Göteborg, 2019

Cell-based models for studying paediatric high-grade gliomas

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson Hörsal,
Academicum, Medicinaregatan 3, onsdagen den 29 maj 2019, klockan 9.00.
av **Susanna Larsson**

Fakultetsopponent:

Professor Silvia Marino

Queen Mary University of London, United Kingdom

Avhandlingen baseras på följande delarbeten

I. Wenger A, **Larsson S**, Danielsson A, Juul Elbæk K, Kettunen P, Tisell M, Sabel M, Lannering B, Nordborg C, Schepke E and Carén H.
Stem cell cultures derived from pediatric brain tumors accurately model the originating tumors.
Oncotarget, 2017, 8(12):18626-18639. doi: 10.18632/oncotarget.14826

II. **Larsson S**, Wenger A, Dosa S, Sabel M, Kling T and Carén H.
Cell line-based xenograft mouse model of paediatric glioma stem cells mirrors the clinical course of the patient.
Carcinogenesis, 2018 Oct 8;39(10):1304-1309.
doi: 10.1093/carcin/bgy091.

III. **Larsson S**, Kettunen P, Carén H.
Invasion of human paediatric high-grade gliomas in zebrafish.
Manuscript

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Cell-based models for studying paediatric high-grade gliomas

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Abstract

Brain tumours are the largest group of solid tumours in children and accounts for most cancer-related deaths. Astrocytoma is the largest group, representing almost half of the brain tumours, where high-grade glioma is one of the most devastating forms with very poor prognosis due to lack of efficient treatments. A better understanding of the disease and new treatment options are urgently needed.

In **paper I**, we assessed the possibility of culturing glioma stem cells (GSC) from primary paediatric high-grade brain tumours, adherently, in serum-free neural stem cell media. Cells maintained proliferative capacity long-term, displayed neural stem cell markers and responded to differentiation cues. Moreover, cell lines initiated tumour growth when orthotopically transplanted into NOG mice.

In **paper II**, survival of GSC-transplanted NOG mice was monitored, and the histological and molecular features of the developed xenograft tumours were studied. The survival of mice correlated with the survival of the patients. Moreover, the xenograft tumours showed the same growth pattern as the patient tumours with similar genetic and epigenetic alterations as the originating tumour and GSC line.

In **paper III**, we explored zebrafish as an animal model to study paediatric high-grade gliomas. The tumour-initiating potential and invasive properties were studied. The take-rate of transplanted GSC in the fish was high, and the cells invaded the surrounding brain tissue of the fish after only a few days.

In this thesis, three pre-clinical models were established which can be used to generate new knowledge and explore new treatment options for paediatric brain tumours.

Keywords: paediatric brain tumour, glioblastoma, glioma stem cell, primary culture, xenograft tumour, zebrafish

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