Breast Cancer Liquid Biopsy Stratification

Summary

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Supervisor:	Prof. Dr. Michael Speicher
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between July 15, 2019 00:00 and September 15, 2019 23:59 (Europe/Zurich)

Description

Background:

Breast cancer is the most common cancer in Austrian women. Currently, clinical routine stratification of tumors is mostly based on hormone receptor, HER2 status and estimation of proliferation. However, a more robust and objective classification of tumors can be achieved by elucidation of further biological properties, which is also of increasing significance as novel anticancer therapies are based on biological mechanisms. For this project the classification of the METABRIC consortium, which is based on combining gene expression and somatic copy number alterations (SCNAs), referred to as integrative clusters (IntClust) (1) is most relevant as it represent to date the most extensive molecular-based taxonomy of breast cancer (2). These integrative clusters are based on the observation that a significant proportion of the gene expression landscape is determined by SCNAs that drive expression in cis. “Liquid biopsies” are based on the analysis of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), or tumor-derived extracellular vesicles, which have been shed from tumors and their metastatic sites into the blood (3). Our group has extensive expertise in the analysis of plasma DNA. Of note, we showed recently that the detailed analyses of plasma DNA even allows inferring the expression status of genes within a tumor genome by nucleosome position mapping (4). As the aforementioned integrative clusters in breast cancer are based on SCNAs and gene expression the purpose of this project is to test whether these subgroups can be established directly from plasma DNA and whether this results in an improved stratification of women with breast cancer.

Hypotheses:

Hypothesis 1: Integrative breast cancer clusters can be directly established from plasma DNA and improve stratification of patients.

Hypothesis 2: SCNA analyses together with our nucleosome mapping strategy can resolve the impact of narrow versus broader amplification or the level of the amplification or amplitude, respectively, and establish the cancer driver genes in over-represented regions.

Hypothesis 3: The combination of high-resolution panel sequencing and nucleosome positioning patterns will contribute to an improved understanding between distinct mutations and their association to gene expression.

Objectives:

- Detailed characterization of the genome of metastatic breast cancer, which represents a frequent disease stage, by non-invasive means.
- Innovative characterization of high-level amplifications, which belong to the most important biomarkers in breast cancer, by nucleosome position mapping.
- Identification of novel predictive and prognostic biomarkers, which can then be used for stratification of patients into clinical trials.

Methodology:

Whole-genome sequencing with high coverage: High coverage sequencing is a prerequisite for nucleosome positioning mapping from plasma DNA.

Plasma-Seq: Whole-genome sequencing with a shallow coverage conducted according to our previously published protocols (5).

Nucleosome position mapping: as described in our publication (4).

Copy number analyses and focal amplification mapping: We described our analyses pipelines for establishing copy number profiles extensively in our previous publications [for an example see (6)], which is based on segmented z-scores as well as genome-wide z-scores (i.e. established z-score statistics to detect aberrant genomic content in plasma).

Targeted Cancer Panel; molecular barcoding, digital PCR: For analyses of plasma samples with low ctDNA variant allele frequency (VAF) we will use various protocols involving molecular barcoding.

Statistical methods, bioinformatics, data analyses, and integration with clinical data: A number of innovative statistical and bioinformatic tools will be applied.

References:

1. Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, Speed D, Lynch AG, Samarajiwa S, Yuan Y, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012; 486:346-52
2. Russnes HG, Lingjaerde OC, Borresen-Dale AL, Caldas C. Breast Cancer Molecular Stratification: From Intrinsic Subtypes to Integrative Clusters. Am J Pathol. 2017; 187:2152-62
3. Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet*. 2019; 20:71-88
4. Ulz P, Thallinger GG, Auer M, Graf R, Kashofer K, Jahn SW, Abete L, Pristauz G, Petru E, Geigl JB et al. Inferring expressed genes by whole-genome sequencing of plasma DNA. *Nat Genet*. 2016; 48:1273-8
5. Heitzer E, Ulz P, Belic J, Gutschi S, Quehenberger F, Fischereder K, Benezeder T, Auer M, Pischler C, Mannweiler S, Pichler M, Eisner F, Haeusler M, Riethdorf S, Pantel K, Samonigg H, Hoefler G, Augustin H, Geigl JB, Speicher MR. Tumor-associated copy number changes in the circulation of patients with prostate cancer identified through whole-genome sequencing. *Genome Med.* 2013; 5(4):30
6. Ulz P, Belic J, Graf R, Auer M, Lafer I, Fischereder K, Webersinke G, Pummer K, Augustin H, Pichler M, et al. Whole-genome plasma sequencing reveals focal amplifications as a driving force in metastatic prostate cancer. *Nat Commun*. 2016; 7:12008

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