Project abstract

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PROJECT PROPOSAL

A major focus of our past and current work is on epigenomic alterations associated with breast and prostate cancer[1–3], two of the most common cancer types worldwide. Modifications of DNA and the histone proteins around which DNA is packaged (DNA methylation, histone modifications) are important in regulating gene expression.

Endocrine therapy is highly effective in blocking the estrogen receptor pathway in hormone receptor positive/HER2 negative early breast cancer (EBC). However, up to 40% of patients experience relapse during or after adjuvant endocrine therapy. Accumulating evidence suggests that non-genetic mechanisms are major contributors to treatment resistance. In a large collaborative study on EBC, we used genomic alterations and DNA methylomes of samples collected after three weeks of anti-hormonal therapy to develop a computational model to predict treatment response[4]. In a planned multi-disciplinary project in triple-negative breast cancer, we will characterize epigenetically defined, drug-tolerant persister cells (PCs) that are predisposed to survive treatment and drive disease recurrence. We hypothesize that single cell epigenetic heterogeneity contributes to treatment resistance.

Methodologically, our group is interested in novel sequencing technologies, including native nanopore sequencing of long DNA fragments and cell-free plasma DNA. The advantage of nanopore sequencing is the ability to simultaneously detect genomic and epigenomic alterations on the same DNA fragments, and to derive allele-specific information. Novel technological developments in nanopore sequencing also allow the simultaneous detection of open chromatin regions[5,6].

Prostate cancer is characterized by high levels of epigenetic alterations and genomic structural variants (SVs) such as deletions, duplications and translocations, rather than recurrent cancer driver mutations. Building on our large and comprehensive prostate cancer cohort of fresh-frozen and multi-regional samples, including metastatic tissue, together with clinical outcome data we plan to use nanopore sequencing to answer the question why certain regions of the genome are more prone to acquire genomic alterations during cancer development. The frequency of SVs in the genome correlates with changes in epigenomic modifications, but the mechanisms and interplay between these two processes are poorly understood. We expect to provide a solid scientific basis for the use of long-read sequencing data to transform the analysis of genome-epigenome interactions in cancer and elucidate novel oncogenic mechanisms and potential cancer vulnerabilities.

References:

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