

NOVEL BIOMARKERS ASSOCIATED WITH HISTOTYPE AND CLINICAL OUTCOME IN EARLY-STAGE OVARIAN CARCINOMA

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, den 7 maj 2020, kl. 9.00

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Avhandlingen baseras på följande delarbeten

- I. **Engqvist H**, Parris TZ, Werner Rönnerman E, Söderberg E, Biermann J, Mateoiu C, Sundfeldt K, Kovács A, Karlsson P, Helou K. Transcriptomic and genomic profiling of early-stage ovarian carcinomas associated with histotype and overall survival. *Oncotarget* (2018).
- II. **Engqvist H**, Parris TZ, Kovács A, Nemes S, Werner Rönnerman E, De Lara S, Biermann J, Sundfeldt K, Karlsson P, Helou K. Immunohistochemical validation of COL3A1, GPR158 and PITHD1 as prognostic biomarkers in early-stage ovarian carcinomas. *BMC Cancer* (2019).
- III. **Engqvist H**, Parris TZ, Kovács A, Werner Rönnerman E, Sundfeldt K, Karlsson P, Helou K. Validation of novel prognostic biomarkers for early-stage clear-cell, endometrioid and mucinous ovarian carcinomas using immunohistochemistry. *Frontiers in Oncology*, section Women's Cancer (2020).
- IV. **Engqvist H**, Parris TZ, Biermann J, Werner Rönnerman E, Larsson P, Sundfeldt K, Kovács A, Karlsson P, Helou K. Integrative genomics approach identifies molecular features associated with early-stage ovarian carcinoma histotypes. Submitted (2020).

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Abstract

Ovarian cancer is a collective name for multiple malignancies deriving from or involving the ovary, mainly comprising five histotypes of epithelial origin (clear-cell (CCC), endometrioid (EC), high-grade serous (HGSC), low-grade serous (LGSC), and mucinous carcinomas (MC)) with varying clinical (*e.g.* risk factors, survival outcome, response to therapy) and molecular behavior (*e.g.* origin, genetic characteristics). Despite known differences in disease states, the majority of ovarian carcinomas are still treated as one entity with surgery, followed by chemotherapy. This treatment regimen is not adequate, which is reflected in relatively poor 5-year overall survival rates (55%) for ovarian cancer patients. Hence, there is a strong need for novel biomarkers for improved stratification of ovarian carcinoma patients based on a combination of individual molecular tumor characteristics and conventional clinicopathological features, which can further form the basis for the future development of novel targeted treatment options for ovarian cancer histotypes.

This doctoral thesis focuses on early-stage (stage I and II) ovarian carcinomas for which limited information is available regarding molecular profiles associated with the diagnosis and prognosis of the different histotypes. In the first work, novel mutation and gene signatures were associated with histotype, overall survival (*e.g.* the tumor suppressor *MTUS1*), ovarian cancer (*e.g.* gene expression patterns for the long non-coding RNA *MALAT1*), and tumor aggressiveness (*e.g.* *COL3A1*). In the second and third works, histotype-specific prognostic gene signatures were validated on the protein level using immunohistochemistry identifying 20 prognostic biomarkers (11 CCC-associated biomarkers (ARPC2, CCT5, GNB1, KCTD10, NUP155, PITHD1, RPL13A, RPL37, SETD3, SMYD2, and TRIO), three EC-associated biomarkers (CECR1, KIF26B, and PIK3CA), five MC-associated biomarkers (CHEK1, FOXM1, GPR158, KIF23, and PARPBP), and *COL3A1* for the main histotypes). In the fourth work, a multi-omics approach (genome- and transcriptome-wide analyses) integrating DNA methylation, DNA copy number alteration, and RNA sequencing data was applied to identify novel putative oncogenes and tumor suppressor genes associated with the CCC, EC, HGSC and MC histotypes.

Taken together, the current doctoral thesis presents novel insights into molecular features associated with early-stage ovarian carcinoma that may improve patient stratification and subclassification based on histotype and clinical outcome.

Keywords: ovarian carcinoma, histotype-specific diagnosis and prognosis, molecular biomarker, outcome prediction, integrative analysis