Methylation Profiling in Rhabdomyosarcoma

Project

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Sarcomas account for some of the most malicious and aggressive pediatric malignancies, with frequent metastasis and high relapse rates. Over the last 40 years, cure rates have significantly increased. This was mainly achieved through a better understanding of the pathophysiology of the disease, and by treating the patients according to cooperative international treatment protocols. Nevertheless, despite continuous optimization of therapy protocols, advances have plateaued during the last two decades, and the overall survival rate of patients with advanced, metastasized or relapsed disease remains poor. This prompts the necessity for new treatment strategies which consider the molecular and epigenetic background of patient tumors, as the epigenetic status might predict risk profiles but also the sensitivity to certain cancer medicines. So far, only a limited number of studies have explored the epigenetic status of rhabdomyosarcomas (RMS), such as their DNA methylation state. Furthermore, no studies have correlated the methylation state with clinical outcome while considering different patient characteristics in detail. However, we believe that similar to the influence of genetic characteristics, including specific translocations, on the patients' risk profile, epigenetic patterns too can be directly correlated with the patients' outcome. We therefore propose to use a large collection of RMS samples and corresponding clinical data to perform a DNA methylation analysis, including correlation of the data to a large spectrum of clinical parameters. To gain novel insights into the epigenetic status of RMS and its correlation with clinical outcome, we will address the following specific aims:

Aim 1

We will use an array-based DNA-methylation profiling approach to measure DNA methylation profiles in a large collection of primary and relapse RMS samples covering all subtypes. These methylation profiles will be correlated with multiple clinical parameters and the outcome of each patient, extracted from the patient charts. We assume that methylation profiles will uncover novel entities within histological subgroups that can be used for a novel classification scheme.
Further correlation with the clinical features will help us to identify risk groups by means of their methylation profile. Comparison of the methylation profiles of primary and relapsed samples from the same patient will help us to better understand mechanisms leading to onset of relapse and drug resistances.

Aim 2

We will identify markers for drug response in the methylation data by performing methylation profiling of our established RMS patient-derived xenografts (PDX), by comparing these profiles with the profiles from the patient samples and by correlating this data with already existing drug profiles of the PDX.

Aim 3

We will identify relevant genes affected by deregulated DNA methylation. For this, we will use RNA sequencing to investigate gene expression profiles from our patient and PDX samples as well as from control cells of the myogenic lineage. We assume that differential methylation is reflected on the mRNA level and might reveal genes responsible for outcome, risk of relapse and drug resistance patterns.

Overall, we expect that this study will provide both new and relevant insights into the molecular biology of RMS. By combining state-of-the-art molecular profiling of patient-derived material with clinical outcome parameters, this study will contribute to a more accurate risk profiling of the individual patient and help to guide treatment strategies and decisions. This is a translational project to directly use benchside created data in clinical practice.