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SNO abstract

A GSK-3/ β -catenin/ARHGAP axis regulates glioblastoma invasion

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Introduction: Glycogen synthase kinase-3 (GSK-3) has been implicated as a potential target in glioblastoma migration and invasion. Here we investigated the effects of GSK-3 inhibition on downstream effector genes and discovered a novel GSK-3 / β -catenin/ARHGAP migration axis that drives glioblastoma invasion.

Methods: Expression arrays of glioblastoma cells treated with the GSK-3 inhibitor 6-bromoindirubin-3'-oxime (BIO) were performed. Functional validation was carried out using 2D and 3D migration assays, siRNA knockdown and orthotopic xenograft models. Protein expression was investigated in patient glioblastoma samples.

Results: Microarray data analysis identified deregulation of expression of members of the ARHGAP gene family of GTPase regulators after BIO treatment of U251 cells. This was confirmed at the protein level by Western blotting and immunostaining. siRNA treatment indicated a specific promigratory role for ARHGAP29. U251 cells exposed to BIO displayed a decrease in migration as evidenced by loss of polarity and reduction in cell velocity. This was associated with a rearrangement of actin filaments and β -catenin translocation from the cell surface to the nucleus, where it is known to act as a transcription factor downstream of GSK-3 inhibition. We then found that ICG001, an inhibitor of β -catenin-induced transcription, essentially mimicking GSK-3 activation, induced transcription of ARHGAP29 and led to a partial increase of ARHGAP29 protein expression, reduction of β -catenin target gene expression and the ability of cells to migrate. *In vivo* studies, as well as data from glioblastoma patients, confirmed a pro-migratory role for ARHGAP29 as evidenced by elevated protein levels in migratory cells at the invasive front in orthotopic xenograft models and its association with disease recurrence.

Discussion: We demonstrate for the first time signalling events downstream of GSK-3 activation and β -catenin nuclear translocation which reveal a new pathway regulating glioblastoma migration through the transcription of the GTPase regulator ARHGAP29.