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Activation of the Wnt pathway by natural ligands or small molecule inhibitors activates latent HIV

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Background: Highly Active Antiretroviral therapy (HAART) is very effective in suppressing replication of HIV. However, during HAART, HIV persists lifelong as a latent virus in the patient's memory CD4+T cells. This latent HIV reservoir is transcriptionally competent and cessation of HAART leads to renewed active viral replication. Therefore, in order to eradicate HIV from infected patients, this latent viral reservoir has to be targeted and activated for subsequent elimination by HAART.

Methods: Using J-Lat and S-Lat CD4+ T cell line models as well as ex vivo infected primary CD4+ T cell models reflecting HIV latency we examined the role of the Wnt signaling pathway in regulation of transcription of the latent HIV LTR. We also used various biochemical assays probing the nucleosomal landscape of the latent and Wnt-activated HIV LTR to delineate the mechanism by which Wnt signaling regulates HIV.

Results: We find that activation of the Wnt pathway by natural ligands or small molecule inhibitors resulted in activation of the latent HIV LTR. Treatment of latently HIV infected cells with activators of the Wnt pathway resulted in recruitment of TCF/LEF and b-catenin, the molecular effectors of Wnt signaling, to the latent HIV LTR. Wnt-mediated activation of the latent HIV LTR was synergistically enhanced in the presence of histone deacetylase inhibitors, a class of drugs currently under clinical investigation for activation of latent HIV.

Conclusions: Targeting the Wnt pathway by small molecules and Wnt agonists may be an attractive strategy in a combinatorial therapy aimed at activation of latent HIV infected cells followed by their elimination in the presence of HAART.