Research Group Details

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Short Introduction to the lab

Professor Jussi Taipale holds a joint appointment at the University of Helsinki, and at Karolinska Institutet. The Taipale lab at the University of Helsinki is part of the Academy of Finland's Center of Excellence in Cancer Genetics (2012-2017). Our group is interdisciplinary, and composed of both biomedical and computer scientists. Our main scientific interest is in understanding of how growth factors and oncogenes drive cell proliferation.

Project Outline

Title

Systematic identification of factors regulating cellular quiescence using next generation FUCCI sensors

Short introduction to the research problem

In multicellular organisms only a very limited number of cells is actively proliferating, while the remainder of the cells either permanently exit the cell cycle to undergo terminal differentiation or acquire a reversible state termed cellular quiescence (reviewed by Coller 2007). The quiescent state is also referred to as G0 phase and was initially recognized in cultivated cells (Pardee 1974). It is believed that the quiescent state of cultivated cells closely resembles the quiescence of stem cells in vivo (Buttitta and Edgar 2007), but due to the lack of robust markers for quiescent cells we have only limited knowledge about the regulation of this fundamental process. Because cancer is often associated with deregulated cellular quiescence, have factors involved in maintaining cellular quiescence enormous potential for the use as diagnostic markers and development of novel anti cancer drugs.

Statement of experimental aims and methods

This project aims to systematically screen for factors regulating cellular quiescence. Crucial to the project is a newly developed reporter system that allows robust visualization of the G1-G0 transition in cultivated cells and model organism. This reporter system is a modification of the popular FUCCI technology (reviewed by Zielke and Edgar 2015), which allows faithful tracking of cell cycle phasing in living cells. FUCCI sensors provide a reliable readout for cell proliferation that can be applied in individual live imaging experiments as well as microscopy-based high-content screening approaches. To identify potential regulators of cellular quiescence we will combine these 2nd generation FUCCI sensor with recently developed technologies for gene regulation based on nuclease-deactivated Cas9 (reviewed by Dominguez et al. 2015) that allow systematic evaluation of loss (CRISPRi) and gain (CRISPRa) of function effects. The cell-based screen will be conducted in parallel in two well-characterized cell lines (human h-tert RPE1 and mouse NIH 3T3 fibroblasts). To evaluate the in vivo

relevance the identified candidate genes will be further characterized the in the stem cells of the Drosophila midgut.

Project time table

The first year of the PhD project will be mainly deal with optimizing the screening procedure and performing a pilot screen. The actual genome-wide screen will only require a few weeks, so that most of the second year can be spend with secondary screening to verify the hits from the primary screen. The second half of the PhD project (years 3-4) will be utilized for the in vivo evaluation of the candidate genes.

Collaborators or external secondments relevant to the project

The cell-based screen will be conducted in conjunction with the Karolinska High Throughput Center (KHTC) **http://www.scilifelab.se/facilities/khtc/.**

Max 5 references relevant to the project

- Buttitta, L. A. & Edgar, B. A. Mechanisms controlling cell cycle exit upon terminal differentiation. Curr Opin Cell Biol 19, 697–704 (2007).
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- Dominguez, A. A., Lim, W. A. & Qi, L. S. Beyond editing: repurposing CRISPR–Cas9 for precision genome regulation and interrogation. Nat Rev Mol Cell Biol 1–11 (2015). doi:10.1038/nrm.2015.2
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