DLK1-DIO3 Region as a Source of Candidate Tumor Suppressor miRNAs in Papil- Lary Thyroid Carcinoma

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Abstract

Background: DLK1-DIO3 genomic region comprises one of the largest microRNA (miRNAs) clusters in human genome. In previous studies we showed the downregulation of several miRNAs from the genomic region in papillary thyroid carcinoma (PTC). Due to the large number of miRNAs within this region the individual contribution of these molecules to PTC development and progression remains unclear.

Methods: We used different computational resources to clarify the contribution of DLK1-DIO3-derived miRNAs to PTC.

Results: Our analysis suggests that 12 miRNAs from this region cooperate to modulate distinct cancer-relevant biological processes, potentially responding for most of the impact of DLK1-DIO3-derived miRNAs to PTC development and progression. The overexpression of miR-485-5p in two PTC cell lines decreased proliferation and migration, confirming the biological relevance of in silico data.

Conclusion: Our results shed light on the role of DLK1-DIO3 region, harboring several tumor suppressor miRNAs in thyroid cancer and open perspectives for the functional exploration of these miRNAs as therapeutic targets for PTC.

Full Text

This preprint is available for download as a PDF.

Figures

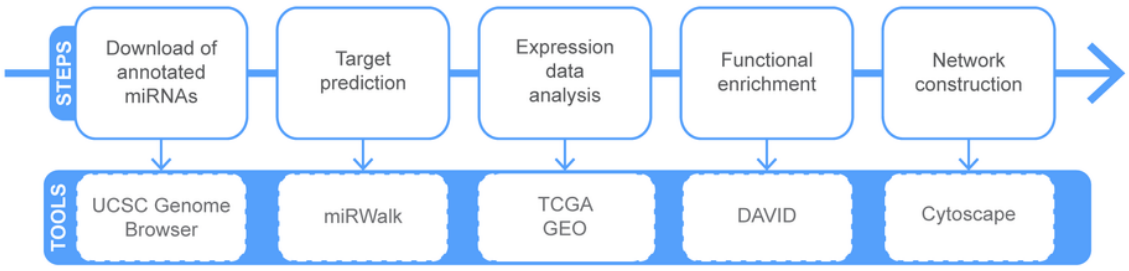

Figure 1

Firstly, miRWalk platform was used to identify the list of targets for each of the mature miRNAs situated in the DLK1-DIO3 region. Only interactions predicted by at least 8 out of the 12 algorithms were considered valid, resulting in a list of 6,231 targets.

Figure 2

Overall, most of miRNAs from DLK1-DIO3 are downregulated in PTC and other types of cancer, such as kidney papillary carcinoma and chromophobe renal cell carcinoma, breast invasive carcinoma and head and neck squamous cell carcinoma

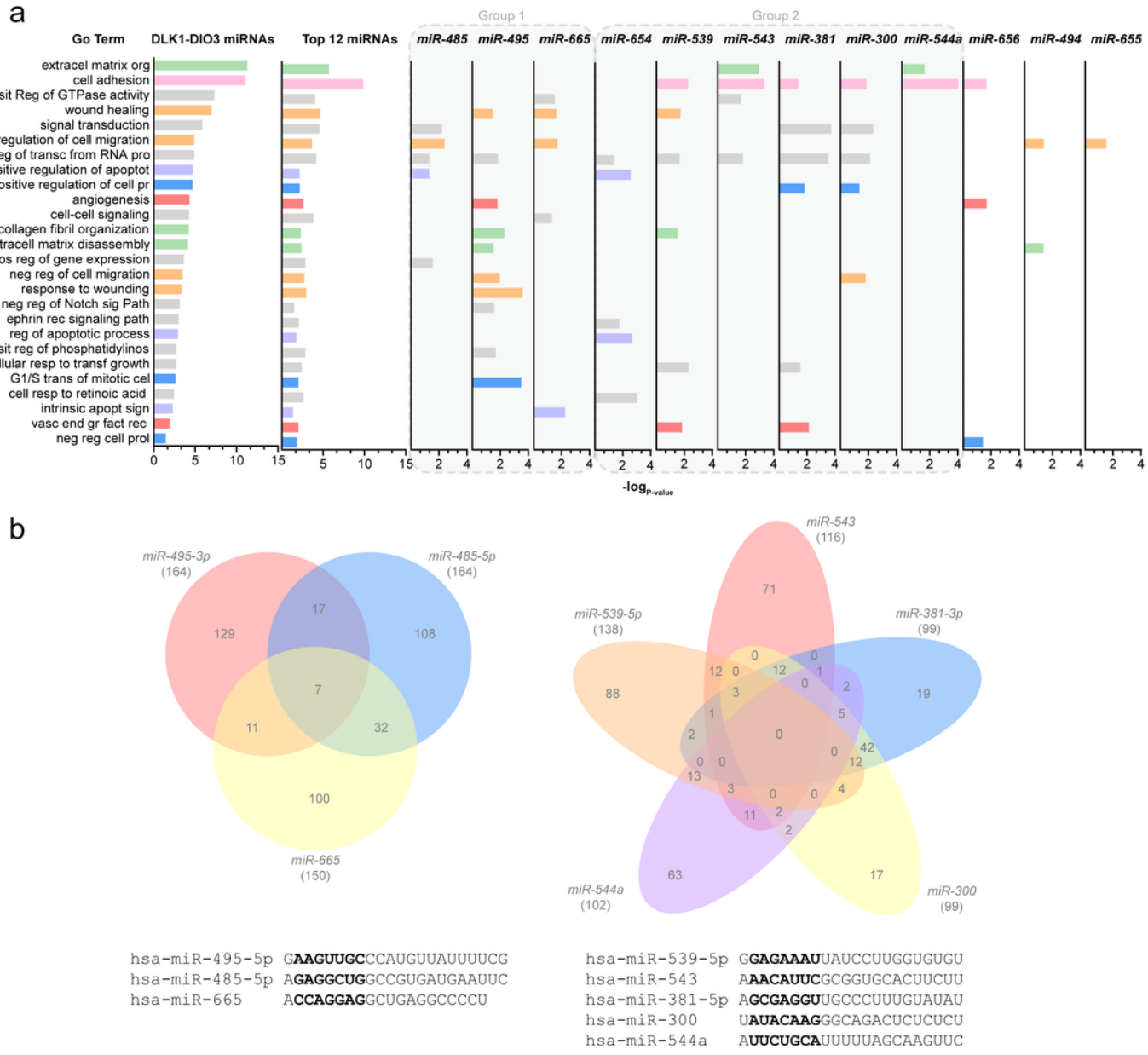

Figure 3

Thus, each small group of miRNAs could contribute with PTC development and progression through deregulation of different biological process. Most of the top-12 miRNAs genes (except for miR-665, miR-370-3p and miR-432-5p) span a 39.8 kb region (chr14:101028292-101068115) upstream from MEG9 gene, along with 22 other miRNA genes, with no apparent correlation between their genomic location, sequence conservation and biological function (data not shown).

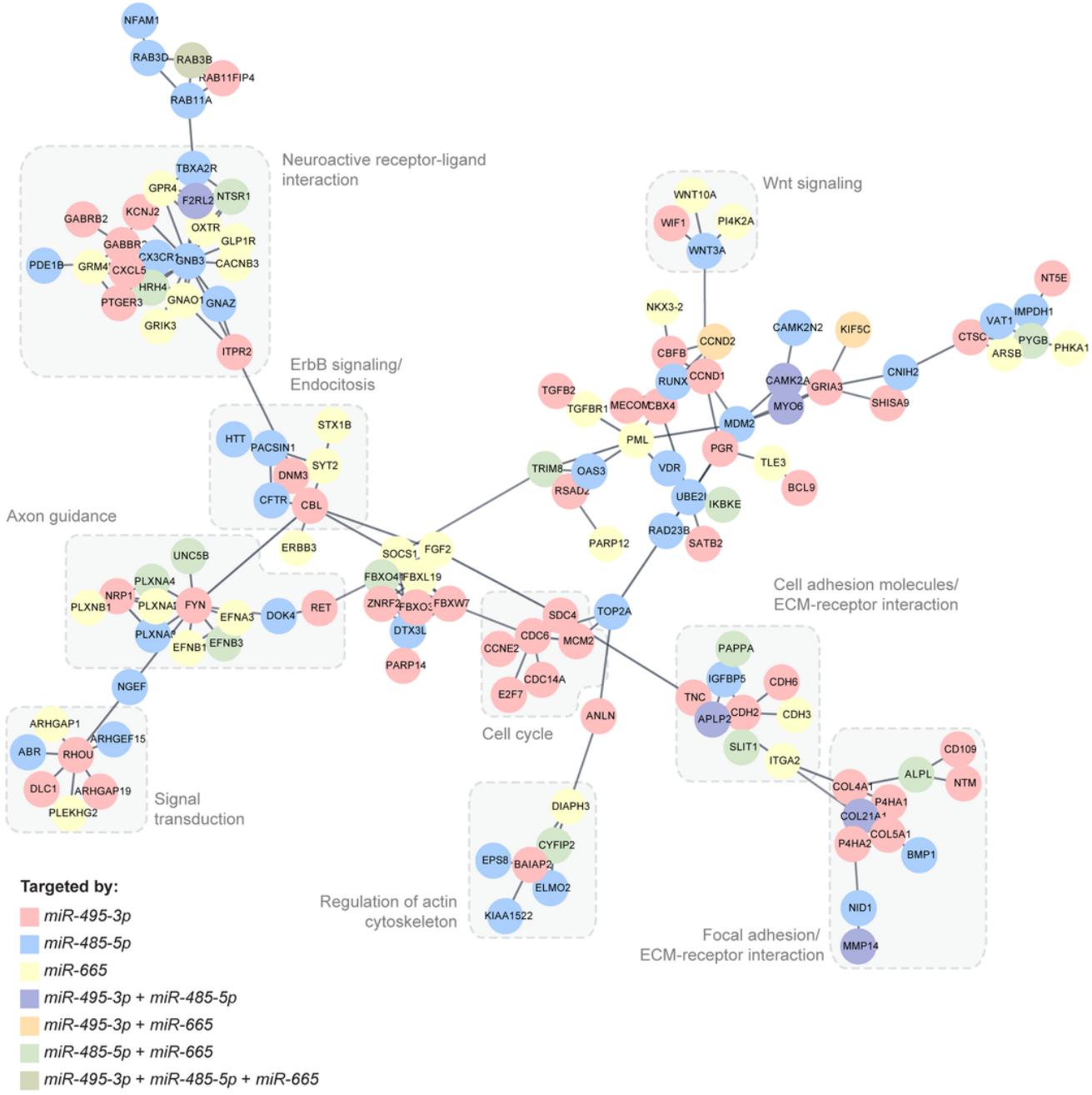

Figure 4

where we observe that miRNAs from group 1 (miR-495-3p, miR-485-5p, miR-665) cooperate to modulate different cancer-related processes, such as cell cycle, signal transduction and extracellular matrix remodeling, where simultaneous targeting is rarely observed.

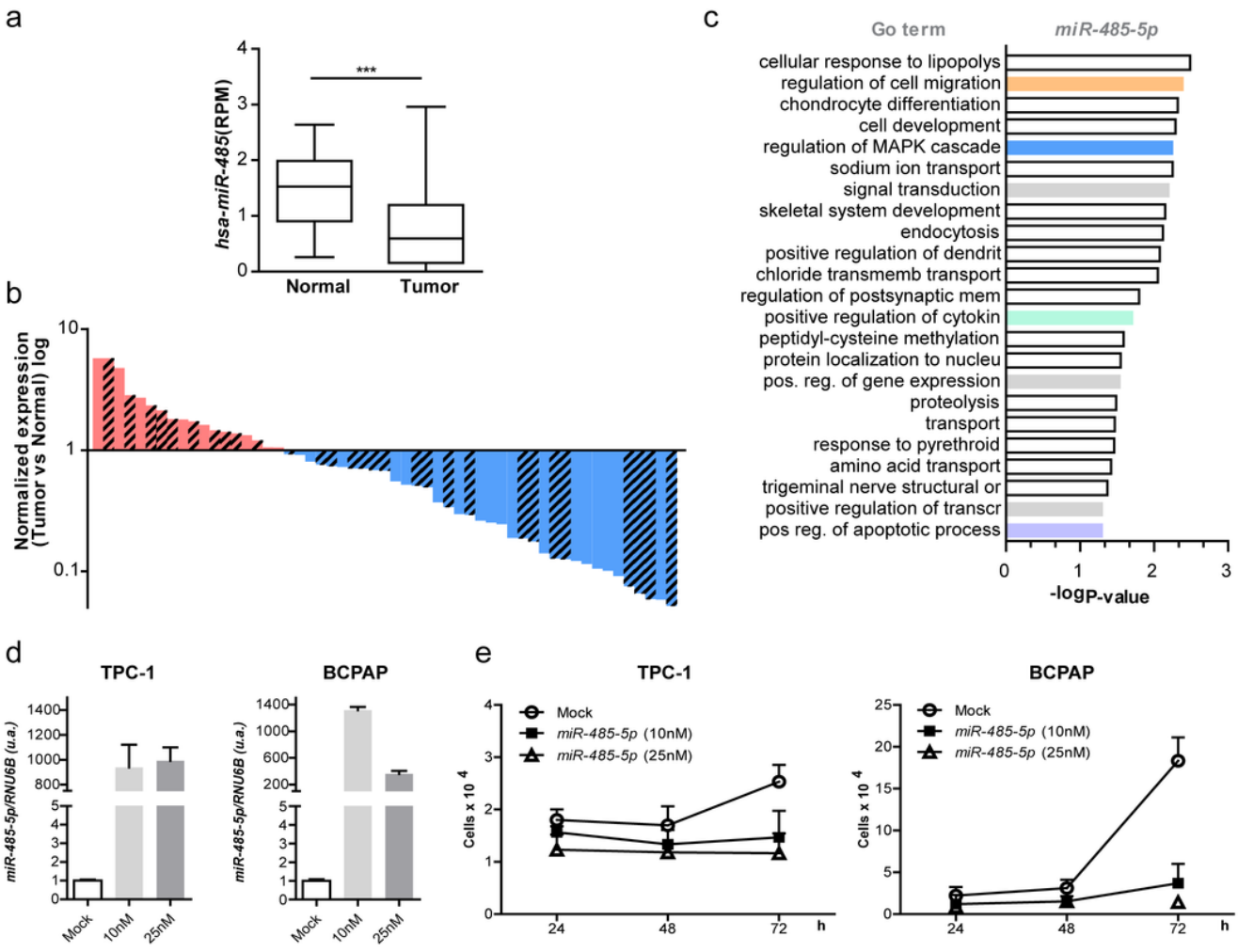

Figure 5

The enriched biological processes and signaling pathways among miR-485-5p targets include relevant processes for PTC, such as “regulation of cell migration”, "regulation of MAPK cascade” and “signal transduction” (Fig. 5c). As expected, the transfection of miR-485-5p commercial mimetic abolished cell proliferation of two PTC cell lines (TPC-1 and BCPAP)

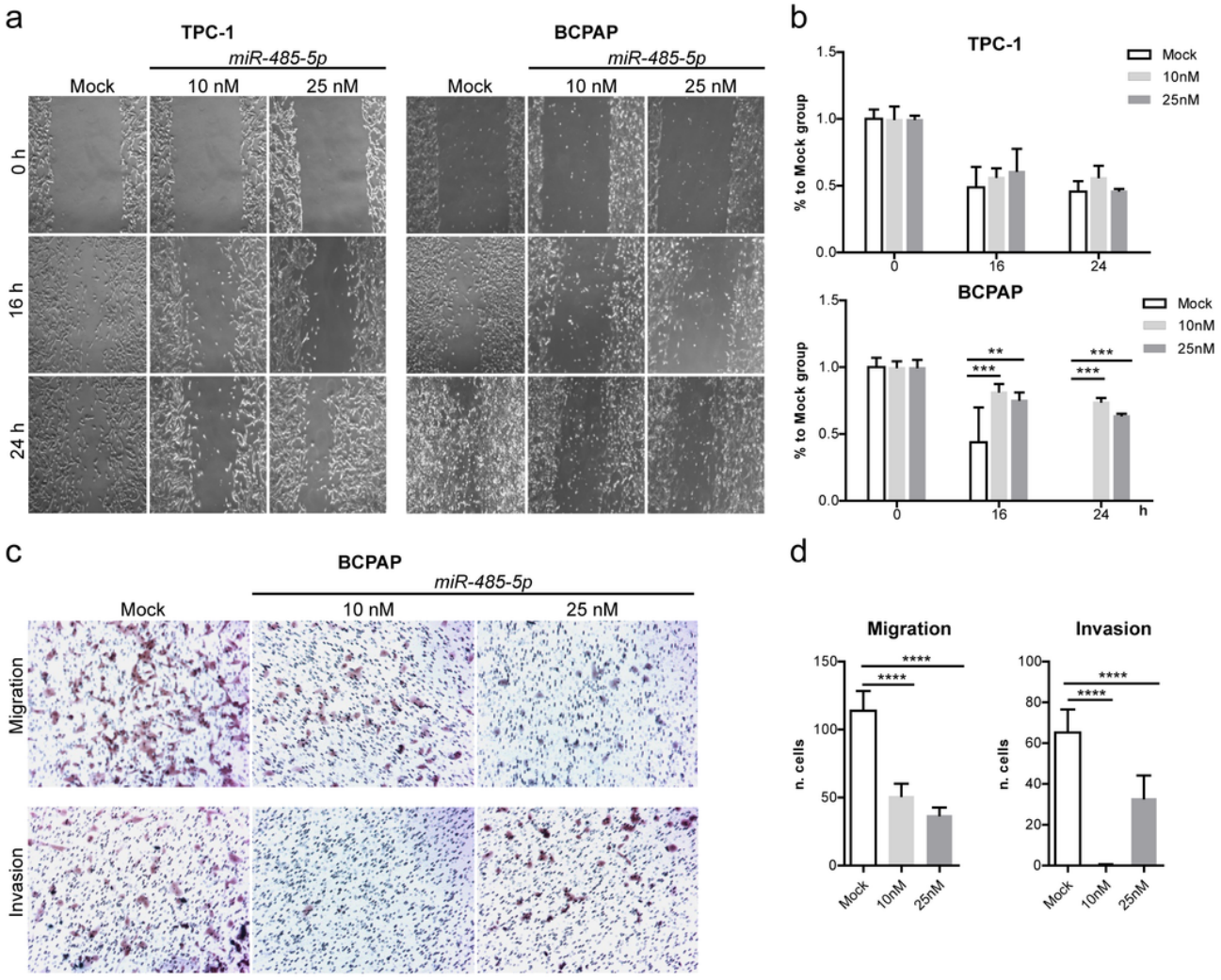

Figure 6

The suppression of migratory behavior is dependent on the onco genic background of the cell line, as the BRAF1799A-positive BCPAP cells showed a significant decrease of the migratory capacity after the transfection of miR-485-5p. In contrast, no significant changes were observed in TPC-1 cells, which harbor the RET/ PTC1 rearrangement. The role of miR-485-5p on the suppression of migration of the BRAF-mutated BCPAP cell line was confirmed by Transwell assay