MKRN1 Degrades AGC1 to Trigger Chemotherapy Resistance of Colorectal Cancer

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Abstract

Oxaliplatin (Oxa) has been extensively utilized in the treatment of colorectal cancer (CRC), yet the frequent occurrence of chemotherapy resistance continues to pose a significant obstacle to achieving long-term disease-free survival for CRC patients. In this study, we established an Oxa-resistant CRC cell line and employed a CRISPR/Cas9 sgRNA library targeting 1,117 human epigenome-related genes to screen for key regulators of Oxa resistance, ultimately identifying Makorin Ring Finger Protein 1 (MKRN1) as a gene associated with Oxa resistance. Clinically, MKRN1 is highly expressed in CRC, and its upregulation is correlated with poor therapeutic response, disease progression, and worse overall survival rates in CRC patients treated with Oxa-based regimens. In CRC cells, gain- and loss-of-function studies of MKRN1 respectively altered the sensitivity to Oxa treatment, as evidenced by changes in IC50 values and cell apoptosis. Mechanistic analysis revealed that MKRN1 interacts with Aspartate/Glutamate Carrier 1 (AGC1), facilitating the degradation of AGC1 via K11- and K29-linked ubiquitination, thereby affecting mitochondrial energy metabolism. Through metabolic reprogramming, this process enhances the expression of heat shock proteins while reducing oxidative stress, ultimately contributing to the development of Oxa resistance in CRC cells. Gene set enrichment analysis of RNA sequencing data

from MKRN1- and AGC1-deficient CRC cells indicated that mitochondrial energy metabolism and antioxidant responses are primary targeted functions. Moreover, in CRC xenograft mouse models, AGC1 knockdown reversed the tumor-inhibiting and heightened Oxa sensitivity effects caused by MKRN1 knockdown. Virtual screening identified Rabdosiin as a potential inhibitor of MKRN1, and combination therapy with Rabdosiin and Oxa significantly reduced tumor volume and improved survival rates in xenograft models. Taken together, our findings highlight the pivotal role of MKRN1 in regulating CRC chemotherapy resistance and offer novel therapeutic strategies aimed at overcoming Oxa resistance and improving patient prognosis.

Key Words: Colorectal Cancer; Oxaliplatin Resistance; Ubiquitination; Antioxidant Responses; MKRN1; AGC1;