University of Birmingham

Dr Andy Turnell

Senior Lecturer

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About

Andy Turnell is a Senior Lecturer in the School of Cancer Sciences. He is interested in how viruses regulate host cell transcription programmes and cell cycle checkpoints in order to promote viral replication and cellular transformation. He is particularly interested in how adenovirus oncoproteins modulate the function of host cell proteins to regulate chromatin, the ubiquitin-proteasome pathway and DNA damage pathways. He is also interested in how the cellular proteins targeted by adenovirus function to control fundamental cellular pathways.

Qualifications

- BSc Medical Biochemistry, University of Birmingham.
- PhD Biochemistry, University of Birmingham.

Biography

- Senior Lecturer: 2009-present
- Lecturer: 2008-2009
- RCUK Birmingham Fellow in Cancer Virology: 2005-2010
- Post-Doctoral work on adenovirus at UoB: 1994-2004

Teaching

MRes Endocrine Cancer
(i) module lead
(ii) lecture on oncogenes and tumour suppressor gene function

Medicine and Surgery MBChB (/undergraduate/courses/med/medicine.aspx) II
(i) SGT lead on p53- from mutation to treatment
(ii) lecture on tumour suppressor gene function
(iii) SGT tutor on Viruses and Cancer

Medical Science BMedSc (/undergraduate/courses/med/medical-sci.aspx) III
(i) Lecture on cell growth and senescence
(ii) supervise final year lab-based projects

Clinical Science BMedSc - Intercalated Degree (/undergraduate/courses/med/ClinicalScienceBMedSc-IntercalatedDegree.aspx)
(i) lecture on cell cycle and apoptosis

Clinical Oncology MSc/Postgraduate Diploma (/postgraduate/courses/taught/med/clinical-oncology.aspx)
(i) lecture on cell growth, senescence and tumour suppressor gene function

Postgraduate supervision

Andy currently supervises PhD projects investigating:

(i) the role of adenovirus early region proteins in viral replication and cellular transformation.

(ii) the role of the Anaphase-Promoting Complex/Cyclosome in the cell cycle.

If you are interested in pursuing a PhD in either of these areas please contact Andy directly by e-mail.

Andy also supervises lab-based projects for MRes and MSc students.

Research

Research Themes:

Viral Oncology, Cancer Cell Biology

Research Activity:

i) Regulation of ubiquitin-proteasome and DNA damage signalling pathways by adenovirus

In recent years it has become apparent that in order to replicate efficiently viruses have evolved to selectively activate/inactivate DNA damage response signalling pathways in order to promote viral replication. In this regard we have determined that different Ad serotypes differentially regulate DNA damage signalling pathways during infection (Blackford *et al*., 2008; Forrester *et al*., 2011). These studies have also determined that the adenovirus E1B55K-binding protein, E1B-AP5 (also known as hnRNPUL1) is an integral component of ATR signalling pathways activated during infection (Blackford *et al*., 2008).

It has previously been determined that Ad5 utilizes a cullin 5-RING ubiquitin ligase to target p53 and the Mre11-Rad50-NBS1 component, Mre11 for proteasomal-mediated degradation during infection in order to inactivate p53 and ATM signalling pathways. Recent work from our lab has determined that Ad12 preferentially utilizes a cullin 2-RING ubiquitin ligase to target p53 for degradation during infection, and that Ad12 also uses this ubiquitin ligase to target the ATR activator, TopBP1 for proteasomal degradation during infection (Blackford *et al*., 2010). Ad12-mediated degradation of TopBP1 ensures that the checkpoint kinase, Chk1 is not activated during infection.

We are currently employing proteomic techniques to identify novel adenovirus early region-binding proteins in adenovirus-infected and adenovirus-transformed cells. We anticipate that this approach will help identify proteins that function in DNA damage response pathways or anti-viral/stress response pathways and that are targeted by adenovirus in order to facilitate viral replication and/or promote adenovirus-mediated cellular transformation. In order to determine to what extent adenovirus targets the ubiquitin-proteasome pathway during infection we also employ proteomic techniques in order to identify those proteins whose expression is affected significantly by adenovirus infection or during the process of adenovirus-mediated cellular transformation.

ii) Regulation of the Anaphase-Promoting Complex/Cyclosome (APC/C)

The anaphase-promoting complex/cyclosome (APC/C) is a multicomponent E3 ubiquitin ligase that, by targeting protein substrates for 26S proteasome-mediated degradation through ubiquitylation, coordinates the temporal progression of eukaryotic cells through mitosis and the subsequent G1 phase of the cell cycle. Work in our lab established that the APC/C subunits APC5 and APC7 possess within their primary sequence CBP and p300 protein-protein interaction domains that are evolutionarily conserved in adenovirus E1A (Turnell *et al*., 2005) In this regard we determined that the APC/C and CBP/p300 cooperate to regulate transcription and cell cycle progression and that E1A targets APC/C-CBP/p300 complexes to promote cellular transformation.

In collaboration with Dr Grant Stewart we recently investigated the role of the DNA damage response protein, Mediator of DNA damage Checkpoint 1 (MDC1) in mitosis. We determined that MDC1 regulates metaphase-to-anaphase transition through its ability to bind directly to the APC/C-Cdc20 and modulate its E3 ubiquitin ligase activity (Townsend *et al*., 2009). The ability of MDC1 to regulate metaphase-to-anaphase transition was found to be independent of both the Spindle Assembly Checkpoint and ATM/ATR activation, but depended upon its ability to regulate the Cdc20-dependent activation of the APC/C (Townsend *et al*., 2009).

In light of these studies, current work in the lab is focused towards establishing how CBP/p300 and DNA damage signalling pathways regulate APC/C function, and determining the role of the APC/C in CBP/p300 transcription programmes and DNA damage signalling pathways. We have also identified novel APC/C-interacting proteins by mass spectrometry and are consequently interested in establishing the role of these proteins in cell cycle control as well as determining their functional relationship to the APC/C.

Other activities

Core Member of BBSRC committee D: Molecules, Cells and Industrial Biotechnology

Editorial Board, Journal of General Virology

School of Cancer Sciences Chemical Safety Advisor

Member of School Health and Safety Executive committee

Publications

Selected publications:

Sedgwick G. G., Townsend K., Martin A., Shimwell N. J., Grand R. J. A., Stewart G. S., Nilsson J., and Turnell A. S. (2012) Transcriptional Intermediary Factor 1γ binds to the Anaphase-Promoting Complex/Cyclosome and promotes mitosis. Oncogene. doi: 10.1038/onc.2012.501. [Epub ahead of print].

Turnell A. S. and Grand R. J. (2012). DNA viruses and the cellular DNA-damage response. *J. Gen. Virol.* 93:2076-2097.

Forrester N. A., Patel R. N., Speiseder T., Groitl P., Sedgwick G. G., Shimwell N. J., Seed R. I., Ó Catnaigh P, McCabe C. J., Stewart G. S., Dobner T., Grand R. J., Martin, A. and Turnell A. S. (2012). Adenovirus E4orf3 targets Transcriptional Intermediary Factor 1γ for proteasome-dependent degradation during infection. *J. Virol.* 86:3167-3179.

Forrester N. A., Sedgwick G.G., Thomas A,. Blackford A.N., Speiseder T., Dobner T., Byrd P.J., Stewart G.S., Turnell A.S. and Grand R.J. (2011). Serotype-specific inactivation of the cellular DNA damage response during adenovirus infection. *J Virol.* 85:2201-2211.

Blackford A. N., Patel R. N., Forrester, N. A., Theil K., Groitl P., Stewart G. S., Taylor A. M. R., Morgan I. M., Dobner T., Grand R. J. A. and Turnell A. S. (2010) Adenovirus 12 E4orf6 inhibits ATR activation by promoting TOPBP1 degradation *Proc. Natl. Acad. Sci. USA.* 107:12251-12256.

Townsend K., Mason H., Blackford A. N., Miller E. S., Chapman J.R., Sedgwick G. G., Barone G., Turnell A. S. and Stewart G. S. (2009) MDC1 regulates mitotic progression. *J. Biol. Chem.* 284:33939-48.

Blackford A. N., Stewart G. S., Taylor A. M. R., Dobner T., Grand R. J. and Turnell A. S. (2008) A role for E1B-AP5 in ATR kinase signalling pathways during adenovirus infection *J. Virol.* 82:7640-7652.

Bruton R. K., Rasti M., Mapp K. L., Young N., Carter R. Z., Abramowicz I. A., Onion D. F., Shuen D. F., Mymryk J. S., Turnell A. S. and Grand R. J. A. (2007) CtIP binds directly to AdE1A through its N terminal region and CR3. *Oncogene* 26:7467-7479.

Rasti M., Grand R. J. A., Yousef Y. F., Shuen M., Mymryk J. S., Gallimore P. H. and Turnell A. S. (2006) Roles for APIS and the 20S proteasome in adenovirus E1A-dependent transcription. *EMBO J.* 25:2710-2722.

Turnell A. S., Stewart G. S., Grand R. J. A., Rookes S. M., Martin A., Yamano H., Elledge S. J. and Gallimore P. H. (2005) The APC/C and CBP/p300 cooperate to regulate transcription and cell-cycle progression. *Nature* 438:690-695.

Rasti M., Grand R. J. A., Mymryk J. S., Gallimore P. H. and Turnell A. S. (2005) Recruitment of CBP/p300, TBP and S8 to distinct regions at the N-terminus of adenovirus E1A. *J. Virol.* 79:5594-5605.

Turnell A. S. , Grand R. J. A., Gorbea C., Xhang X., Wang W., Mymryk J. S. and Gallimore P. H. (2000) Regulation of the 26S proteasome by adenovirus E1A. *EMBO J.*

19:4759-73.

Hutton F. G., Turnell A. S., Gallimore P. H. and Grand R. J. A. (2000) Consequences of disruption of the interaction between p53 and the larger adenovirus early region 1B protein in adenovirus E1 transformed cells. *Oncogene* 19:452-62.

Turnell A. S., Grand R. J. A. and Gallimore P. H. (1999) The replicative capacities of large E1B-null group A and group C adenoviruses are independent of host cell p53 status. *J. Virol.* 73:2074-83.