Cell, Molecular, and Tumor Biology: Oncogenes/Tumor Suppressor Genes

The functional relation of vitamin D receptor and p53 in cancer cells.

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Abstract

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Epidemiologic studies, in-vitro and animal studies indicate that vitamin D3 may have anti-cancer benefits. The evidence that higher vitamin D levels through increased sunlight exposure or dietary or supplement intake inhibit colorectal carcinogenesis is substantial. And vitamin D3 and its analogues induce cell cycle arrest and apoptosis, so it potentially could be used for cancer prevention. VDR gene, which encodes a nuclear receptor that mediates the effects of vitamin D3 and has potential tumor-suppressive activity. Through our study on the identification of the transcriptional targets of p53, we found that expression of the VDR gene is directly up-regulated by p53. Because both p53 and vitamin D3 have antitumor activity, we further investigated the functional relation of p53 and VDR in cancer cells. First, we confirmed VDR expression was induced by p53 and p53 family genes in variety cancer cell lines. ChIP assays showed that candidate p53-binding sequences located in the VDR first intron could directly interact with the p53 protein in vivo, and Luciferase assays confirmed the p53-response sequence was functional. Overexpression of VDR increased the sensitivity to vitamin D3 treatment, and suppressed colony growth of colorectal cancer cells. We observed several p53 target genes were up-regulated by vitamin D3 treatment under VDR overexpression condition. Expression of VDR and its target genes by p53, p63, and p73 was enhanced by the addition of vitamin D3, so VDR enhances the transcriptional activation of TP53 downstream genes. Furthermore down-regulation of VDR decreased the transcriptional activation of a subset of p53 target genes and decreased the numbers of
apoptotic cells induced by Ad-p53 or Ad-p63. These data suggest that VDR plays a novel role in the p53 signaling pathways. p53 might sensitize cells to the anti-proliferative actions of vitamin D3 by increasing VDR levels. Some studies show that VDR is downregulation in high-grade carcinomas and the efficacy of therapy with vitamin D3 analogues is lost at late steps of tumour progression. So the alteration of p53 may be one of the causes of this VDR dysregulation and it may thus be used as an indicator of patients who are unlikely to respond to this therapy.