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MAIN FIELDS OF RESEARCH; ABSTRACT

Tumour heterogeneity, or the existence of multiple genetically distinct subclones within a tumour, is an important but poorly understood phenomenon. Often following a pattern of branched evolution, cells within the tumour mass undergo genetic and epigenetic alteration. These subclones may acquire advantages within the tumour microenvironment or allow for cell migration out of the primary tumours, invasion of neighbouring tissues and infiltration into more distant organs.
Genetic murine cancer models are a powerful tool, but the existing tools have some limitations, specifically in probing the consequences of tumour heterogeneity. We are in the process of validating a novel genetic tool to generate sparse clones of marked genetically manipulatable cells within a tumour mass. This model will then be implemented in the Tyr::N-RasQ61K/Ink4a$^{-/-}$ melanoma mouse model. Our focus is on the Wnt-pathway, subclones with either activated or abolished canonical Wnt-signalling will be generated in melanocytic nevi and behaviour of the clones will be monitored within the primary tumour tissue as well as for their capacity for invasion and metastasis formation.
In another line of experimentation, we are developing a method to transfect colon epithelial cells in vivo. In order to generate sporadic, metastasizing models of colorectal cancer, using the CRISPR-Cas9 system. In 80-90% of the cases of colorectal cancer (CRC) the loss of the APC tumour suppressor gene is proposed to be the initiating step. Multiple genetically engineered mouse models have been developed to evaluate the role of APC loss of function in CRC. Late-stage investigations have proved difficult however, as the high tumour burden and the consequent need for euthanasia prevents studying the progression of the tumour to a metastatic stage. Using multiplex CRISPR to knock down Apc in combination with different other tumour suppressor genes in a subset of colon epithelial cells, we aim to generate sporadic but fast developing tumours in order to allow for late stage development.

SPECIAL TECHNIQUES AND EQUIPMENT

In vivo experiment using and generating new mouse models, primary cell culture, FACS, real time quantitative PCR, fluorescence microscopy, single molecule FISH