What is the Molecular Basis of Vitamin D Receptor and β-Catenin Cross Regulation?

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Epidemiological studies show a relationship between the dietary intake or UV-activation of pre-vitamin D and the incidence of colon cancers. This relationship indicates that vitamin D may have a chemopreventive action and animal studies have confirmed the preventive efficacy of vitamin D and its analogues in colon cancer. However in many instances human cancer cells and tumors become resistant to treatment. Another major concern is the high incidence of side effects unrelated to the anti cancer actions of vitamin D. Even though both the cancer- and some of the non-cancer-related actions of vitamin D are mediated via interaction with its nuclear receptor (VDR) it is not clear if they can be separated. A detailed understanding of these pathways may lead to the development of agents or dietary regimens that are effective in patients that are resistant to vitamin therapy and/or to the development of treatments with fewer side effects. The β-catenin/TCF oncogenic pathway, almost universally activated very early in colon cancer, is a key intermediary in the preventive action of vitamin D and its analogues in colon cancer. The β-catenin -regulated transcriptional repressor snail is also a key regulator of VDR expression in the colon. Acetylation of the β-catenin C-terminal discriminates between the ability of vitamin D to repress β-catenin signaling and the ability of β-catenin to activate the VDR. Many mutations of the VDR have been discovered in families with hereditary vitamin D resistant rickets (HVDRR). Most mutants fail to activate a vitamin D responsive promoter and also fail to bind β-catenin or regulate its activity. However, one point mutation in the AF2 domain of the VDR (E420Q) abrogates the ability of the VDR to activate vitamin D response element-containing promoters but does not affect its interaction with β-catenin or activation of heterologous promoters. Remarkably, this mutant VDR can activate VDRE-reporters in the presence of elevated β-catenin, but not classical VDR co-activators. These data indicate that this mutant VDR could be selectively activated in situations in which β-catenin is elevated such as colon cancer. Similarly, we find that certain VDR analogues (partial antagonists) **do not** allow recruitment of classical co-activators and therefore cannot activate VDR in most cells. However, these analogues **do** activate VDR when β-catenin is activated.

To identify additional and more potent analogues, we performed a limited simulation study using our newly developed Common Reference Binding Mode (CRBM) strategy, which takes into account receptor/ligand "breathing." This study yielded six new compounds with the structural potential to activate VDR in the presence of β-catenin. We seek to explore and exploit the concept that the vitamin D pathway can be <u>preferentially</u> activated in colon cancer cells expressing high levels of activated β-catenin. Such a strategy might offer the additional benefit of repressing β-catenin signaling at the same time as VDR is activated. Vitamin D and the VDR are also important mediators of the innate immune system that regulates inflammatory responses in the colon. These data together with the growing realization that inflammatory bowel disease is a significant risk factor for colon cancer emphasizes the importance of the vitamin D/β-catenin axis in GI malignancies.