THYROID INFLAMMATION ASSOCIATES WITH DOWN-REGULATION OF FOXE1 AND ENRICHMENT FOR A STEM CELL TRANSCRIPTOME IMPLICATING EPITHELIAL DEDIFFERENTIATION AS A MECHANISM OF THYROID CANCER RISK DUE TO THYROIDITIS

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Background/Purpose: Inflammation is a risk factor for thyroid cancer, which occurs in Hashimoto's disease, Grave's disease, and other thyroiditis types. Several studies have correlated hypo-function polymorphisms in *FOXE1* with increased risk of thyroid cancer.
Methods: Microarray expression data of human thyroiditis tissues compared to thyroid hyperplasias and adenomas was analyzed via hierarchical clustering. Expression correlation analysis identified genes co-expressed with FOXE1. Significance of Analysis of Microarray (SAM) identified gene profiles between experimental groups. ConceptGen software quantified strength of gene profile overlaps.
Results: *FOXE1* transcript is consistently down-regulated in thyroid tissues from various forms of thyroiditis, but not in thyroid hyperplasias or adenomas. Expression correlation analysis revealed that other thyroid differentiation genes such as *TSHR* and *NKX2-1* were down-regulated along with *FOXE1* specifically in thyroiditis. SAM derived gene profiles of thyroiditis tissues versus thyroid hyperplasias (>2-fold, FDR<5%) across multiple data sets. Thyroiditis profiles showed strong overlap with mammary stem cell and thyroid progenitor gene profiles (50 to 80 overlapping genes; p=3.2E-17 to p=7.8E-31). This overlap was not observed in a profile representing a comparison of normal thyroids to adenomas.
Discussion & Conclusion: Since stem cells have been proposed as the targets of transformation in a number of solid cancers, and stem cells have been isolated from goiters, a partial dedifferentiation program at the transcriptomic level may increase the pool of stem-like cells that undergo transformation. This data suggests an organ-wide dedifferentiation program associated with thyroid inflammation, which may account for the increased risk of thyroid cancer after thyroiditis.