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Epigenetic mechanisms that operate in mammals

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ABSTRACT

Epigenetic mechanisms act to change the accessibility of chromatin to transcriptional regulation locally and globally *via* modifications of the DNA and by modification or rearrangement of nucleosomes. Epigenetic changes can be defined as stable molecular alterations such as the gene expression they are heritable during cell divisions but do not involve changes in the DNA sequence. Epigenetics consist in several molecular mechanisms: histone modifications, small non-coding or antisense RNAs and DNA methylation; that are closely interconnected.

KEYWORDS

Epigenetics;
DNA methylation;
Histone modification;
Non coding RNAs;
miRNA.

INTRODUCTION

Historically, the word "epigenetics" was used to describe events that could not be explained by genetic principles.

Conrad Waddington (1905–1975), who is given credit for coining the term, defined epigenetics as "the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being"[1].

Much of today epigenetic research is converging on the study of covalent and noncovalent modifications of DNA and histone proteins and the mechanisms by which such modifications influence overall chromatin structure. Chromatin, the complex of DNA and its intimately associated proteins, provides an attractive candidate for shaping the features of a cell epigenetic landscape.

Epigenetic phenomena have recently led researchers to conserved molecular mechanisms involving chromatin modification, a theme reinforced throughout this special issue. We favor the view that the macromolecular entities described below all significantly contribute to the physiologically relevant organization of most eukaryotic genomes. These entities, and possibly others yet unknown, should be considered collectively when exploring epigenetic mechanisms.

EPIGENETICS

In biology and specifically genetics, epigenetics is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms, other than changes in the underlying DNA sequence. It refers to functionally relevant modifications to the genome that

do not involve a change in the nucleotide sequence. Epigenetics refer to changes in phenotype and gene expression that occur without alterations in DNA sequence. Epigenetic modifications of the genome can be acquired de novo and are potentially heritable. These changes may remain through cell divisions for the remainder of the cell life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism, instead of non-genetic factors cause the organism genes to behave differently.

There are three major mechanisms of epigenetic regulation, including methylation of CpG islands, mediated by DNA methyltransferases, modification of histone proteins, and microRNAs. There are substantial interactions between these epigenetic mechanisms (Figure 1).

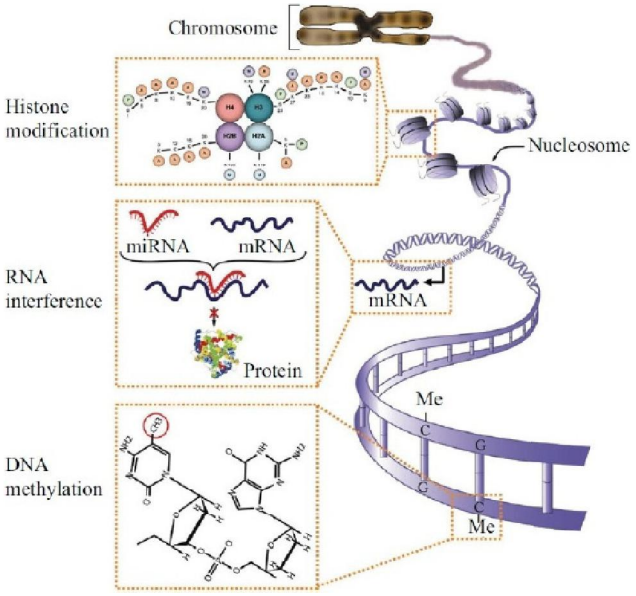

Figure 1 : Schematic of the mechanisms of epigenetic regulation. DNA methylation, histone modification and RNA-mediated gene silencing constitute three distinct mechanisms of epigenetic regulation. DNA methylation is a covalent modification of the cytosine (C) that is located 5' to a guanine (G) in a CpG dinucleotide. Histone (chromatin) modifications refer to covalent post-translational modifications of N-terminal tails of four core histones (H3, H4, H2A, and H2B). The most recent mechanism of epigenetic inheritance involves RNAs[2].

DNA METHYLATION

DNA methylation is the most studied mechanism, provides suppression of gene expression, embryonic development, transcription, chromatin structure, X-chromosome inactivation, genomic imprinting regulation and functional preservation of the stability of chromatin.

In mammals, methylated cytosine is predominantly observed in the context of CpG dinucleotides and is involved in a range of processes including embryogenesis, genomic imprinting and tumorigenesis.

DNA methylation is an essential component of the epigenetic machinery in regulating gene expression and interacting with nucleosomes that control DNA packaging, affecting entire domains of DNA[2].

The only known epigenetic modification of DNA in mammals is methylation of cytosine at position C_5 in CpG dinucleotides[3]. By contrast, the other main group of epigenetic modifications (the post-translational modification of histones) shows a high level of diversity and complexity[4]. The mammalian DNA methylation machinery is composed of two components, the DNA methyltransferases (DNMTs), which establish and maintain DNA methylation patterns, and the methyl-CpG binding proteins (MBDs), which are involved in reading methylation marks[5]. DNA methyltransferases (DNMTs) catalyze genome-wide DNA methylation and are associated with histone modifying enzymes (*e.g.* histone deacetylases (HDACs)), histone methyltransferases (SUV (39) H1/2 and EZH2), and ATP dependent chromatin remodeling enzymes[6] (Figure 2). The methyl moiety of methyl cytosine resides in the major groove of the DNA helix, where many DNA-binding proteins make contact with DNA, and exerts its effect by attracting or repelling various DNA-binding proteins. A family of proteins that can bind to DNA containing methylated CpG dinucleotides, known as methyl-CpG-binding proteins, have been shown to recruit repressor complexes to methylated promoter regions and thereby contribute to transcriptional silencing. Certain transcription factors bind to CpG-containing DNA sequences only when they are unmethylated.

DNA methylation may affect the transcription of genes in two ways. First, the methylation of DNA itself may physically impede the binding of transcriptional proteins to the gene, and second, and more important, methylated DNA may be bound by proteins known as methyl-CpG-binding domain proteins (MBDs). MBD proteins then recruit additional proteins to the locus, such as histone deacetylases and other chromatin remodeling proteins that can modify histones, thereby

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forming compact, inactive chromatin, termed heterochromatin[7] (Figure 2).

Maintenance methylation activity is necessary to preserve DNA methylation after every cellular DNA replication cycle. Without the DNA methyltransferase (DNMT), the replication machinery itself would produce daughter strands that are unmethylated and, over time, would lead to passive demethylation.

DNMT1 is the proposed maintenance methyltransferase that is responsible for copying DNA methylation patterns to the daughter strands during DNA replication. Mouse models with both copies of DNMT1 deleted are embryonic lethal at approximately day 9, due to the requirement of DNMT1 activity for development in mammalian cells[7].

It is thought that DNMT3a and DNMT3b are the *de novo* methyltransferases that set up DNA methylation patterns early in development. DNMT3L is a protein that is homologous to the other DNMT3s but has no catalytic activity. Instead, DNMT3L assists the *de novo* methyltransferases by increasing their ability to bind to DNA and stimulating their activity. Finally, DNMT2 (TRDMT1) has been identified as a DNA methyltransferase homolog, containing all 10 sequence motifs common to all DNA methyltransferases. However, DNMT2 (TRDMT1) does not methylate DNA but instead methylates cytosine-38 in the anticodon loop of aspartic acid transfer RNA[7-9].

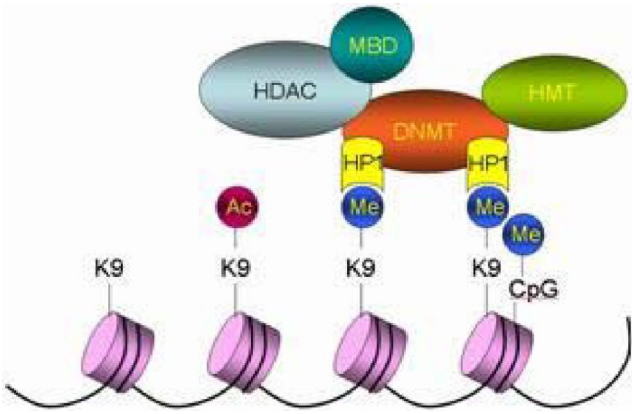

Figure 2 : Schema of the DNA methylation components[35]

HISTONE MODIFICATION

Chromatin proteins serve as building blocks to package eukaryotic DNA into higher order chromatin fibers. Each nucleosome encompasses approximately146 bp of DNA wrapped around an octamer of histone proteins. These octamers consist of double subunits of H2A, H2B, H3, and H4 core histone proteins (Figure 1). The histone proteins coordinate the changes between tightly packed DNA (heterochromatin) that is inaccessible to transcription and exposed DNA (euchromatin) that is available for binding and regulation of transcription factors[10,11] (Figure 3). These changes occur due to structural characteristics of the nucleosome that are known as "histone tails," which extend from the core octamer. These tails consist of N-termini of the histone proteins and are the major sites for post-translational modifications.

Chromatin is a highly dynamic structure and must keep the balance between being folded as much as needed and being accessible whenever necessary to cope with genome templated processes such as replication, transcription and DNA repair. The functional state of chromatin is partially regulated through post-translational modifications (PTMs) of histones. Thereby these modifications are involved in regulating the gene expression. Numerous types of histone modifications exist and they are divided into two groups. First group

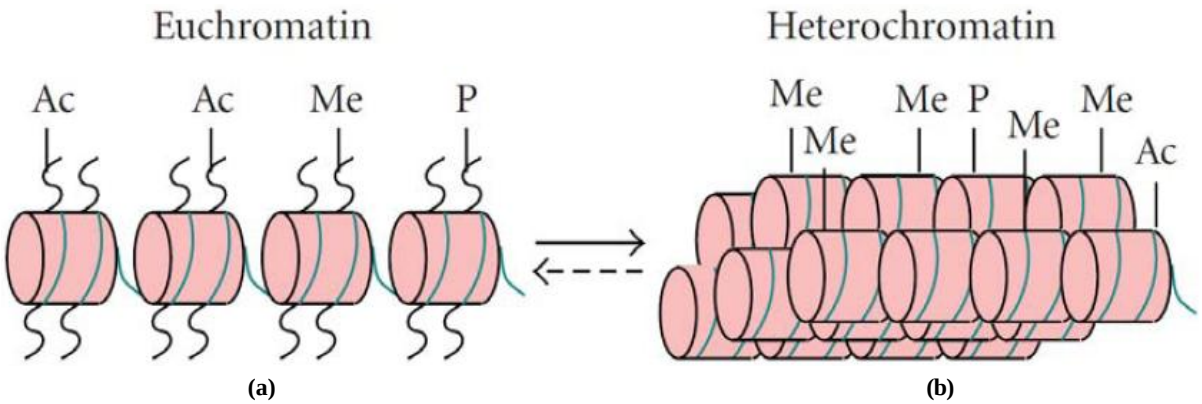

Figure 3 : Euchromatin and Heterochromatin. Histone tails have three types of modification including acetylation (Ac), phosphorylation (p), and methylation (Me)[14].

belong acetylation of lysines, phosphorylation of serines and threonines and methylation of arginines and lysines as they convey small chemical groups. Second, there are larger peptides such as ubiquitination and sumoylation of lysines and ADP-ribosylation of glutamic acid (TABLE 1). There are several mechanisms how histone posttranslational modifications can influence chromatin. First, histones and their modifications can alter the chromatin structure and thus regulate DNA accessibility. The other one is PTMs on histones facilitates the binding of a protein to chromatin by creating a specific binding site[12,13].

Acetylation of histone proteins correlates with transcriptional activation and a dynamic equilibrium of histone acetylation is governed by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone acetylation status results from an intricate cross-talk between HATs and HDACs[2]. HDACs are a class of enzymes catalyzing the opposite action to HATs. They influence a myriad of cell processes including signal transduction, apoptosis, cell cycle regulation, and cell growth[15]. HDACs catalyze deacetylation of both histone and non-histone proteins and, similar to HATs, can be either nuclear or cytoplasmic. Aside from histones, many transcriptional regulators, chromatin modifiers, and intracellular signal transducers are posttranslational modified by acetylation. Importantly, HDACs are associated with a number of other epigenetic repression mechanisms, including histone methylation[16], PcG-mediated repression[17], and DNA methylation. Importantly, HDAC activity is often crucial to prepare the histone template for methyltransferases by removing acetyl groups obstructing methylation[11].

Histone methylation also plays a major role in gene expression regulation[14]. Histone methylation is associated with transcriptional repression or activation depending on the affected specific amino acid. For example, methylation of histone H3 lysines 4 and 36 is associated with active gene expression. However methylation of histone H3 lysines 9 and 27 is associated with gene silencing. Histone methylation is catalyzed by a large number of enzymes. Similar to acetylation/deacetylation, histone methylation is reversible and catalyzed by 2 families of histone demethylases (HDMTs), namely the lysine-specific demethylase 1 (LSD1) and the Jumonji domain-containing enzymes[18,19]. Histone methylases and HDMTs are usually part of large protein complexes that regulate gene transcription[2,3,11].

Phosphorylation is in addition to acetylation and methylation of histone. Important progress has also been made in the studies of other types of covalent modifications including phosphorylation of histone H3 at Ser10 (H3-S10)[20]. This has important implications regarding signal transduction. It suggests that the mainly cytoplasmic protein phosphorylation cascades that have dominated signal transduction processes for many years may have a more direct effect on gene expression through the phosphorylation of chromatin[10]. Also phosphorylation in chromatin generates a barrier for the repair of DNA damage. Two phosphorylation sites on this histone have a role in doublestrand break repair via nonhomologous end joining: H2AS129 mediated by Mec1 and H4S1 mediated by Caesin kinase II[21].

Ubiquitylation very large modification has been found on H2A (K119) and H2B (K20 in human and K123 in yeast)[22]. A role for this modification has been demonstrated in transcriptional elongation by the histone chaperone fact[23]. How ubiquitylation functions is unclear. It is likely to recruit additional factors to chromatin but may also function to physically keep chromatin open by a "wedging" process, given its large size[10,24].

Sumoylation is like ubiquitylation. Sumoylation is a very large modification and shows some low similarity to ubiquitylation. This modification has been shown to take place on all four core histones, and specific sites have been identified on H4, H2A, and H2B[25]. Sumoylation antagonizes both acetylation and ubiquitylation, which occur on the same lysine residue, and consequently this modification is a repressive for transcription in yeast.

ADP Ribosylation this histone modification is badly defined with respect to function. ADP ribosylation can be mono- or poly-, and the enzymes that mediate it are MARTs (Mono-ADP-ribosyltransferases) or PARPs (poly-ADP-ribosepolymerases), respectively[26]. In addition the Sir families of NAD-dependent histone deacetylases have been shown to have low levels of this activity, so they may represent another class of this family. There are many reports of ADP ribosylation of histones, but only one site, H2BE2ar1, has been definitively mapped. Although the function of the enzymes has often been linked to transcription, evidence that the catalytic activity is involved has been lacking.

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Recently, a role for PARP-1 activity in transcription has been demonstrated but only under conditions where DNA repair is induced. Double-strand breaks mediated by Topoisomerase II b activate the PARP-1 enzyme, which then directs chromatin changes to the estrogen-regulated *PS2* gene[27].

TABLE 1 : Different classes of modifications identified on histones[10,13,28]

Chromatin Modifications	Modified Residues	Regulated Functions
Acetylation	K-ac	Transcription Repair, Replication, Condensation
Methylation (lysines)	K-me1 K-me2 K-me3	Transcription Repair
Methylation (arginines)	R-me1 R-me2a R-me2s	Transcription
Phosphorylation	S-ph T-ph	Transcription Repair Condensation
Ubiquitylation	K-ub	Transcription Repair
Sumoylation	K-su	Transcription
ADP ribosylation	E-ar	Transcription
Deimination	R > Cit	Transcription
Proline Isomerization	P-cis > P-trans	Transcription

NONCODING RNAs

Non-coding RNA (ncRNA) molecules are those RNAs that do not encode proteins, but instead serve some other functions in the cell. Small noncoding RNAs refer to a family of RNAs that, by complementarity to the 3' untranslated region of messenger RNAs, lead to their degradation and subsequent inhibition of gene expression[29]. Part of this family of noncoding RNAs are 20- to 22- nucleotide microRNAs (miRNAs), resulting from the sequential splicing of primary then pre-RNAs. miRNAs are involved in post-transcriptional control of gene expression. miRNAs transcripts are generated either by RNA polymerase II or III as long primary transcripts (pri- miRNAs) carrying the mature miRNA sequence in a stem loop structure[30].

In the nucleus, cleavage of the pri-RNA stem loop by the RNase III endonuclease DROSHA releases a 60-70 nucleotide long precursor RNA, called pre-RNA, which is subsequently transported into the cytoplasm and is further processed by Argonaute2 and DICER[31]. One stand of the DICER cleavage product carrying the mature miRNA sequence is further incorporated into the RNA-induced silencing complex (RISC)[32]. Due to the complementarities of miRNAs to the 3' UTR of mRNAs, the active RISC recognizes target transcripts and promotes translation inhibition or mRNA destabilization, both resulting in the reduction of target protein level[32,33]. miRNAs are then incorporated in the RNA-induced silencing complex and transported back in the nucleus, where they exert their biological effect. Through Watson-Crick base pairing, miRNAs bind to complementary sequences of mRNAs and induce either degradation or translational silencing of the target mRNAs[2]. Small RNA pathways are often entangled. Despite our growing understanding of the mechanism and function of small RNAs, their evolutionary origins remain obscure. It is interesting to note that miRNAs are also themselves epigenetically regulated at their promoter level, and target many genes that play important roles in such processes as cell cycle progression, apoptosis, and differentiation. A single miRNA can have hundreds of target mRNAs, highlighting the implication of this gene regulation system in cellular functions[32]. The study of miRNAs has become the subject of intense interest, especially after the discovery of the fundamental role of these small, noncoding RNAs in a countless of cellular and biological processes ranging from development to disease states[29,32,33].

ncRNAs appear to comprise a hidden layer of internal signals that control various levels of gene expression associated with physiological and developmental processes. ncRNAs, especially small ncRNAs, play a significant role in cellular physiology, specifically, epigenetic regulation of gene expression. Epigenetic regulation is a heritable change in gene expression that cannot be associated with genetic variation.

Approximately 1,000 miRNA genes have been computationally predicted in the human genome, with each miRNA targeting multiple protein coding transcripts. Although miRNA are vital to normal cell physiology their misexpression has been linked to carcinogenesis, and miRNA profiles are now being used to classify human cancers[34]. A list of some of the miRNAs whose expression is altered during carcinogenesis is presented in TABLE 2. The influence of miRNA on the

epigenetic machinery and the reciprocal epigenetic regulation of miRNA expression suggest that its deregulation during carcinogenesis has important implications for global regulation of epigenetics and cancer.

TABLE 2 : MicroRNA alterations in various human cancers[4,31,33]

MicroRNAs	Target Gene(s)	Cancer Type
miR-125	AKT, ERBB2-4, FGF, FGFR, IGF, MAPKs, MMP11, SP1, TNF, VEGF	breast
miR-205	VEGF-A, ErbB3	breast
miR-10b	Rho C	breast
miR-335	SOX4, TNC	breast
miR-29a	TTP	breast
miR-9	CDH1	breast cancer
miR-520	CD44	breast cancer
miR-146	NF-kB	breast, pancreas and prostate cancers
miR-10b	HOXD10	metastatic breast cancer
miR-372,miR-373	RAS, p53, CD44	testicular germ cell tumor and breast cancer
miR-342	ER, PR and HER2	breast and colon cancer
miR-145	ER	colon and breast cancer
miR-126	CRK1,PIK3R2,SPRED1, VCAM1	breast and lung cancer
miR-200 family	ZEB1, ZEB2	NCI-60 cell lines; breast, ovary
miR-218, miR-145	PXN	breast, lung and prostate cancer
miR-155	RHOA	Burkitt's lymphoma, breast, colon, and lung cancers
miR-21	PDCD4,PTEN,TPM1,RECK, TIMP3,BCL2	glioblastoma, breast, lung, prostate, colon and cervical cancer
miR-15a, miR-16-1	CCND1, Wnt3A	prostate
miR-101	Fos, EZH2	HCC, prostate
miR-127	Bcl-6	bladder cancer
miR-124	CDK6	colon cancer
miR-223	NFI-A, MEF2C	acute myeloid leukemia
miR-34b/34c	p53 network, CDK6, E2F3	colon cancer
miR-17, miR-92	c-MYC	lung cancer
miR-92b	PRMT5	brain primary tumors
miR-29c	ECM proteins	NPC
miR-127, miR-199a	BCL6, E2F1	cervical cancer
miR-421	CBX7, RBMXL1	gastric cancer
miR-32, miR345, miR-1228,miR-195, miR30b	CDKN2A,NF2,andJUN	Malignant mesothelioma (MM)
miR-190, miR-196	HGF	pancreatic cancer
miR-34a	c-Met	HCC
miR-146a, miR-146b	ROCK1, IRAK1,TRAF6	prostate cancer and papillary thyroid carcinomas
miR-340, miR-421, miR-658	MYC, RB, PTEN	lymph node metastasis and gastric cancer
let-7a-3	RAS, IGF-II	lung and ovarian cancer
miR-9	NF-_B	ovarian and lung cancer

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MicroRNAs	Target Gene(s)	Cancer Type
miR-221, miR-222	CDKN1C/P57 and CDKN1B/P27	hepatocellular carcinoma
miR-25, miR-32, miR-142	ITGA_1	lung cancer and solid tumor
miR- 124, miR-183	ITGB_1	lung cancer
miR-143	ERK5	cervical cancer
miR-372, miR-373	LATS2	testicular germ cell cancer
miR-370	MAP3K8 MzChA-1, KMCH-1,	cholangiocarcinoma downregulation
miR- 124, miR-183	ITGB1 _	lung cancer

Abbreviations: CDK6, cyclin D kinase 6; MEF2C, myocyte enhancer factor 2C; NFIA, Nuclear factor 1 A-type; p53, tumor protein 53; RAS, Rat Sarcoma; CD44, cluster differentiation 44; PDcD4, programmed cell death 4; TPM1, tropomyosin 1; PTEN, phosphatase and tensin homolog ; BCL2, B-cell lymphoma 2 protein; RECK, reversion Inducing cysteine rich protein kazal motif; ROHA, ras homolog gene family member A; NF-_B, nuclear factor-_appaB; PRNT5, protein arginine N-methyltransferase 5; HOXD10, homeobox D10; CDH1, Cadherin-1; CBX7, chromobox 7; RBMX L1, RNA binding motif protein X-linked; CDNK2A, cyclin-dependent kinase inhibitor 2A; NF2, neurofibromatosis, type 2; HGF, hepatocyte growth factor; ERBB2-4= or (HER4), human epidermal growth factor Receptor 4; JUN, janus N-terminal kinases; FGFR, fibroblast growth factor receptor; MAPKs, mitogen-activated protein kinase; MMP11, matrix metalloproteinase11; VEGF, vascular endothelial growth factor; TNF_, tumor necrosis factor-alpha; CRK1, Cdc2-related kinase1; PIK3R2, phosphatidylinositol 3-kinase egulatory subunit beta; SPRED1,sprouty-related, EVH1 domain containing 1; VCAM, vascular cell adhesion molecule; ROCK1, rho-associated, coiled-coil containing protein kinase 1; IRAK1, interleukin-1 receptor associated kinase-1; TRAF6, TNF receptor associated factor 6; Rb, retinoblastoma; IGF-II, insulin-like growth factor 2; PXN, paxilin; ITG_1, integrin beta-1; ERK5, extracellular signal-regulated kinase 5; LATS2, large tumor suppressor homolog 2; ER, estrogen receptor; PR, progesterone receptor, TNC, tenascin C; HCC, hepatocellular carcinoma; BT-IC, breast tumor initiating cells; NPC, nasopharyngeal carcinoma.

CONCLUSION

In summary, recent studies revealed that deregulation of a number of epigenetic mechanisms may favour appearance of genetic alterations. Understanding the complexity of the epigenome and the actors involved in modulating its interactions within genomic sequences, it will open new horizons in our search to know all the mechanisms governing cellular fate.

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