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The BET bromodomain inhibitor JQ1 and the histone deacetylase inhibitor panobinostat induce synergistic anticancer effects by repressing LIN28B and N-Myc expression

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Patients with neuro blastoma associated with MYCN oncogene amplification experience a very poor prognosis. BET bromodomain inhibitors are emerging as one of the most promising novel classes of anticancer agents by blocking the BET bromodomain proteins BRD3 and BRD4 from activating transcription of oncogenes such as MYC and MYCN. However, treatment with BET bromodomain inhibitors alone does not result in cancer remission. Here we show that BRD3 and BRD4 directly bound to the LIN28B gene promoter and activated LIN28B gene transcription, and that knocking down LIN28B expression reduced the expression of N-Myc protein, but not N-Myc mRNA. Combination therapy with the BET bromodomain inhibitor JQ1 and the histone deacetylase inhibitor panobinostat synergistically suppressed LIN28B gene expression, reduced N-Myc mRNA expression to the same extent as JQ1 treatment alone, but considerably and synergistically reduced N-Myc protein expression. JQ1 and panobinostat induced synergistic growth inhibition and apoptosis in neuroblastoma cells, but not normal non-malignant cells in vitro. Importantly, in neuroblastoma-bearing mice, JQ1 and panobinostat combination therapy synergistically and considerably reduced N-Myc protein expression in tumor tissues and blocked tumor progression. Our findings have therefore identified a potential strategy to reduce N-Myc onco-protein expression and a novel therapeutic approach for the treatment of aggressive neuroblastoma.

Biography

Jeyran Shahbazi is working as a Research Officer at Children's Cancer Institute, Lowy Cancer Research Centre, UNSW. Her research interests include Cell Biology, Cancer Research, Molecular Biology.

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