

GRANT/FELLOWSHIP REPORT

Grant Holder Name	Alison K Ramsay
Department(s) in which the Fellowship was held	Urology Research Group (R8), Beatson Institute for Cancer Research, Garscube Estate, Switchback Rd, Glasgow
Type of Grant/Fellowship; Project Title;	Joint RCSEd / RCPSG Davies Fund Research Fellowship Validation of the MEK5 and ERK5 pathway as targets for drug development for prostate cancer and analysis of the proteomic basis of ERK5 induced function
Period grant held	February 2007-February 2009
From:	
To:	

Lay Summary (no more than 200 words)

Prostate cancer is a major public health issue. Its treatment remains unsatisfactory; and there is with an urgent need for novel therapies. The MEK5/ERK5 signalling pathway has recently been strongly implicated in prostate cancer with over expression being associated with advanced and aggressive disease. In this study we have shown that knockdown of ERK5 signalling in prostate cancer cells reduces the cells malignant potential i.e. proliferation, migration and invasion. We have also shown that ERK5 is over expressed in human metastatic prostate cancer. This data supports previous published results and confirms that targeting ERK5 in prostate cancer is an attractive therapeutic candidate. There is limited understanding at present about ERK5 signalling and its interacting proteins. Potential downstream targets of ERK5 were therefore investigated using prostate cancer cells. A novel relationship between ERK5 and another member of its signalling family, ERK1 was identified however further work is required to outline its role in the ERK5 signalling network.

Grant Report (no more than 1800 words)

(a) Clinical and Scientific Significance of advances made

Extracellular signal-regulated protein kinase 5 (ERK5) has been implicated in prostate carcinogenesis. In this study we further investigated the role of ERK5 in prostate cancer and examined its relationship with 2 other MAP Kinases, ERK1 and ERK2. Using siRNA to target ERK5 expression, we found that reduced ERK5 expression significantly inhibited cellular proliferation, motility and invasion in prostate cancer PC3 cells when compared to the controls, ($p < 0.005$). We have previously reported upregulated ERK5 expression in primary human prostate cancer specimens. In the present study, we were able to validate these results and demonstrate moderate-strong levels of cytoplasmic staining in 63% cases of PIN/PIA. High levels of cytoplasmic (55%) and nuclear (73%) immunoreactivity was also shown in a range of metastatic prostate tumours ($n=11$). Potential 'cross-talk' between ERK5 and ERK1/2 signaling was investigated using siRNA for each individual isoform of ERK1/2. ERK1 knockdown resulted in increased ERK5 activation in addition to prolonged ERK2 phosphorylation. Proliferation studies were also performed in PC3 cells, the results of which support published data that ERK1 acts as a negative regulator and ERK2 as a positive regulator of cell proliferation.

Our results validate the importance of the MEK5-ERK5 signaling pathway as a potential target for therapy in prostate cancer and highlight a novel functional and biochemical relationship between ERK1 and ERK5 signaling. A drug development programme coordinated by Cancer Research Technology continues to work towards the development of an ERK5 small molecule inhibitor for use in human prostate cancer.

ERK5 has been shown to regulate the activity of several transcription factors including MEF2, c-Fos and Fra-1, Sap-1, c-Myc and NF κ B. In order to further investigate the ERK5 signalling network we attempted to immunoprecipitate ERK5 and use mass spectrometry analysis to identify any interacting proteins. This work is still being analysed.

(b) Problems encountered and steps taken to overcome them

Initial immunoprecipitation experiments identified insufficient levels of ERK5 in PC3 cells to continue with endogenous ERK5 pulldown. HEK293 cells were therefore transfected with FLAG-tag ERK5. Abundant levels of exogenous ERK5 were immunoprecipitated in order for mass spectrometry analysis to be performed.

(c) Collaborations established

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

Publications

Aberrant expression of extracellular signal-regulated kinase 5 in human prostate cancer

SRC McCracken, **A Ramsay**, R Heer, ME Mathers, BL Jenkins, J Edwards, CN Robson, HY Leung
Oncogene 2008; 27(21):2978-88.

Signalling pathways in prostate carcinogenesis- Potentials for Molecular Targeted Therapy

Ramsay AK, Leung HY
Clinical Science. *In production, April 2009.*

Oral Presentations

Validation of the MEK5 and ERK5 pathway as targets for drug development for prostate cancer

Ramsay AK, Leung HY
West of Scotland Urology Group Meeting, Glasgow October 2007

The role of ERK5 signalling in human prostate cancer

Ramsay AK, Leung HY
Scottish Society of Experimental Medicine, Glasgow November 2007

The importance of NF κ B and its relationship with ERK5 in Prostate Cancer

Ramsay AK, Zhang L, Leung HY
West of Scotland Urology Group, Glasgow November 2008

ERK5 signalling in prostate cancer and its relationship with ERK1/2

Ramsay AK, Seywright M, Leung HY
Scottish Urology Society, Lanarkshire April 2009
(Winner of registrar presentation prize)

Poster Presentations

Validation of the MEK5 and ERK5 pathway as targets for drug development for prostate cancer

Ramsay AK, Leung HY
Northern England and South of England Prostate Cancer Collaborative, Cambridge
November 2007

Validation of the MEK5 and ERK5 pathway as targets for drug development for prostate cancer

Ramsay AK, Leung HY
BAUS Society of Academic Urology, London January 2008

ERK5 is overexpressed in prostate cancer and represents a potential target for drug development

Ramsay AK, Seywright M, Keller E, Leung HY
BAUS Annual Meeting, Manchester

June 2008

The importance of NF_κB and its relationship with ERK5 in Prostate Cancer

Ramsay AK, Zhang L, Leung HY

Northern England and South of England Prostate Cancer Collaborative, Cambridge
November 2008

(E) Acknowledgements

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