The nuclear vitamin D receptor (VDR) modulates gene transcription in 1,25-dihydroxyvitamin D (1,25D) target tissues such as kidney, colon, and bone. The 1,25D hormone is derived from vitamin D in the skin from the diet, and binds to and activates the VDR. We have previously shown that resveratrol, an antioxidant found in the skin of red grapes, has the ability to activate the VDR signaling pathway. Moreover, cells treated with both resveratrol and 1,25D resulted in an additive or even synergistic stimulation of VDR-mediated transcription compared to cells treated with 1,25D alone. Based on these initial results, experiments were designed to test the significance of mutations in the hormone-binding domain of VDR. Identical hormone treatments were applied to “wild-type” (non-mutated) and single point VDR mutations. 1,25D displayed a significant drop in activity caused by these mutations, while the ability of resveratrol to activate VDR was only modestly attenuated. One possible interpretation of these results is that resveratrol may affect VDR activity indirectly, perhaps via the ability of resveratrol to activate SIRT1, an enzyme which has been shown to deacetylate (and thereby activate) other nuclear receptors such as the liver X receptor (LXR). In support of this hypothesis, radiolabeled 1,25D displacement assays revealed an increase in bound radiolabeled 1,25D only in the presence of resveratrol, suggesting that direct binding of resveratrol to VDR is unlikely. Additionally, we observed increased transcriptional activity response to resveratrol in a subset of other nuclear receptors, including the liver X receptor (LXR), which is known to be deacetylated by SIRT1. Finally, we tested receptor-mediated transcriptional activity in a system containing VDR in the absence and presence of overexpressed SIRT1. Transcriptional activity was higher in cells expressing SIRT1, and synergistic activity of 1,25D combined with resveratrol was observed. We are currently conducting additional experiments employing the VDR/SIRT1 assay in multiple cellular contexts. In conclusion, this study elucidates a potential novel pathway for “crosstalk” between VDR/SIRT1, for the first time, a potential novel pathway for “crosstalk” between VDR/SIRT1 assay in multiple cellular contexts. In conclusion, this study elucidates a potential novel pathway for “crosstalk” between VDR/SIRT1 assay in multiple cellular contexts. In conclusion, this study elucidates a potential novel pathway for “crosstalk” between VDR/SIRT1 assay in multiple cellular contexts.