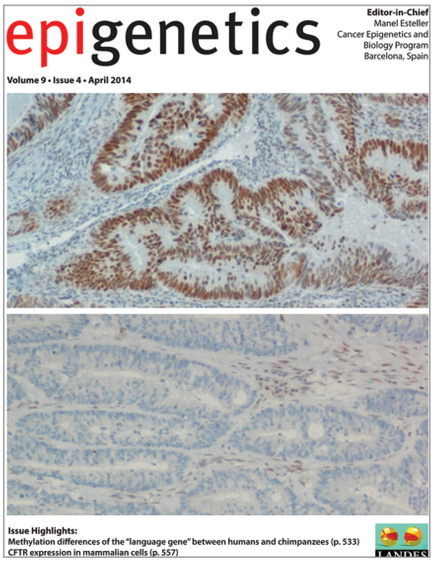
Nucleus 5:4, 279–280; July/August 2014; © 2014 Landes Bioscience

Landes Highlights

Set5 and Set1 cooperate to repress gene expression at telomeres and retrotransposons

Eukaryotic genomes are packaged into discrete regions of transcriptionally active genes (euchromatin) and transcriptionally silenced genes (heterochromatin). The establishment and maintenance of these chromatin regions is essential for virtually all nuclear processes and requires the dynamic posttranslational modification of histones. The coordinated activities of these chromatin modifiers in the regulation of gene expression are not fully understood. It was previously reported that the budding yeast histone H4 methyltransferase Set5 functions together with Set1, the H3K4 methyltransferase, in specific cellular contexts. In a new study, Dr Ashby Morrison and colleagues set out to investigate the relationship between these evolutionarily conserved enzymes in the regulation of gene expression. They generated a comprehensive genetic interaction map of the functionally uncharacterized Set5 methyltransferase and expanded the existing genetic interactome of the global chromatin modifier Set1, revealing functional overlap of the two enzymes in chromatin-related networks, including transcription. Furthermore, gene expression profiling via RNA-Seq revealed an unexpected synergistic role of Set1 and Set5 in repressing transcription of Ty transposable elements and genes located in subtelomeric regions. This study uncovers novel pathways in which the methyltransferase Set5 participates and, more importantly, reveals a partnership between Set1 and Set5 in transcriptional repression near repetitive DNA elements in budding yeast. Together, the results define a new functional relationship between histone H3 and H4 methyltransferases, whose combined activity may be important for preserving genomic integrity.



Reference

Martín GM, King DA, Green EM, Garcia-Nieto PE, Alexander R, Collins SR, Krogan NJ, Gozani OP, Morrison AJ. Set5 and Set1 cooperate to repress gene expression at telomeres and retrotransposons. Epigenetics 2014; 9:513-22; PMID:24442241

Functional non-CpG methylation in mammalian cells

DNA methylation involves the addition of a methyl group to cytosine at the carbon atom 5 to create 5-methylcytosine. In mammalian genomes, the methylation of cytosine residues within CpG dinucleotides is crucial to normal development and cell differentiation. However, methylation of cytosines in the contexts of CpA, CpT, and CpC (non-CpG methylation) has been reported for decades, yet it remains poorly understood. In recent years, whole genome bisulphite sequencing (WGBS) has confirmed significant levels of non-CpG methylation in specific tissues and cell types. Non-CpG methylation has several properties that distinguish it from CpG methylation. In a recent review Dr Luke Hesson and colleagues summerize the current literature describing non-CpG methylation in mammalian cells. They describe the important characteristics that distinguish it from CpG methylation and discuss possible mechanisms of its establishment and maintenance, as well as its functional importance.

Reference

Patil V, Ward RL, Hesson LB. The evidence for functional non-CpG methylation in mammalian cells. Epigenetics 2014; 9; PMID:24717538; http://dx.doi.org/10.4161/epi.28741

Telomerase enzymatic component hTERT: Dual role in regulating telomere length

Telomere lengths are tightly regulated within a narrow range in normal human cells. Previous studies have extensively focused on mechanisms how short telomeres are extended and have demonstrated that telomerase plays a central role in elongating short telomeres. However, very little is unknown about the molecular mechanisms regulating excessively long telomeres. In a new report, Dr Qin Yang and colleagues demonstrate that the telomerase enzymatic component, hTERT, plays a dual role in the regulation of telomere length. It shortens excessively long telomeres and elongates short telomeres simultaneously in one cell, maintaining the optimal telomere length at each chromosome for efficient protection. This novel hTERT-mediated telomere-shortening mechanism not only exists in cancer cells, but also in primary human cells. The hTERT-mediated telomere shortening was found to require hTERT's enzymatic activity, but the telomerase RNA component, hTR, was not involved in that process. The authors found that expression of hTERT increases telomeric circular DNA formation, suggesting that telomere homologous recombination is involved in the telomere-shortening process. They further demonstrated that shelterin protein TPP1 interacts with hTERT and recruits hTERT to telomeres, suggesting that TPP1 might be involved in the regulation of telomere shortening. Taken together, the study reveals a novel function of hTERT in telomere length regulation and adds a new element to the current molecular model of telomere length maintenance.

Reference

Zheng Y-L, Zhang F, Sun B, Du J, Sun C, Yuan J, Wang Y, Tao L, Kota K, Liu X, et al. Telomerase enzymatic component hTERT shortens long telomeres in human cells. Cell Cycle 2014; 13:1765-76; PMID:24721976; http://dx.doi.org/10.4161/cc.28705

Biological role of HBO1-JADE1 chromatin shuttling during organ regeneration

Acetylation of histones within the chromatin context is a post-translational modification that can regulate DNA replication, repair, and gene transcription. The histone acetyl transferase (HAT) HBO1 is known to interact with 2 isoforms of JADE1 (gene for apoptosis and differention-1) protein: the truncated splice variant JADE1S and the full-length protein JADE1L. JADE1 promotes acetylation of nucleosomal histones by HBO1. The HBO1–JADE1 complex facilitates cell proliferation by unclear mechanisms. In a recent study, Dr Maria Panchenko and colleagues reported intracellular chromatin shuttling of HBO1-JADE1 complex during mitosis coupled to phosphorylation of JADE1. In interphase of dividing cells JADE1S was localized to the nucleus and associated with chromatin. As cells approached mitosis, JADE1S dissociated from chromatin during prophase and localized to the cytoplasm. JADE1S chromatin re-association began in telophase and paralleled nuclear envelope membrane reassembly. By early G1, JADE1S was completely re-associated with chromatin and localized exclusively to the nucleus. Importantly, cytoplasmic but not chromatin-associated JADE1 protein was phosphorylated. Mass-Spectrometric analysis of JADE1S protein isolated from G2/M-arrested cells identified six phosphorylated amino acid residues: S89, T92, S102, S121, S392, and T468, including three novel sites. Temporally, JADE1S phosphorylation and dephosphorylation during mitosis correlated with JADE1S chromatin dissociation and recruitment. Interestingly, also the levels of global histone H4 acetylation correlated with chromatin recruitment of JADE1S. The biological relevance of this phenomenon was supported by results from in vivo studies in mouse kidneys, where JADE1S transiently accumulated in the cytoplasm of tubular epithelial cells during kidney regeneration. The transient increase in the number of cells with cytoplasmic JADE1S directly correlated with activation of tubular cell proliferation and inversely correlated with the number of cells with nuclear JADE1S staining, supporting a biological role of HBO1-JADE1 shuttling during organ regeneration.

Reference

Siriwardana NS, Meyer R, Havasi A, Dominguez I, Panchenko MV. Cell cycle-dependent chromatin shuttling of HBO1-JADE1 histone acetyl transferase (HAT) complex. Cell Cycle 2014; 13:1885-901; PMID:24739512; http://dx.doi.org/10.4161/cc.28759