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Landes Highlights

Effects of microRNA on mRNA translation and stability

MicroRNAs (miRs) are short endogenously expressed RNAs that regulate gene expression post-transcriptionally. It is known, that both messenger RNA (mRNA) degradation and suppression of mRNA translation can mediate reduced protein levels following miR targeting of an mRNA. However, the relative contributions of these two mechanisms have remained elusive. According to a previous genome-wide study in mammals employing RNA-sequencing to measure miR effects on mRNA translation and stability, 84–89 percent of miR-induced suppression of gene expression was found to be mediated by degradation of target mRNAs. Drs Ola Larsson and Robert Nadon re-analyzed this data set and applied a number of analysis modifications revealing that the contribution of miR-regulated mRNA translation was likely underestimated for some mRNA subsets. In contrast to the original analysis, this new analysis indicated that suppression of mRNA translation precedes mRNA degradation upon miR targeting. The study findings thereby increase the understanding of miR mediated genome wide suppression of gene expression in mammals.

Reference

Larsson O, Nadon R. Re-analysis of genome wide data on mammalian microRNA-mediated suppression of gene expression. Translation 2013; 1:e24557; http://dx.doi.org/10.4161/trla.24557

Chromatin patterns associated with lung adenocarcinoma progression

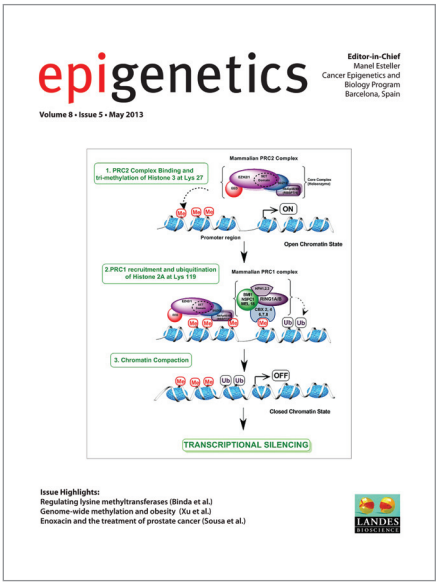
The development and progression of lung adenocarcinoma, one of the most common cancers, is driven by the interplay of genetic and epigenetic changes, but the role of chromatin structure in malignant transformation remains poorly understood. A new study used systematic nucleosome distribution and chromatin accessibility microarray mapping platforms to analyze the genome-wide chromatin structure from normal tissues and from primary lung adenocarcinoma of different grades and stages. Dr Jonathan Dennis and colleagues identified chromatin-based patterns across different patients with lung adenocarcinoma of different cancer grade and stage. Low-grade cancers had nucleosome distributions very different compared with the corresponding normal tissue but had nearly identical chromatin accessibility. Conversely, nucleosome distributions of high-grade cancers showed few differences. Substantial disruptions in chromosomal accessibility were seen in a patient with a high-grade and high-stage tumor. These data imply that chromatin structure changes during the progression of lung adenocarcinoma. The authors therefore developed a model in which low-grade lung adenocarcinomas are linked to changes in nucleosome distributions, whereas higher-grade tumors are linked to large-scale chromosomal changes. These results provide a foundation for the development of a comprehensive framework linking the general and locus-specific roles of chromatin structure to lung cancer progression. The authors propose that this strategy has the potential to identify a new class of chromatin-based diagnostic, prognostic and therapeutic markers in cancer progression.

Reference

Druliner BR, Fincher JA, Sexton BS, Vera DL, Roche M, Lyle S, et al. Chromatin patterns associated with lung adenocarcinoma progression. Cell Cycle 2013; 12:1536-43; PMID:23598721; http://dx.doi.org/10.4161/cc.24664

Human subtelomeric chromatin dynamics upon cellular senescence

Subtelomeres are patchworks of evolutionary conserved sequence blocks and harbor the transcriptional start sites for telomere repeat containing RNAs (TERRA). Recent studies suggest that the interplay between telomeres and subtelomeric chromatin is required for maintaining telomere function. To further characterize chromatin remodeling of subtelomeres in relation to telomere shortening and cellular senescence, Dr Silvère Van der Maarel and colleagues systematically quantified histone modifications and DNA methylation at the subtelomeres of chromosomes 7q and 11q in primary human WI-38 fibroblasts. Chromatin state was assessed by quantifying markers for euchromatin (histone acetylation) and constitutive (CpG methylation, H3K9me3) and facultative (H3K27me3, H3K36me3) heterochromatin along the subtelomere. Together with chromosome specific analysis of TERRA promoters and transcripts, a complex picture of both common and chromosome specific epigenetic changes at human subtelomeres upon cellular senescence emerged. In particular, the authors observed a senescence-associated reduction of constitutive heterochromatin markers, which was accompanied by a gain of facultative repressive marks. The data indicate that the repressed state is preserved during senescence as neither increased levels of euchromatin markers nor derepression of the only annotated gene in the studied region were found. Furthermore, this study also revealed distinct regulation of two TERRA promoter sites at subtelomeres of 7q and 11q. Taken together, this work provides a detailed description of human subtelomeric chromatin dynamics and shows distinct regulation of the TERRA promoters of 7q and 11q upon cellular senescence.

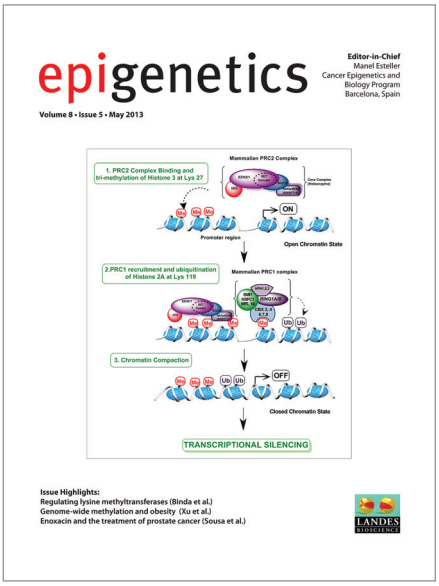


Reference

Thijssen PE, Tobi EW, Balog J, Schouten SG, Kremer D, El Bouazzaoui F, et al. Chromatin remodeling of human subtelomeres and TERRA promoters upon cellular senescence: Commonalities and differences between chromosomes. Epigenetics 2013; 8:512-21; PMID:23644601; http://dx.doi.org/10.4161/epi.24450

Interactions between lysin methyltransferases and their substrates

Lysine methylation of histones and non-histone proteins has emerged in recent years as a posttranslational modification with wide-ranging cellular implications far beyond epigenetic regulation. Lysin methyltransferases (KMTs) are fundamental players in the regulation of chromatin signaling. This is emphasized by several reports showing that functional defects of KMTs can lead to cancer, growth defects, neurological disorders, and other human pathologies. The molecular interactions between lysine methyltransferases and their substrates appear to be regulated by posttranslational modifications of sites surrounding the lysine methyl acceptor. Specific histone modifications appear to dictate whether or not a KMT can further modify its substrate. SET [Su(var)3–9, Enhancer-of-zeste, Trithorax] domain-containing methyltransferases seem to be particularly sensitive to the sequence and posttranslational modifications surrounding the target lysine site. Two very interesting examples of this cross-talk between methyl-lysine sites are found in the SET domain-containing lysine methyltransferases SET7 and SETDB1, whereby the histone H3 trimethylated on lysine 4 (H3K4^{me3}) modification prevents methylation by SETDB1 on H3 lysine 9 (H3K9), and the histone H3 trimethylated on lysine 9 (H3K9^{me3}) modification prevents methylation by SET7 on H3K4. A similar cross-talk between posttranslational modifications regulates the functions of non-histone proteins such as the tumor suppressor p53 and the DNA methyltransferase DNMT1. In a recent Review, Dr Olivier Binda discusses the cross-talk between cis lysine methylation sites and other adjacent posttranslational modifications within histones H3 and H4 as well as a few non-histone proteins.



Reference

Binda O. On your histone mark, SET, methylate! Epigenetics 2013; 8:457-63; PMID:23625014; http://dx.doi.org/10.4161/epi.24451