

MicroRNA Signatures and Transcriptional Regulatory Networks in Glioblastoma

by
Michael Henriksen

The overall objective of this thesis was to gain a better understanding of the molecular mechanisms that underpin the invasive nature of GBM. The dysregulation of key signalling pathways plays a role in tumourgenesis and relapse giving rise to GBM hallmarks. One of the most prominent hallmarks of GBM is the invasive or infiltrative nature which can in part be due to a population of cells called cancer stem cells (CSCs), which supports the tumour growth in a heterogeneous hypoxic niche. Gene regulation, pre- and post-transcriptional (microRNA), and how this can be linked in some way to the expression of stem cell like proteins that are dysregulated has been the main focus point in this thesis and by looking at these in combination with clinicopathological features, we have learnt more about the underlying pathology of this disease and its progression.

This thesis is a compilation of several papers, which are subdivided into two parts based on theme. Part one, "MicroRNA in Glioblastoma", explores the role of microRNA (miRNA) in GBM and their association with survival. An overview of signatures or patterns of miRNAs, which are of prognostic potential, was established to find a common miRNA profile and to identify miRNAs associated with survival, clinical outcome and the modulation of the mesenchymal mode of migration and invasion (MMMI). A number of these were associated with differential expression in GBM patients, including miR-125b which had an inverse correlation with Nestin expression and correlated with overall survival in GBM patients, eloquently illustrating how clinicopathological findings and molecular profiling may be a relevant combination to predict patient outcome.

The second part, "Brain Specific Fatty Acid Binding Protein in Glioblastoma", looks extensively into the regulation of the brain fatty acid binding protein (FABP7), a highly upregulated protein in GBM and part of its underlying invasive nature. FABP7 is a stem cell marker in GBM and was early on recognised as a gene involved in GBM biology. However, the fundamental aspects of regulation within cancer are, at the moment, still elusive. The regulatory landscape of FABP7 is comprised of many aspects, with some revealed but most still elusive. A comprehensive map of the binding of transcription factors, the primal regulator, was generated, describing the function of 27 transcription and signalling factors with reference to their effect on FABP7 expression, their role in neural development, and in GBM. A majority of these are associated with regulatory modules in GBM, confirming FABP7 as a target gene in GBM. Though FABP7 is highly upregulated in GBM, it is notoriously lacking from many GBM cell lines (e.g. U87) or primary cell cultures. It was found that FABP7 is lost upon cultivation of GBM tissue, however, for some cultures, the protein could be re-expressed upon neurosphere formation or xenografting. This elusive behaviour was hypothesised to be in part a function of the molecular subtype which led to the finding that FABP7 belongs to the classical subtype, along with Nestin, another known stem cell marker.

The functional role of many differentially regulated microRNAs are still to be elucidated, however, it is apparent that microRNAs have a huge impact on the biology of GBM. Of the microRNAs that were found differentially regulated across the tumour samples, 36 were predicted to target FABP7. Since miRNAs have a huge impact on the biology of GBMs and due to their connection with the clinicopathological features, it would be highly relevant to find miRNAs that target FABP7, since only one miRNA to date (miR-21) has been found to regulate FABP7 in mouse.

The interconnected web of regulatory elements is vast, and to this end, this thesis only scratches the surface.

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PhD lecture

by

Michael Henriksen

Thursday 17 August 2017



DEPARTMENT OF HEALTH SCIENCE AND TECHNOLOGY
AALBORG UNIVERSITY

This thesis is based on
Michael Henriksen's research work at:

Department of Health Science and Technology
Aalborg University, Denmark

To fulfill the requirements for the PhD degree, Michael Henriksen has submitted the thesis: "MicroRNA Signatures and Transcriptional Regulatory Networks in Glioblastoma", to the Faculty Council of Medicine at Aalborg University.

The Faculty Council has appointed the following adjudication committee to evaluate the thesis and the associated lecture:

Professor Pranela Rameshwar
Rutgers University
USA

Professor Bjarne Winther Kristensen
Odense Universitet
Denmark

Chairman:
Professor Karen Dybkær Sørensen
Aalborg University Hospital/Aalborg University
Denmark

Moderator:
Associate Professor Meg Doroux
Aalborg University
Denmark

The PhD lecture is public and will take place on:

Thursday 17 August 2017 at 13:00
Aalborg University – Room D2-106
Fredrik Bajers Vej 7D2
9220 Aalborg Øst

Program for PhD lecture on

Thursday 17 August 2017

by

Michael Henriksen

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Glioblastoma

Chairman: Professor Karen Dybkær Sørensen

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| 13.00 | Opening by the Moderator |
| 13.05 | PhD lecture by Michael Henriksen |
| 13.50 | Break |
| 14.00 | Questions and comments from the Committee
Questions and comments from the audience at the
Moderator's discretion |
| 16.00 | Conclusion of the session by the Moderator |

After the session a reception will be arranged