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Discovery of small molecule SUMO1 inhibitors for cancer therapy

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Orderly progression through the cell cycle is driven by oscillation of cyclin-dependent kinase (CDK) activity that is controlled by periodic ubiquitin-mediated degradation of CDK activating cyclins; however, the mechanism that maintains the constant levels of CDK proteins through the cell cycle are unknown. In human glioblastoma, the elevation of CDK proteins has been reported and linked to the gene amplifications; yet, the amplifications occur only in a small fraction of the cancers according to the cancer genome. Here, we show that the G1 phase CDK6 is modified by small ubiquitin-like modifier 1 (SUMO1) and the CDK6 sumoylation stabilizes CDK6 protein and its kinase activity in glioblastoma. CDK6 sumoylation at Lys 216 structurally blocks its ubiquitination at Lys 147, inhibits the ubiquitin-mediated CDK6 degradation and drives the cell cycle through G1/S transition. In a feedback loop, the G2/M phase CDK1 phosphorylates the SUMO conjugating enzyme, ubiquitin-conjugating enzyme 9 (UBC9), which mediates CDK6 sumoylation from G2/M to G1 phase through the cell cycle. In screening of a library with a cell-based assay, we identify a lead compound small molecule SUMO1 specific inhibitor. Treatment with the lead compound SUMO1 inhibitor specifically blocks SUMO1 conjugation pathway, induces CDK6 ubiquitination and degradation, causes G1 arrest and suppresses the progression of glioblastoma xenografts. Thus, SUMO1-CDK6 conjugation constitutes a new mechanism of the cell cycle control in human glioblastoma and the small molecule SUMO1 specific inhibitor may prove to be a novel therapeutic agent in treating human glioblastoma.

Biography

Chunhai Charlie Hao has completed M.D., Ph.D. and clinical neuropathology residency. He is the attending neuropathology at Emory University Hospitals. He has published more than 80 papers in peer-reviewed journals and serving as an editorial board member of *Open Journal of Apoptosis*.

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