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MDM2 Degrades Deacetylated Nucleolin through Ubiquitination to Promote Glioma Stem-like Cell Enrichment for Temozolomide Resistance

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Glioblastoma multiform (GBM) is the most fatal of all brain cancers, and the standard care protocol for GBM patients is surgical tumor resection followed by radiotherapy and temozolomide (TMZ)-mediated chemotherapy. However, tumor recurrence frequently occurs, and recurrent GBM exhibits more malignancy and less sensitivity in response to chemotherapy. The malignancy and drug resistance primarily reflect the small population of glioma stem-like cells (GSC). Therefore, understanding the mechanism that controls GSC enrichment is important to benefit the prognosis of GBM patients. Nucleolin (NCL), which is responsible for ribosome biogenesis and RNA maturation, is overexpressed in gliomas. However, the role of NCL in GSC development and drug resistance is still unclear. In this study, we demonstrate that NCL attenuated GSC enrichment to enhance the sensitivity of GBM cells in response to TMZ. In GSC enrichment, NCL was significantly reduced at the protein level as a result of decreased protein stability. In particular, the inhibition of HDAC activity by suberoylanilide hydroxamic acid rescued NCL acetylation accompanied by the loss of mouse double minute 2 homolog (MDM2)-mediated ubiquitination. Moreover, NCL inhibited the formation of stem-like spheres by attenuating the expression of Sox2, Oct4 and Bmi1. Furthermore, NCL sensitized the response of GBM cells to TMZ. Based on these findings, NCL is a potential marker to predict chemotherapeutic efficiency in GBM patients.

Key words: glioblastoma, glioma-stem-like cell, nucleolin, temozolomide