Growth regulation in thyroid development
Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Ragnar Sandberg, Medicinaregatan 7A, torsdagen den 24 maj 2018, klockan 9.00

av Shawn Liang

Fakultetsopponent:
Professor Christophe Pierreux
Université Catholique de Louvain, Belgien

Avhandlingen baseras på följande delarbeten


II. Liang S, Fagman H, Nilsson M. Thyroid developmental growth depends on Fgf10 gene dosage. Manuscript

III. Liang S, Moccia C, Fagman H, Nilsson M. Mutant Braf (Braf^{v600e}) accelerates embryonic thyroid growth without interfering with glandular morphogenesis and de novo thyroid differentiation. Manuscript
Growth regulation in thyroid development

Shawn Liang

Sahlgrenska Cancer Center

Department of Medical Biochemistry and Cell Biology, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Abstract

The fundamental aspects of developmental mechanisms that regulate embryonic and postnatal thyroid growth gaining the final size of the gland are still largely undetermined. In embryonic development, various organs and glands are composed of branched structures, designed to maximize efficiency and function. Branching morphogenesis is the developmental process that gives rise to these multicellular tubular networks. This growth process, which involves a range of paracrine and cell-autonomous factors including Fgf10 and Sox9, are utilized by the lung and numerous exocrine glands. In thyroid, an endocrine gland, postnatal growth involving thyroid stimulating hormone (TSH) from the pituitary differs to embryonic growth, which is TSH independent and thus rely on local factors of yet unknown identity. This thesis investigates thyroid growth regulation by Fgf10, Sox9, Shh and mutant Braf in normal (wildtype) and genetically modified mice engineered to constitutively or conditionally delete or express the targeted genes of interest.

In paper I, we show that branching morphogenesis is a key process in glandular development of the embryonic thyroid. Sox9, Fgfr2b and Ki-67 are co-expressed at distal tips of branching epithelial buds. Mesenchymal Fgf10 is crucial for embryonic thyroid growth. The Fgf10⁻/⁻ mutant thyroid has a normal anatomical shape and uninterrupted functional differentiation but is severely hypoplastic due to defective branching. These findings uncover a novel mechanism of thyroid development in which branching growth generated by reciprocal mesenchymal-epithelial interactions determines final organ size.

Paper II investigates postnatal thyroid growth regulation. This identified growth retardation comprising reduced numbers of Ki-67⁺ proliferating cells in the thyroid of Fgf10⁻/⁻ mutant mice. Thyroid growth is rescued postnatally in Fgf10⁻/⁻;Shh⁻/⁻ double mutant animals, suggesting Shh regulation over Fgf10 signalling. This demonstrates for the first time gene dosage dependent regulation of postnatal thyroid growth accomplished through reciprocal interactions between Fgf10 and Shh signalling pathways.

In Paper III, we examine effects of conditionally expressed Brafᵀᴱᴼᴼᴼₑ oncprotein in Nkx2-1⁺ progenitors on growth and differentiation of the embryonic thyroid. Constitutive activation of MAPK pathway by mutant Braf in thyroid progenitors lead to a global growth response and a 4-fold increase in thyroid size at birth, however without disturbing the natural morphogenesis to a bilobed gland or the differentiation into functional follicular cells. Thyroid specific gene analysis confirmed expression of Tg, Nis, Tpo, Tshr and Pax8, suggesting capability of iodination and thyroid hormone production in mutant embryonic cells. These results indicate that mechanisms of de novo thyroid differentiation in mouse embryos resist dedifferentiation as regularly observed in MAPK-activated adult thyroid cells. A potential clinical importance of this novel finding relies on the fact that thyroid tumour cells carrying BRAFᵀᴱᴼᴼᴼₑ mutation are insensitive to radioiodine treatment due to repressed thyroid gene expression.

Keywords: Thyroid, growth regulation, branching morphogenesis, Fgf10, Sox9, Shh, Brafᵀᴱᴼᴼᴼₑ