Topic: ONSET OF FETAL THYROID FUNCTION

Title: Sodium/Iodide Symporter (NIS) gene expression is the limiting step for the onset of thyroid function in the human fetus.

Authors: Szinnai G, Lacroix L, Carré A, Guimiot F, et al. (Paris, France)

Reference: Journal of Clinical Endocrinology & Metabolism 92: 70-76, 2007

SUMMARY

Context: Terminal differentiation of the human thyroid is characterized by the onset of follicle formation and thyroid hormone synthesis at 11 gestational weeks (GW).

Objective: This study aimed to investigate the ontogeny of thyroglobulin (Tg), thyroid peroxidase (TPO), sodium/iodide symporter (NIS), pendrin (PDS), dual oxidase 2 (DUOX2), thyroid stimulating hormone receptor (TSHR), and thyroid transcription factor 1 (TITF1), forkhead box E1 (FOXE1) and paired box gene 8 (PAX8) in the developing human fetus.

Design: Thyroid tissues from 45 human embryos and fetuses (7-33 GW) were analysed by quantitative PCR to monitor mRNA expression for each gene and by immuno-histochemistry to determine the cellular distribution of TITF1, TSHR, Tg, TPO, NIS, and the onset of T₄ production. A broken line regression model was fitted for each gene to compare the log-linear increase in expression before and after the onset of T₄ production.

Results: TITF1, FOXE1, PAX8, TSHR, and DUOX2 were stably expressed from 7 to 33 GW. Tg, TPO, and PDS gene expressions were detectable as early as 7 GW and were correlated with gestational age (P < 0.01). The slope of the regression line was significantly different before and after the onset of T₄ synthesis at 11 GW (P < 0.01). NIS expression appeared last and showed the highest fit by the broken line regression model of all genes (correlation age: P < 0.0001; broken line regression: P < 0.0001). Immuno-histochemical studies detected TITF1, TSHR, and Tg in unpolarized thyrocytes before follicle formation. T₄ and NIS labelling were only found in developing follicles from 11 GW on.

Conclusion: These results imply a key role of NIS for the onset of human thyroid function.

COMMENT

The developing human thyroid gland undergoes a series of complex changes during embryogenesis in order to become functional. Morphogenesis is completed when the thyroid reaches its definitive pretracheal position – at 7 weeks gestation – but, at this early stage, the gland is mainly composed of undifferentiated thyrocyte precursors.

Three morphological differentiation stages can be distinguished: precolloid, beginning colloid, and follicular growth stage. Differentiation includes several changes: the polarization of thyrocyte precursors (with basal & apical poles), followed by follicle formation (allowing colloid to be accumulated), and the expression of thyroid-specific functional genes, such as thyroglobulin ‘Tg’ (the matrix on which
thyroid hormone can be produced), thyroperoxidase ‘TPO’ (the enzyme needed to catalyse iodine incorporation onto the Tg matrix), thyroid-stimulating hormone receptor ‘TSHR’ (main regulator – at the basolateral thyrocyte membrane level – of thyroid growth & function, via hypothalamic-pituitary control), and sodium/iodide symporter ‘NIS’ (the pump needed to trap iodide from the circulation).

The present study is fascinating as it is the first attempt to investigate the sequence of this molecular program of human thyroid differentiation. The results show essentially that a precisely timed expression program exists. DUOX2 expression is stable already at 7 weeks gestation. A second group of genes (Tg, TPO, PDS) are expressed at low levels first, then increase significantly before 11 weeks gestation, and their increased expression is correlated with the onset of thyroid function. NIS is the last gene to appear, and its expression is the most strongly correlated with the rapid onset of thyroid hormone synthesis at 11 weeks gestation. This expression pattern suggests that NIS expression is the rate limiting step for the onset of thyroid function in man. In other words, all parts of the complex puzzle must first be in place for iodide to be actively trapped and organified within an already organized thyroid gland, allowing thyroid hormone to be produced.

It is important to note that this study is purely qualitative, as it does not allow to assess which quantitative fraction of the overall fetal thyroid hormone environment is related to the onset of T₄ synthesis at such early embryonic stage (first trimester of gestation). Therefore, the presence of T₄ in the anatomical structures bathing the developing embryo (amniotic and coelomic fluid) remains presumably mostly due to maternal transfer of thyroid hormone. Even though fetal T₄ synthesis may be starting around 11-12 weeks, it is not until 16-20 weeks gestation that the fetal hormone contribution to this crucial environment may become relevant. (Daniel Glinoer, M.D.; Ph.D.)

See Figure below