The Roles of TRβ and Runx2 in Promoting Thyroid Tumor Progression

Abstract:

Background: Thyroid cancer is the most common endocrine cancer. Incidence has been increasing worldwide for the past few decades. Thyroid hormone receptors (TR) are critical development regulators that play an imperative role in regulation of cellular response to thyroid hormones (TH) by binding to them and activating or repressing target genes. Mutations and altered expression of TRs have been associated with tumor progression. Recent studies have suggested that another critical development regulator, Runt-related transcription factor 2 (Runx2), may act as a tumor promoter. Previous studies in our laboratory revealed reciprocal expression of TRB and Runx2 in benign and malignant human thyroid cells confirmed in tissue biopsy samples.

Hypothesis: TRB expression directly correlates with Runx2 levels in human thyroid cells.

Methods: TRB knockdown by siRNA will be transiently established in human thyroid cell lines derived from benign tissue. Confirmation of altered protein levels will be by Western analysis. Transfections of siRNA against TRβ were done in two different benign thyroid cell lines (NORI and THJ) in order to study its effect on tumorigenesis. Changes in TRβ levels, after being blocked with siRNA, were quantified using Western blotting. Changes in levels of a suspected target of TRβ, Runx2, were also measured by Western analyses. Changes in Runx2 target genes including known tumorigenic factors VEGF and MMP 3 will be determined by qRT-PCR. Analyses of TRB sequences in the benign and malignant cells will be determined by Sanger sequencing.

Results: siRNA knockdown of TRβ increased Runx2 protein levels in both benign cell lines. The effects on target genes are currently being determined.

Conclusions: These results imply regulation of Runx2 by TRβ. This project identifies some of the consequences of a loss of function of TRβ in benign thyroid cells. Because of its proposed function as a tumor suppressor, it was expected that
the loss of TRβ in benign cells would induce characteristics similar to those seen in malignant cells, and the amount of Runx2 found in the cells would increase. This data is some of the first indication of TRβ regulation of Runx2 expression and is consistent with the loss of TRβ contributing to Runx2 tumor promotion.