Nature Reviews Endocrinology | Published online 10 November 2015; doi:10.1038/nrendo.2015.193

THYROID FUNCTION

Differentiated pluripotent stem cells restore thyroid function

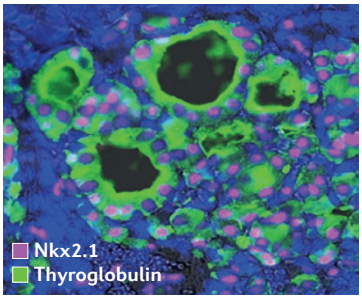
Functional human thyroid cells can be generated from patient-derived induced pluripotent stem cells, according to findings reported in *Cell Stem Cell*. Furthermore, the research team showed that in a mouse model of hypothyroidism, thyroid function is restored by transplantation of mouse thyroid cells generated using this technique.

Pluripotent stem cells have been used to derive several cell lineages, yet a lack of knowledge of the mechanisms that regulate early thyroid development has precluded the derivation of mature thyroid cells without forcibly overexpressing transcription factors. The researchers had previously shown that a cocktail of factors could induce mouse pluripotent stem cells to form endoderm progenitor cells expressing homeobox protein Nkx-2.1, a protein expressed only in lung or thyroid epithelia within endoderm-derived tissue. Although these progenitor cells expressed thyroid-specific genes, they did not become fully mature thyroid cells; the researchers aimed to address this problem in a new study.

In this paper, the team report that a combination of the growth factors FGF2 and BMP4 in the growth media was sufficient to induce thyroid fate. Mouse or *Xenopus* embryos exposed to inhibitors of BMP or FGF signalling showed markedly reduced specification of thyroid progenitor cells. Culturing thyroid progenitor cells in a 3D culture system with a cocktail of thyroid maturation factors resulted in stable expression of thyroid-specific genes and the formation of follicular-like cell clusters, or organoids. Importantly, the organoids were capable of organification (incorporation of iodine into thyroglobulin) and the production of small amounts of T_4.

Next, the investigators transplanted either undifferentiated stem cells or thyroid follicular organoids into a mouse model of hypothyroidism. 8 weeks after surgery, circulating levels of T_3 and T_4 in the mice that received thyroid follicular organoids were similar to levels observed in normal mice. By contrast, mice with hypothyroidism that received only undifferentiated stem cells showed no improvement in levels of thyroid hormones.

"These findings then gave us confidence that the same growth factors might accomplish the goal of engineering human thyroid progenitors ... from the stem cells made from patients," says author Darrell Kotton. Induced pluripotent stem cells were generated from dermal fibroblasts obtained from children with hypothyroidism and cultured with BMP4 and FGF2, resulting in thyroid progenitor cells. "When human induced pluripotent stem cells were cultured using the same growth factors used to differentiate mouse thyroid progenitors, we found robust expression of thyroid differentiation and maturation markers," says co-author Maria Serra.



Immunofluorescence micrograph of transplanted thyroid follicles. Image courtesy of D. Kotton.

"Although there are good drugs available to replace thyroid function, we can now envision a way children or adults might ... receive sustained rescue of their thyroid function by transplanting their own thyroid cells regenerated in the laboratory from cells made by reprogramming their skin or blood cells," concludes co-author Anthony Hollenberg.

Hugh Thomas

ORIGINAL ARTICLE Kurmann, A. A. *et al.* Regeneration of thyroid function by transplantation of differentiated pluripotent stem cells. *Cell Stem Cell* **17**, 1-16 (2015)