inducible VDR expression on cell growth, we examine the influence of elevated p53 on the response to 1,25-dihydroxyvitamin D3 by RT-PCR, colony formation assay, FACS analysis and so on. And these experiments show that the expressing p53 exhibits increased response to 1,25-Dihydroxyvitamin D3. Taken together, these results demonstrate that the vitamin D receptor gene is a target for transcriptional activation by
p53 and suggest that p53 might sensitize cells to the anti-proliferative actions of 1,25-dihydroxyvitamin D3 by increasing VDR levels.