Emerging genes and pathways in thyroid differentiation and tumorigenesis.

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Thyroid cancer remains the most common endocrine malignancy worldwide and its incidence and mortality has increased steadily over the last four decades. In general, it has a good outcome; however, some patients develop aggressive forms of thyroid cancer that are untreatable and the molecular bases are poorly understood. These aggressive forms have lost NIS (Na/I Symporter) function, one of the most important hallmarks during thyroid cancer progression, as it leads to radioiodine-resistant metastatic disease. Our work has contributed to understand the mechanisms involved in iodide uptake repression and tumor progression. We have found that BRAF activation decreases NIS expression and impairs NIS trafficking to the membrane of follicular thyroid cells, and accordingly causes (RAI)-refractory metastatic disease in patients with papillary thyroid cancer. We have demonstrated that the mechanism by which BRAF impairs NIS function is mediated by a TGFβ autocrine loop. Furthermore, by next-generation sequencing and gene expression analysis we have identified a master miRNA (miR) regulatory network involved in essential biological process such as thyroid differentiation. Among those miRNAs, the most abundantly expressed in thyroid tumors is the miR-146b and we found that it binds to the 3′-UTR region of thyroid differentiation genes such PAX8 and NIS, leading to impaired protein translation and subsequently a reduction of iodide uptake. Besides, we show that miR-146b and PAX8 regulate each other sharing common target genes, thus highlighting a novel regulatory circuit that govern differentiated phenotype in thyroid tumors. Furthermore, we have shown that the overexpression of miR-146b induces an hyperactivation of the PI3K/AKT pathway, via PTEN suppression, leading to a more aggressive tumoral behavior. In summary, our work described molecular determinants that may be exploited therapeutically to modulate thyroid cell differentiation and iodide uptake for improved treatment of advanced thyroid cancer.

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