Universität Basel

Research Project

Exploring the genomic, epigenomic and transcriptomic landscapes of adenosquamous and pleomorphic lung cancer

Third-party funded project

Project title Exploring the genomic, epigenomic and transcriptomic landscapes of adenosquamous and pleomorphic lung cancer
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Lung cancer remains the leading cause of cancer related death worldwide with approximately 1.8 million new cases and 1.6 million deaths per year. Fortunately, there have been significant improvements in the last decade. Better treatment options guided by the discovery of targetable genomic alterations have been identified and improved patient's survival. However, personalized medicine with targeted therapeutics is suitable for less than 20-30% of Western patients. Landmark studies investigating the genomics of non-small cell lung cancer (NSCLC) have focused mainly on the most frequent types of NSCLC, namely lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). In contrast, rare but clinically relevant subtypes of NSCLCs, such as adenosquamous carcinoma (ASC) and pleomorphic carcinoma (PMC), have not yet been thoroughly investigated, despite affecting large patient numbers globally. The here proposed study draws upon the experiences and developments made in the previous SNF studies with LUAD (310030_138513) and LUSC (320030_162781), especially for the potential of whole-exome sequencing (WES) for the analysis of tumor evolution. Over the course of said studies, we have improved our bioinformatic pipeline and approaches from genomic analysis of targeted panel sequencing (310030_138513) to WES (320030_162781). Always in the context with our refined technology of multiparameter ploidy profiling (MPP), which allows separation of tumor population with high purity enabling the genomic analysis of complex tumor samples and tumors with low tumor cell content. The main aim of this study is to explore the molecular and genetic background of tumor heterogeneity and evolution in ASC and PMC in a comprehensive manner. For this purpose, we will analyze the morphological distinct tumor components of the two rare NSCLC subtypes ASC and PMC, which are defined by their distinct morphological heterogeneity and aggressive clinical behavior. We selected 20 patients with ASC and 20 patients with PMC from our pathology archive. In both cohorts, tumor regions will be separated by histology (adenosquamous carcinoma and squamous cell carcinoma components in ASC; adenocarcinoma or squamous cell carcinoma and spindle and/or giant cell components in PMC) using macrodissection or the above-mentioned MPP approach in tumor specimens with low tumor cell proportion. DNA of all separated tumor regions will be tested for the presence of mutations, insertions- and deletions, copy number aberrations and mirrored allelic imbalances using WES. Further, epigenomic and transcriptomic profiles will be assessed using DNA methylation arrays and genome-wide gene expression arrays, respectively. This will allow us to elucidate the genomic, epigenomic and transcriptomic background of morphologically different histologies in the two rare NSCLC subtypes, ASC and PMC that are defined by the striking intratumoral heterogeneity of their morphology. Importantly, we will be able to define to which extent each of the three 'Omic' profiles contribute to the morphological heterogeneity and to decipher

the evolution of these tumors. This may not only provide new fundamental insights into the molecular mechanisms of morphological tumor heterogeneity in general but also pinpoint new therapeutic avenues in these NSCLC subtypes, which are known for their aggressive clinical behavior. We anticipate that the here proposed study will lead to a better understanding of the evolution and the underlying clonal composition of rare NSCLC subtypes and thus contribute to the further development of personalized cancer medicine in patients with ASC and PMC.

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