Description for the general public

Identification of epigenetic mechanisms contributing to glioma drug resistance

Our understanding of cancer treatment has increased over the years and as a result personalized treatments became available. However, for patients with aggressive brain tumors, glioblastomas, the prognosis has not changed much and an average survival is still shorter than 15 months. Systematic analyses confirmed that the treatment resistance is associated with the multicellular composition of glioblastoma. Glioblastoma consists of many different cell types, which makes the treatment difficult and mostly unsuccessful. In particular, the presence of the non-differentiated cells called 'cancer stem cells' is one of the major obstacles in a successful therapy.

In living cells DNA is not a standalone molecule, but is organized into a chromatin, which comprise DNA, RNA and proteins. Although it is believed that alternations in a genome (mutations of DNA, repetition of a gene etc.) are the main cause of cancer, there is a rising number of evidence showing that alternations in epigenetic mechanisms, i.e. mechanisms involved in chromatin organization, play an important role in tumor formation. Importantly, it was also shown that epigenetic regulation is crucial for maintenance of a non-differentiated state. However, up to date, there is no publicly available data on chromatin accessibility in glioblastoma stem-like cells and its contribution to drug resistance.

The aim of this project is to identify epigenetic characteristics of glioblastoma stem-like cells and regulatory networks that contribute to tumor drug resistance and reoccurrence. First, epigenetic characteristics and gene expression levels will be profiled in glioblastoma stem-like cells and differentiated cells derived from them. An analysis of matched pairs will facilitate identification of glioblastoma stem-like characteristic features. Subsequently, both stem-like and differentiated cells will be treated with temozolomide (TMZ; a commonly used chemotherapeutic). The epigenetic characteristics and gene expression levels in the treated cell lines will be assessed. This way, a bioinformatic analysis will be able to provide a comprehensive map of epigenetic glioblastoma stem-like characteristics involved in stem-like maintenance and/or drug resistance. Finally, the gathered data will allow understanding epigenetic regulatory mechanisms of the stemness-associated tumor recurrence.

The results will elucidate the role of epigenetic mechanisms in glioblastoma self-renewal and drug resistance potentials. Our approach can likely identify novel epigenetic variants that would allow better diagnostics and reveal novel targets for the glioma therapy. The identified characteristics will have impact on personalized patient care, where decisions can be made based on individual genomic profiles.