5-2023

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Background: Neuroblastoma is a challenging cancer to treat in pediatric patients. Despite intense treatment regimens, the prognosis for high-risk pediatric neuroblastoma patients remains poor, with less than 40% survival.

Significance of the Problem: One of the major obstacles to effective immunotherapy in neuroblastoma is the defective immune cells. Neuroblastoma tumors generally have impaired T-cell anti-tumor activity due to restricted MHC class I expression on tumor cells. This makes natural killer (NK) cells an attractive alternative for neuroblastoma immunotherapy, as they are not restricted by MHC class I expression on tumor cells. However, the overexpression of immune checkpoint molecules like B7-H3 (gene: CD276) helps tumor cells to escape NK immune surveillance, hindering the effectiveness of NK cell-mediated immunotherapy in neuroblastoma.

Objective: Micro RNAs (miRNAs or miR) play critical roles in nervous system development and post-transcriptional regulation of genes involved in neuroblastoma development. Therefore, exploring the role of upstream miRNAs that can target B7-H3 and regulate NK-mediated anti-tumor immune response in neuroblastoma could lead to the identification of novel therapeutic targets for neuroblastoma treatment.

Methods: Using the TARGET, neuroblastoma patient dataset, we applied the robust bioinformatic workflows incorporating differential expression, co-expression, survival, heatmaps, and box plots.

Results: We present here the role of miRNAs belonging to the miR-29 family, including miR-29a, miR-29b, and miR-29c, in regulating B7-H3 and antitumor immunity in neuroblastoma. Using different neuroblastoma patients' microarray data sets, we show that miR-29a, miR-29b, and miR-29c levels in the tumors were associated with good clinical outcomes and inversely correlated with B7-H3. Higher B7-H3 mRNA was associated with disease progression and poor survival in patients with neuroblastoma. MiR-29a, miR-29b, and miR-29c inhibited B7-H3 expression in neuroblastoma cells. B7-H3 downregulation induced NK cell activation and enhanced its cytotoxic functions against neuroblastoma cells, boosting NK-mediated antitumor immunity. Furthermore, miR-29a, miR-29b, and miR-29c treated neuroblastoma tumors had a large influx of infiltering activated NK and T cells, which is associated with tumor shrinkage, reduced tumor microvessel density, low macrophage infiltration, and enhanced tumor cell apoptosis. In cell culture, overexpression of miR-29a, miR-29b, and miR-29c inhibited proliferation, colony formation, migration, and neurospheres forming ability of neuroblastoma cell lines.

Conclusions: Overall, our findings highlight the therapeutic potential of miR-29a, miR-29b, and miR-29c to boost NK and T cell-mediated immune surveillance of neuroblastoma tumors, strengthening natural anti-tumor immunity and response to anticancer therapies.

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