GSK3β regulates Bcl2L12 and Bcl2L12A anti-apoptosis signaling in glioblastoma and is inhibited by LiCl.


Source

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Abstract

BCL2L12 has been reported to be involved in post-mitochondrial apoptotic events in glioblastoma, but the role of BCL2L12A, a splicing variant of BCL2L12, remains unknown. In this study, we showed that BCL2L12 and BCL2L12A were overexpressed in glioblastoma multiforme (GBM). Large-scale yeast two-hybrid screening showed that BCL2L12 was a GSK3b binding partner in a testis cDNA library. Our data demonstrated that GSK3b interacts with BCL2L12 but not BCL2L12A, whose C terminus lacks a binding region. We found that a BCL2L12(153-191) fragment located outside of the C-terminal BH2 motif is responsible for GSK3b binding. In contrast, no interaction was detected between BCL2L12A and GSK3b. In vitro kinase and l-phosphatase assays showed that GSK3b phosphorylates BCL2L12 at S156, while this site is absent on BCL2L12A. Moreover, our data also showed that the BCL2L12(153-191) fragment directly interrupted GSK3b-mediated Tau phosphorylation in a dose-dependent manner. Ectopic expression of GFP-fused BCL2L12 or BCL2L12A in U87MG cells leads to repression of apoptotic markers and protects against staurosporine (STS) insults, indicating an antiapoptotic role for both BCL2L12 and BCL2L12A. In contrast, no anti-apoptotic ability was seen in BCL2L12(S156A). When BCL2L12-expressing U87MG cells were co-administrated with STS and LiCl, cells underwent apoptosis. This effect could be reversed by LiCl. In short, we established a model to demonstrate that GSK3b interacts with and phosphorylates BCL2L12 and might also affect BCL2L12A to modulate the apoptosis signaling pathway in glioblastoma. These findings suggest that LiCl may be a prospective therapeutic agent against GBM.

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