Göteborg, 2022

Deregulated epigenetics and cancer stem cells in brain tumours

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, fredagen den 3 juni 2022, klockan 9.00.

av **Anna Wenger**

Fakultetsopponent:
Professor Sebastian Brandner, University College London, United Kingdom

Avhandlingen baseras på följande delarbeten

I. **Wenger A**, Larsson S, Danielsson A, Elbæk KJ, Kettunen P, Tisell M, Sabel M, Lannering B, Nordborg C, Schepke E, Carén H. Stem cell cultures derived from pediatric brain tumors accurately model the originating tumors. *Oncotarget. 2017;8(12):18626-39*.

II. Larsson S, **Wenger A**, Dósa S, Sabel M, Kling T, Carén H. Cell line-based xenograft mouse model of paediatric glioma stem cells mirrors the clinical course of the patient. *Carcinogenesis. 2018; 39(10):1304-1309*.

III. **Wenger A**, Karlsson I, Kling T, Carén H. CRISPR-Cas9 knockout screen identifies essential genes for paediatric glioma stem cell growth. *Manuscript*.

IV. **Wenger A**, Ferreyra Vega S, Kling T, Olsson Bontell T, Jakola A.S., Carén H. Intratumor DNA methylation heterogeneity in glioblastoma: implications for DNA methylation-based classification. *Neuro-oncology. 2019;21(5):616-27*.

V. **Wenger A**, Ferreyra Vega S, Schepke E, Löfgren M, Olsson Bontell T, Tisell M, Nilsson D, Kling T, Carén H. DNA methylation alterations across time and space in paediatric brain tumours. *Manuscript*.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

Göteborg, 2022

Deregulated epigenetics and cancer stem cells in brain tumours

Anna Wenger

Department of Laboratory Medicine, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Glioblastoma (GBM) is an incurable brain tumour with dismal prognosis as the median survival for afflicted patients is only 8 months. Aberrations of epigenetic processes, which govern gene expression, are involved in cancer, but these epigenetic mechanisms are reversible and can potentially be corrected by treatment. One epigenetic mark, DNA methylation, can also be used for tumour classification. The aim of this thesis was to 1) establish a representative model system of paediatric GBM and use it to identify new epigenetic treatment targets, and 2) profile the epigenetic heterogeneity in adult and paediatric brain tumours and its effect on methylation-based classification.

Patient-derived cancer stem cell (CSC) lines were established in **paper I** from paediatric GBM, and the cells retained the methylation pattern of the originating tumours. The CSC were injected into mice orthotopically in **paper II** and formed GBM tumours similar to the patient tumours. The survival of the injected mice correlated significantly with the survival of the patients, and the model thus reflects the clinical course of the patients. In **paper III**, we performed a CRISPR knockout screen with an epigenetic library and identified several novel genes as essential for the growth of CSC. **Paper IV** demonstrated that multiple methylation subclasses coexist within *adult* GBM, and that the methylation status of the clinically used biomarker *MGMT* varied. In contrast, the subclasses were stable across space and time in *paediatric* brain tumours in **paper V**.

In conclusion, we showed that intratumour methylation heterogeneity is a feature of adult GBM and should be considered for methylation-based biomarkers and classification. The methylation classification was however homogeneous within paediatric brain tumours, which is promising as it is in clinical use for this patient group. We also established a representative *in vitro* and *in vivo* model system of CSC derived from paediatric GBM. With this model system, we identified candidate genes as tumour drivers and potential therapeutic targets in paediatric GBM.

Keywords: Cancer stem cell, glioblastoma, paediatric, methylation, heterogeneity, CRISPR

ISBN: 978-91-8009-749-9 (TRYCK) http://hdl.handle.net/2077/70928
ISBN: 978-91-8009-750-5 (PDF)