6-mer peptide for anti-cancer therapeutic use

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Technology description

A 6-mer peptide (Win6mer) has been designed which has potential as an anti-cancer therapeutic. The Win6mer disrupts MLL1 and SETd1A core complex assembly, but does not inhibit isolated SET domain activity. MLL I belongs to the SETI family of histone H3 lysine 4 (H3K4) methyltransferases, comprised of MLLl-4 and SETdlA/B. MLLl translocations are present in acute leukemias and mutations in several family members are associated with cancer and developmental disorders. MLL I associates with a sub-complex containing WDR5, RbBP5, ASH2L, and DPY-30 (WRAD), forming the MLLl core complex required for H3K4 mono- and dimethylation and transcriptional activation. Core complex assembly requires interaction of WDR5 with the MLLl WDR5 interaction (Win) motif, which is conserved across the SETI family. Agents that mimic the SETI family Win motif inhibit the MLL I core complex and have become an attractive approach for targeting MLL I in cancers. Like MLLl other SETI family members interact with WRAD, but the roles of the Win motif in complex assembly and enzymatic activity remain unexplored. Here, we show that the Win motif is necessary for interaction of WDR5 with all members of the human SETI family. Mutation of the Win motif-WDR5 interface severely disrupts assembly and activity of MLLl and SETdlA complexes, but only modestly disrupts MLL2/4 and SETdlB complexes without significantly altering enzymatic activity in vitro. Notably, in the absence of WDR5, MLL3 interacts with RAD and shows enhanced activity. To further probe the role of the Win motif-WDR5 interaction, we designed a peptidomimetic that binds WDR5 (Kd~3nM) and selectively inhibits activity of MLLl and SETdlA core complexes within the SETI family. Our results reveal that SETI family complexes with the weakest Win motif-WDR5 interaction are more susceptible to Win motif-based inhibitors.

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