Medical University of Graz

Cause and consequence of structural DNA damage in cancer.

Summary

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Supervisor:	PD Dr. Karl Kashofer
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between March 24, 2021 00:00 and May 05, 2021 23:59 (Europe/Zurich)

Description

Background:

Cancer is a genetic disease. Much is already known about the impact of mutations in the coding regions of genes. These protein amino acid changes deregulate pathways, activate cellular processes and present targets for treatment. Changes to the structure of DNA present a different kind of somatic changes in neoplasia. Cancer cells can accumulate copy number changes, translocations, loss of heterozygosity and other genomic imbalances. There are several pathways leading to these DNA changes, notably HRR gene mutation or methylation and defects in cell division and chromatid separation, often in conjunction with TP53 mutations. These genetic changes lead to aberrant gene expression and the creation of neoantigens, activating the immune system and subsequently inducing immune evasion in the tumor. Immune checkpoint inhibitors are a class of drugs that can be used to re-activate the immunological response to the tumor cells and have shown promising results in clinical studies. More recently, PARP inhibitors have emerged as potent therapeutic drugs in tumors with homologous recombination deficiency demonstrated by BRCA1/2 mutation and/or genomic scarring.Our lab is structured into a core diagnostic laboratory providing molecular pathology based diagnostics in southern Austria serving approximately 1.2 million citizens, and a research and development department which strives to transition innovative and novel analysis methodologies from the basic research setting into clinical diagnostics.

Hypothesis and Objectives:

- Structural DNA damage leads to immunogenicity and subsequent immune evasion
- Structural damage by HRD is a distinct phenomenon and diagnostically targetable
- Immune checkpoint inhibitors can play a role in urogenital cancers with structural DNA damage
- PARP inhibitor efficacy is correlated to specific features of structural DNA damage

Methodology:

We have access to well characterized cohorts of penile, vulvar and cervical cancers and are currently recruiting a cohort of patients with ovarian cancer who already have a genomic diagnostic analysis performed with the proprietary Myriad myChoice CDx test. We use NGS sequencing of tumor cohorts to assess mutational profiles and genomic scarring, available datasets include low density WGS (whole genome sequencing), TCR repertoire sequencing, amplicon panel sequencing, exome sequencing and full WGS from Ion Torrent and Illumina platforms. The successful candidate will use modern bioinformatics workflows to characterize and correlate mutational profiles, genomic scarring and cyclic multi-color immunofluorescence image series of tumor tissues to generate hypotheses on the correlation of genomic features, immune cell infiltrates and clinical data of patients. Wetlab experiments will involve multi-color immunofluorescence, NGS sequencing and establishing and manipulating cell line models of select tumors from the cohorts. Our bioinformatics setup includes a linux cluster environment on which we deploy dockerized workflows. All our IT infrastructure is based on Debian GNU/Linux and we have a strong dedication to free and open source software.

References:

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