Göteborg, 2022

Studies of molecular features and novel prognostic biomarkers of cutaneous melanoma

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Åke Göransson, Medicinaregatan 11, den 14 december 2022, klockan 9:00

av **Iva Johansson**

Fakultetsopponent:
Docent Johan Botling
Uppsala Universitet, Uppsala, Sverige

Avhandlingen baseras på följande delarbeten

I. Sanna A, Harbst K, **Johansson I**, Christensen G, Lauss M, Mitra S, Rosengren F, Hakkinen J, Vallon-Christersson J, Olsson H, Ingvar A, Isaksson K, Ingvar C, Nielsen K, Jonsson G. Tumor genetic heterogeneity analysis of chronic sun-damaged melanoma. Pigment Cell Melanoma Res 2020;33(3): 480-489.

II. **Johansson I**, Tempel D, Dwarkasing JT, Rentroia-Pacheco B, Mattsson J, Ny L, Olofsson Bagge R.Validation of a clinicopathological and gene expression profile model to identify patients with cutaneous melanoma where sentinel lymph node biopsy is unnecessary. Eur J Surg Oncol. 2022 Feb;48(2):320-325.

III. Mulder EEAP*, **Johansson I***, Grünhagen DJ, Tempel D, Rentroia-Pacheco B, Dwarkasing JT, Verver D, Mooyaart AL, van der Veldt AAM, Wakkee M, Nijsten TEC, Verhoef C, Mattsson J, Ny L, Hollestein LM*, Olofsson Bagge R*. Using a Clinicopathologic and Gene Expression (CP-GEP) Model to Identify Stage I-II Melanoma Patients at Risk of Disease Relapse. Cancers (Basel). 2022 Jun 9;14(12):2854.

IV. **Johansson I**, Arheden A, Jespersen H, Carstam L, Matsson J, Akyürek L, Olofsson BaggeR, Ny L. Presence of CD8+ and CD20+ lymphocytes and tertiary lymphoid structures in the invasion zone of primary cutaneous melanoma and the association to brain metastasis. Manuscript.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Studies of molecular features and novel prognostic biomarkers of cutaneous melanoma

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Abstract

Cutaneous malignant melanoma is a highly heterogeneous disease. Immunotherapy has revolutionized the treatment of stage IV disease and is now successfully administered as adjuvant treatment in stage III and soon in stage II. Correct identification of the patients at high risk for progressive disease who will benefit from the treatment is crucial. Important prognostic features in the early phase of the disease are to be found within the primary tumor and sentinel lymph node, but plenty is still to be investigated. Sentinel lymph node biopsy (SLNB) status is one of the independent prognostic factors guiding treatment decisions, but not without controversy. Approximately 80% of the SLNB are negative, contrasting to a wide range of prognosis in node-negative patients.

In **paper I,** we explored the molecular features of melanoma arising in chronic sun-damage skin, proving that this type of melanoma is a distinct molecular entity with a different progression compared to the more common melanoma in intermittently sun-exposed skin.

In **papers II and III**, we evaluated a novel non-invasive prognostic test to be utilized in primary cutaneous melanoma. In our investigation, the CP-GEP test was able to safely identify the patients where the sentinel lymph node biopsy is unnecessary. The same CP-GEP test was able to stratify the patients with high and low risk of disease progression, but the test algorithm still needs to be optimized for this purpose in a clinical setting.

In **paper IV**, we showed that digital quantification of crucial inflammatory cells in the primary tumor microenvironment using immunohistochemistry has a potential to further stratify primary melanoma at risk of brain metastasis.

Keywords: Primary cutaneous melanoma, chronic sun-damage skin, gene expression profiling, immunohistochemistry, tertiary lymphoid structures, B cells, CD8+ T cells

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