

Supervisor: Dr Alan McIntyre

Project title: Functional investigation of pH sensing mechanisms in Kidney Cancer

Description:

Kidney cancer is the 8th most common cancer in the UK with >10,000 new cases annually. Nearly 30% of patients will die of the disease within 5 years. A major type of kidney cancer is clear cell renal cell carcinoma (ccRCC) and >90% of ccRCC have a mutation in the von Hippel–Lindau (VHL) protein which result in stabilisation of the hypoxia inducible factors (HIF1 α and HIF2 α) in normoxic conditions. Regions of low oxygen (hypoxia) are frequently found in solid tumours and arise from the combination of high metabolic and proliferative rate and aberrant tumour vascularisation. Hypoxia is associated with therapy resistance, metastasis and worse patient outcome. HIF1 α and HIF2 α are transcription factors and their stabilisation (normally just in hypoxia) leads to changes in key genes which trigger more aggressive growth and survival, and contribute to the major hallmarks of cancer. In particular the HIF proteins change the expression of metabolic genes. The hypoxic tumour extracellular microenvironment is also acidic because of increased production of metabolic acids, CO₂ and lactic acid (from glycolysis) and longer diffusion distances to functional blood vessels. The optimal range of intracellular pH is narrow, such that only a fraction of a pH-unit change can lead to aberrant function or even death. I recently identified increased expression of a protein that senses changes in pH in response to anti-angiogenic therapy of xenograft tumours *in vivo*, a treatment which increases tumour hypoxia. Taking advantage of the large published cancer genome atlas data sets, I investigated the expression of acid sensing proteins and identified that high expression of many of these is associated with worse patient survival in kidney cancer. This project aims to investigate the expression and role of pH sensing proteins in kidney cancer using a combination of molecular and cell biology approaches including 3-dimension cell culture.

Theme(s): Functional studies of pH sensing genes associated with worse kidney cancer patient survival.

Keywords: pH sensing, acid sensing, kidney Cancer, hypoxia, metabolism, pH regulation, functional analyses, 3D culture.

Fee band: High cost laboratory-based research

Available to Home & EU students/International Students

Please email a CV with a covering letter to Dr Alan McIntyre (alan.mcintyre@nottingham.ac.uk), who can also supply more information to interested parties.

<http://www.nottingham.ac.uk/medicine/people/alan.mcintyre>