Medical University of Graz

Genetic events in the progression from precancerous lesions to invasive carcinoma

Summary

Karl Kashofer, Diagnostic & Research Institute of Pathology; Medical University of Graz

Supervisor:	PD Dr. Karl Kashofer
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 18, 2021 00:00 and October 04, 2021 23:59 (Europe/Zurich)

Description

Background:

Human papilloma virus (HPV)-induced invasive cervical squamous cell cancer (SCC) develops via the precursor lesion high-grade squamous intraepithelial lesion (HSIL). Our group is investigating the events leading to progression of the precursor lesions thin and thick HSIL to microinvasive and fully invasive SCC. Different HPV genotypes show a wide range in their oncogenicity and vary greatly in the study groups. Thin HSIL has a prevalence of 22.5% of non-high-risk HPV genotypes compared to less than 3% in thick HSIL and invasive SCC. Genetic mutations of driver genes are not apparent in precursor lesions but seem to play an important role in later stages and we have described a very high prevalence of TP53 and CDKN2a mutations in SCC of the cervix and related penile cancers. However, little is known about the interplay of HPV infection and genetic mutation in these different stages of cancer development. Our lab is structured into a core diagnostic laboratory providing molecular pathology based diagnostics in southern Austria and a research and development lab which strives to transition innovative and novel analysis methodologies from the basic research setting into clinical diagnostics. Our research activities are centered around anogenital cancers, with emphasis on penile, vulvar and cervical cancer.

Hypothesis and Objectives:

- HPV infection by specific viral genotypes is sufficient to drive proliferation but not carcinogenesis
- Genetic changes are needed for the progression from precursor lesions to SCC
- TP53 and CDKN2a mutations play an important role in the carcinogenisis of anogenital cancers
- Structural DNA damage is contributing to the evolution of SCC

Methodology:

We have access to cohorts of penile, vulvar and cervical cancers which have been characterized by histology, immunohistochemistry and focused NGS panel analysis. We want to expand on this genetic analysis using exome sequencing based on a new NovaSeq 6000 instrument recently made available to our lab. Genetic analysis combined with transcriptome sequencing will inspire hypotheses on the interplay of HPV infection, HPV genotype, structural DNA damage and genetic mutation of driver and tumor suppressor genes in these progressive stages of cancer development. We want to further establish a tissue culture based system to test the oncogenicity of different HPV strains in combination with genetic changes in-vitro and possibly also in-vivo in murine xenotransplantation models. Introduction of genetic mutations will be performed with the CRISPR/Cas system by recapitulating oncogenic mutations known from the genetic screenings, or by modifying the DNA repair system leading to structural DNA changes.

The successful PhD candidate will use cutting edge sequencing technology and bioinformatics to characterize and correlate mutational and transcriptional profiles, genomic scarring and HPV infection in retrospective cohorts of anogenital cancers. Subsequently we will focus on the generation and characterization of meaningful tissue culture models to study the progression of anogenital cancers from precursor lesions to squamous cell carcinoma.

References:

Thin variant of high-grade squamous intraepithelial lesion - relationship with high-risk and possibly carcinogenic human papilloma virus subtypes and somatic cancer gene mutations.

Regauer S, Reich O, Kashofer K. Histopathology. 2019 Sep;75(3):405-412. doi: 10.1111/his.13869. Epub 2019 Jun 28. PMID: 30927371

Time series analysis of TP53 gene mutations in recurrent HPV-negative vulvar squamous cell carcinoma.

Regauer S, Kashofer K, Reich O. Mod Pathol. 2019 Mar;32(3):415-422. doi: 10.1038/s41379-018-0141-4. Epub 2018 Oct 5. PMID: 30291345

HPV-negative penile squamous cell carcinoma: disruptive mutations in the TP53 gene are common.

Kashofer K, Winter E, Halbwedl I, Thueringer A, Kreiner M, Sauer S, Regauer S. Mod Pathol. 2017 Jul;30(7):1013-1020. doi: 10.1038/modpathol.2017.26. Epub 2017 Apr 7. PMID: 28387325