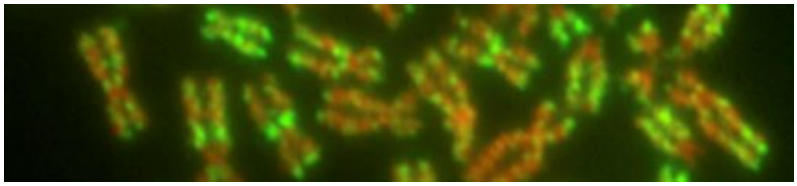
Chromatin and Gene Expression



Group Leader: **Professor Bryan Turner (/staff/profiles/cancer/turner-bryan.aspx)**

Overview

DNA is packaged into the nuclei of all eukaryotic cells as a complex with histone proteins, known as chromatin. DNA packaging itself has a major effect on whether genes are expressed or silent, while chemical modification of histones by families of enzymes, provides a signalling system that can target regulatory proteins to specific genes, thereby adding further levels of regulation.

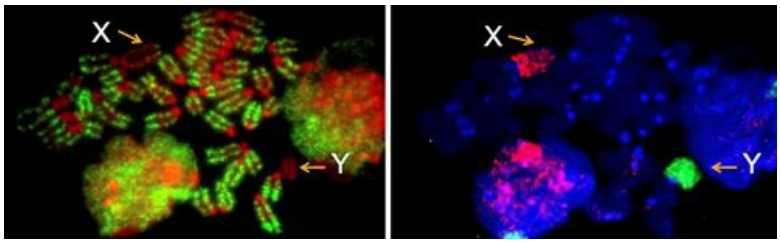
Our Research Group

The Chromatin and Gene Expression Group explores the mechanisms by which epigenetic marks, especially histone modifications, regulate patterns of gene expression through differentiation and development. We have a particular interest in the ways in which environmental agents, including therapeutic drugs and dietary components, can trigger epigenetic change, and in identifying circumstances in which such changes can be heritable, through the cell cycle, from one cell generation to the next.

We work with histone deacetylase (HDAC) inhibitors, particularly sodium valproate, a widely used anti-epileptic, a potential chemotherapeutic agent and a known teratogen. Although VPA induces global histone hyperacetylation, its effects on gene expression are complex and surprisingly restricted. We are beginning to unravel the mechanisms involved. We have shown a close link between changes in histone acetylation and methylation at specific amino acids mediated by the methyltransferase MLL, and this link is being explored.

The group uses model systems based on cultured human or mouse cells, including embryonic stem cells and human lymphoblastoid cell lines. Experimental approaches are based on the use of antibodies specific for particular modified histones, in chromatin immunoprecipitation (ChIP) and immunomicroscopy. Novel approaches have been developed to work with small numbers of cells and thereby to explore environmentally induced epigenetic changes in the early embryo or in cell sub-populations isolated by flow cytometry (FACS), including cells in different stages of the cell cycle.

Sophisticated microscopical approaches provide information on the distribution of histone modifications in single cells, and across metaphase chromosomes, potentially providing new biomarkers to monitor cancer progression or identify subtypes. Mapping histone modificatons across metaphase chromosomes at much higher resolution is being accomplished by ChIP using chromatin from metaphase cells (isolated by FACS) coupled to next generation sequencing.



Metaphase chromosomes immunostained to detect histone H4 mono-methylated at lysine 4 (green, left panel). X and Y chromosomes (identified with DNA probes, right) are depleted in this modification.

Current Projects...

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Defining an early transcriptional response to histone deacetylase inhibitors: regulation by chromatin and effects on cell survival (Turner, Nightingale, Halsall)

Drugs that inhibit a family of enzymes known as histone deacetylases (HDACs) are undergoing clinical trials against a variety of cancers. While they have been found to be remarkably effective against a few rare cancers, they are much less effective against the most common cancers.

We will test the hypothesis, based on our preliminary data, that resistance to HDAC inhibitors in both normal cells and most cancers, is due to an ancient, evolutionarily conserved defence mechanism that serves to protect the cell's carefully regulated patterns of gene expression from the disruptive effects of environmental enzyme inhibitors. Understanding how this defence mechanism works will point the way to treatments that can make tumour cells more sensitive to existing HDAC inhibitors.

Exploring the metaphase epigenome in normal and leukaemic cells (Turner, Rutledge, Terrenoire)

When the cell divides (ie. at mitosis) the chromosomes become highly compacted and can be seen with a light microscope. We have devised a method for staining these chromosomes with antibodies to particular family of proteins that gives each chromosome its own distinctive pattern of bright and dim bands. Our continuing work will use both microscopy and molecular biology/biochemistry to ask how these bands relate to the function of genes aligned along the chromosome, whether the banding patterns differ in normal and cancer cells, and if so, why?

Regulation of the histone methyl-transferase MLL (Nightingale, Wiersma)

Histone methylation plays an important role in activating or silencing genes, depending on the specific histone residue that is modified. The MLL family of histone methyl-transferases plays an important role in development, and mis-regulation by MLL 'fusion' proteins is causal for a number of leukaemias. Our ongoing research focuses on how the extracellular environment, through marks in chromatin, regulates MLL activity, and how this is dysregulated in tumours.

Epigenetic marks through the cell cycle in embryonic stem cells (O'Neill, Goss)

The Carrier Chromatin ImmunoPrecipitation (CChIP) technique developed in our laboratory is being used to assay embryonic stem cells in different cell cycle phases, isolated by flow cytometry. The work will show how histone modifications across key genes change as cells grow and divide.

Recent Publications...

O'Neill, L.P. et al. (2006) Epigenetic characterization of the early embryo with a chromatin immunoprecipitation protocol applicable to small cell populations. Nature Genetics 38, 835-841

Nightingale, K.P. et al. (2007) Cross-talk between histone modifications in response to histone deacetylase inhibitors: MLL4 links histone H3 acetylation and histone H3K4 methylation. J.Biol.Chem. 282, 4408-4416

Lin, H. et al. (2007) Dosage compensation in the mouse balances up-regulation and silencing of X-linked genes. PLoS Biology 5 (12) e326

O'Neill, L.P. et al. (2008) Differential loss of histone H3 isoforms mono-, di- and tri-methylated at lysine 4 during X-inactivation in female embryonic stem cells. Biol. Chem. 389, 365-70

VerMilyea, M.D. et al. (2009) Transcription independent heritability of induced histone modifications in the mouse preimplantation embryo. PLoS One 4 (6) e6086

Thorne, J.L. et al. (2010) Epigenetic control of a VDR-governed feed-forward loop that regulates p21waf1/cip1 expression and function in non-malignant prostate cells. Nuc.Acids Res. 39 (6) 2045-56

Terrenoire, E. et al. (2010) immunostaining of modified histones defines high-level features of the human metaphase epigenome. Genome Biol. 11 (11) R110.

Lin H, et al. (2011) Relative overexpression of X-linked genes in mouse embryonic stem cells is consistent with Ohno's hypothesis. Nature Genetics 43 (12) 1169-70.

Halsall J, et al. (2012) Genes are often sheltered from the global histone hyperacetylation induced by HDAC inhibitors. PLoS One 7(3) e33453

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