Origins of thyroid progenitors and tumor-initiating cells

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av **Ellen Johansson**

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Avhandlingen baseras på följande delarbeten

I. Ellen Johansson, Louise Andersson, Jessica Örnros, Therese Carlsson, Camilla Ingeson-Carlsson, Shawn Liang, Jakob Dahlberg, Svante Jansson, Luca Parrillo, Pietro Zoppoli, Guillermo O Barilla, Daniel L Altschuler, Daniela Padula, Heiko Lickert, Henrik Fagman, Mikael Nilsson
Revising the embryonic origin of thyroid C cells in mice and humans
Development 2015(142):3519-3528

II. Ellen Johansson, Shawn Liang, Henrik Fagman, Pina Marotta, Mario De Felice, Bengt R Johansson, Mikael Nilsson
Guidance of parafollicular cells (C cells) to the embryonic thyroid involves remodeling of basement membrane
Manuscript

III. Elin Schoultz, Ellen Johansson, Iva Jakubikova, Shawn Liang, Therese Carlsson, Bengt R Johansson, Henrik Fagman, Konrad Patyra, Jukka Kero, Martin Bergö, Mikael Nilsson
Follicular origin of tumor heterogeneity in a mouse model of sporadic papillary thyroid cancer
Manuscript

IV. Ellen Johansson, Carmen Moccia, Henrik Fagman, Mikael Nilsson
Tracing tumor-initiating cells in Braf^{V600E}-induced thyroid cancer
Manuscript

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Origins of thyroid progenitors and tumor-initiating cells

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Abstract

The thyroid gland located in the anterior neck consists of two main cell types. First, the follicular cells that form the functional units, the follicles, in which thyroid hormones are produced and stored before release into the blood circulation; second, the parafollicular cells or C cells that produce calcitonin, a hormone that takes part in calcium regulation. These two cell types can give rise to different forms of cancer. Understanding basic mechanisms that govern the development and differentiation in the embryo may shed light on cell-specific mechanisms in tumor development.

In non-mammalian vertebrates neuroendocrine C cells retain in the ultimobranchial glands instead of being incorporated into the thyroid. Early quail-chick transplantation studies indicated that the C cells derive from the neural crest (i.e. are neuroectodermal), but this was not confirmed in mammals. In paper I, lineage tracing using a double fluorescent reporter (mTmG) showed that thyroid C cells in mouse embryos derive from pharyngeal endoderm instead of the neural crest. It was further shown that endoderm markers (Foxa1 and Foxa2) are dynamically regulated in invasive medullary thyroid carcinomas in humans. The actual entry of C cell precursors into the embryonic thyroid was investigated in paper II. Immunofluorescence and ultrastructural analysis with transmission electron microscopy indicated that the basement membrane of the ultimobranchial bodies is degraded before fusing with the thyroid primordium and that the process required Nkx2-1, a thyroid transcription factor. This suggested that migration and final parafollicular positioning of thyroid C cells is intrinsically regulated during development.

In paper III, we modified an inducible mouse model of papillary thyroid cancer (the most common type of thyroid cancer). This mouse model is based on the Cre/loxP-system in which a $Braf^{V600E}$ mutation (constitutively activating the MAPK pathway) is conditionally activated only in thyroid follicular cells upon induction with tamoxifen. We discovered occurrence of sporadic Cre activity in the absence of tamoxifen and that microtumors developed clonally with functionally normal thyroid follicles side by side. Eventually, multifocal papillary thyroid carcinomas of different phenotypes (classical, tall-cell, hobnail, cystic and solid variants) developed within the same gland. Thus, this model enabled the detailed study of different stages in tumor development under conditions that closely resemble tumor development in humans. In paper IV, TgCre;$Braf^{V600E}$ mice were recombined with the mTmG reporter to trace mutant cells before overt tumorigenesis. A great diversity in proliferation rate among primary GFP-labeled cells that rarely developed into microtumors suggested the possibility of oncogene-induced senescence. Treatment with vemurafenib, a specific inhibitor of mutant Braf, inhibited focal tumorigenesis at an early stage, suggesting feasibility of the model in drug testing.

Keywords: Thyroid gland, thyroid cancer, mouse model, developmental biology, lineage tracing

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