c-Myc-miR-29c-REV3L signalling pathway drives the acquisition of temozolomide resistance in glioblastoma.


Abstract

See Happold and Weller (doi:10.1093/awv301) for a scientific commentary on this article. Resistance to temozolomide poses a major clinical challenge in glioblastoma multiforme treatment, and the mechanisms underlying the development of temozolomide resistance remain poorly understood. Enhanced DNA repair and mutagenesis can allow tumour cells to survive, contributing to resistance and tumour recurrence. Here, using recurrent temozolomide-refractory glioblastoma specimens, temozolomide-resistant cells, and resistant-xenograft models, we report that loss of miR-29c via c-Myc drives the acquisition of temozolomide resistance through enhancement of REV3L-mediated DNA repair and mutagenesis in glioblastoma. Importantly, disruption of c-Myc/miR-29c/REV3L signalling may have dual anticancer effects, sensitizing the resistant tumours to therapy as well as preventing the emergence of acquired temozolomide resistance. Our findings suggest a rationale for targeting the c-Myc/miR-29c/REV3L signalling pathway as a promising therapeutic approach for glioblastoma, even in recurrent, treatment-refractory settings.

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KEYWORDS: c-Myc/miR-29c/REV3L signalling; glioblastoma; temozolomide resistance

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