ABSTRACT

TRANSCRIPTIONAL REGULATION OF THYROID DEVELOPMENT:

POSSIBLE INTERPLAY OF ENDODERM- AND MESODERM-DERIVED MORPHOGENETIC SIGNALS

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Congenital hypothyroidism (CH) affects 1 in 3000 children and is the major cause of treatable mental retardation. Most cases are due to malformations of the gland, collectively named thyroid dysgenesis. The disease results from defective thyroid organogenesis during embryonic life. However, the molecular mechanisms of pathogenesis are largely unknown. In recent years, identification and functional analysis of thyroid developmental genes in murine models have indicated that both cell-autonomous and non-cell-autonomous mechanisms, involving the thyroid progenitors themselves and the surrounding embryonic tissues, respectively, are of importance. In this thesis, four important morphogenetic regulatory molecules were investigated for novel putative functions in mouse thyroid development.

In paper I, the thyroid expression and function of the T-box transcription factor Tbx1 were examined in wild-type and *Tbx1* null mutant mouse embryos. Tbx1 immunoreactivty was present in the splanchic mesoderm adjacent to the thyroid but not in the thyroid progenitors. The thyroid of *Tbx1* deficient embryos was severely dysplastic resembling hemiagenesis and lacked C-cellls. It was further evidenced that the *Tbx1-/-* thyroid phenotype was related to delayed budding and failure of the disclosed thyroid rudiment to establish contact with embryonic vessels of the cardiac outflow tract.

The LIM homeodomain transcription factor Isl1 was found to be expressed in both thyroid progenitors and surrounding mesenchyme (paper II). The Isl1 expression pattern was altered in a distinct spatiotemporal manner during the different developmental steps (budding, migration and fusion of the thyroid primordia). However, thyroid specification was not affected in *Isl1* null mutants. In late development Isl1 identified the C-cell precursors, but Isl1 was largely down-regulated in mature adult C-cells. In addition, *Isl1* transcript was detected in human medullary thyroid cancer.

In paper III, the forkhead transcription factor Foxa2 was found to be an embryonic marker of pharyngeal endoderm, lateral thyroid anlagen (ultimobranchial bodies) and C-cells. The Foxa2 expression was maintained in adult C-cells. However, Foxa2 was specifically excluded from the follicular progenitors in the median thyroid bud, and was not expressed in the thyroid follicles.

Foxa2 and calcitonin expression were employed to investigate the origin and fate of C-cell precursors in mouse embryos deficient of the secreted morphogen Sonic hedgehog (Shh) (paper IV). This showed that C-cell precursors did not colonize the embryonic thyroid but were aberrantly located in the pharyngeal endoderm and other endoderm derivatives. The *Shh-/-* phenotype was linked to impaired fusion of thyroid primordia, primarily caused by failure of the ultimobranchial bodies to bud from the fourth pharyngeal pouch. Paper IV also revealed that genetically fate mapped *Shh* expressing endoderm progenitors were largely excluded from the thyroid primordia. However, Shh was neo-expressed in a subset of follicular progenitors in late development of the prospective thyroid lobes.

Taken together, the results of this thesis identify Tbx1 and Shh as novel regulators of mammalian thyroid organogenesis. This is likely manufactured in part by morphogenetic mechanisms superimposing on the development of the entire pharyngeal apparatus and also cell-autonomous regulatory networks. Isl1 and Foxa2 are proven to be novel embryonic markers of C-cell precursors. Collectively, the data support the hypothesis of an endoderm origin of mouse thyroid C-cells.

Key words: thyroid, congenital hypothyroidism, dysgenesis, Tbx1, Shh, Isl1, Foxa2, C-cells.
ISBN: 978-91-628-7558-9

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AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Göteborgs universitet kommer att offentligen försvaras i hörsal ” Arvid Carlsson”, Academicum, Medicinaregatan 3, Göteborg, fredag den 31 oktober, klockan 09.00

av

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Fakultetsopponent: Professor Gijs Van Den Brink, Leiden, Nederländerna

Avhandlingen baseras på följande delarbeten:

I. **Fagman H*, Liao J*, Westerlund J*, Andersson L, Morrow BE, Nilsson M.** The 22q11 deletion syndrome candidate gene Tbx1 determines thyroid size and positioning.
Human Molecular Genetics. 2007 Feb1; 16(3):276-85.
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II. **Westerlund J, Andersson L, Carlsson T, Zoppoli P, Fagman H, Nilsson M**. Expression of Islet1 in thyroid development related to budding, migration and fusion of primordia.
Developmental Dynamics (in press).

III. **Westerlund J*, Andersson L*, Carlsson T, Fagman H, Nilsson M.** Foxa family members mark embryonic progenitor cells differentiating into C-cells in the developing thyroid gland.
Manuscript.
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IV. **Westerlund J, Andersson L, Carlsson T, Fagman H, Nilsson M.** Sonic hedgehog regulates the fusion of midline and lateral embryonic thyroid primordia and entry of C-cell precursors to the thyroid gland.
Manuscript.

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