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Development of a functional thyroid model based on an organoid culture system

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ABSTRACT

The low turnover rate of thyroid follicular cells and the lack of a long-term thyroid cell culture system have hampered studies of thyroid carcinogenesis. We have now established a thyroid organoid culture system that supports thyroid cell proliferation in vitro. The established mouse thyroid organoids performed thyroid functions including thyroglobulin synthesis, iodide uptake, and the production and release of thyroid hormone. Furthermore, transplantation of the organoids into recipient mice resulted in the formation of normal thyroid–like tissue capable of iodide uptake and thyroglobulin production in vivo. Finally, forced expression of oncogenic NRAS ($NRAS^{Q61R}$) in thyroid organoids established from p53 knockout mice and transplantation of the manipulated organoids into mouse recipients generated a model of poorly differentiated thyroid cancer. Our findings suggest that this newly developed thyroid organoid culture system is a potential research tool for the study of thyroid physiology and pathology including thyroid cancer.

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1. Introduction

Mammalian thyroid follicular cells have an intrinsically low turnover rate (about five renewals per lifetime in human) [1,2], which has presented a challenge to the long-term culture and propagation of such primary cells. A long-term culture system for stem cells of the small intestine or colon has been developed in which single stem cells derived from an organ digest form stereotypic organoid structures [3–5]. In this organoid culture system, the tissue stem cells are able to replicate and to generate differentiated cells in the presence of specific niche factors. Organoid culture protocols have also been established for several additional organs including the stomach [6], esophagus [7], pancreas [8], liver [9], and prostate [10,11], but not for the thyroid. Given that the characteristics of thyroid stem cells have remained largely unknown [2,12,13], the establishment of thyroid organoids containing such cells might prove useful for their characterization. The presence of highly proliferative thyroid stem cells in an organoid might also be beneficial for gene transfer experiments focused on exploration of thyroid physiology or pathology.

Tumors derived from thyroid follicular cells include papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), poorly differentiated thyroid cancer (PDTC), and anaplastic thyroid cancer (ATC) [2]. Differentiated thyroid cancers (DTCs) including PTC and FTC are slow-growing tumors with 10-year relative survival rates of 93% and 85%, respectively [14]. In contrast, the 10-year survival rate of

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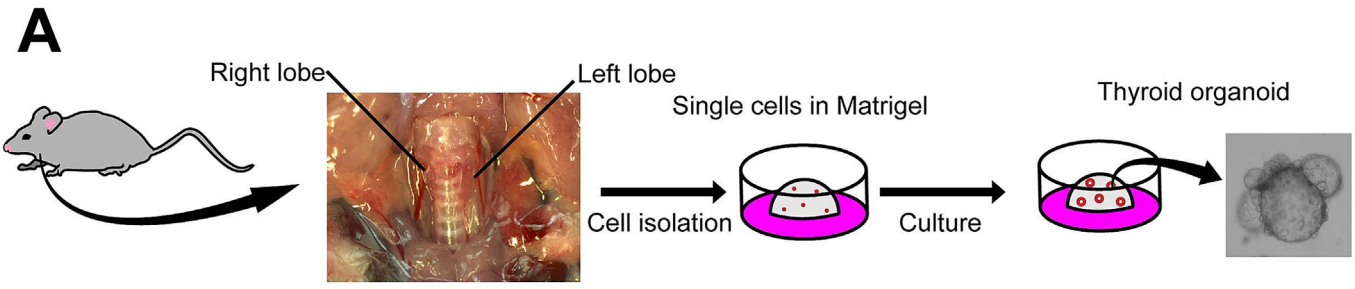
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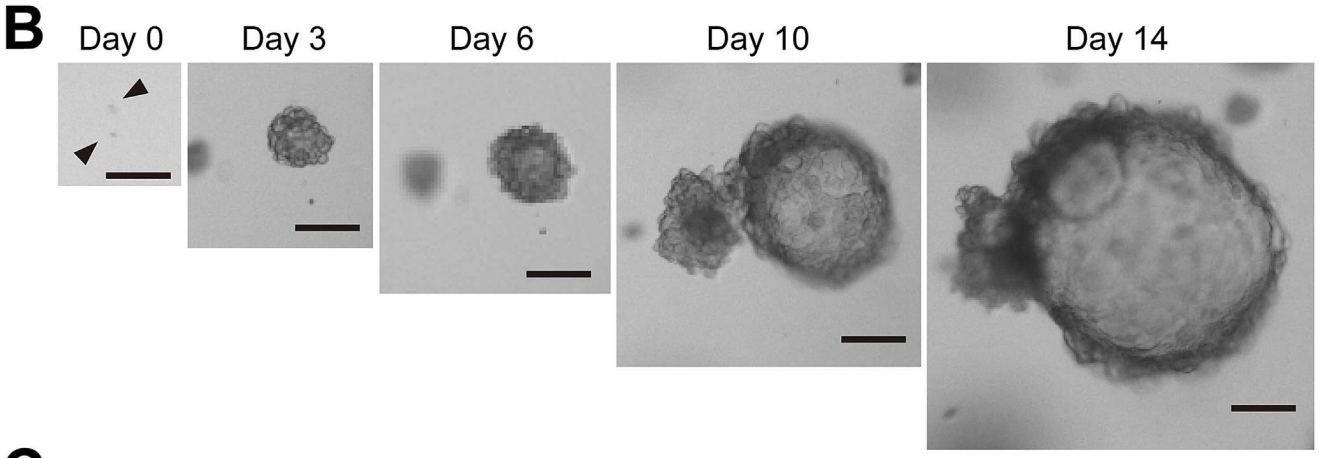
Left lobe
Single cells in Matrigel
Thyroid organoid
Cell isolation
Culture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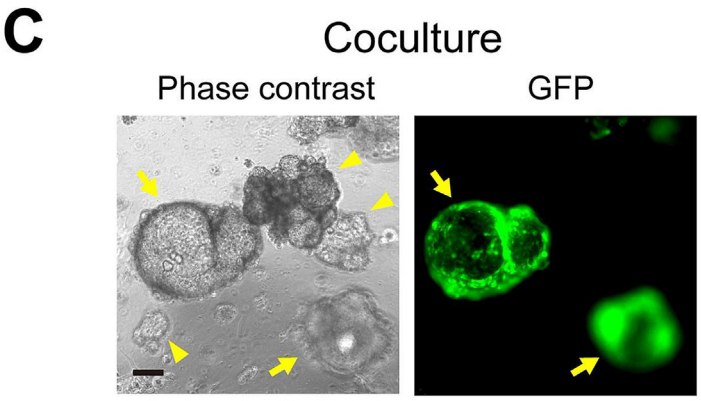
Day 14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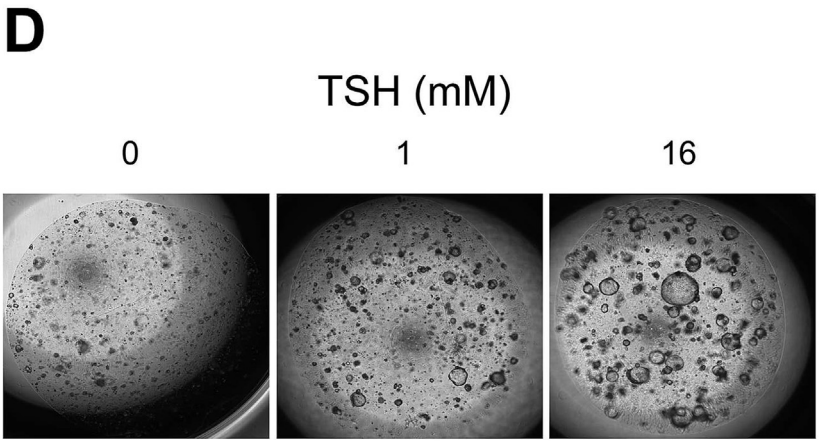
GFP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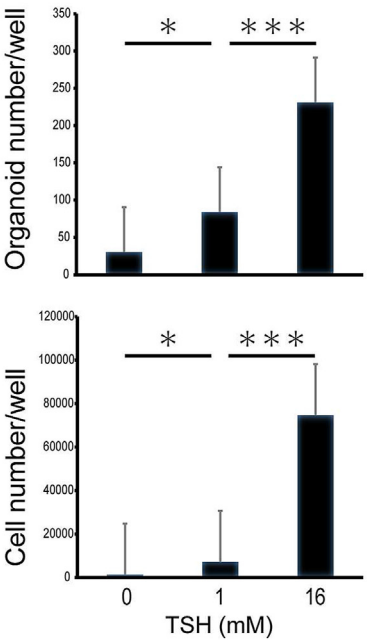
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Cell number/well
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16
TSH (mM)

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