Finding and understanding somatic mutations and their contribution to development of colorectal cancer

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Research area:
Cancer/oncology

Brief description
We are looking for students with an interest in functional studies or genetics of cancer, or in development of computer tools for large sequence data analysis.

Aim

We aim at finding and understanding somatic mutations involved in cancer development, particularly in colorectal cancer. We are also pursuing development of diagnostics and strategies for utilization of genetic information from the tumor for targeted treatment.

Background

Mutations that cause normal cells to lose control over cell division and maintenance are important contributors to cancer development. For many of the somatic mutations acquired by cancer cells the contribution to tumor development is unknown, impeding understanding of tumor biology. The presence of genetic alterations in a tumor also provides opportunity for e.g. diagnosis, disease monitoring and therapy.

Our research spans many aspects of somatic mutations and their role in cancer, being centered around the following topics: (1) identification of cancer-causing mutations, (2) investigation of how specific mutations contribute to tumor development or metastasis, (3) strategies to utilize the specific genetic properties of cancer cells for targeted treatment, and (4) development of methods and procedures to aid or improve diagnosis.

Project plan

We have several projects where students can apply to join.

1. Early detection and monitoring of cancer by analysis of circulating tumor DNA and other blood biomarkers has potential to reduce cancer mortality. However, several different types of analytes need to be determined in the one and same patient to achieve high sensitivity and specificity. Currently, this requires several different blood samples from the same patient processed in different and often intricate ways which limits clinical implementation. We are therefore developing

a new pre-analytical technology to isolate several different fractions from the same blood sample which has potential to radically improve the implementation of liquid biopsies in the clinical workflow.

The work includes design, development and testing of an integrated system with hardware, software and consumables. The project has opportunities for several students with engineering competencies, such as electrical engineering, programming of embedded systems, mechanical engineering and molecular biotechnology.

2. Hundreds of genes have been proposed as cancer drivers through cancer genomics studies. Functional validation of candidate genes is essential to understand and utilize this information clinically. In a series of projects we have used rAAV gene targeting constructs to knock-out or knock-in function of candidate cancer genes in human cells to investigate their contribution to cancer associated phenotypes. We currently have a project for extensive characterization of non-synonymous mutations in the oncogene *KRAS* where a student is welcome to join. Isogenic cell lines are subjected to proteomic, transcriptomic and metabolomic profiling and the project will include follow-up of these analyses. Techniques that may be used include widely used methods such as cell culturing, RT-qPCR and western blot.
3. We have recently reported non-synonymous mutations of EPHB1 and their role in metastatic colon cancer (Mathot et al, *Cancer Research* 2017). As an extension to this project, we have screened for additional mutations of EPHB1 and EPHB2 in metastatic colon cancer using unique bioinformatics filtering. Identified EPHB1 and EPHB2 mutations will be subject to validation *in vitro* by generation of isogenic cell models that are screened and characterized as described in Mathot et al, 2017. The project will consist of extensive wet lab experimentation, involving e.g. cell culture, FACS sorting, RT-qPCR and western blot.
4. Targeted cancer therapy is based on finding conditions resulting in selective killing of cancer cells while sparing the normal tissues of the patient. We propose a concept based on exploitation of the natural genetic variation in the human population and the cancer specific phenomenon loss of heterozygosity (LOH) to identify tumors that are sensitized to certain drugs relative to the normal tissues. We have identified and ranked human enzymes that may constitute targets and are now evaluating a selection of these experimentally. For the candidate NAT2 we constructed and validated CRC cell model systems which in drug discovery efforts uncovered a compound with 3-fold increased cytotoxicity in cells lacking NAT2 *in vitro* and *in vivo*. Worldwide >50 000 colorectal cancer patients with NAT2 LOH could benefit from such treatment each year. In a similar effort we are now developing cell models for a promising candidate target enzyme that will be studied during the course of this project. Techniques used in the project may include cell culturing, transfection, functional cell analysis assays, western blot and PCR.
5. We have developed software tools for rapid and accurate mutational analysis of deep sequencing data from solid tumors with significant content of normal cells.

These tools have superior indel calling capabilities, a major challenge in mutational analysis, as compared to state of the art. For this application, novel statistical mathematics has been developed and patented (Swaminathan et al, *Pattern Recognition* 2016). The current challenge is to perform quality assessment of the somatic mutations reported by our software and to evaluate the overall mutation concordance when comparing the data to the analysis performed by several competing solutions. We are looking for a highly motivated student with basic bioinformatics skills, but knowledge of Python is a benefit. The technical side of the project includes the manipulation of data from several next-generation sequencing platforms and programming tasks aiming at analysis of large datasets.

Contact details

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