Supervisor: Dr Alan McIntyre

Project title: Functional analyses of DNA amplified and highly expressed pH regulators in tumours

Description:
Altered metabolism is a hallmark of cancer. Tumour metabolic requirements shift based on phenotypic adaptation, including increased proliferation and survival in the low oxygen (hypoxic) and nutrient-depleted tumour microenvironment. Regions of low oxygen (hypoxia) are frequently found in solid tumours. Hypoxia results from high tumour metabolic demand and proliferative rates combined with inadequate tumour vascularisation. Clinically, hypoxia is associated with poor patient prognosis and resistance to chemotherapy and radiotherapy. Therefore developing new strategies to target the hypoxic microenvironment is critical in improving patient outcome. HIF1α and HIF2α are transcription factors that are stabilised in hypoxia leading 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. This changes the metabolism to become more glycolytic and produce more lactic acid. The hypoxic tumour extracellular microenvironment is also acidic because of increased production of metabolic acids, CO_2 and lactic acid (from glycolysis) and longer diffusion distances to functional blood capillaries. A mismatch between acid production and venting can have major effects on cell survival because H^+ ions are highly reactive and target essentially all protein-dependent processes. pH homeostatic mechanisms are challenged by the low extracellular pH of tumours. Indeed the expression of many pH-regulating enzymes is increased in response to HIF stabilization. Hypoxia also drives tumour DNA copy number aberrations and we hypothesized that hypoxia induced changes in the copy number of pH regulatory genes could offer a survival advantage to tumour cells. To identify novel pH regulatory oncogenes, we investigated pH regulation genes across 10 cancer types (>6000 patient samples) to identify those that had correlated increases in DNA copy number and RNA expression. A number of genes fulfilled these criteria in multiple tumour types. This project aims to investigate the expression and role of the identified pH regulation genes across multiple cancer types using a combination of molecular and cell biology approaches including 3-dimension cell culture.

Theme(s): Functional studies of pH regulatory genes which have correlated increases in DNA copy number and RNA expression

Keywords: Cancer, pH regulation, hypoxia, metabolism, 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