Succinate dehydrogenase and exosomes in gastrointestinal stromal tumours

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This PhD studentship offers the opportunity for a translational tumour project which gives the opportunity to gain sound knowledge in cell culture and molecular cloning including CRISPR/CAS9 technique. The project within the Aerodigestive Programme also includes PCR and pyrosequencing®, ultracentrifugation, electron microscopy, confocal microscopy, time-lapse imaging, micro-fluid chamber systems and in-vivo studies. The student will gain insight into molecular pathology with next generation sequencing. Additionally the student will get the opportunity if desired to engage in direct interaction with patients as part of the national wild type GIST campaign. Presentation of the data at national and international meetings is expected and a publication of the data in a peer reviewed journal is anticipated.

The group further focuses on myofibroblasts in the tumour microenvironment.

Project Description

Gastrointestinal (GI) stromal tumours (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract (1). GISTs are driven by mutation in the KIT (75%), PDGFRα (7%), BRAF (2%) kinase genes, or succinate dehydrogenase (SDH) complex deficiency (5%).

SDH inactivation in SDH-deficient GISTs leads to the accumulation of HIF-1α. The HIF-1α dimerizes with HIF-1β in cell nuclei to form an intact HIF which acts as a transcription factor to induce the expression of downstream genes including IGF and VEGF. This will result in growth promotion and inhibition of apoptosis in tumour cells (2).

Exosomes are small membrane vesicles (40-120 nm) with an endosome origin that are released by cells into the extracellular environment. They carry a cargo of proteins, lipids, and nucleic acids and transfer them to the recipient cells leading to alteration of biochemical composition and gene regulation in the recipient cell. Both tumour cells and stromal cells release exosomes not only into the cancer environment but also into the circulation. This opens the potential for exosomes to be used as a diagnostic tool (3).
We hypothesise that GIST can develop via different signalling pathway implying different gene mutations. A recent publication has outlined that the risk stratification of wild type GIST alters significantly from the more common KIT or PDGFRα mutant tumours (4). The mechanisms underlying the current unpredictable biological behaviour with regards to metastasis and survival remains to be explored. With this in mind, we would like to investigate the profile of exosomes isolated from GIST cell lines and examine their effect on the tumour microenvironment and metastasis.

With the use of the CRISPR/Cas9 system we will modify druggable genes in GIST cells, study their gene expression and compare the exosomes contents as well as their effect on other cell lines. In a second step we aim to harvest circulating exosomes from GIST patients to see whether different exosome types help to stratify metastatic risk.

In addition, we will investigate the DNA methylation pattern in the above cells and explore their relationship in GIST.

Cambridge is one of the UK centres for GIST therapy and specialises in wild type GIST. Our clinical collaborator Dr Ramesh Bulusu has ethical approval for a large cohort of wild type GIST patients for genetic investigation. We have access to a nation wide collection of wild type GIST including clinical data.

The department of molecular pathology has a longstanding history of national leading molecular pathology analysis with the largest spectrum of molecular tests offered.

The aim of the study is to gain further insight into the nature of wild type GIST leading to a better risk stratification and identification of pathological, potentially druggable pathways.

References


Applications

To apply for this studentship please see http://www.cambridgecancercentre.org.uk/studentships

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