

Metabolomics and proteomics studies of brain tumors - a chemometric bioinformatics approach

Lina Mören

Akademisk avhandling

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Fakultetsopponent: Docent, Anders Malmendal,
Department of Biomedical Sciences, University of Copenhagen,
Danmark



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Author
Lina Mörén

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Abstract

The WHO classification of brain tumors is based on histological features and the aggressiveness of the tumor is classified from grade I to IV, where grade IV is the most aggressive. Today, the correlation between prognosis and tumor grade is the most important component in tumor classification. High grade gliomas, glioblastomas, are associated with poor prognosis and a median survival of only 14 months at best including all available treatments. Low grade meningiomas, usually benign grade I tumors, are in most cases cured by surgical resection. However despite their benign appearance grade I meningiomas can, without any histopathological signs, in some cases display bone invasive growth and become lethal. Thus, it is necessary to improve conventional treatment modalities, develop new treatment strategies and improve the knowledge regarding the basic pathophysiology in the classification and treatment of brain tumors.

In this thesis, both proteomics and metabolomics have been applied in the search for biomarkers or biomarker patterns in two different types of brain tumors, gliomas and meningiomas. Proteomic studies were carried out mainly by surface enhanced laser desorption ionization time of flight mass spectrometry (SELDI-TOF-MS). In one of the studies, isobaric tags for relative and absolute quantitation (iTRAQ) labeling in combination with high-performance liquid chromatography (HPLC) was used for protein detection and identification. For metabolomics, gas-chromatography time-of-flight mass spectrometry (GC-TOF-MS) has been the main platform used throughout this work for generation of robust global metabolite profiles in tissue, blood and cell cultures. To deal with the complexity of the generated data, and to be able to extract relevant biomarker patterns or latent biomarkers, for interpretation, prediction and prognosis, bioinformatic strategies based on chemometrics were applied throughout the studies of the thesis.

In summary, we detected differentiating protein profiles between invasive and non-invasive meningiomas, in both fibrous and meningothelial tumors. Furthermore, in a different study we discovered treatment induce protein pattern changes in a rat glioma model treated with an angiogenesis inhibitor. We identified a cluster of proteins linked to angiogenesis. One of those proteins, HSP90, was found elevated in relation to treatment in tumors, following ELISA validation. An interesting observation in a separate study was that it was possible to detect metabolite pattern changes in the serum metabolome as an effect of treatment with radiotherapy and that these pattern changes differed between different patients, highlighting a possibility for monitoring individual treatment response. In the fourth study of this work, we investigated tissue and serum from glioma patients that revealed differences in the metabolome between glioblastoma and oligodendroglioma, as well as between oligodendroglioma grade II and grade III. In addition, we discovered metabolite patterns associated to survival in both glioblastoma and oligodendroglioma. In our final work, we identified metabolite pattern differences between cell lines from a subgroup of glioblastomas lacking argininosuccinate synthetase (*ASS1*) expression, (*ASS1* negative glioblastomas), making them auxotrophic for arginine, a metabolite required for tumor growth and proliferation, as compared to glioblastomas with normal *ASS1* expression (*ASS1* positive glioblastomas). From the identified metabolite pattern differences we could verify the hypothesized alterations in the arginine biosynthetic pathway. We also identified additional interesting metabolites that may provide clues for future diagnostics and treatments. Finally, we were able to verify the specific treatment effect of *ASS1* negative cells by means of arginine deprivation on a metabolic level.

Keywords: glioblastoma, glioma, meningioma, metabolomics, proteomics, mass-spectrometry

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