epigenética

...heritable changes in gene expression that are not due to any alteration in the DNA sequence...

1

Epigenética: cambios en la expresión génica que pueden permanecer durante divisiones celulares sucesivas (memoria celular) que no se deben a cambios en la secuencia de DNA...

La metilación de la citosina de los residuos CpG es un mecanismo esencial para la regulación de la expresión génica.

"the causal interactions between genes and their prod- ucts, which bring the phenotype into being," CP Waddington, 1939

La acetilación y de-acetilación de histonas, así como la metilación de los residuos de lisina de la histona H3, entre otros, también regulan la expresión génica

2

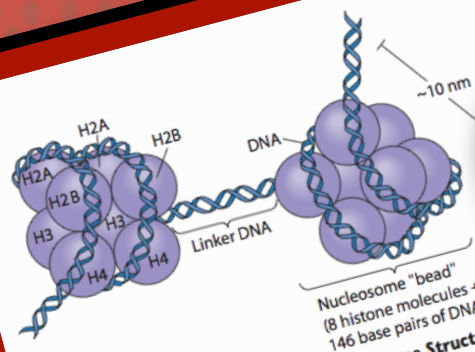


FIGURE 18-21 A Closer Look at Nucleosome Structure. Each nucleosome consists of eight histone molecules (two each of histones H2A, H2B, H3, and H4) associated with 146 base pairs of DNA and a stretch of linker DNA about 50 base pairs in length. The diameter of the nucleosome "bead," or core particle, is about 10 nm. Histone H1 (not shown) is thought to bind to the linker DNA and facilitate the packing of nucleosomes into 30-nm fibers.

3

Los complejos remodeladores dependientes de ATP son también mecanismos epigenéticos de regulación de la expresión génica.

nombre: mauricio lema medina

mom

METILACIÓN DEL DNA

La metilación del DNA ocurre - casi exclusivamente - en la Citosina en los residuos CpG del DNA

LAS 5 METIL-CITOSINAS PUEDEN SUFRIR DESAMINACIONES ESPONTÁNEAS CONVIRDIÉNDOSE EN TIMINA... TRANSICIÓN C A T

HAY VARIAS DNA CITOSINA METIL TRANSFERASAS: DNMT1, DNMT2, DNMT3A, NMT3B, DNMT3L

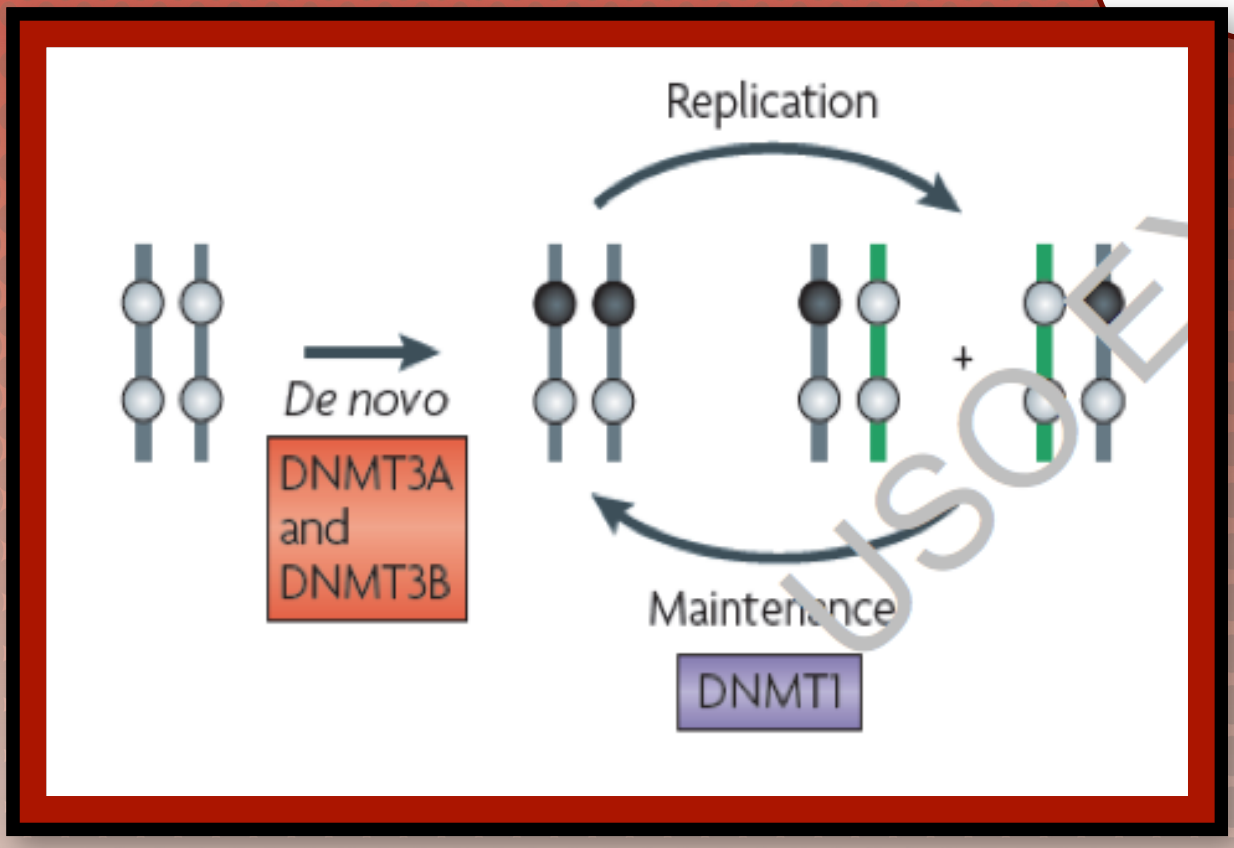
TAMBIÉN HAY DEMETILACIÓN POR LAS ENZIMAS TET

Se han detectado casi 29000 islas ricas en CpG que no están metiladas... ubicadas cerca de los promotores de los genes "house-keeping"

LA DNMT1 ES DE MANTENIMIENTO... MANTIENE LA INTEGRIDAD DE EPIGENO

LA DNMT2 SE ENCARGA DE LA METILACIÓN EN EL RNA NUCLEOLAR ...

LAS DNMT3A Y 3B SE ENCARGAN DE LAS METILACIONES DE NOVO. LA 3L ES IMPORTANTE EN EL IMPRINTING



EPIGENÉTICA VÍA HISTONAS

LAS HISTONAS ACETILASAS (HAT) LE AGREGA GRUPOS ACETILO A LAS HISTONAS

LAS HDAC (HISTONAS DEACETILASAS) REMUEVEN LOS GRUPOS ACETILO

las histonas pueden tambien ser modificadas adicionando / quitando residuos de acetilo, metilo, etc

LAS HISTONAS METIL TRANSFERASAS LE AGREGA GRUPOS METILO A LOS RESIDUOS DE LISINA EN LA HISTONA H3/H4

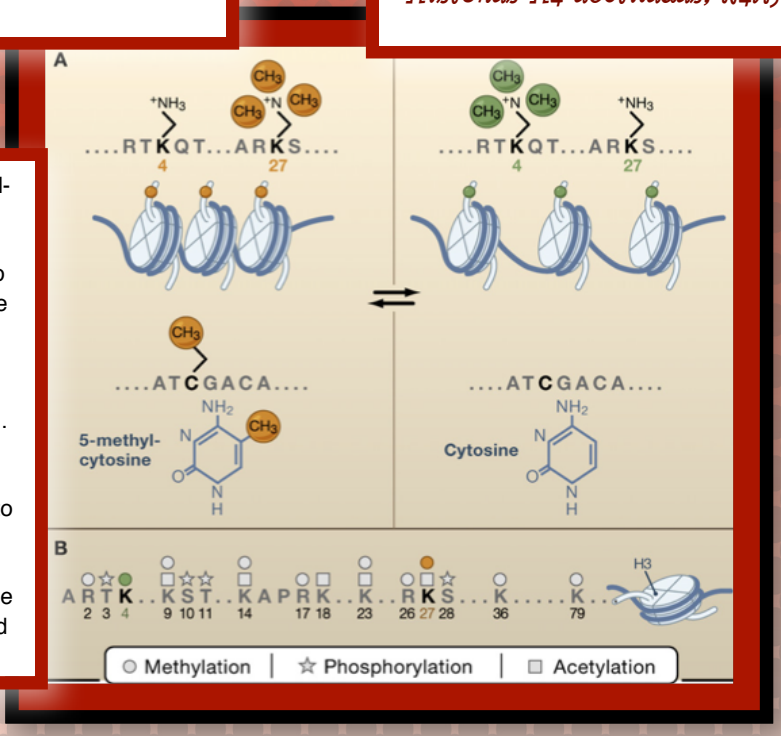
OTRAS ALTERACIONES DE LAS HISTONAS: FOSFORILACIÓN, UBIQUITINIZACIÓN, SUMOILACIÓN, RIBOSLACIÓN E ISOMERIZACIÓN

CÓDIGO EPIGENÉTICO

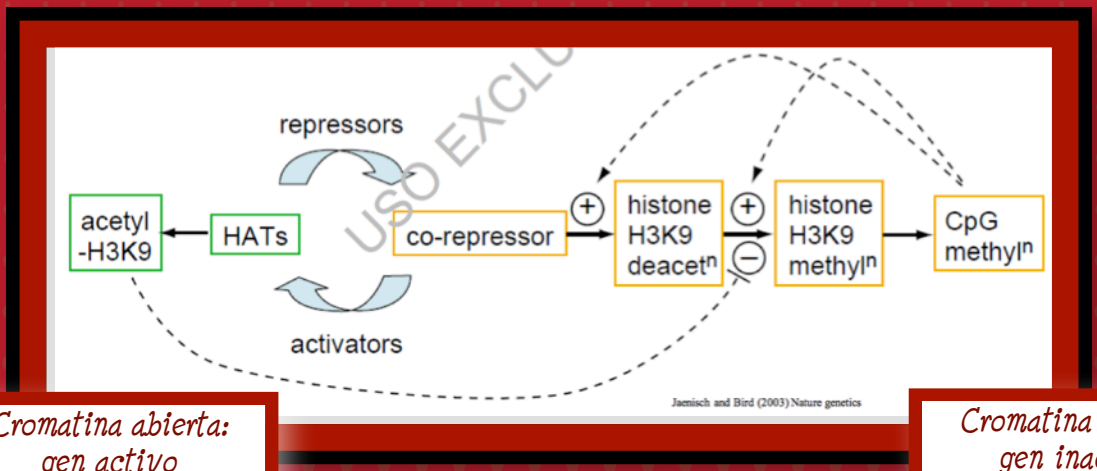
Las modificaciones epigenéticas establecen si el gen es activo o silenciado...

gen inactivo: GpG metilados, Histonas H3 y H4 de-acetilada, K4H3 desmetilada, K9H3 metilada, K27H3 trimetilada

gen activo: GpG sin metilación, Histonas H4 acetiladas, K4H3 dimetilada

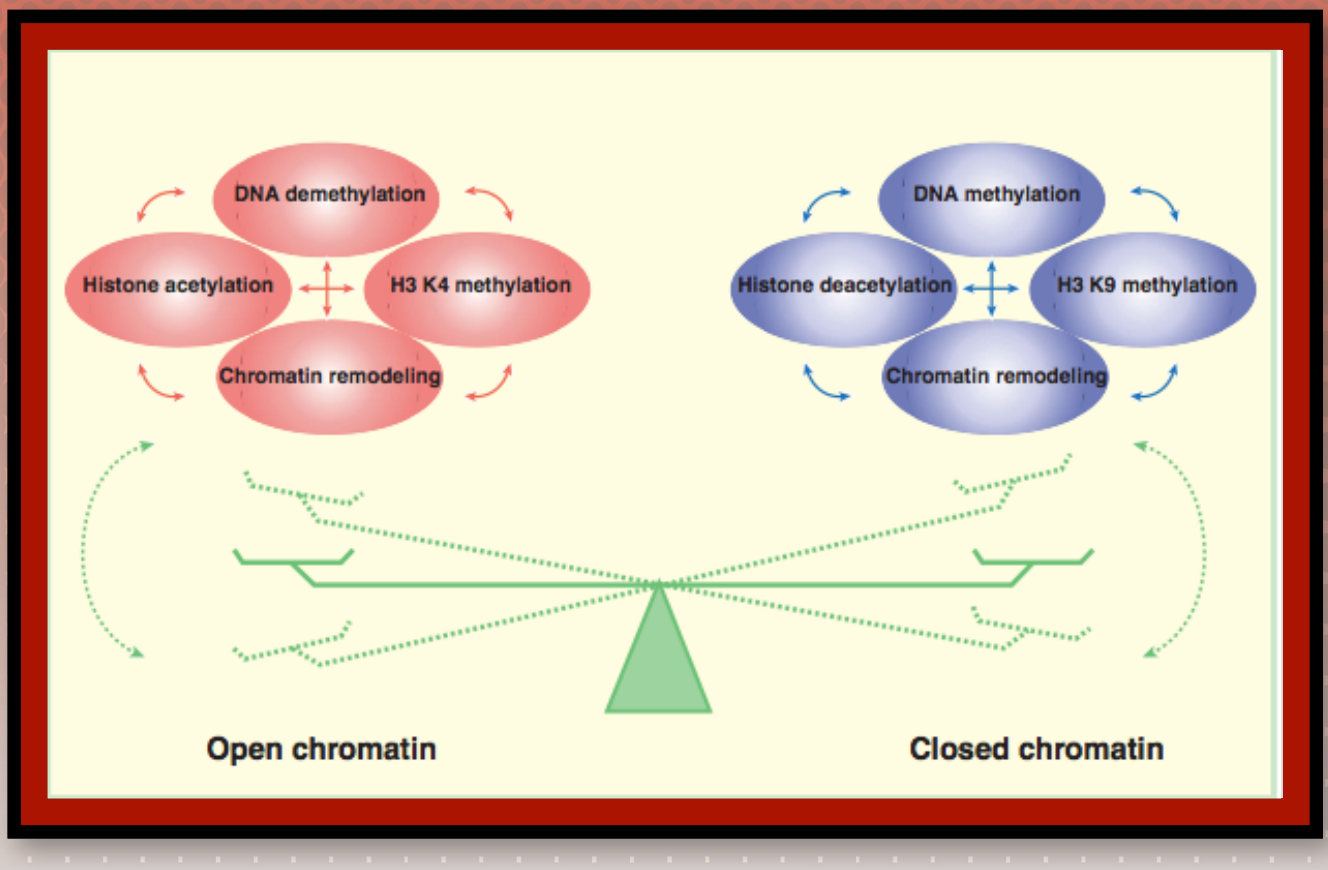


The effect of lysine acetylation reflects, in part, neutralization of the charge interaction between the DNA backbone and the histone tails. However, histone modifications also function to recruit other enzymes to specific regions of the genome. Acetylated lysines are recognized by bromodomains within nucleosome remodeling complexes. An interaction between methylated H3K4 and the Chd1 chromodomain appears to recruit activating complexes to chromatin... In contrast, methylated H3K9 and H3K27 are bound by HP1 and Polycomb, respectively, which mediate chromatin compaction ... A given lysine can have up to three methyl groups, and this "methyl state" can influence chromodomain binding. Polycomb preferentially interacts with trimethylated H3K27, while HP1 shows preference for both di- and tri- methylated H3K9



Cromatina abierta: gen activo

Cromatina cerrada: gen inactivo



IMPRINTING

Cambios epigenéticos durante la gametogénesis (precigóticos)

CARACTERÍSTICAS EPIGENÉTICAS DE LA CROMATINA DE LAS CÉLULAS PLURIPOTENTES

1. cromatina abierta

EXPRESIÓN DE CHD1 QUE REMODELA LA CROMATINA HACIA EUCROMATINA

2. Alta expresión de las proteínas represoras Polycomb-group

Expresión bivalente de h3k27me3 (silenciadora) y de H3k4me3 (activadora)

H3K4ME1 SOBRE LOS ENHANCERS

LYON, CAMBIOS AMBIENTALES... TRANSMITIDOS A HIJOS, ETC

EPIGENÉTICA Y CÁNCER

ACTIVACIÓN CROMOSÓMICA, PÉRDIDA DE IMPRINTING, ACTIVACIÓN DE ONCOGENES

HIPOMETILACIÓN GLOBAL PROGRESIVA

HIPERMETILACIÓN PROGRESIVA DE TSG Y GENES METASTÁSICOS Y MICRORNA

MODIFICACIONES PROGRESIVAS DE LAS HISTONAS

COMPROMISO DE MUCHOS GENES IMPORTANTES EN EL DESARROLLO EMBRIONARIO

DE UNOS GENES ESPECÍFICOS, PROGRESIVA

MODIFICACIONES PROGRESIVAS EN LOS GENES DE LAS HISTONAS...

LOS CAMBIOS EPIGENÉTICOS PUEDEN NO SER ALEATORIOS

HIPOMETILACIÓN

INACTIVACIÓN DE TSG Y MICRORNAS

HIPERMETILACIÓN

MLH1, MGMT... GENES DE REPARACIÓN

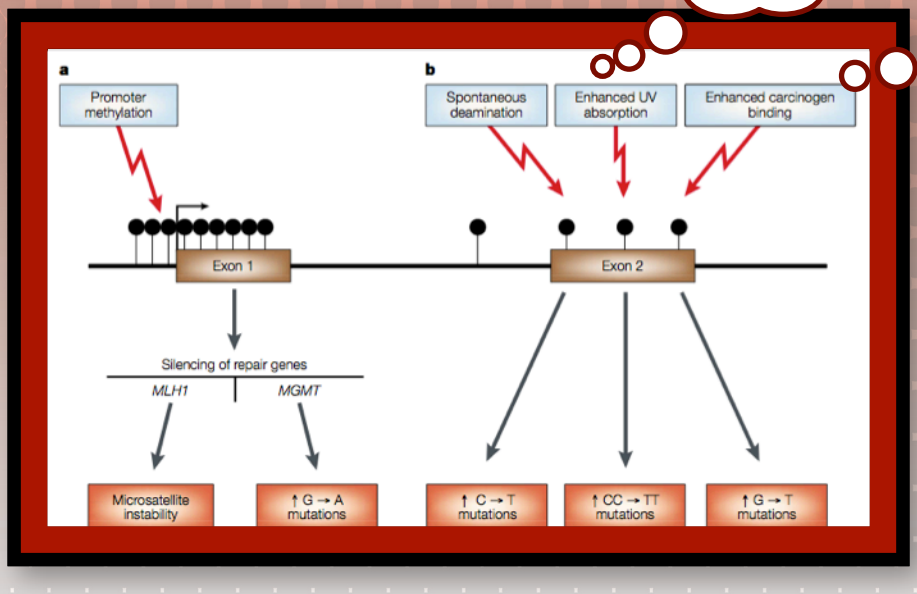
PÉRDIDA DEL IMPRINTING

LA COMBINACIÓN DE HIPOMETILACIÓN GLOBAL CON HIPERMETILACIÓN SELECTIVA PUEDE SER EXPLOSIVA... LA HIPOMETILACIÓN DE LOS SEGMENTOS PERICENTROMÉRICOS NORMALMENTE REPRIMIDOS PUEDE DAR ORIGEN A INESTABILIDAD GENÓMICA ... Y LA HIPERMETILZACIÓN DE LAS ISLAS DE CPG PUEDE SILENCIAR GENES SUPRESORES DE TUMORES...

LA HIPERMETILACIÓN PUEDE SER MUTAGÉNICA

CÁNCER DE PIEL

BENZO(A)PIRENO EPÓXIDO... ALQUITRÁN... CÁNCER DEL PULMÓN



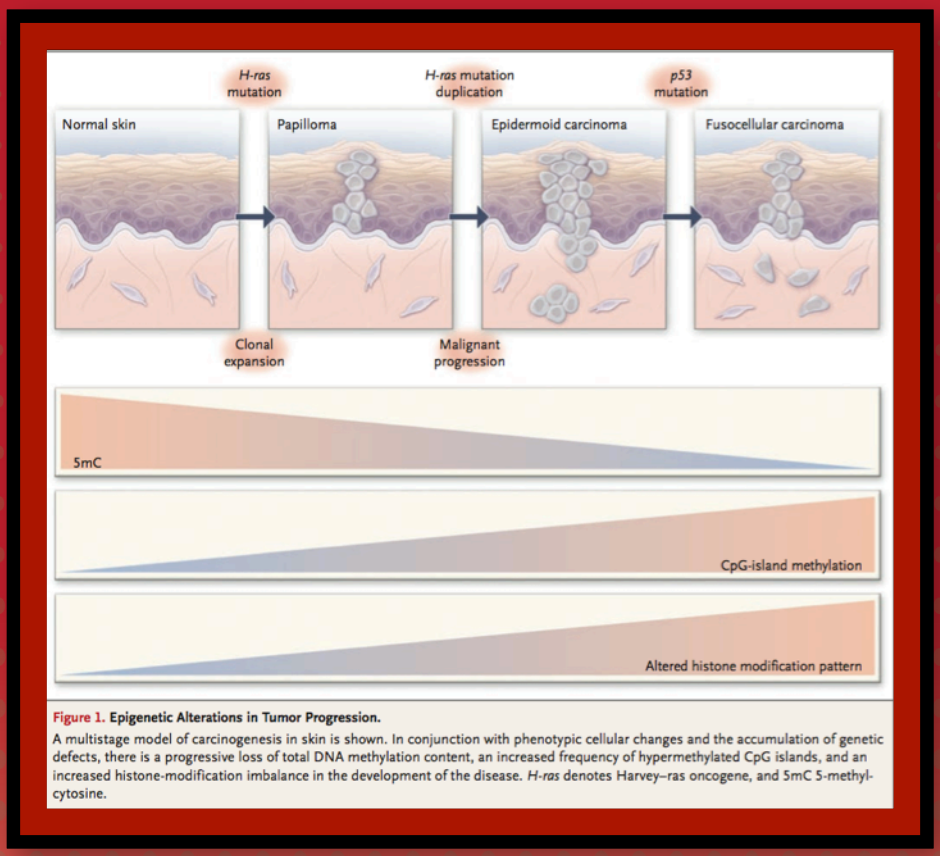


Figure 1. Epigenetic Alterations in Tumor Progression.
A multistage model of carcinogenesis in skin is shown. In conjunction with phenotypic cellular changes and the accumulation of genetic defects, there is a progressive loss of total DNA methylation content, an increased frequency of hypermethylated CpG islands, and an increased histone-modification imbalance in the development of the disease. *H-ras* denotes Harvey–ras oncogene, and 5mC 5-methylcytosine.

hipometilación generalizada y cáncer: mecanismos...

...generation of chromosomal instability, reactivation of transposable elements, and loss of imprinting...

RECOMBINACIÓN MITÓTICA, MUTACIONES Y DELECIONES, ANEUPLOIDÍA

REACTIVACIÓN DE DNA ENDOPARASÍTICO... L1 Y ALU (TRANSPOSONES)

LA PÉRDIDA DEL IMPRINTING PUEDE AUMENTAR LA CARGA TRANSCRIPCIONAL... AUMENTANDO EL RIESGO DE TUMORES

Hipermetilación de los promotores de los genes supresores de tumores y los genes de reparación del DNA... (silenciamiento)

Hypermethylation of the CpG islands in the promoter regions of tumor-suppressor genes is a major event in the origin of many cancers. The initial reports of hypermethylation of the CpG islands in the promoter region of the retinoblastoma tumor-suppressor gene (Rb) were followed by the findings that hypermethylation of the CpG island was a mechanism of inactivation of the tumor-suppressor genes VHL (associated with von Hippel–Lindau disease), $p16_{INK4a}$, hMLH1 (a homologue of MutL Escherichia coli), and BRCA1 (breast-cancer susceptibility gene 1).

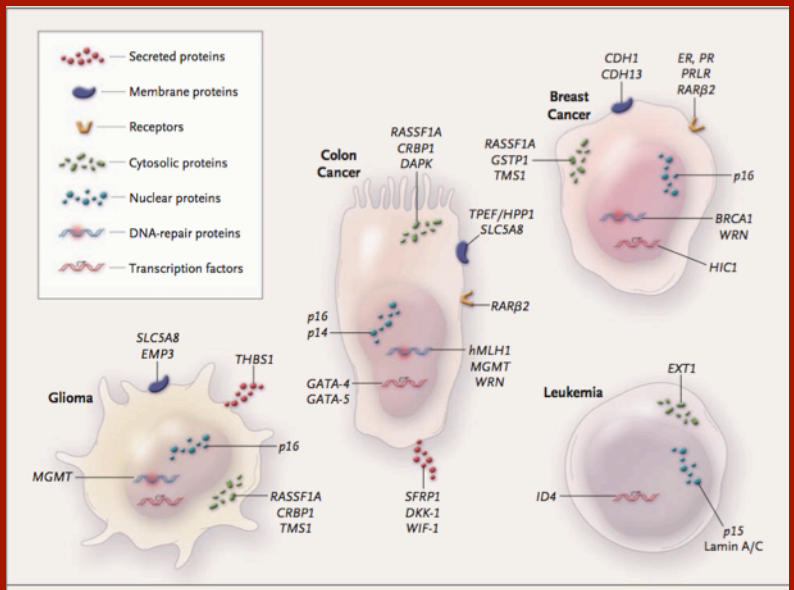


Figure 2. Profile of Hypermethylation of the CpG Island in the Promoter Region of Tumor-Suppressor Genes in Human Cancer.

Four tumor cells are shown undergoing transcriptional silencing by DNA hypermethylation of the regulatory regions of tumor-suppressor genes. In colon cancer, entrance into the cell cycle occurs by means of $p16^{INK4a}$ methylation. In leukemia cells, $p15^{INK4b}$ methylation initiates proliferation. In breast-cancer cells, defects in DNA repair are related to methylation of *BRCA1*, and in glioma cells, methylation of O^6-methylguanine–DNA methyltransferase (*MGMT*) initiates defects in DNA repair. Other depicted hypermethylated tumor-suppressor genes are *CDH1* (cadherin 1), *CDH13* (cadherin 11), *CRBP1* (cellular retinol binding protein 1), *DKK-1* (dickkopf homologue 1), *ER* (estrogen receptor), *GATA-4* (GATA-binding protein 4), *GATA-5* (GATA-binding protein 5), *HIC1* (hypermethylated in cancer 1), *PR* (progesterone receptor), *PRLR* (prolactin receptor), *RARβ2* (retinoic acid receptor β 2), *SLC5A8* (solute carrier family 5 iodide transporter member 8), *WIF-1* (WNT inhibitory factor 1), and lamin A/C.

Table 1. Epigenetic Aberrations among Different Tumor Types.*

Type of Cancer	Epigenetic Disruption
Colon cancer	CpG-island hypermethylation (*hMLH1*, $p16^{INK4a}$, $p14^{ARF}$, *RARB2*, *SFRP1*, and *WRN*), hypermethylation of miRNAs (*miR-124a*), global genomic hypomethylation, loss of imprinting of *IGF2*, mutations of histone modifiers (*EP300* and *HDAC2*), diminished monoacetylated and trimethylated forms of histone H4
Breast cancer	CpG-island hypermethylation (*BRCA1*, E-cadherin, *TMS1*, and estrogen receptor), global genomic hypomethylation
Lung cancer	CpG-island hypermethylation ($p16^{INK4a}$, *DAPK*, and *RASSF1A*), global genomic hypomethylation, genomic deletions of *CBP* and the chromatin-remodeling factor *BRG1*
Glioma	CpG-island hypermethylation (DNA-repair enzyme *MGMT*, *EMP3*, and *THBS1*)
Leukemia	CpG-island hypermethylation ($p15^{INK4b}$, *EXT1*, and *ID4*), translocations of histone modifiers (*CBP*, *MOZ*, *MORF*, *MLL1*, *MLL3*, and *NSD1*)
Lymphoma	CpG-island hypermethylation ($p16^{INK4a}$, *p73*, and DNA-repair enzyme *MGMT*), diminished monoacetylated and trimethylated forms of histone H4
Bladder cancer	CpG-island hypermethylation ($p16^{INK4a}$ and *TPEF/HPP1*), hypermethylation of miRNAs (*miR-127*), global genomic hypomethylation
Kidney cancer	CpG-island hypermethylation (*VHL*), loss of imprinting of *IGF2*, global genomic hypomethylation
Prostate cancer	CpG-island hypermethylation (*GSTP1*), gene amplification of polycomb histone methyltransferase *EZH2*, aberrant modification pattern of histones H3 and H4
Esophageal cancer	CpG-island hypermethylation ($p16^{INK4b}$ and $p14^{ARF}$), gene amplification of histone demethylase *JMJD2C/GASC1*
Stomach cancer	CpG-island hypermethylation (*hMLH1* and $p14^{ARF}$)
Liver cancer	CpG-island hypermethylation (*SOCS1* and *GSTP1*), global genomic hypomethylation
Ovarian cancer	CpG-island hypermethylation (*BRCA1*)

BRCA1 denotes breast-cancer susceptibility gene 1, *BRG1* BRM/SWI2-related gene 1, *CBP* cyclic AMP response-element–binding protein (CREB)–binding protein, *DAPK* death-associated protein kinase, *EMP3* epithelial membrane protein 3, *EP300* E1A binding protein p300, *EXT1* exostosin 1, *EZH2* enhancer of zeste drosophila homologue 2, *GSTP1* glutathione S-transferase 1, *HDAC2* histone deacetylase 2, *hMLH1* homologue of MutL *Escherichia coli*, *ID4* inhibitor of DNA binding 4, *IGF2* insulin-like growth factor 2, *JMJD2C/GASC1* Jumonji domain-containing protein 2C, *MGMT* O^6-methylguanine–DNA methyltransferase, *MLL1* mixed-lineage leukemia 1, *MLL3* mixed-lineage leukemia 3, *MORF* monocytic leukemia zinc finger protein–related factor, *MOZ* monocytic leukemia zinc finger, *NSD1* nuclear receptor binding SET-domain protein 1, *RARβ2* retinoic acid receptor β 2, *RASSF1A* ras association domain family protein 1, *SFRP1* secreted frizzled-related protein 1, *SOCS1* suppressor of cytokine signaling 1, *THBS1* thrombospondin 1, *TMS1* target of methylation-induced silencing 1, *TPEF/HPP1* hyperplastic polyposis gene 1, *VHL* von Hippel–Lindau disease, and *WRN* Werner's syndrome.

HIPERMETILACIÓN EN CÁNCER

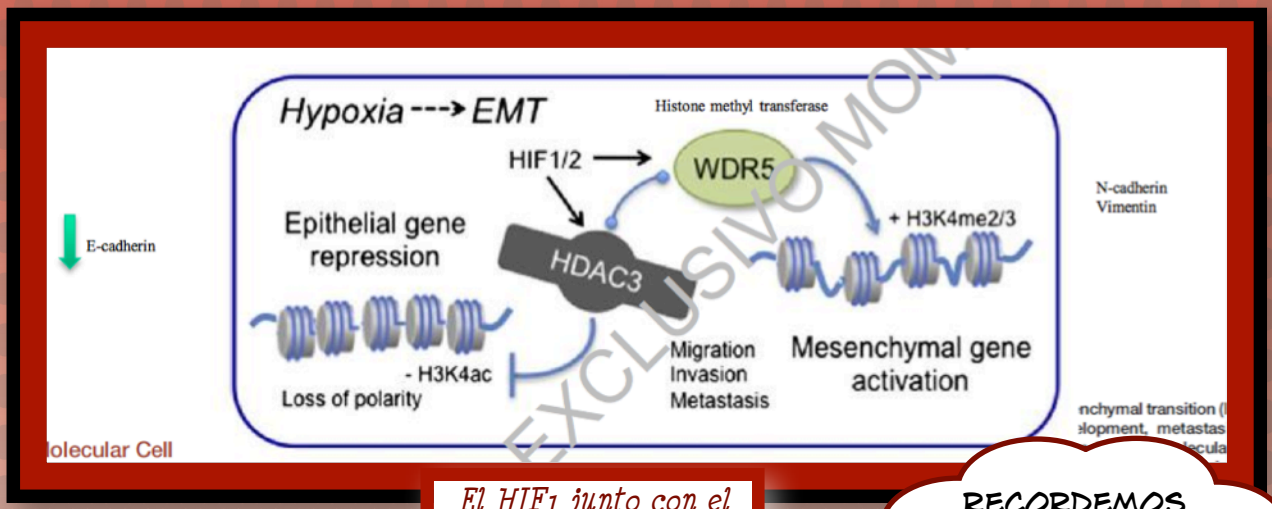
NO OCURRE AL AZAR... IE PML-RAR INDUCE METILACIÓN DE PROMOTORES DE TSG...

Parece ser selectiva, y ayuda a mediar efectos oncogénicos

LA ACTIVACIÓN DEL K-RAS MEDIA EL SILENCIAMIENTO EPIGENÉTICO DEL FAS

EPITHELIAL-MESENCHYMAL TRANSITION

HIPOXIA...



Durante la hipoxia el HIF1 no se destruye

El HIF1 junto con el WDR5 inducen cambios en el HDAC... inactivan la H3K4ac, y promueven la H3k4me2/3

RECORDEMOS QUE LA ACETILACIÓN REPRIME EL GEN, Y LA HIPERMETILACIÓN LO ACTIVA...

MIENTRAS MÁS DIFERENCIADO, MÁS REPRIMIDO. AL REACTVAR MÁS GENES SE VUELVE MÁS PRIMITIVA (MESENQUIMAL) LA CÉLULAS... CON MAYOR POTENCIAL DE INVASIÓN Y METÁSTASIS

BRCA1 MANTIENE LA HETEROCROMATINA

En ausencia de BRCA1 (ie, mutaciones) se disminuye la heterocromatina (DNA condensado) que es inactivo

SE AUMENTA LA ACTIVACIÓN DE LOS GENES EN LOS SATÉLITES DE DNA

EL BRCA1 SE UNE A LOS DNA SATÉLITES Y FAVORECE LA UBIQUILACIÓN DE LA HISTONA H2A... MANTIENE LA HETEROCROMATINA

CIMP

CpG Island Methylator Phenotype

CIMP se encontró en cáncer de colon

Hipermetilación en promotores de genes como P16, MLH1, etc

Se asocia a inestabilidad microsatelital

Frecuentes mutaciones del KRAS u BRAF

MUTACIÓN DE IDH1

Interfiere con el silenciamiento epigenético... causando GLIOMAS

Glossary

Acetylation: A reaction that introduces a functional acetyl group into an organic compound. Deacetylation is the removal of the acetyl group. Acetylation is a post-translational chemical modification of histones, tubulins, and the tumor suppressor p53.

Bisulfite sequencing: The bisulfite treatment of DNA in order to determine its pattern of methylation. Treatment of DNA with bisulfite converts cytosine residues to uracil but leaves 5-methylcytosine residues unaffected.

Chromatin: The complex of DNA and protein that composes chromosomes. Chromatin packages DNA into a volume that fits into the nucleus, allows mitosis and meiosis, and controls gene expression. Changes in chromatin structure are affected by DNA methylation and histone modifications.

CpG islands: Regions in DNA that contain many adjacent cytosine and guanine nucleotides. The "p" in CpG refers to the phosphodiester bond between the cytosine and the guanine. These islands occur in approximately 40% of the promoters of human genes.

DNA methylation: The addition of a methyl group to DNA at the 5-carbon of the cytosine pyrimidine ring that precedes a guanine.

DNA methyltransferases: Family of enzymes that catalyze the transfer of a methyl group to DNA, using S-adenosylmethionine as the methyl donor.

Epigenome: The overall epigenetic state of a cell.

Genomic imprinting: The epigenetic marking of a locus on the basis of parental origin, which results in monoallelic gene expression.

Histone: The main protein components of chromatin. The core histones — H2A, H2B, H3, and H4 — assemble to form the nucleosome; each nucleosome winds around 146 base pairs of DNA. The linker histone H1 locks the DNA into place and allows the formation of a higher-order structure.

Histone deacetylase: A class of enzymes that remove acetyl groups from an N-acetyl-lysine amino acid on a histone.

Transposons: Sequences of DNA that can move around within the genome of a single cell. In this process, called transposition, the sequences can cause mutations and change the organization of DNA in the genome.