Direct Inhibition of the Notch Transactivation Complex

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Direct inhibition of transcription factor complexes is a central challenge in the discipline of ligand discovery. Efforts to develop potent direct-acting inhibitors of most transcription factors have failed to date, principally because these proteins lack surface involutions suitable for high-affinity binding of small molecules. Drawing on structural and genetic insights, we have designed a synthetic, cell-permeable molecule (SAHM1) that targets a critical protein-protein interface in the Notch transactivation complex. We demonstrate that tight, direct ligand binding prevents assembly of the active transcriptional complex. Inappropriate NOTCH activation is directly implicated in the pathogenesis of numerous disease states, including T-cell acute lymphoblastic leukemia (T-ALL). Treatment of leukemic cells with SAHM1 results in genome-wide suppression of Notch-activated genes. Direct antagonism of the Notch transcriptional program further translates into potent, Notch-specific anti-proliferative effects in cultured cells and in a mouse model of Notch-driven T-ALL. As a direct-acting transcription factor antagonist, SAHM1 should prove broadly useful for elucidating the role of Notch signaling in development and in disease biology.