EMBRYONIC ORIGIN AND DEVELOPMENT OF THYROID PROGENITOR CELLS

An experimental study focused on endoderm, EphA4 and Foxa2

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademien vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson Medicinaregatan 3, Göteborg, fredagen den 4:e juni 2010 kl. 09:00

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Avhandlingen baseras på följande delarbeten;

I. **Fagman H, Andersson L and Nilsson M**.
The developing mouse thyroid: embryonic vessel contacts and parenchymal growth pattern during specification, budding, migration, and lobulation.
Dev Dyn. 2006 Feb;235(2):444-55

II. **Andersson L*, Westerlund J*, Carlsson T, Lania G, Baldini A, Fagman H and Nilsson M**
Foxa2 expressing mouse embryonic C-cells originate from progenitors in the foregut endoderm
Manuscript
* contributed equally to the study

III. **Andersson L, Westerlund J, Carlsson T, Amendola E, Fagman H and Nilsson M**
Role of EphA4 forward signaling in thyroid development: Embryonic expression pattern and regulation of folliculogenesis and C-cell lineage expansion
Endocrinology (*Accepted*)

IV. **Andersson L, Liang S, Carlsson T, Liao X, Weiss R.E and Nilsson M** Impaired thyroid growth in *EphA4* deficient mice in an experimental goitrogenesis model
Manuscript

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ABSTRACT

EMBRYONIC ORIGIN AND DEVELOPMENT OF THYROID PROGENITOR CELLS

An experimental study focused on endoderm, EphA4 and Foxa2

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The thyroid gland consists of two endocrine cell types, the follicular cells that produce the thyroid hormones T3 and T4 and the parafollicular C-cells that synthesize calcitonin. It is well-known that these cells have different embryonic origin, although details of their specification and development during organogenesis are still largely lacking. Tumors arising from the two cell types are distinct entities with different treatment and prognosis.

In paper I mouse thyroid morphogenesis was investigated to provide a detailed map of the different stages: specification and placode formation (Embryonic day 8.5-9.5), budding (E10.5), migration (E11.5), fusion and bilobation (E13.5), and eventually differentiation (E15.5 and onwards). Special interest was paid to patterns of proliferation of progenitor cells and relationship to embryonic vessels in the neck. Results of this study formed a platform for further investigation in papers II-IV.

Paper II was designed to investigate by genetic and biochemical tracing of cells expressing T-box (Tbx1) and forkhead (Foxa1 and Foxa2) transcription factors the germ layer origin of C-cell precursors. This showed that mouse C-cells in all probability arise from the pharyngeal endoderm, at difference with the prevailing concept of a neural crest origin originally identified for birds. Microarray analysis indicates that Foxa2 is a novel marker of human medullary thyroid carcinoma cells.

Paper III and IV identified the EphA4 receptor as a novel modulator of follicular and C-cell proliferation in post-natal life. The effect on the C-cell lineage was obviously cell non-autonomous as EphA4 was expressed only in the follicular cells. EphA4 was further found to be expressed in the embryonic thyroid in a distinct spatiotemporal pattern, although no thyroid malformation was detected in *EphA4* null embryos presumably due to redundant functions of other Eph receptors. The cognate ephrin ligands interacting with EphA4 in the thyroid awaits to be identified.

Key words: thyroid, C-cells, Tbx1, Foxa1, Foxa2, EphA4, neural crest, endoderm

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