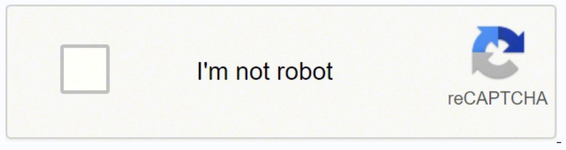
Dna methylation and histone acetylation



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Dna methylation and histone acetylation

Dna methylation and histone acetylation are examples of. Difference between dna methylation and histone acetylation. How does dna methylation and histone acetylation affect gene expression. Dna methylation and histone acetylation quizlet. Dna methylation and histone acetylation are examples of quizlet. Dna methylation and histone acetylation mcat. Genomic imprinting dna methylation and histone acetylation. Dna methylation and histone acetylation are examples of which of the following processes.

Epigenetics is the study of hermetic changes in gene expression that are not mediated at DNA sequence level. Molecular mechanisms that mediate epigenetic regulation include DNA methylation and chromatin/istone modifications. With the identification of historic key-modifying enzymes, the biological functions of many post-translational iston modifications are beginning to be elucidate. Histone's methylation, in particular, plays critical roles in many epigenetic phenomena. In this review, we provide an overview of recent discoveries that shape the current paradigms regarding the roles of the iston methylation and the iston variants in heterochrometotinic assembly and the maintenance of the boundaries between heterochromatin and euchromatin. We also highlight some of the enzymes that mediate istone methylation and discuss the stability and legacy of this modification. THE REGION How a single cell can differ in different cell types in a multicellular organism has long led to the postulation that additional information that regulate genomic functions must exist beyond the genetic code level. This concept led to the introduction of the term "epigenethics" back in the 1940s - a term that has now evolved to mean inherited changes in gene expression that do not involve changes in the DNA sequence (1, 2). Epigenetic regulation is not only critical for the generation of cell diversity during mammal development, but it is also important to maintain stability and integrity of expression profiles of different cell types. Interesting, while these epigenetic changes are inherited and normally maintained stably, they are also potentially reversible, as evidenced by the success of cloning entire organisms through nuclear transfer methods using nuclei of differentiated cells (3). Therefore, understanding of the basic mechanisms that mediate epigenetic regulation is invaluable to our knowledge of cell differentiation and genome programming. Studies on the molecular basis of epigenetics have largely focused on mechanisms such as DNA methylation and chromatin changes (4). In fact, emerging evidence indicates that both mechanisms act in concert to provide a stable and inherited silence in higher eukaryotic genome. In this review, we will focus mainly on color changes and highlight some recent discoveries in the field of chromatic dynamics that functionally connect istone changes and epigenetic adjustment. To provide a wide overview of current results and paradigms, we have taken observations from a wide range of studies using different model organisms such as Saccharomyces cerevisiae, Schizosaccharomyces pombe,mouse, etc. Histone proteins are highly preserved from germ yeast (S. cerevisiae) to man, and the ways of adjusting mediated by chromatin are of and great evolution also preserved. These routes are generally better elucidate in organisms such as yeast andand additional complexity in mammal cells are in many cases still under investigation. chromatic change and histone the structure of chromatin is the packing of the genomic dna through the association with the istone proteins (5.) the nucleosoma, the basic repetition unit of the chromatic, consists of 146 bp of dna wrapped around an octameric istonic nucleus containing two copies each of the istons h2a, h2b, h3, and h4 (6.) the organization of chromatin does not only limit the physical access of nuclear factors to the DNA below, but it is now clear that posttralational modifications of iston proteins can alter the conformation of chromatin and perform regulatory roles directed in gene expression (7.) while most nucleosms in the cell are composed of the same four types of nucleus istons, the huge diversity in the istone/nucleosome structures is generated by a variety of alterations some modifications, including acetylation and phosphorylation, are reversible and dynamic and are often associated with the inducible expression of individual genes. other changes, such as methylation, are found to be more stable and are involved in long-term maintenance of the state of expression of the regions of the genome. These changes occur on multiple but specific sites on istons, and it has been suggested that istons can act as signalling platforms, integrating upstream signaling paths to arouse appropriate nuclear responses such as transcription activation or repression (11.) also, with so many possible combinations of changes that may occur on a variety of iston sites, it has been proposed that different combinations of istone modifications can lead to distinct results in terms of chromatin-reg functions. This idea, formally proposed as the hypothesis of the Histone code (12–14), has been the subject of intense investigation in recent years. heterochromatin and ukromatica the appreciation of the bond between the compaction of chromatin and the gene expression dates back to the cytologic studies of the beginning of the xx century. using the basic dyes to stain the chromatin and display it under the microscope, emil heitz noted that the chromatin of the eukaryotic cells can be widely distinguished in two forms: heterochromatin and euchromatin (15.) heterochrometine has been defined as condensed regions of the nucleus that do not deconense during the interphase, while the eutrondin was easily noticed for decoction has been postulated that heterochromatosis is the regions functionallyof genome and eucaritin is where real gene activity occurs. With the advance to the 21st century, these chromatic chromaticsare much better defined at molecular level: heterochromatic regions are more closed in the conformation of chromatin [as defined by the accessibility of nucleases (16)]; contain few genes actively expressed, and they replicate late in the S-phase (17). On the contrary, the Eucharist is more open and accessible to nucleases, it is rich in genes actively transcriptivable, and it is replicated early during the phase S. Moreover, the euchromatine regions are highly enriched for acetylated istons while the heterochrome contains istons predominantly hypoacetylated. In fact, istone acetylation is now well understood to function in the activation of transcription (18:19), and it is becoming clear that the specific patterns of iston acetylation, as well as methylation, mark these regions and direct the formation of distinct chromatic domains. Around the time of Heitz characterization of heterochromatosis, J. Muller described the phenomenon of varigation effect of position (PEV) in Drosophila where euchromatic genes, when juxtaposed to heterochromatic sequences due to chromosomal rearrangement or transposition, can become transcriptally silenziati (20). The extension of the silence varied from one clonal population to another and thus gave rise to variegated phenotypes. These observations not only supported the link between heterochromate and transcriptional silegation, but also suggested that there is an epigenetically-based cis-spreading silence. Through further genetic studies, several genes have been identified to modify this PEV effect and are classified as E(var)s (ENhancers of PEV) or Su(var)s (PEV suppressors) (21). Characterization of these gene products has shown that some have structural roles in heterochromatic training or functional roles in gene simplification. One of the best examples of these Su(var) genes is Su(var)2–5, which encodes heterochrome protein 1 (HP1) (22). HP1 is a nuclear protein that binds chromatin that is located in heterochromatic regions in Drosophila and in higher eukaryotes. The association of HP1 to specific regions of the genome is thought to be a critical event in initiating and maintaining the conformation of heterochromatotin condensed chromatin. This function, as we know now, is intimately linked to the istone methylation and the remodeling of chromatin. Su(var) And HISTONE METHYLATION It has long been known that the istons, particularly H3 and H4, are metiled in a series of residues of lysine (Lys) and arginine (Arg). The main sites of Lys-methylization on istons so far identified are: Lys4, Lys9, Lys27, Lys36, Lys79 on H3 (see Fig. 1) and Lys20 on H4 (23, 24). In addition, Lys' residue can be metiated in the form of mono, di-, or trimetilation, and this differential methylation provides additional functional diversity to each Lys methylation site. An important turning pointunderstanding of the H3 Lys-methylization function was the discovery that one of the well-studied Su(var) genes actually codifies an istone methyltransferase istoneThe Su(var)3–9 gene in Drosophila, and its homolog, Clr4, in S. pombe fission yeast, were originally identified by genetic screens to have transcriptional silegation roles associated with heterochrome (in Drosophila) and in coupling type silegation (in S. pombe) (25). The biochemical analysis of human homologen, Suv39H1, revealed that this protein has an enzyme activity that specifically metilates H3 historian to Lys9 (26). This result, followed by a convergence of genetic and biochemical data, and helped by the development of highly-specific antibodies for H3 metilates in different sites, quickly outlined a heterochromatic training path (27–29). In S. pombe, for example, heterochromatic formation begins with the deacetylation of istone H3 to Lys9 from a complex of istone deacetylase (HDAC) that clears the way to Clr4 to metilate this unique residue that can be acetylate or metilate. Lys9's methylation on H3 then creates a reason specifically recognized and linked by the HP1 chromodomus. The Clr4 gene disintegration resulted in the loss of location of Swi6 (HP homologs1), illustrating that H3 methylation is necessary in the recruitment of HP1 and heterochrome assembly in vivo (29). Intriguingly, genetic studies in S. pombe and Tetrahymena systems show that heterochromatosis formation also depends on genes that codify RNA interference components (RNAi) machinery (30, 31). It has been suggested that small RNAs are involved in targeting isto-modifying activities to regions that must be silent, and the mechanical details of this process are currently under investigation (32, 33). Open in the new tabDownload slideSummary of the Lys-Metilati Residui on H3 Highlighted in this review Of the five Lys residues on H3 known to be metiated, four are highlighted in this review and figure. Examples from different organisms of enzymes that metilate H3 in the sites indicated are shown above the sequence of amino acids H3. The enzymes that metilate H3 on Lys9, 27 and 4, respectively, belong to the Su(var)3–9, E(Z), and Trx families, and all contain SET domains (named after the enzymes mentioned above) that work as their catalytic nucleus. On the contrary, members of the Dot1 family, which methed H3 on Lys79, do not have SET domains. Also indicated in this figure are the known physical and biological functions (or putative) associated with each site-specific methylation event. Txn, Transcription. In the mouse, the interruption of the two homologs Su(var)3–9, Suv39h1 and Suv39h2, led to alter the feasibility and chromosomal instability in the embryos of the double-round rat (dn) (34). Using antibodies that specifically distinguish the mono, di- and trimethylated state of Lys9-metilated H3, it has been found that fibroblasts derived from dn embryos show a specific loss of Lys9 trimethylized formH3 to pericentric heterocromatotin (35). Interesting, while the location of HP1α HP1αthe cells are compromised, the presence of chromatin condensed in pericentric regions, as indicated by DAPI (4′,6-diamidino-2-phenylindole) dense color, seems to be unchanged (35, 36). In addition, these cells have a concomitant increase in Lys9 monomethylization and H3 Lys27 trimethylation in pericentric regions, suggesting that additional enzyme systems in dn cells can change H3 differently and perhaps function to compensate and maintain heterochromatic stability. SET DOMAIN AND HISTONE METHYLING The structural-functional analysis of Suv39H1 and Clr4 have shown that their HMT activities are mediated by the SET domain of proteins. This highly preserved domain is found in large numbers of proteins from yeast to man, and takes its name from the three founding proteins that share this domain: On(VAR)3–9, zeste enhancer [E(Z)] and trithorax (TRX) (25). In fact, all three of these proteins, as well as an increasing number of other proteins containing SET domains, have now been demonstrated to have HMT activity and each has a exquisite specificity towards different sites on H3 or H4 (24, 37). E(Z) and TRX belong to the families of Polycomb (Pc)- and trx-group genetic products that have previously been identified as proteins that modify the important chromatin to maintain the balanced expression of homeotic genes in Drosophila and mammals. The human EZH2 metilates histone H3 to Lys27, while the homologists TRX [e.g., Set1p in S. cerevisiae, TRX, TRR (linked to trithorax) in Drosophila, and MLL (myeloid or mixed lineage leukemia) in human] all methylated H3 to Lys4 (24). In line with the previously assigned roles of the Pc and Trx complexes in transcription repression and activation, respectively, the H3 Lys27 methylation was correlated with transcription (38, 39), and the H3 Lys4 methylation is now well established as a chromatin brand for active genes (40). Analogue of HP1 chromodome binding to H3 lys9-methylated, Pc protein chromodomain was found to bind lys27-metilated H3, and functions to recruit the Pc complex to start transcriptional silencing Pc-dependent (41). It is interesting to note that the wrapping of HP1 and Pc chromodomins has been enough to change the nuclear localization of these proteins in Drosophila S2 cells, indicating that the binding of the respective chromatin-binding proteins in vivo. H3 Lys4 methylation has been well documented to be associated with Eucharistic regions in different organisms, including S. pombe, Drosophila and mammalian cells; However, no direct role has been found for this change in the activation of transcription. Biochemical pull-down tests have shown that Lys4-metilated H3 can bind to remodeling enzymeIsw1p (42). In addition, Isw1p's association with chromatin depends on the H3 Lys4-methylante Set1p in S. cerevisiae, suggesting suggestingthis change promotes the association of remodeling factors which in turn facilitate transcription. Biochemical data have also suggested that Lys4-metilated H3 can prevent the link of the HDAC NuRD (nucleosome remodeling and HDAC) mammal complex (43). The consensus so far suggests that the H3 Lys4 methylation can play an indirect regulatory role while maintaining the genomic regions associated in a state that is able to activate transcription. DOMAIN-CONTACTS METHYLTRANSFERAS From the first recognition that the SET domain of Suv39H1 has activities of iston methyltransferase, many other proteins containing SET domain have been shown to istons metilate in a variety of Lys residues (Refs. 23 and 24 and Fig. 1). It is important to note that not all proteins containing SET domains are HMT, nor are the activities of all istone Lys-meethyltransferases mediated by SET domains. For example, Dot1p is a non-SET enzyme containing metila H3 to Lys79 (44–47). In contrast to other methylation sites identified on istons, which are located at N-terminal code of H3 and H4 which physically extend from the core core core core core [as determined by the nucleosoma crystal structure (48)], Lys79 is located in the central domain of H3. Dot1p strongly prefers H3 nucleosomal on H3 free as substrate in vitro and presumably requires the nucleosomal context for substrate recognition. Article S. cerevisiae does not have the prototypic form of heterochromatotin found in superior eukaryotes, specific regions of its genome (such as silent-type mating, telomeric regions, and ribosomic DNA locus) are silent by epigenetic-type mechanisms. Instead of the heterochromed assembly mediated HP1, the silence is mediated by the connection of the Sir complex (including Sir2, Sir3, and Sir4) to the mating and telomeric loci, and the connection of the RENT complex (including Sir2, Net1, and Cdc14) to the ribosomal DNA locus (49). In this organism, about 90% of all H3 are mono-, di- or trimetilati to Lys79, which roughly corresponds to the amount of euchromatin in its genome (44). The Dot1 (originally identified by a genetic screen as a telomeric silencing degregator) seems to have an antisilentic function so the overexpression of this protein leads to the loss of silencing in germ yeast. Similarly to the suggestion that H3 Lys4-methylization prevents the connection of the NuRD selegation complex in mammal cells, it has been postulated that Lys79 methylation functions to reject Sir protein binding and thus prevent the spread of Sir proteins in the eucaromatic parts of the S. cerevisiae genome (44, 50). The methylation of H3 to Lys79 is a trademark also preserved in other Eucharistic cells; However, if it also has a role in setting boundaries between heterochromyeuchromatin in other organisms is not clear. Interesting, it was recently reported that mammal DNAprotein, 53BP1, recognizes and binds specifically to Lys79 methilate H3 (51). In addition, its location with double strands of DNA breaks and repair foci requires the function of the H3 Lys79-methyltransferase Dot1L mammal. Since this methylation brand is not only found on DNA break sites in mammal cells, such as H3 Lys79 methylation helps selectively recruit 53BP1 to DNA damage sites is an important question that awaits further investigation. ROLES OF MODIFICATION AND EXTERNAL AND EXTERNAL BOUNDARIO ETEROCHROMATIN-EUCHROMATIN In S. cerevisiae, the location of the Htz1 variant (also known as H2A.Z in mammal cells) has also been suggested to function in the definition of the boundaries between heterochromatin and heterochromatin. While the core istons (H2A, H2B, H3 and H4) represent most istons in all organisms, variant versions of these istons (except H4) exist in low stable state levels, and they are thought to replace their iston core counterparts to strategic positions in the genome for specialized functions (52, 53). For example, the nucleosms of the centromeres contain the variant H3 Cse4/CENP-A (in S. cerevisiae/human), and are thought to perform specific central functions. H2A.X is a variant form of H2A in human cells that is rapidly phosphorized in response to DNA damage and functions to mark the damaged area and to recruit DNA repair complexes. H2A.Z (or Htz1) is another H2A variant that is preserved from germ yeast to humans. The initial studies of this variant in Tetrahymena have discovered that it is specifically enriched in the transcriptive nuclei of this organism (54, 55). In accordance with this result, the deletion of the HTZ1 gene in S. cerevisiae has led to the compromised activation of several inducible genes (56). However, this elimination also affected the transcriptive sizing of mating loci and telomers (57). A recent study with microarray analysis found that 40% of the genes requiring Htz1 for full expression are found in the eucaromatic regions adjacent to the silenziate regions of loci and telomeric type (58). Moreover, the loss of Htz1 has led to the spread of Sir proteins in the euchromatine regions, while the concomitant loss of Htz1 and Sir2 protein has restored the expression levels of Htz1-regulated genes. Therefore, these results suggest that Htz1 has a role in maintaining the integrity of heterochrometo-euchromatin boundaries to ensure proper transcription regulation of genes in both regions. Recently, three independent studies have identified a chromatic remodeling complex, Swr1-complex, which specifically exchanges Htz1 with H2A nucleosomal, and thus works to insert Htz1 into the appropriate genome regions (59–61). These studies have aroused greatin the definition of the links between remodeling and depositioning complexes of iston variations, and the potential of these complex complexesContrary to what is observed in St. cerevisiae, the role of H2A. Z in mammals in association with heterochromatin is less clear. Immunlocation studies have shown that H2A.Z is excluded from the silent transcriptional chromosome X, which supports the idea that H2A.Z is preferentially associated with the active transcriptional regions of the genome (62). However, the same study also found that in early mouse embryos, H2A.Z locates the pericentric heterocromatine, suggesting that this variant can play a role in the functions of heterochromatin during development. Experiments with RNAi showed that the exhaustion of H2A.Z in Cos7 cells leads to the loss of the correct location of HP1± in chromosomal arms, but the location of HP1± in centromeres was not affected (63). A recent report using live cross-linking studies found that HP1± is associated with H2A.Z- but not H2A-cromatine, and in combination with the results of biophysical analysis of reconstituted oligonucleosomic arrays, this study proposed that H2A.Z and HP1± work together in the compaction of chromatin to heterochromatic domains. (64). Taking these results along with studies in Tetrahymena, Drosophila and S. cerevisiae that suggest that H2A.Z has a role in the activation of transcription, it is possible that different organisms have evolved separate functions with euchromatin- and heterochromatin-associated for this variant. It is perhaps interesting to note that the entire genome of S. cerevisiae, apart from the regions defined by Sir proteins, exists in an eucromatic state. Coherently with this concept, the chromatin of this organism does not contain markers of historic methylation such as H3 Lys9 or Lys27, which are associated with repressive chromatic. As a result, in the sprout yeast, Htz1 can only have a single function in maintaining the transcriptional competence of euchromatin genes, while this variant may have additional heterochrometine-associated functions in other eukaryotes. BOUNDARY EETEROCHROMATINA SEPARATED AND EUCROMATINA IN EUCARIOOTI SUPERS In mammal cells, a significant part of the genome consists of genetically poor and transcripically inert regions, maintained in a repressed chromatic state. To prevent the essential genes of euchromatin from being silenced by the spread of heterochromatin, the highest eukaryotes have defined the boundary elements that act as barriers against the nearby effects. In two separate studies, which carried out a large-scale mapping of the istonic modification status of about 50 kb around the mating locus of S. pombe and the chicken locus Î2-globin, it was found that there are distinct and net boundaries between Lys9-methylated H3 associated with heterochromatin and Lys4-methylated H3 associated with euchromatin (65, 66). In fact, the levelsLys9- vs. Lys4-methylate H3 are inversive with each other on these 50 kb domains (i.e. when one is tall, the other is low). Important: cancellation cancellationIR-L and IR-R border elements that flank the mat2 and the mat3 loci in S. pombe have led to the spread of heterocromatotin and H3 Lys9 methlyation in the flanking euchromatin regions normally marked by the methylation H3 Lys4 (65). In the β-globin of chicken locus, a functional boundary element was mapped to the hypersensitive site deoxyribonuclease I called 5′HS4. A recent report has shown that a 250-bp region in this element recruits and binds ubiquitously expressed USF proteins (67). These USF proteins physically associate with iston acetiltransferases p300/cAMP response element protein-binding (CBP) and p300, as well as H3 Lys4 methyltransferase Set7/9. In addition, the intermediate stop of RNAi of the USF expression resulted in a loss of intake of iston modification enzymes, a significant decrease of H3 acetylate and Lys4-methylized and a concomitant increase in the H3 Lys9-methylized to the 5′HS4 element. These studies thus provide a possible mechanism to direct isto-modifying enzymes to border elements through the association with USF proteins to prevent heterochromy in eucaromatic regions. HISTONE METHOD STABILITY One of the definition criteria for epigenetic changes is that they are inherited. For this reason, one of the attractive features of Lys' istone methylation as a potential epigenetic sign is that this modification seems to be very stable (68, 69). The initial studies which examined the turnover rate of iston methylation found that the half-life of the methyl brand on istons is equal to that of the protein itself, and therefore proposed that this change be irreversible. Recently an enzyme has been identified that catalyzes the removal of Arg ethylated istons, indicating that not all types of istone methylation are irreversible (70, 71). Istoni arg methyltransferases is linked to gene activation so recruitment of istone Arg methyltransferases, such as CARM1 (arginine associated with methyltransferasae co-activator) and PRMT1 (protein arginine N-metil transferase), is part of the transcription of genes regulated nuclear hormone (for more details of this group of enzymes). To the extent that the activation of these genes is transient, it is not surprising that the Arg methylation of istons should be reversed to restore the inducible state of genes. Functionally, the identified enzyme, peptidilarginine deiminasi 4 (PAD4 or PADI4), is not a demethylase, but a deiminase that converts Arg residues into citrulline (75). In vitro essays have shown that PAD4/PADI4 can use metilati-histones as substrate, and chromatic immunoprecipitation analyses have demonstrated the coordinated enrichment of Arg-methylized istons, PAD4/PADI4, and citrullinate istons to promote pS2with the expression profile of this estrogen-regulated gene (70, 71). These studies have proposed that the removal of H3 or H4 Arg metilates be mediated throughThe Arg residues to the PAD4/PADI4 citrulline, and the citrullinate istons are then replaced or converted into istons not modified by an unknown mechanism. As it is evident that epigenetic reprogramming occurs during differentiation and development, this argues that at some point there must also be the removal or turnover of methylic-Lys signs on istons. The identification of such enzymatic activity has shown to be elusive until very recently when it was reported that an oxidase hemisphere called LSD1 (Lys-specific demethylase 1) specifically targets H3 methilate to Lys4 (76). LSD1 was initially identified as a component of the Co-REST receptor complex. The in vitro essays have shown that LSD1 converts H3 mono or dimethylated into non-methylated forms, but has no enzymatic effects on quarterly substrates. In addition, this enzyme has an exquisite specificity for Lys4-metilated H3; however, the structural basis for this specificity is not currently known. The arrest induced by RNAi of LSD1 levels has led to an increase in H3 levels etilated by Lys4 and the derepression of a number of known genes to be regulated by the Co-REST complex, suggesting that this enzymatic activity has a role in gene silence. An intriguing point of observation is that the LSD1 homologists and homologists have been identified in a number of eukaryotic organisms; However, they do not seem to be present in S. cerevisiae. This is surprising because this organism is enriched in Lys4-metilated H3. In addition, the amine oxidizing activity of LSD1 does not mean the removal of lis trimetilata, and therefore it is possible that additional and alternative (i.e. one that uses a different kind of enzyme reaction) istone Lys-demethylases can exist (77.) Since both LSD1 and PAD/PADI4 are the first and only relationships of the respective methyl-Arg removal enzymes and methyl-Arg removal activities, many remain from these details. For example, how are these enzymes targeted and regulated in vivo? To the extent that previous studies have discovered that the mass level of iston methylation is very stable, this indicates that only a small fraction of total chromatin is demethylated? Also, given the specificity of LSD1 towards Lys4-metilated H3, are there distinct enzymes that demete each of the site-specifically methed H3 and H4? Finding answers to these questions will undoubtedly remodel our current ideas of the biological roles of the iston methylation. REGULATION OF THE BINDING OF CHROMATIN-ASSOCIATES IN HISSION METHODS Lys9 and Lys27 methylation on H3 is functionally important for determining interactions with iston protein (24,) and this is mediated by the methyl-dependent bond of HP1 and Pc through their chromodomin motifs. The analysis of the crystalline structure of the chromodons of these twohave shown that the preserved positioning of several key aromatic residues form structures similar to those of the cage that bind the lis methulates up(41, 78, 79). As mentioned above, Lys79's H3 metilate is specifically recognized and linked by 53BP1 (51), and in this case the interaction is mediated by the 53BP1 Tudor domain. The Tudor domain and the chromodomain are structurally related and belong to a larger family of domains known as the royal family (80). If other members of this family also bind methin is an interesting question that is the subject of investigation. Taking into account the idea that metillis residues serve to recruit binding partners, some researchers have also raised the question if this link depends on the methylation of factors associated with chromatin is potentially a regulated process. In particular, it has been noted that many of the sites of lis-methylation on istons are adjacent to known Ser/Thr residues or potential phosphorized sites; It has therefore been proposed that the reversible phosphorylation of the neighboring residues may play a role in the regulation of the metilate-dependent bond of chromatic factors such as HP1 (81). The in vitro bond of HP1 to H3 metilate with Lys9 was ablate when the residual serine in position 10 (Ser10) of H3 was phosphorated (81). In addition, the live location of HP1 to chromatin was found related to changes in the H3 modification status during the cell cycle (82). It is interesting to note that the dissociation of HP1 from chromatin occurs only after H3 was phosphorized to Ser10 and acetylate to Lys14. This combination of H3 modifications has previously shown to be related to transcriptional activation of precocious genes in mammal cells (83, 84) and may have additional functions in the antagonism of the transcriptive silencing mediated by HP1. LINKS ARE AND DNA METHODATION As mentioned above, DNA methylation is another mechanism associated with epigenetic silence. DNA methylation occurs specifically at the C5 position of cytosine residues that are in the context of CpG dinucleotides. It has been estimated that 80% of all CpG dinucleotids present in the genome of mammals are metilated (85). The remaining unmatched residues of CpG are mostly found in the regions promoting genes that are constitutionally active and are called CpG islands. The DNA methylation has long been shown to have a transcriptive silentizer function. This effect is partly mediated by the recruitment of HDAC through the methyl-DNA binding motifs of components of different complexes containing HDAC (86, 87). More recently, direct functional links between DNA and the methylation of the iston were discovered. In Neurospora and Arabidopsis, genetic evidence indicates that methylation H3 Lys9 is a prerequisite for DNA methylation (88, 89). Loss of Suv39H1/2 in mouse knockout cells also altered the DNA methylation pattern of their(90). On the other hand, examples of DNA methylation ablation affecting H3 methylation and other istonswere also found in Arabidopsis and human cells (91, 92). It seems that DNA and istone methylation probably have a cyclical and mutually strengthening relationship, and both are necessary for a stable and long-term epigenetic silence. INDUSTRY OF EPIGENETY MARKET Although a substantial detail is known about the inheritance of DNA methylation through the mythical cell division, any similar mechanism for the inheritance of istone modifications are not so clearly understood. As mentioned earlier, the istone methylation does not seem to turn rapidly and presumably persists through the cell division. Also for highly dynamic changes such as acetylation, previous studies have shown that specific sites of acetylation are maintained during mitosis, and such inheritance of acetylation patterns is designed to maintain the expression profiles of genes through successive generations (93, 94). During DNA replication, the pre-existing nucleosms of the parental genome are recycled and deposited on the newly generated daughters' wires, and therefore, any stable istone changes can potentially be transferred from one generation to another. Early studies using radioactive istons labeled strongly suggested that parents' istons are transferred as untouched octadors, and are randomly segregated on the two strands of the daughter's DNA (95, 96). Nucleus assembly complexes then deposit additional synthesizers to fill gaps. It is interesting to note that a recent report suggested that parental nucleosis can actually split in a semi-conservative way where the parental istonic octamer is divided into H2A-H2B/H3-H4 heterodimers which are then equally segregated on the two strands of the daughter's DNA (97). In this scenario, the nucleous assembly complex then deposits istons synthesized recently to complete the pre-existing half of nucleosome (see Fig. 2). This idea is intriguing because it invokes the possibility of a mechanism that can transmit faithfully and fairly the information istone-associated by parents to children of DNA. However, it is unclear how this hypothesis fits with the previous data that showed the transfer of intact iston ottamatists during DNA replication. Open in the new tabDownload slide Two Nucleosome secretion models After the passage of the replication fork, the parental nucleosomes are recycled and deposited on the two daughter threads. In model A, parental istonic ottamers (grain cylindri) remain intact and are randomly segregated to the two daughter threads. The newly assembled nucleos (red cylinders) then fill the gaps not occupied by the parents' octadors. In this scenario, enzymes that change tonography copy historic changes of parentsfrom the Me groups) to the newly assembled adjoining nucleosms (simpbolized by green arrows). In model B, the parental isthonic ottamers are divided in half and are equally segregated to the two daughters' threads (half of cereals). Core assembly complexes then deposit againistons to complete the existing half of nucleosomes (red media) present on the daughter's wires. In this case, istone modifying enzymes copy changes from the old half to the new half of nucleosomes (simpbolized by green arrows.) regardless of the mechanism that segregates and assembles nucleosides on newly divided dna filaments, the successful propagation of iston modification models requires a way to copy/replicate pre-existing changes on newly assembled nucleosomes. in the above mentioned scenarios, it is required to copy the istone modifications from the pre-existing nucleosome to the adjacent nucleosome assembled with newly synthesized istons, while the other requires the copy of the information from the "old half" of the nucleose to the "new half" (fig. 2.) in the DNA methyltransferase process, the copy of the methyltransferase pattern while replication is mediated.1 at the moment, a similar process has not been shown to replicate istone modification. However, it is interesting to note that some hmts such as suv39h1 also contain chromodominic motifs that potentially play a role in targeting these enzymes to selectively modified regions of chromatin. Moreover, several istone acetiltransferases such as cbp and P300/CBP-asssociated factor also contain bromodomins, a reason that has been shown to have acetil-Lys binding properties. While chromiums and bromolomins of these hmts and iston acetiltransferases have not yet been found to bind specific or acetylated methin istons, the functional meaning of these potential modification-binding motives present on istone methyl- and acetiltransferases is nevertheless alluring. conclusions from the time when chromatin was thought only as a static armor for the dna to wrap, our appreciation for the different regulatory functions mediated by chromatin and istone modifications grew up in jumps and limits. Instead of being a structural bystander, istons are now recognized as active effects of gene expression and as suppliers of additional levels of regulation to the standard DNA model. epigenetic information encoded by histonic changes and histonic variants not only defines functional genomic points of reference as heterochromatin and euchromatin, but also regulates more specialized epigenetic phenomena such as inactivation chromosome x and genomic imprinting (arees that are beyond the scope of this review; for recent reviews, see refs. 98–100). Moreover, these changes are fundamental to maintain the integrity of genome expression profiles and the interruptions of these profiles undoubtedly contribute to diseases and diseases. Therefore, our growing understanding of the mechanical details of epigenetic regulation has great promise for the improvement of human health. recognitionrecognize tony tonyfor invaluable discussions on nucleosis segregation patterns. We also want to thank Scott Briggs for the critical review of the manuscript. The work carried out in our laboratory is funded by Canadian Health Research Institutes and the National Cancer Institute of Canada which grants agencies in Canada.

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