Göteborg 2022

ReCREating BRAF-driven thyroid and lung cancer in mice

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Ivarsson, Medicinaregatan 3, den 8 juni 2022, klockan 9.00

av **Elin Schoultz**

Fakultetsopponent:

Christopher J. McCabe,
Professor of Molecular Endocrinology, Institute of Metabolism and Systems Research
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Avhandlingen baseras på följande delarbeten

I. **Elin Schoultz**, Ellen Johansson, Carmen Moccia, Iva Jakubikova, Naveen Ravi, Shawn Liang, Therese Carlsson, Mikael Montelius, Konrad Patyra, Jukka Kero, Kajsa Paulsson, Henrik Fagman, Martin O Bergö, Mikael Nilsson.
Tissue architecture delineates field cancerization in BRAF^{V600E}-induced tumor development. *Disease Models & Mechanisms 2022 Feb1;15(2)*

II. **Elin Schoultz**, Shawn Liang, Therese Carlsson, Stefan Filges, Anders Ståhlberg, Henrik Fagman, Clotilde Wiel, Volkan Sayin, Mikael Nilsson.
Stochastic oncogene targeting of *Nkx2.1*-lineage cells differentially recapitulates BRAF-driven tumor development and progression in lung and thyroid. *Manuscript*

III. **Elin Schoultz**, Carmen Moccia, Thomas Ramo, Therese Carlsson, Mikael Montelius, Henrik Fagman, Martin O Bergö, Mikael Nilsson.
Sex bias of BRAF-inhibitor therapy in mice with papillary thyroid cancer. *Manuscript*

IV. **Elin Schoultz**, Thomas Ramo, Carmen Moccia, Mikael Nilsson.
Heterogeneity of a BRAF^{V600E}-induced cancer inflammation in a mouse model of sporadic thyroid tumorigenesis. *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

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ReCREating BRAF-driven thyroid and lung cancer in mice

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Abstract

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer with a 3:1 female/male incidence. PTC is caused by oncogenic *BRAF* mutation encoding $BRAF^{V600E}$ in 50% of cases. Prognosis is mostly excellent with surgery and radioiodine therapy, but 15% of PTC patients with clinical tumors die of the disease. Transgenic mouse models are invaluable tools in dissecting the mechanisms of thyroid tumor progression, and to monitor novel targeted drug treatments *in vivo*. Conditional expression of $BRAF^{V600E}$ using a thyroid specific Cre driver, e.g. the thyroglobulin (*Tg*) promoter, can be used to activate mutant Braf ($Braf^{CA}$) specifically in the thyroid and with temporal control using tamoxifen-inducible Cre. However, an inborn problem with this procedure is that nearly all thyroid cells are synchronously oncogene-activated. This causes hypothyroidism and unphysiologically high levels of circulating TSH that is goitrogenic, making it difficult to investigate tumor clonality confounded by reactive hyperplasia. In paper I, we developed a new PTC model based on stochastic BRAF activation (due to spontaneous Cre activity in the absence of tamoxifen) by which tumors developed in a normal microenvironment and with maintained systemic thyroid function. Originating from a single follicle, individual tumors had different histologic phenotypes and were initially oligoclonal identified by lineage tracing. We applied this model in paper III to evaluate drug responses to a BRAF-inhibitor (a vemurafenib analog) and found that female mutant mice recovered poorer in thyroid gene expression (*Slc5a5* and *Tshr*) than males and developed larger tumors that progressed more with long-term drug treatment. Analysis of cytokine expression in paper IV revealed differential cytokine expression indicating tumor heterogeneity distinguished by level of inflammation, and that the tumor cells themselves secreted cytokines (IL-1β, IL-6 and TNF-α) in early tumor development. Finally, we confirmed that targeted oncogene activation without induction can generate sporadic tumorigenesis in other tissues. In paper II, using *Nkx2.1*, a transcription factor shared by thyroid and lung, as Cre driver, mutant BRAF independently caused both thyroid and non-small cell lung carcinomas with different growth and progression features consistent with modulation of oncogene activity in an organ-specific fashion. This represents the first mouse model in which lung adenomas progress to adenocarcinomas due to BRAF mutation.

Keywords: Thyroid cancer, BRAF mutation, transgenic models, clonal tracing, BRAF inhibitor, sex differences, lung cancer

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