University of Birmingham

Dr Clare Davies PhD, B.Med.Sc

Birmingham Fellow

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About

Clare Davies is a Research Group Leader at the School of Cancer Sciences. Clare's approaches involve understanding the role of proteins in cancer biology from the molecular level to the whole animal, by using a combination of cell biology, protein-biochemistry and mouse genetics approaches. This enables her to fully understand mechanistically how biochemical pathways within a cell influence the complex interactions that occur between tumour cells and the host microenvironment.

She has recently been awarded a Birmingham Fellowship to establish her group to study the role of protein arginine methylation in cancer development, with a focus on understanding how protein methylation effects gene expression in breast cancer.

Qualifications

- PhD in Cancer Biology (2003)
- B.Med.Sci (Hons) (1998)

Biography

Clare Davies qualified in 1998 with a Bachelor of Medical Science (B.Med.Sc) from the University of Birmingham, and continued her studies in Birmingham obtaining a PhD in Cancer Biology at the School of Cancer Sciences.

Clare was then awarded a CRUK Post-Doctoral Fellowship to work with Dr. Axel Behrens at the CRUK-London Research Institute (LRI) investigating novel mechanisms of gene expression in cancer. She then joined Dr. Cathy Tournier's lab at the University of Manchester where she built on her expertise studying cancer development in vivo using genetically altered mice.

Clare has recently been awarded a Birmingham Fellowship to initiate her own research group, and joined the School of Cancer Sciences in October 2012.

Postgraduate supervision

Dr Davies is interested in supervising doctoral research students in the following areas:

- Genetic analysis of PRMTs in breast cancer development
- Novel substrates and regulators of PRMTs in physiological and pathological conditions
- Methylation of RACO-1 in breast cancer development

If you are interesting in studying any of these subject areas please contact Clare on the contact details above, or for any general doctoral research enquiries, please email: **dr@contacts.bham.ac.uk (mailto:dr@contacts.bham.ac.uk)** or call +44 (0)121 414 5005.

Research

Arginine methylation and gene expression in cancer

Changes in genes expression are crucial for the transformation of a normal cell to a metastatic and malignant cancer cell. Gene activation is incredibly complex and crucially involves two main interconnected events; chromatin remodelling and the recruitment of specific transcription factor complexes. Oncogenic signals modulate these events through the reversible modification of protein function through the addition of chemical/small molecules. Arginine methylation catalysed by protein arginine methyltransferases (PRMTs) is one such important but understudied modification as PRMTs are often found within chromatin remodelling complexes. However, they can also directly modulate gene expression by directly influencing transcription factor complexes as Clare has previously shown that the activity of c-Jun/AP-1 is promoted by the methylation of co-activator RACO-1. This is significant as c-Jun activity is often upregulated in human cancer and emphasis the potential role of protein methylation in tumourigenesis.

The regulation and substrate specificity of PRMTs in Breast Cancer

Since arginine methylation is a newly emerging field of research its role in gene expression in both normal and malignant cells is not well understood. However, recent studies have strongly link this protein modification with breast cancer. Levels of PRMTs are elevated in Estrogen Receptor (ER) breast cancer, key proteins involved in disease progression are arginine methylated and silencing of PRMT1 reduces the growth of breast cancer cells. This is exciting as specific PRMT inhibitors are currently being developed, suggesting that targeting non-conventional forms of protein modification could be a novel strategy in promoting tumour cell death. This is particularly important in breast cancer as current regimes for both ER+ and Her2+ cancers often lead to the development of drug resistance.

The Davies lab aims to increase our molecular understanding of how arginine methylation contributes to breast cancer development. More specifically the questions that we are addressing include:

(1) Do PRMTs initiate or facilitate cancer progression.
(2) How do PRMTs drive tumourigenesis.
(3) How is the activity of PRMTs regulated by oncogenic signals.

(4) Can PRMT expression in breast cancer be a biomarker for disease subtype.

To address these questions, the lab uses mammary 3D cell-culture models and genetically modified mice to investigate the in vivo significance of PRMTs in cancer development, in combination with protein-biochemical approaches to study cellular processes at the molecular level. In particular, the lab investigates the role methylation plays in controlling c-Jun/ AP-1 activation in breast cancer.

Other activities

Member of the Biochemical Society

Publications

Davies CC, Harvey E, McMahon R, Finegan KG, Connor F, Davies RJ, Tuveson DA, Tournier C (2014) Conditional deletion of mkk4 and mkk7 cooperates with KrasG12D expression to accelerate pancreatic ductal adenocarcinoma in mice. Cancer Research 74 (12), 3344-56.

Davies CC and Behrens A (2013) Arginine methylation: Making its mark on AP-1 gene activation. Cell Cycle 12:15, 2333–2334.

Davies CC, Chakraborty A, Diefenbacher ME, Skehel M, and Behrens A (2013) Arginine methylation of thec-Jun co-activator RACO-1 is required for c-Jun/AP-1 activation. The EMBO Journal 32, 1556 – 1567.

Davies C and Tournier C (2012). Exploring the function of the JNK (c-Jun N-terminal kinase) signalling pathway in physiological processes to design novel therapeutic stratagies. Biochem Soc Trans. (40):85-9.

Knox PG*, Davies CC*, Ioannou M, and Eliopoulos AG (2011). The death domain kinase RIP1 links immunoregulatory CD40 receptor to apoptotic signalling in carcinoma cells. The Journal of Cell Biology,(192):391-399
*Equal contribution to this work.

Davies CC, Chakraborty A, Cipriani F, Haigh K, Haigh JJ and Behrens A (2010). RACO-1 links AP-1 activity to growth factor signalling. Nature Cell Biology, (10): 963-72
*Signalling Gatway Featured Article of the Week

Davies CC, Mak TW, Young LS, Eliopoulos AG (2005). TRAF6 is required for TRAF2 dependent CD40 signal transduction in nonhemopoietic cells. Mol. Cell Biol. (25): 9806-19

Davies CC, Bem D, Young LS, Eliopoulos AG (2005). NF-kB overrides the apoptotic program of TNF receptor 1 but not CD40 in carcinoma cells. Cell Signal (17): 723-38

Davies CC, Mason J, Wakelam MJ, Young LS, Eliopoulos AG (2004). Inhibition of PI3K and ERK MAPK-regulated protein synthesis reveals the pro-apoptotic properties of CD40 ligation in carcinoma cells. J Biol Chem. (279): 1010-19

Eliopoulos AG, Davies C, Blake SS, Murray P, Najafipour S, Tsichlis PN, Young LS (2002). The oncogenic protein kinase Tpl-2/Cot contributes to Epstein-Barr virus-encoded latent infection membrane protein 1-induced NF-kappaB signaling downstream of TRAF2. J Virol. (76):4567-79.

Eliopoulos AG, DAVIES C, Knox PG, Gallagher NJ, Afford SC, Adams DH, Young LS (2000). CD40 induces apoptosis in carcinoma cells through activation of cytotoxic ligands of the tumor necrosis factor superfamily. Mol Cell Biol. (20):5503-15.