Medical University of Graz

In silico evaluation of DNA methylation signatures as regulators of therapy resistance and tumor progression within clinically relevant subgroups of lung and breast cancer patients

Summary

Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz

Supervisors:	Dr. Marija Balic Dr. Sebastian Vosberg
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background:

Lung and breast cancer are two of the most common and deadly cancer types, and treatment resistance is a significant problem in these entities, especially in patients with advanced disease. Human tumors are known to be caused not only by DNA mutations [1, 2] but also by epigenetic alterations, such as DNA methylation [3, 4]. With ongoing disease, tumors accumulate such molecular alterations, which promote tumor progression, the invasion of healthy surrounding tissue as well as the formation of metastases. Yet, the molecular mechanisms of disease progression are still not fully understood, and many late-stage cancers lack clear driver events. For individual patient subgroups, effective targeted therapies exist, yet most patients still do not sufficiently respond to the treatment and/or develop resistances. Such patients are in the highest medical need of novel effective treatment options. Identifying clinically relevant biomarkers allows to gain insights into the molecular mechanisms of treatment response and tumor progression, with the potential to reveal novel treatment targets.

Hypothesis and Objectives:

This project aims at identifying and characterizing DNA methylation changes that are associated with the progression of lung and breast cancer using well defined clinically relevant patient subgroups. This includes to unravel their regulatory function on downstream targets and to identify clinically relevant biomarkers for the response towards individual therapy approaches as well as the risk of disease recurrence. To this end, DNA methylation profiles of cancer patients will be integrated with gene expression profiles in a systematic approach which allows to describe the regulatory mechanisms of treatment failure across a broad spectrum of molecular alterations. Integrating such molecular signatures with detailed clinical records improves our understanding of tumor biology and finally also disease control and management.

Methodology:

Molecular profiles of breast and lung cancer patients are collected within the Medical University of Graz, alongside with comprehensive clinical records. Further, publicly available data from TCGA [5, 6], TRACERx [7], and METABRIC [8] will be included in the project as well. Molecular characterization includes profiling of DNA methylation and gene expression of primary tumor samples at different time points during the course of the disease, as well as of metastatic lesions. Individual computational approaches which are needed to analyze this unique data collection will be developed during the project and will be combined with state-of-the-art bioinformatic analysis pipelines [9, 10]. Subsequently, candidate mechanisms may be evaluated *in vitro* using cutting edge molecular approaches such as the CRISPR/Cas9 system.

Medical University of Graz

During this PhD project, the candidate will use modern computational approaches to characterize and correlate DNA methylation profiles with respect to cancer development and treatment response in retrospective cohorts of lung and breast cancer patients. The successful completion of the project will contribute to our understanding of the biology of cancer progression and pave the way for more effective treatment approaches as well as informed clinical decision making, both ultimately optimizing patient care in the future.

References:

1. Nowell, P.C. and D.A. Hungerford, Chromosome studies on normal and leukemic human leukocytes. J Natl Cancer Inst, 1960. 25:85-109.

2. Nowell, P.C., The clonal evolution of tumor cell populations. Science, 1976. 194:23-8.

3. Berdasco, M. and M. Esteller, Aberrant epigenetic landscape in cancer: how cellular identity goes awry. Dev Cell, 2010. 19(5):698-711.

4. Esteller, M., Cancer epigenomics: DNA methylomes and histone-modification maps. Nat Rev Genet, 2007. 8(4):286-98.

5. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50.

6. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012 Oct 4;490(7418):61-70.

7. Jamal-Hanjani M et al. Tracking genomic cancer evolution for precision medicine: the lung TRACERx study. PLoS Biol. 2014 Jul 8;12(7):e1001906.

8. Curtis C, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52.

9. Greif PA*, Hartmann L*, Vosberg S*, et al. Evolution of Cytogenetically Normal Acute Myeloid Leukemia During Therapy and Relapse: An Exome Sequencing Study of 50 Patients. Clin Cancer Res. 2018 Apr 1;24(7):1716-1726. *authors contributed equally

10. Kerbs P, Vosberg S, et al. Fusion gene detection by RNA sequencing complements diagnostics of acute myeloid leukemia and identifies recurring NRIP1-MIR99AHG rearrangements. Haematologica. 2021 Jun 17.

To get more information or to apply online, visit https://mug.glowbase.com/positions/265 or scan the the code on the left with your smartphone.