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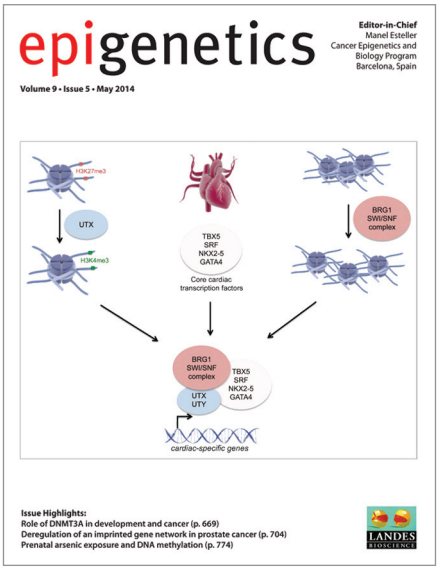
Landes Highlights

Hierarchical model of chromatin folding questioned

Several hierarchical levels of DNA packaging are believed to exist in chromatin, starting from a 10-nm chromatin fiber that is further packed into a 30-nm fiber. While transitions between the 30-nm and 10-nm fibers were thought to be essential for the control of chromatin transcriptional status, recent studies have demonstrated that in the nuclei, DNA is packed in tightly associated 10-nm fibers that are not compacted into 30-nm fibers. Additionally, the accessibility of DNA in chromatin seems to depend on the local mobility of nucleosomes rather than on decompaction of chromosome regions. A recent review by Drs Sergey Razin and Alexey Gavrilov summarizes these findings, which argue for reconsidering the hierarchical model of chromatin packaging and some of the basic definitions of chromatin organization. The authors emphasize that chromatin domains can be considered as three-dimensional structures, which may include genomic regions that do not necessarily constitute a continuous domain on the DNA chain. Future studies should focus on elucidating the mechanims that control the assembly of 3D chromatin domains that incorporate segments of different chromosomal regions. Current progress in the development of high-resolution microscopic techniques, allowing the study of living cells, promises exciting new discoveries in the chromatin field.

Reference

Razin SV, Gavrilov AA. Chromatin without the 30-nm fiber: constrained disorder instead of hierarchical folding. Epigenetics 2014; 9:653-7; PMID:24561903; http://dx.doi.org/10.4161/epi.28297



Histone acetylation regulates alternative splicing

Histone acetylation modulates alternative splicing of several hundred genes. In a recent study, Dr David Stanek and colleagues tested the role of the histone acetyltransferase p300 in alternative splicing and showed that knockdown of p300 promotes inclusion of the alternative fibronectin (FN1) EDB exon. p300 associates with CRE sites in the promoter via the CREB transcription factor. The authors created mini-gene reporters driven by an artificial promoter containing CRE sites. Both deletion and mutation of the CRE site affected EDB alternative splicing in the same manner as a p300 knockdown. The authors also showed that p300 controls histone H4 acetylation along the FN1 gene. Consistently, p300 depletion and CRE deletion and/or mutation both reduced histone H4 acetylation on mini-gene reporters. Finally, the effect of CRE inactivation on H4 acetylation and alternative splicing was shown to be counteracted by the inhibition of histone deacetylases. In summary, these data suggest that histone acetylation could be one of the mechanisms how the promoter and promoter binding proteins influence alternative splicing.

Reference

Dušková E, Hnilicová J, Staněk D. CRE promoter sites modulate alternative splicing via p300-mediated histone acetylation. RNA Biol 2014; 11; PMID:25019513; http://dx.doi.org/10.4161/rna.29441

An artificial cellular system for inducing and following replication fork block formation

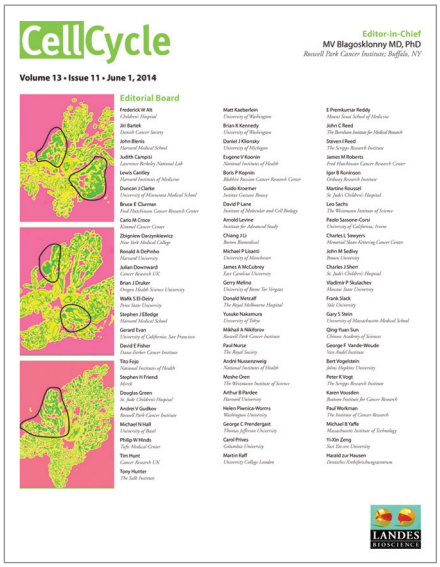
In order to maintain genome stability it is important that at every cell division, each daughter cell inherits only one copy of the completely duplicated genome. Obstacles such as replication fork blocks (RFBs) can impede correct execution of this process, leading to incomplete replication and genomic instability, consequences that have been associated with several hereditary disorders and cancer. In a recent study, Dr Geneviève Almouzni and colleagues investigated the mechanisms that lead to RFBs and the means to bypass them. They used integrated LacO and/or TetO arrays as a tractable system to follow in time a process in individual cells at a single locus. They showed that induction of the binding of LacI and TetR proteins, and not the presence of the repeats, is key to form the RFB. Binding of these proteins to the arrays during replication caused a prolonged persistence of replication foci at these site. This, in turn, induced a local DNA damage repair (DDR) response, with the recruitment of proteins involved in double-strand break (DSB) repair, such as TOPBP1 and 53BP1, and the phosphorylation of H2AX. Furthermore, the appearance of micronuclei and DNA bridges after mitosis was consistent with an incomplete replication. The authors discuss how the many DNA binding proteins encountered during replication can be dealt with and the consequences of incomplete replication. Future studies exploiting this system may help analyzing how an RFB, along with bypass mechanisms, are controlled in order to maintain genome integrity.

Reference

Beuzer P, Quivy J-P, Almouzni G. Establishment of a replication fork barrier following induction of DNA binding in mammalian cells. Cell Cycle 2014; 13:1607-16; PMID:24675882; http://dx.doi.org/10.4161/cc.28627

Telomerase enzymatic component hTERT can do both: Elongate and shorten telomeres

Telomere lengths are tightly regulated within a narrow range in normal human cells. Previous studies have extensively focused on how short telomeres are extended and have demonstrated that telomerase plays a central role in elongating short telomeres. However, much about the molecular mechanisms of regulating excessively long telomeres is unknown. In a new study, Dr Yun-Ling Zheng and colleagues demonstrated 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 chromosomal end for efficient protection. This novel hTERT-mediated telomere-shortening mechanism was found to exist not only in cancer cells, but also in primary human cells. The hTERT-mediated telomere shortening required 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 onto telomeres, suggesting that TPP1 might be involved in regulating telomere shortening. This 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