



Scottish Chromatin Group



7th Scottish Chromatin Group Meeting and 2010 Tenovus-Scotland Medal Lecture

Wednesday 9th June 2010

Charles Wilson Lecture Theatre, University of Glasgow.

Preliminary programme

10.00 Tea/coffee welcome

7th Scottish Chromatin Group meeting

10.30 - 11.10 **Kevin Hiom**, University of Dundee

Ubiquitylation of histone H2A in chromatin: what does it do?

11.10 - 11.40 **John Thomson** (Adrian Bird's group), University of Edinburgh

DNA Sequence at CpG islands influences chromatin structure via the CpG binding protein Cfp1

CpG islands (CGIs) are prominent in the mammalian genome due to their GC-rich base composition and high density of CpG dinucleotides, but their function is unknown. We found that the CpG binding protein Cfp1 colocalises with CGIs and is essential for the maintenance of histone H3 lysine 4 trimethylation at these loci. Insertion of artificial clusters of CpG created novel H3K4me3 peaks, suggesting that DNA sequence can direct the modification state of surrounding chromatin via interactions with CpG binding proteins.

See Thomson J.P. et al. (2010) CpG islands influence chromatin structure via the CpG-binding protein Cfp1. *Nature* 464, 1082-1086.

11.40 - 12.25 **Peter Fraser**, Babraham Institute, Cambs

Spatial transcription networks between co-regulated genes

Genome-wide e4C screens for genes sharing transcription factories with the mouse α - and β -globin genes has revealed hundreds of preferred intra- and inter-chromosomal transcription partners. We show that genes positively regulated by the erythroid kruppel-like factor Klf1 preferentially share a discrete number of specialized transcription factories in erythroid nuclei.

See Schoenfelder S., et al. (2010) Preferential associations between co-regulated genes reveal a transcriptional interactome in erythroid cells. *Nature Genetics* 42:53-61.

12.25 - 13.25 Buffet lunch

13.25 - 13.55 **Kelly Chiang** (Dave Vetrie's group), University of Glasgow

Defining the relationships between histone modifications and gene splicing

13.55 - 14.40 **Jane Mellor**, University of Oxford

Histone modifications, transcription factors, ncRNA and gene loops in transcription.

The majority of yeast genes are transcribed on both the sense and antisense strand, even when repressed. There are often two antisense transcripts (ncRNAs), one of which extends into the promoter region and one which terminates around the transcription initiation site and these may function to either repress or promote sense transcription. The 3' region of many regulated genes contains both the sequences (consensus 8bp TATA box) and chromatin organisation to promote antisense transcripts.

In this talk I will discuss the role played by

- (i) transcription factors that respond to nutrient cues and the cell cycle,
- (ii) post-translational modifications on histone H3,
- (iii) nucleosome organisation and
- (iv) the sua7-1 mutation in TFIIB in regulating sense and antisense transcripts at a number of genes.

14.40 - 15.20 Tea/coffee

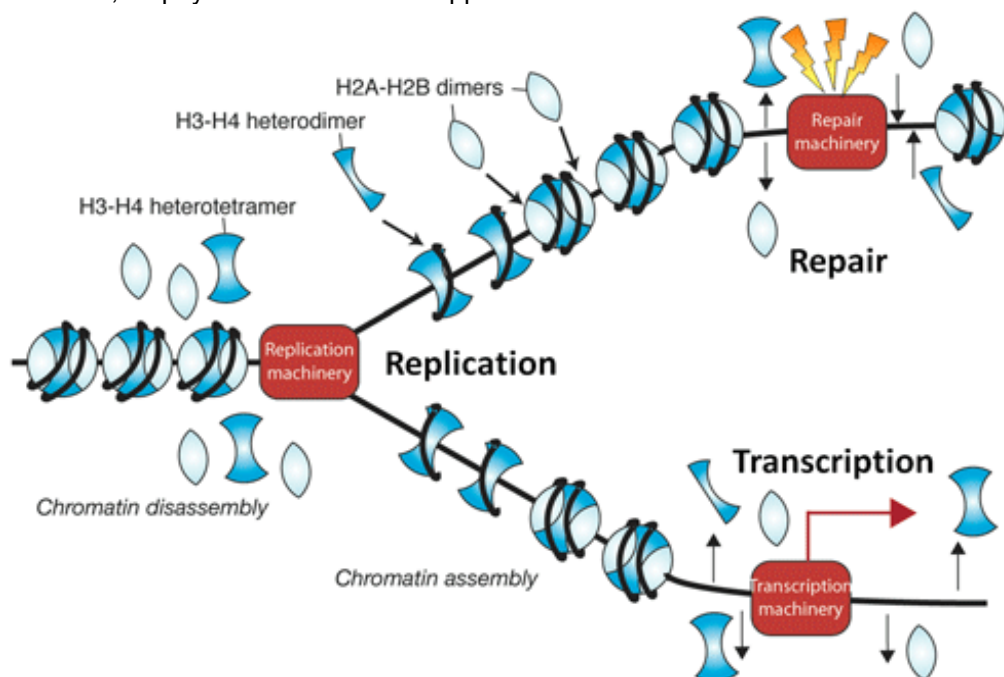
15.20 - 15.30 **2010 Tenovus-Scotland Medal Lecture**

Introduction by Prof. Sir Roddy MacSween, Chairman of Tenovus-Scotland

15.30 - 16.30 **Jessica Tyler**, University of Texas MD Anderson Cancer Center, Houston, USA

Regulation of genomic processes by chromatin assembly and disassembly

The packaging of the eukaryotic genome into chromatin is essential for normal growth, development, and differentiation. The fundamental repeating unit of chromatin is the nucleosome, comprising DNA wrapped around histone proteins H3, H4, H2A, and H2B. It is well established that histones are removed from the DNA prior to DNA replication and that the newly-replicated DNA is repackaged into chromatin. However, the machinery, mechanisms and cellular impact of chromatin assembly and disassembly were unknown. Furthermore, exactly how chromatin structures are accurately reassembled in order to reinstate the epigenetic information carried by the chromatin is still unclear. My discovery (as a postdoc) of the ubiquitous histone chaperone Anti-Silencing Function 1 (Asf1), that together with Chromatin Assembly Factor 1 (CAF-1) deposits histones onto newly-replicated DNA *in vitro*, provided the entry point to investigate these critically important issues. Our studies have utilized a combination of yeast molecular genetics, tissue culture studies, biochemical, biophysical and structural approaches.



Until recently, chromatin disassembly and reassembly were believed to only occur during DNA replication. Our hypothesis was that all genomic processes that utilize the DNA, including transcription, DNA repair, and recombination, would necessitate chromatin disassembly and reassembly. In agreement with the high degree of conservation of chromatin structure and genomic processes among eukaryotes, we have shown that human Asf1 can functionally replace budding yeast Asf1. Using yeast, we discovered that Asf1 mediates the disassembly of chromatin during transcription. Furthermore, we discovered that the disassembly and assembly of chromatin at promoter regions is essential for transcriptional regulation *in vivo*. Contrary to the previous dogma for transcriptional activator function, we showed that the sole role of at least some activators *in vivo* is to stimulate the loss of nucleosomes from promoters. We have also established that chromatin assembly and disassembly occur during DNA repair; Asf1 and CAF-1 are critical for genomic stability and viability following double-strand DNA repair due to their roles in assembling chromatin around DNA lesions. Our studies have also revealed that chromatin assembly after DNA repair, not repair of the DNA *per se*, is the event that signals to the DNA damage cell cycle checkpoint that repair is complete.

Mechanistically, it was widely assumed that histones H3/H4 always exist as a heterotetramer and are deposited onto DNA in this form. However, we unequivocally proved using biophysical methods and x-ray crystallography that the Asf1-H3/H4 complex comprises one molecule of Asf1 bound to an H3/H4 heterodimer. Indeed, Asf1 physically blocks formation of the H3/H4 heterotetramer. As such, the current proposed mechanisms of chromatin assembly and disassembly now need to be reevaluated.

More recently, we have expanded our studies of chromatin dynamics towards a better understanding of human disease, including aging and cancer. Asf1 is required for the acetylation of histone H3 on lysine 56 – a histone mark that loosens the intrinsic structure of the nucleosome. We have recently discovered a new mechanism of aging in yeast that is due to this epigenetic mark and have exploited our finding to achieve life-span extension. To date, the vast majority of studies on the acetylation of histone H3 on lysine 56 have been limited to yeast. We have recently discovered that this epigenetic mark also occurs in humans and *Drosophila*. Moreover, we have found a striking correlation between acetylation of histone H3 K56 and cancer. Consequently, studies of chromatin assembly and disassembly are fundamentally important for understanding all the activities of the genome, genomic instability, aging and cancer.

Ransom M, Dennehey BK, Tyler JK. (2010) Chaperoning histones during DNA replication and repair. *Cell*. 140: 183-95.

Das C., et al. (2009) CBP/p300-mediated acetylation of histone H3 on lysine 56. *Nature* 459:113-7.

Chen C.C., et al. (2008) Acetylated lysine 56 on histone H3 drives chromatin assembly after repair and signals for the completion of repair. *Cell* 134:231-43.

English C.M., et al. (2006) Structural basis for the histone chaperone activity of Asf1. *Cell* 127:495-508.

16.30 - 16.40 Medal presentation by Prof Anton Muscatelli, Principal, University of Glasgow.

16.40 Wine reception

Directions and maps

The meeting will be held in the Charles Wilson Lecture Theatre, a converted church located at the corner of Gibson Street and Kelvin Way on the main University of Glasgow campus. It is labelled as 'E15' on the University campus map (attached).

Limited pay-and-display parking is available locally. The nearest underground station is Kelvinbridge.

Further travel directions and information on disabled access can be found at

www.scottishchromatin.co.uk