University of Birmingham

Dr Grant Stewart

Reader in Cancer Genetics

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About

Dr Grant Stewart is a CR-UK Career Development and Lister Institute Fellow, who runs a laboratory within the College of Medicine and Dentistry, School for Cancer Sciences.

The principle focus of the research ongoing within Dr. Stewart's laboratory is understanding how the cellular recognises and responds to genetic damage, such as DNA breaks and DNA inter-strand cross-links, which are caused by exposure to ionising radiation and certain chemotherapeutic drugs. One of the primary research goals of the laboratory is to understand how the ubiquitin and SUMO system function to regulate the recruitment of repair proteins to sites of DNA damage and how defects in this pathway contribute the development of human disease and cancer.

Qualifications

- Reader in Cancer Genetics. 2012
- Lister Institute Fellow. 2009
- CR-UK Career Development Fellow. 2005
- Ph.D. Institute for Cancer Studies, University of Birmingham. 2000
- BSc (Hons) University of Bristol. 1996

Biography

Dr. Grant Stewart received his first degree in Cellular and Molecular Pathology at the University of Bristol (1996). He subsequently joined the laboratory of Professor Malcolm Taylor at the University of Birmingham to do a Ph.D. studying the heterogeneity of the chromosomal instability syndrome, Ataxia-Telangiectasia (A-T), and the role of the ATM (Ataxia-Telangiectasia Mutated) gene in sporadic leukaemia. During the course of his Ph.D., he identified mutations in DNA double strand break (DSB) gene, hMRE11, also contributed to the development of a syndrome similar to A-T (A-T-like disorder or ATLD), firmly establishing a genetic link between the hMre11 DSB repair complex and ATM.

Continuing his growing interest in the cellular response to DNA damage, he moved in 2002, with a European Molecular Biology Organisation (EMBO) Long Term Fellowship, to the laboratory of Professor Stephen Elledge at Baylor College of Medicine (Houston, Texas). Whilst at Baylor, he identified a novel DNA double strand break repair protein called Mediator of DNA Damage Checkpoint 1 (MDC1) and demonstrated it played a role in recruiting other DSB responsive proteins to the sites of DNA breaks to facilitate repair and cell cycle checkpoint activation.

In 2005 Dr. Grant Stewart moved back to the University of Birmingham with a CR-UK Career Development Fellowship to start up his own laboratory investigating the function of the DNA DSB repair proteins, MDC1 and 53BP1, during the cellular response to DNA damage and also how defects in pathways controlled by these proteins contribute to human disease and tumourigenesis. Recently his group has identified a novel human immunodeficiency syndrome associated with defective repair of DNA DSBs called RIDDLE syndrome. 'RIDDLE' is an acronym describing its common clinical features: Radiosensitivity, ImmunoDeficiency, Dysmorphic facial features and LEarning difficulties. Through a collaboration his laboratory was able to identify the gene mutated in RIDDLE syndrome as RNF168 and that the encoded protein facilitates the recruitment of DSB repair proteins, such as 53BP1 and BRCA1, to sites of DNA damage by promoting relaxation of the chromatin structure surrounding the break.

Despite these findings, very little is known about the function of RNF168 during the cellular response to DNA DSBs and how defects in this pathway contribute to human immunodeficiency. Currently Dr. Grant Stewart's laboratory is focusing on RIDDLE syndrome and determining how RNF168 and the ubiquitin/SUMO system functions in the cell to coordinate DNA DSB repair, which is in part funded by CR-UK and a Lister Institute Research Prize.

Teaching

- Science undergraduate students: BMedSci (Year 2 and 3).
- Medical undergraduate students: MBChB (Year 2 course on 'Cancer; causes to cures')
- Postgraduate MSc students: (Clinical Oncology)

Postgraduate supervision

Grant is interested in supervising doctoral research students in the following areas:

- Regulation of the cellular response to DNA damage by the ubiquitin/SUMO system
- Identification of novel human disease genes involved in the repair of DNA damage by total genome sequencing
- Functional regulation of the DNA damage response by phosphorylation/dephosphorylation

If you are interesting in studying any of these subject areas please contact Grant 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

The cellular response to DNA double strand breaks (DSB) is a complex, integrated network of pathways that function to preserve the integrity of the genome. Following the recognition of DNA damage, a cascade of repair protein recruitment is initiated that is essential for the timely and accurate repair of the DNA lesion. This occurs in a highly ordered, hierarchical manner, principally controlled by mediator proteins, such as MDC1 and 53BP1. Mediator proteins function as molecular scaffolds that facilitate the recruitment and localized activation of repair and checkpoint proteins within the microenvironment surrounding the damage.

Access of repair proteins to sites of DNA damage requires the controlled relaxation of the surrounding chromatin. This process is regulated by the post-translational modification of histones adjacent to the DNA break, which involves enzymes that coordinate protein phosphorylation, ubiquitylation, SUMOylation, methylation and acetylation.

The research ongoing in the laboratory of Dr. Grant Stewart centres on understanding how the cell coordinates the relocalisation of repair/checkpoint proteins to the sites of DNA damage and how defects in this pathway contributes to the development of human disease and cancer. The identification of mutations in the RNF168 gene as the underlying genetic cause of the human immunodeficiency disorder, RIDDLE Syndrome, by Dr. Stewart's laboratory has highlighted the importance of the ubiquitin system in facilitating repair of programmed DNA breaks that occur during immune system development. Based on this, research projects within Dr. Stewart's laboratory currently focus on determining how the ubiquitin/SUMO system regulates the recognition and repair of DNA damage, the identification of novel proteins that function to regulate this process and whether components of this pathway are mutated in human syndromes characterised by nervous/immune system abnormalities and cancer predisposition.

Other activities

Memberships:

- Biochemical Society (2006)
- European Society for Immunodeficiencies (2006)
- British Association for Cancer Research (2010)
- European Association for Cancer Research (2010)

Editorial experience:
Reviewer of manuscripts submitted to EMBO Journal, EMBO Reports, Molecular and Cellular Biology, Oncogene, Journal of Cell Science, Experimental Cell Research, Journal of Cell Biology, Journal of Experimental Medicine, Biochemical Journal, Nucleic Acids Research, DNA repair, Cell Cycle, Nature Cell Biology, Nature Structure and Molecular Biology and Nature.

Grant reviewing experience:
I review grant applications submitted to the Medical Research Council (MRC), Cancer Research UK (CR-UK), INCa French National Cancer Institute, Leukaemia and Lymphoma Research (LLR), Biotechnology and Biological Sciences Research Council (BBSRC), European Research Council (ERC), Association for International Cancer Research (AICR), Breast Cancer Campaign (BCC) and the Lister Institute.

Publications

Stewart GS**, Stankovic T, Byrd PJ, Wechsler T, Miller ES, Huissoon A, Drayson MT, West SC, Elledge SJ, Taylor AM. (2007). RIDDLE immunodeficiency syndrome is linked to defects in 53BP1-mediated DNA damage signaling. Proc Natl Acad Sci U S A. 104:16910-5. (** Corresponding author)

Spycher C, Miller ES, Townsend K, Pavic L, Morrice NA, Janscak P, Stewart GS, Stucki M. (2008). Constitutive phosphorylation of MDC1 physically links the MRE11/RAD50/NBS1 complex to damaged chromatin. J. Cell Biol. 181:227-40

Blackford AN, Bruton RK, Dirlik O, Stewart GS, Taylor AMR, Dobner T, Grand RJA, and Turnell AS (2008) A role for E1B-AP5 in ATR signalling pathways during adenovirus infection J. Virol. 82:7640-52

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Zlatanou A, Despras E, Braz-Petta T, Boubakour-Azzouz I, Pouvelle C, Stewart GS, Nakajima S, Yasui A, Ishchenko AA, Kannouche PL. (2011). A novel pathway involving hMsh2-hMsh6 complex, mono-ubiquitinated PCNA and pol eta in response to oxidative DNA damage in human cells. Mol Cell. 43:649-662.

Polo SE, Blackford AN, Chapman JR, Baskcomb L, Gravel S, Rusch A, Thomas A, Blundred R, Smith P, Dobner T, Taylor AMR, Turnell AS, Stewart GS, Grand RJA, Jackson SP. (2012). Regulation of DNA-end resection by hnRNPU-like proteins promotes DNA double-strand break signaling and repair. Mol Cell. 45:505-16.

Byrd PJ, Srinivasan V, Last JI, Smith A, Biggs B, Carney EF, Exley E, Abson C, Stewart GS, Izatt L, Taylor AMR. (2012). Severe reaction to radiotherapy for breast cancer as the presenting feature of ataxia telangiectasia. Br. J. Cancer 106:262-8.

Ogi T, Walker S, Stiff T, Hobson E, Limsirichaikul S, Carpenter G, Prescott K, Suri M, Byrd PJ, Matsuse M, Mitsutake N, Nakazawa Y, Vasudevan P, Barrow M, Stewart GS, Taylor AMR, O'Driscoll M, Jeggo PA. (2012). Indentification of the first ATRIP-deficient patient and novel mutations in ATR define a clinical spectrum for ATR-ATRIP Seckel Syndrome. PLoS Genet. (In press).