Clinical THYROIDOLOGY
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Will Stem Cell Autotransplants Be Clinically Effective for Treating Some Causes of Hypothyroidism?

Antonica F, Kasprzyk DF, Opitz R, Iacovino M, Liao X-H, Dumitrescu AM, Refetoff S, Peremans K, Manto M, Kyba M, Costagliola S. Generation of functional thyroid from embryonic stem cells. Nature. October 10, 2012 [Epub ahead of print]. doi:10.1038/nature11525.

SUMMARY

Background

Embryonic stem-cell research has a translational goal of replacing the function of defective or destroyed organs. Dozens of genes are specifically enriched in the cell bud that forms in the floor of the embryonic pharynx and develops into the thyroid gland (1). A number of research groups have tested various combinations of intrinsic and extrinsic factors on stem-cell preparations in attempts to find which are necessary and sufficient for thyroidogenesis. This exciting report from an international collaboration between several labs now provides a specific combination of factors and exposure times that promotes functional thyroid tissue in hypothyroid mice, and seems to hold promise for the development of human thyroid autotransplants in the future.

Methods

Mouse embryonic stem cells were engineered to overexpress two transcription factors: PAX8 and NKX2-1 (also called TTF-1) only when doxycycline was added to the culture medium. The cells were cultured in hanging drops for 4 days to differentiate into embryoid bodies, which were grown in Matrigel; doxycycline was then added. After various times, mRNA from treated embryoid bodies was tested for Foxe1, (another transcription factor needed for thyroid development), TSH receptor, sodium/iodide symporter (NIS), and thyroglobulin mRNA; the histology of embryoid bodies was also examined.

Results

All of the mRNAs mentioned above were detected, and of particular interest, prominent autocrine production of endogenous Nkx2-1 and Pax8 was also seen, but the cells did not form follicular structures. However, if the doxycycline treatment was limited to days 4 to 6, and then TSH was added, the cells formed three-dimensional structures resembling follicles by 21 days. These cells expressed NIS and e-cadherin on the basolateral side of the follicles, and they also iodinated thyroglobulin. These follicle-like organoids were then grafted under the kidney capsule of hypothyroid mice. Within a month, the grafts had formed a network of small vessels, and the mean serum level of thyroxine in the mice rose, TSH fell, and the body temperature of the mice normalized.

Conclusions

Transient overexpression of the transcription factors NKX2-1 and PAX8 in cultured mouse embryonic stem cells, followed by TSH stimulation for several weeks, caused differentiation into thyroid follicular cells that formed functional thyroid tissue in hypothyroid mice.

ANALYSIS AND COMMENTARY

Obtaining human-induced stem cells is not yet a routine procedure, and there is no guarantee that the specific method described for mouse embryonic stem cells will work, but eventually a way to reprogram pluripotent stem cells obtained from a patient's skin will probably be found. True, clinical trials are not just around the corner, but someday thyroid autotransplants will become available. It seems time to start mulling over clinical questions. For example, congenital thyroid dysgenesis is a common problem, but few causative mutations have been identified.

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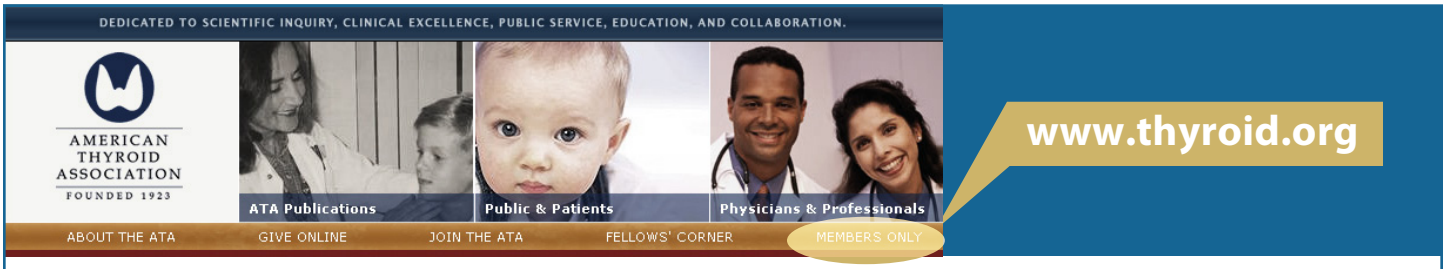
Would pluripotent stem cells from these patients remain defective in differentiating into thyroid tissue, or would epigenetic programming be reset so that thyrocyte precursors would survive and develop normally? If a patient who had a total thyroidectomy for cancer were to be given a thyroid autograft, would the new thyroid develop the same cancer? Would patients previously treated for Hashimoto's or Graves' disease who received thyroid autografts have recurrent disease? These will be fascinating questions to answer in the coming era of genetic engineering of stem cells so that they produce specific organs, as pioneered by this year's two winners of the Nobel Prize in Physiology or Medicine, John B. Gurdon and Shinya Yamanaka.

— Stephen W. Spaulding, MD

Reference

1. Fagman H, Amendola E, Parrillo L, Zoppoli P, Marotta P, Scarfò M, De Luca P, de Carvalho DP, Ceccarelli M, De Felice M, Di Lauro R. Gene expression profiling at early organogenesis reveals both common and diverse mechanisms in foregut patterning. Dev Biol 2011;359:163-75. Epub September 1, 2011; doi: 10.1016/j.ydbio.2011.08.015.



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