

Meeting report

Chromatin remodeling and genome stability

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A report on the 12th Tenovus Scotland Symposium 'Stability and Regulation of Genes and Genomes', Glasgow UK, 6-7 April 2006.

A feature of many cancer cells is loss of genome stability. They become more prone to mutation and accumulate chromosomal rearrangements. The factors that impinge on genome stability are thus of great interest, and a recent meeting in Glasgow sponsored by the cancer charity Tenovus Scotland was an opportunity for researchers in disciplines such as DNA replication, repair, and recombination, and the epigenetic control of gene regulation, to learn about the overlapping mechanisms of chromatin remodeling and epigenetics in controlling these diverse functions.

Lessons from archaea and yeast

With the focus of the meeting mainly on higher eukaryotic cells, crossover of information from an unusual model system featured in the Tenovus-Scotland Medal lecture by Stephen Bell (MRC Cancer Cell Unit, Cambridge, UK). Genome stability depends on the faithful replication of DNA, and the DNA replication machinery of the unicellular archaea is a helpfully simplified version of that found in eukaryotes. Like eukaryotic chromosomes, the DNA of the archaeon *Sulfolobus solfataricus* contains multiple origins of replication, and its primase is a stripped-back version of the eukaryotic DNA polymerase-primase, being composed of a small and a large primase subunit only. It appears that histidine residues at the primase active site change conformation to help release the primer, and Bell noted that small molecules designed to block this conformational change, and thus to block DNA replication in actively dividing cells, might have potential as drugs against cancer. In both archaeal and human cells, the primase is coupled to the progression of the replication fork via a protein complex called the GINS complex. The GINS complex is consequently a

marker of proliferating cells and Bell demonstrated its promise in cancer detection.

In eukaryotic cells, sister chromatids are held together after replication by cohesins, proteins that encircle the duplicated chromatids. In a genome-wide analysis of the budding yeast *Saccharomyces cerevisiae*, Frank Uhlmann (Cancer Research UK, London, UK) reported that once cohesin is initially loaded onto the chromosome by the Scc2/Scc4 protein complex in the G₁ phase of the cell cycle, it surprisingly relocates to sites in the DNA where transcription is converging from different directions. This movement away from the loading machinery helps stabilize the cohesin ring, and Uhlmann suggested that the transcriptional machinery may 'push' cohesin towards the 3' ends of genes. As cohesin is loaded onto the DNA before the start of DNA replication, this raises the question of what happens when the replication fork meets a cohesin molecule. The replication fork might pass through the cohesin ring, or cohesin might be removed and then reassembled after fork progression. Uhlmann noted that the presence at replication forks of proteins required to help establish cohesin, such as the acetyltransferase Eco1 and the chromatin-associated protein Ctf4, might suggest the reassembly model.

Chromatin remodeling

A common role for chromatin-remodeling complexes in both DNA replication and DNA repair was introduced by Patrick Varga-Weisz (Babraham Institute, Cambridge, UK). The remodeling complex WICH is conserved in vertebrates and is targeted to sites of replication and may function to keep nucleosomes mobile, allowing the re-binding of *trans*-acting regulatory proteins after replication. If a component of this complex, the Williams syndrome transcription factor (WSTF), is knocked down, chromatin becomes more compact and transcription is impaired. As several chromatin-remodeling complexes are involved in recombination and repair, one outstanding question is how they are targeted. Varga-Weisz

proposed that histone modifications such as ubiquitination are involved. Proteins with CUE domains (named after the yeast protein Cue1) can interact with monoubiquitinated proteins, and one chromatin remodeler, Fun30, a yeast homolog of the human protein SMARCA4, contains these domains. Overexpression of SMARCA4 has been associated with genetic instability. Fun30 has ATPase activity and was shown to interact with ubiquitinated histone H4, and to be able to slide nucleosomes; if its ATPase activity is abolished, cells become sensitive to DNA damage, indicating a role for Fun30 in DNA repair.

Alain Verreault (Université de Montréal, Montreal, Canada) discussed a novel histone modification involved in the repair of DNA double-strand breaks. Abundant acetylation of lysine 56 (K56) of histone H3 is found predominantly in newly synthesized histones that are incorporated into nucleosomes during S phase of the cell cycle, and the lysines become deacetylated in G2. H3 K56 is located at the DNA entry/exit point on the nucleosome core and Verreault reported that mutations affecting its acetylation lead to increased sensitivity to agents that cause double-strand breaks. The persistence of K56 acetylation when double-strand breaks are present is due to the presence of DNA damage checkpoint proteins, and it is therefore important for the replication fork progression in the presence of DNA damage.

Epigenetic regulation

Epigenetic regulation deals with reversible changes to DNA or the state of chromatin that have long-term influences on gene expression. DNA methylation is considered a classic example of a repressive epigenetic chromatin mark. In *Xenopus* embryos, no transcription occurs until the mid-blastula transition, concomitant with a wave of DNA demethylation. Richard Meehan (MRC Human Genetics Unit, Edinburgh, UK) described how antisense knockdown of the maintenance methyltransferase Dnmt1 led to an upregulation of 25% of the genes analysed. Meehan presented data suggesting that Dnmt1 can act as a repressor in addition to its role in DNA methylation maintenance.

A hierarchical order in the appearance of epigenetic marks at a gene can be crucial to controlling gene expression. Jane Mellor (University of Oxford, UK) provided the example of K36 methylation of histone H3, which is required for the recruitment of Eaf3, which in turn is required for histone deacetylation. A failure to deacetylate by Eaf3 can facilitate transcription from cryptic promoters. Mellor also introduced the idea that many of the epigenetic marks analyzed by researchers are dynamic, as illustrated by data from the *MET16* gene in yeast. The epigenetic marks (both histone acetylation and methylation) may often only be present for short periods of time, and their order of arrival is crucial to setting up a 'cascade' of marks through interactions with remodelling complexes such as NuA4, which contains Eaf3.

The HS4 region of the chicken β -globin locus acts as a 'barrier' element to protect against the spreading of the surrounding chromatin status into the locus. Gary Felsenfeld (National Institutes of Health, Bethesda, USA) described a protein complex found at HS4 that contained both the transcription factor USF and the methyltransferase PRMT1. Knockdown of *PRMT1* led to a decrease in H4 methylation on arginine 3 (R3) and a loss of many of the 'active' marks throughout the β -globin locus. It appears that methylation of R3 is essential for the subsequent establishment of many of the 'active' marks. It remains to be seen what proteins interact with R3 methylation to achieve this remodeling.

Moved to expression

Taking a step back from the analysis of chromatin remodeling at this level, Wendy Bickmore (MRC Human Genetics Unit) proposed that clustering of genes with similar expression patterns disrupts long-range condensation of chromatin and allows the genes to be transcribed more easily. This may be the evolutionary driving force behind the clustering of similarly expressed genes in the genome. She also described how genes also move in and out of their chromosomal territories within the nucleus, depending on their expression status. This positioning concerns the expression not only of individual genes, but also of other genes close by. For example, β -globin is surrounded by 'off' genes and has to move before it can express, whereas α -globin is surrounded by 'active' genes and stays within its territory when it is expressed.

Genes often loop out of their territories and end up sharing transcription factories with other similarly expressed genes. Peter Fraser (Babraham Institute) suggested that the driving force for sharing factories is the high local concentration of transcription factors, which can be recruited to help reinitiate transcription of the factory. One fascinating result of genes sharing transcription factories is an increased level of chromosomal translocations between these genes. For example, *c-myc* and the immunoglobulin heavy-chain locus co-localize despite being on different chromosomes, and translocations between them are found in a high percentage of cancer cells, such as in Burkitt's lymphoma. Co-localizations within factories may therefore be of crucial influence in the mechanisms leading to translocations.

The Tenovus meeting was a great opportunity to hear from researchers in the wide-ranging fields of DNA recombination, repair and epigenetics. What became clear were the obvious mechanistic links between all these processes and how much can be learned from these separate fields. DNA repair and recombination mechanisms must work within the context of chromatin, and conversely chromatin 'marks' must be established and maintained within the context of the cell's life cycle. The meeting highlighted the benefits of bringing researchers in different fields together, which can only become more useful as these fields converge.