miR-551b and SEMA3D as Potential Therapeutic Targets in Papillary Thyroid Cancer

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Abstract

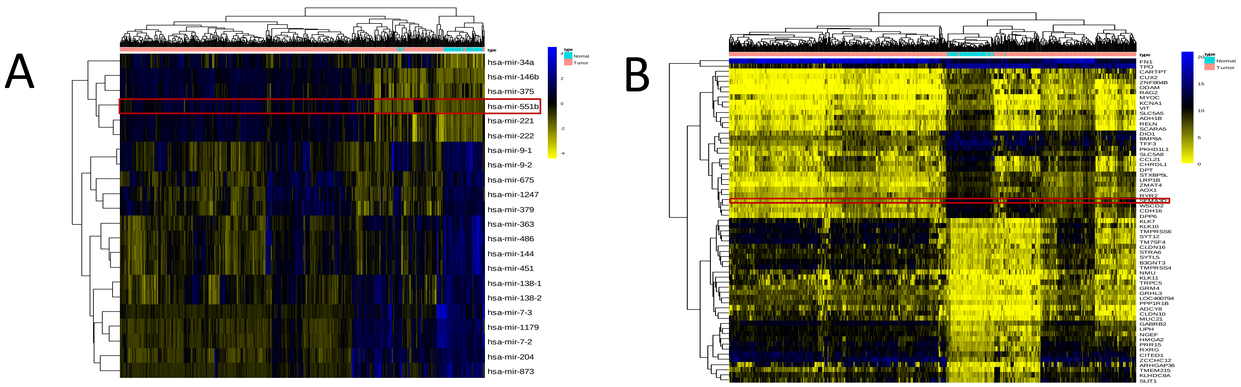
Objectives: We aim to identify microRNAs and mRNAs differentially expressed in papillary thyroid cancer that correlate with clinical characteristics of the disease.

Methods: Level 3 miR-Seq data and mRNA-Seq data of thyroid cancer from The Cancer Genome Atlas (TCGA) were used for analysis. The expression level of microRNAs and mRNAs between normal and primary tumor samples were compared. The correlation between differentially expressed miRNAs/mRNAs and patients' clinical characteristics, including tumor size (T1/2 vs. T3/4), lymph node status, metastatic status, extrathyroidal extension (ETE), BRAF mutation, and AJCC tumor stage (TI/II vs. TIII/IV) were tested.

Results: 65 miRs and 2483 mRNAs were differentially expressed in papillary thyroid carcinoma primary tumors compared to adjacent normal tissues with more than 2-fold change. Many differentially expressed miRs were significantly correlated with BRAF^{V600E} mutation, lymph node involvement, ETE, tumor stage, tumor size, but not with tumor metastatic status. The miR-551b was the second upregulated miRs in primary tumor compared to normal tissues (7.6 fold, p<0.0001), and was further increased in tumors from patients with lymph node metastasis or BRAF mutation. Among differentially expressed mRNAs, SEMA3D expression was significantly decreased (31.7 fold, p<0.0001) in PTC, and was further decreased in tumors from patients with lymph node metastasis, tumor stage III / IV, ETE, or BRAF mutation. SEMA3D shows significant negative correlation with miR-551b in PTC patients (r=-0.66 and p<.0001), and miRDB predicts SEMA3D as a target of miR-551b. Both miR-551b and SEMA3D has been reported as a potential therapeutic target in other cancers [1,2]. Recently, SEMA3D was included in a 15-gene biomarker panel to identify malignancy among cytologically indeterminate thyroid tumors [3]. **Therefore, miR-551b and SEMA3D may play a critical role in thyroid cancer tumorigenesis and/or progression.**

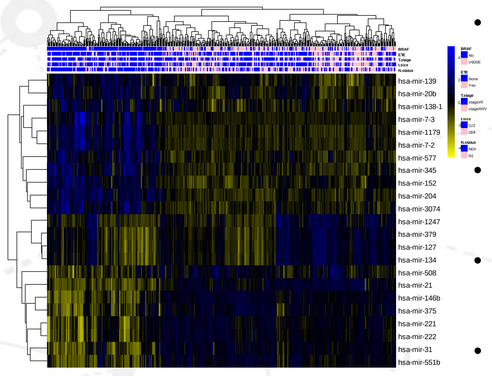
Conclusions: Deregulated miR-551b and SEMA3D may play a critical role in tumorigenesis and/or progression and they may serve as potential therapeutic targets in PTC.

Top deregulated miRs and mRNAs in papillary thyroid carcinoma



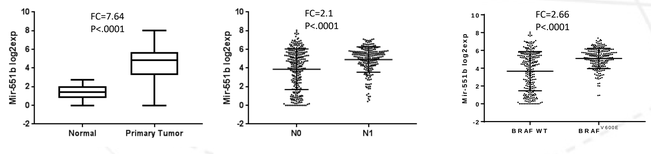
A. Top differentially expressed miRs with >3 fold change. B. Top differentially expressed mRNAs with >20 fold change in PTC. Thyroid cancer TCGA mRNA-Seq and miRNA-Seq data were compared between the paired normal and primary PTC samples. miRs and mRNAs that meet the significance cutoff (p-value<0.0001)and with more than 2 fold change were selected for further association tests with patient clinical characteristics (65miRs and 2483 mRNAs were selected).

MiRs associated with patient clinical characteristics



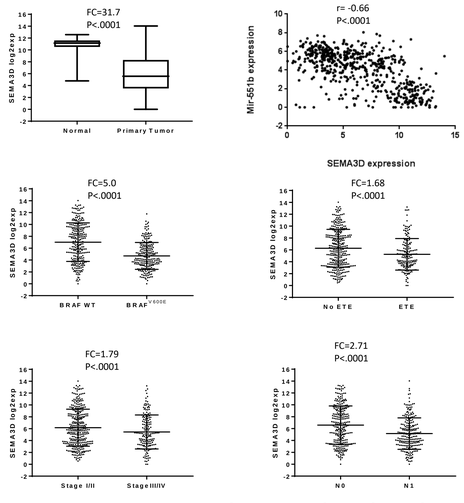
- The expression of the upregulated miRs, including miR-551b, -31, -221, -222, -375, -146b, -21, -508, are further increased; and the downregulated miRs, including miR-139, -20b, -138-1, -7-3, -1179, -7-2, -577, -345, -152, -204, are further decreased in tumors with BRAF^{V600E} mutation (P<.0001 for BRAF association test).
- miR-1247, miR-127, miR-134, miR-379 are significantly downregulated in primary tumors, but their expression was significantly increased in tumors with BRAF^{V600E} mutation (P<.0001 for BRAF association test).
- Most of the miRs significantly associated with BRAF^{V600E} mutation are also associated with lymph node involvement, tumor stage III/IV, tumor size 3/4, or ETE
- None of the differentially expressed miRs are associated with metastatic status.

MiR-551b associated with BRAF^{V600E} mutation and lymph node involvement



miR-551b is further increased in tumors from patients with BRAF^{V600E} mutation or lymph node involvement.

SEMA3D associated with miR-551b, BRAF^{V600E} mutation, tumor stage (III/IV) , ETE, and lymph node involvement



- SEM3D is negatively correlated with miR-551b and is a predicted target of miR-551b.
- SEMA3D was significantly downregulated in PTC, and was further decreased in tumors from patients with lymph node involvement, BRAF^{V600E} mutation, tumor stage III/IV, or ETE.

Conclusion

- miR-551b is associated with BRAF^{V600E} mutation and lymph node involvement.
- SEMA3D, a predicted target of miR-551b, is associated with BRAF^{V600E} mutation, ETE, lymph node involvement, and tumor stage (III/IV).
- Therefore, miR-551b and SEMA3D axis may play a critical role in thyroid cancer tumorigenesis and/or progression.

Reference

1. Xu XL, Wells A , Padilla M, Kato K, Kim K and Lin Y. A signaling pathway consisting of miR-551b, catalase and MUC1 contributes to acquired apoptosis resistance and chemo resistence. 2014. Carcinogenesis. vol.35 no.11 pp.2457–2466.
2. Worzfeld T, Offermanns S. Semaphorins and plexins as therapeutic targets. Nat. Rev. Drug Discov. 2014; 13:603–621. [PubMed: 25082288]
3. Gomez-Rueda H, Palacios-Corona R, Gutiérrez-Hermosillo H, Trevino V. A robust biomarker of differential correlations improves the diagnosis of cytologically indeterminate thyroid cancers. Int J Mol Med. 2016 May; 37 (5):1355-62. [PubMed:27035928]

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