AN INTEGRATIVE APPROACH TO CHARACTERIZE AND EXPLOIT THE EPIGENETIC LANDSCAPE IN GLIOBLASTOMA

EIN INTEGRATIVER ANSATZ ZUR CHARAKTERISIERUNG DER EPIGENETISCHEN LANDSCHAFT BEIM GLIOBLASTOM

TUNCAY BAUBEC
Department of Molecular Mechanisms of Disease, Laboratory of Systems Biology of Gene Regulation
University of Zurich

MICHAEL WELLER
Department of Neurology, Laboratory of Molecular Neurooncology, University Hospital and University of Zurich

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SUMMARY

There is increasing evidence for epigenetic alterations in glioblastoma, the most common and most aggressive primary brain tumor in adults. Despite surgery, radiotherapy and chemotherapy the tumors inevitably recur and the prognosis of patients with glioblastoma remains poor. Therefore, there is an urgent need for a better understanding of targetable molecular mechanisms at different disease stages and for novel treatment options. Epigenetic mechanisms are potential therapeutic targets because of their reversible nature. However, the gene regulatory landscape, comprising epigenetic alterations as well as transcriptional and chromatin regulators, in glioblastoma at different disease stages and upon chemoradiotherapy has remained largely unexplored. We will address this gap of knowledge and use a novel integrative approach to characterize the gene regulatory landscape in glioblastoma at different disease stages in a quantitative and functional manner. We will perform longitudinal epigenetic profiling of glioblastoma patient samples obtained at diagnosis and at recurrence after standard treatment with chemoradiotherapy. For this, we apply single-cell transcriptomics, genome-wide DNA methylation, ATAC-seq and a novel mass spectrometry-based technology to analyze the landscape of histone modifications. We will functionally characterize the role of the identified epigenetic marks for tumor growth *in vitro* and *in vivo* and the susceptibility to irradiation or temozolomide chemotherapy. This will include targeted manipulations of chromatin marks as well as genetic and pharmacological inhibition of chromatin regulating enzymes in human glioblastoma cell lines followed by epigenetic profiling and state-of-the-art molecular biology methods. Furthermore, we will investigate novel epigenetic-based therapies alone or in combination with irradiation or temozolomide in complex glioblastoma samples using pharmacoscopy, a novel approach that combines high-throughput microscopy and machine learning algorithms to characterize drug responses at a single-cell level. This work will provide an unprecedented deep molecular and functional insight into the gene regulatory landscape of glioblastoma at different disease stages and exploit this for novel epigenetic-based therapeutic concepts. It shall build the basis for future developments of epigenetic therapy for cancer with the aim to improve the prognosis of patients and to translate this knowledge to other malignancies.