Centro Universitario Rivera

SEDE TACUAREMBÓ

CENUR NORESTE

UNIVERSIDAD DE LA REPÚBLICA URUGUAY

7a Clase

EPIGENÉTICA

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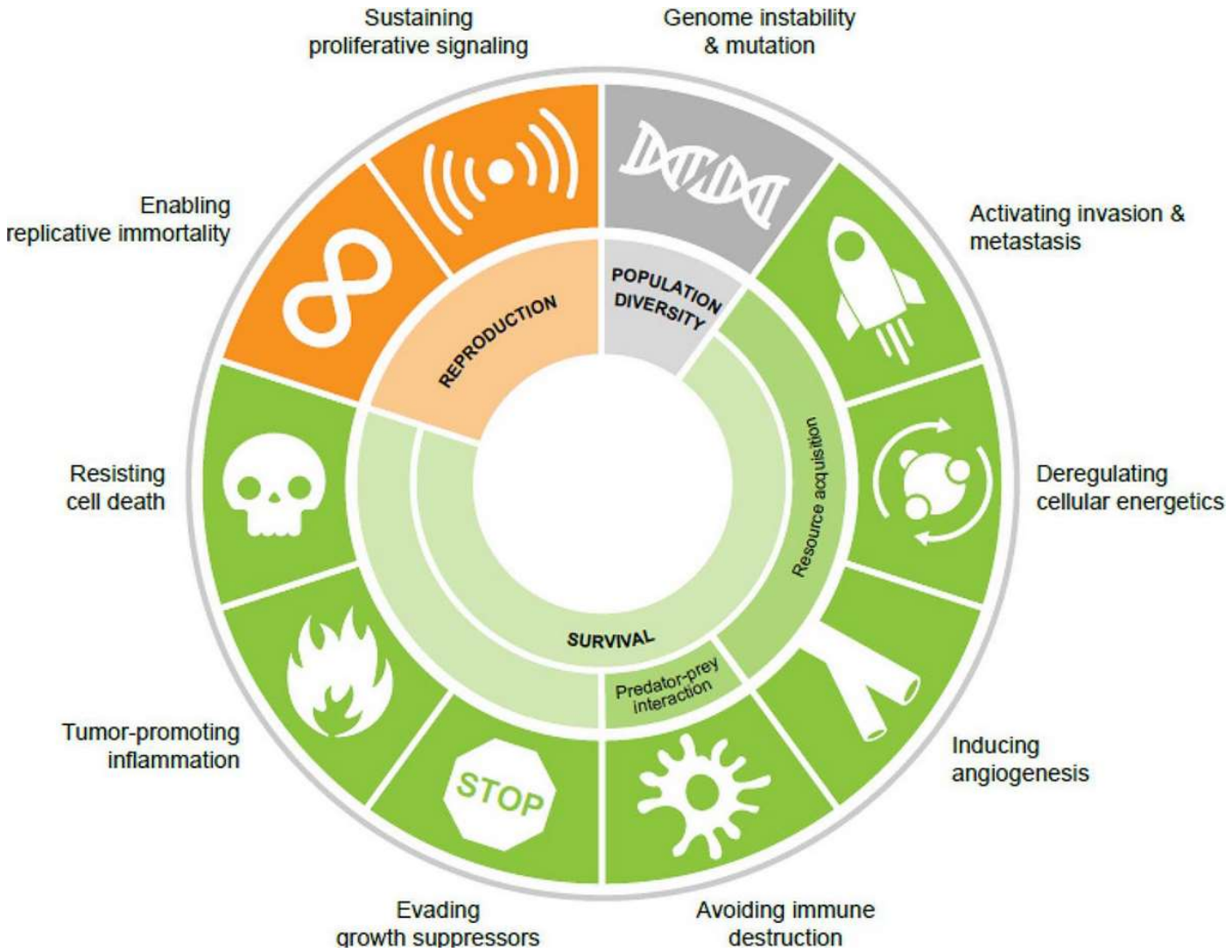
CONTENIDO

- Cáncer y alteraciones epigenéticas
  - Metilación del ADN
  - Modificaciones de las Histonas
  - ARNs no codificantes
- Patrones de variación epigenética en las poblaciones humanas
- Epigenética en el envejecimiento

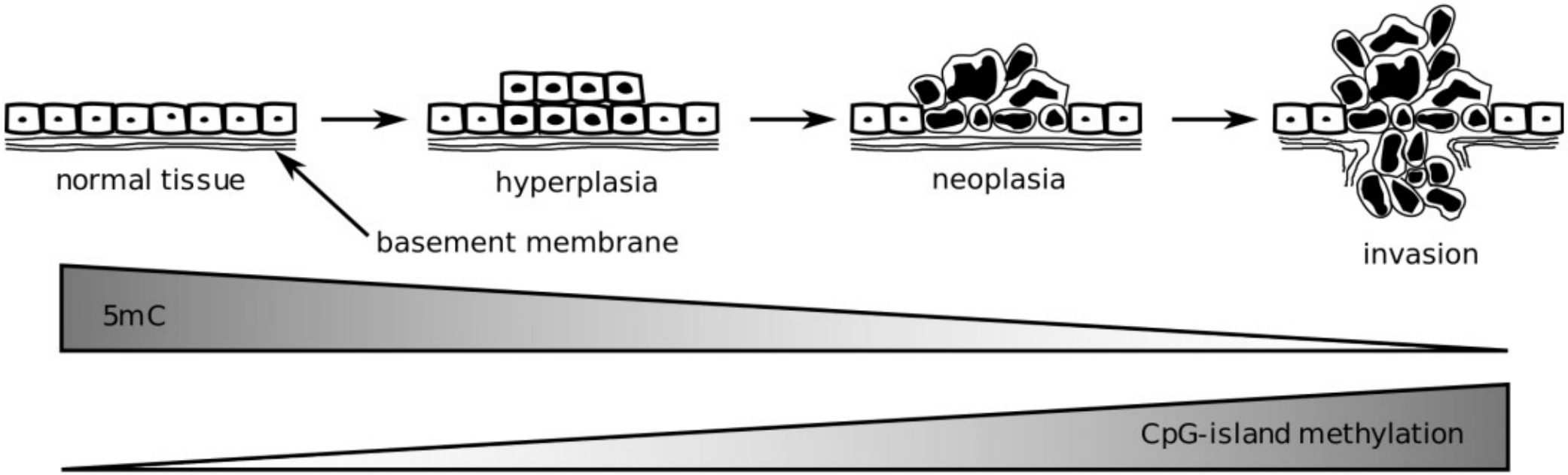

Sustaining proliferative signaling
Genome instability & mutation
Enabling replicative immortality
Activating invasion & metastasis
Resisting cell death
Deregulating cellular energetics
Tumor-promoting inflammation
Inducing angiogenesis
Evading growth suppressors
Avoiding immune destruction
REPRODUCTION
POPULATION DIVERSITY
Resource acquisition
SURVIVAL
Predator-prey interaction
STOP

CÁNCER

1. Activación de oncogenes

2. Inactivación de genes supresores de tumor.

La activación o inactivación se puede dar por mecanismos genéticos o epigenéticos.



ALTERACIONES EPIGENÉTICAS EN EL CÁNCER

Metilación del ADN

– Hipermetilación locus específica.

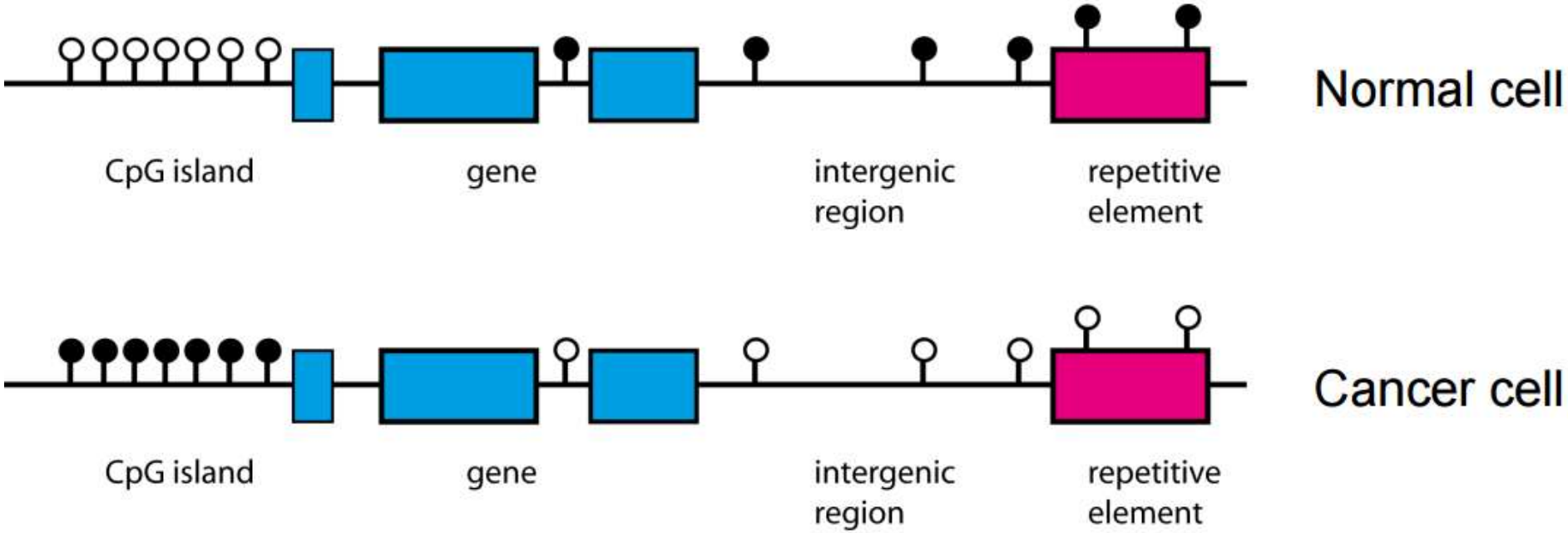
• Islas CpG de genes supresores de tumor

• ICRs – pérdida de impronta

– Hipometilación global.

• Elementos repetitivos
• ICRs – pérdida de impronta

ALTERACIONES EPIGENÉTICAS EN EL CÁNCER



HIPERMETILACIÓN EN LAS ISLAS CpG

- Ocurre en genes supresores de tumor más frecuentemente que las mutaciones.
- El perfil de CpGs hipermetiladas varía dependiendo del tipo de tumor.
- En los tumores, las células con epimutaciones son rápidamente seleccionada.
- La metilación aumenta con el tiempo, incrementa con la edad.

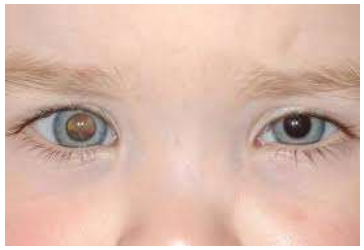
HIPERMETILACIÓN EN LAS ISLAS CpG. Ejemplos.

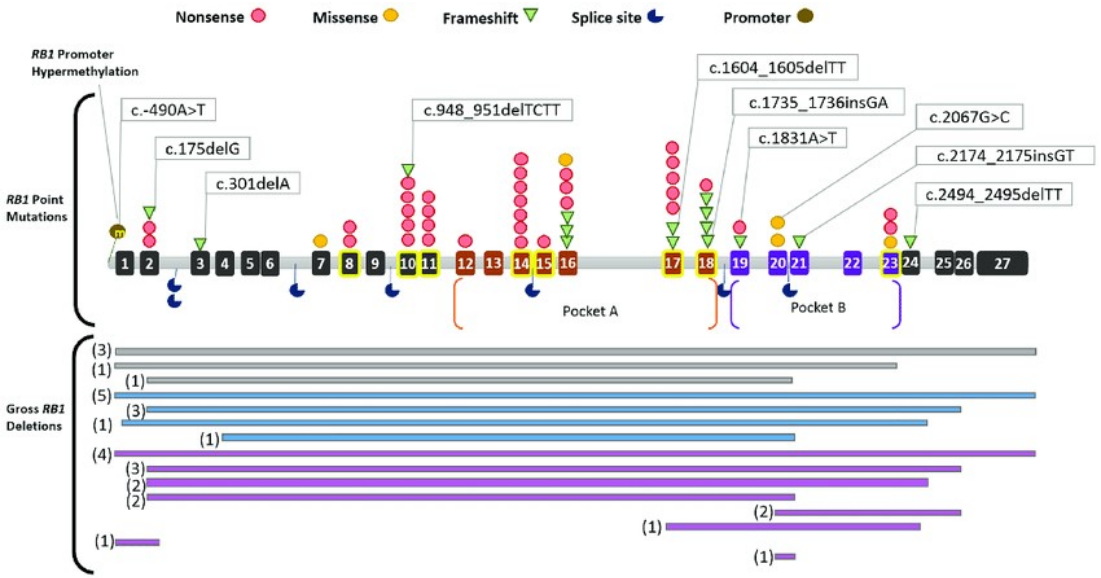
– ***RB*** en retinoblastoma

– ***MLH1*** en cáncer colorrectal

– ***BRCA1*** en cáncer de mama

Gen RB1 en retinoblastoma





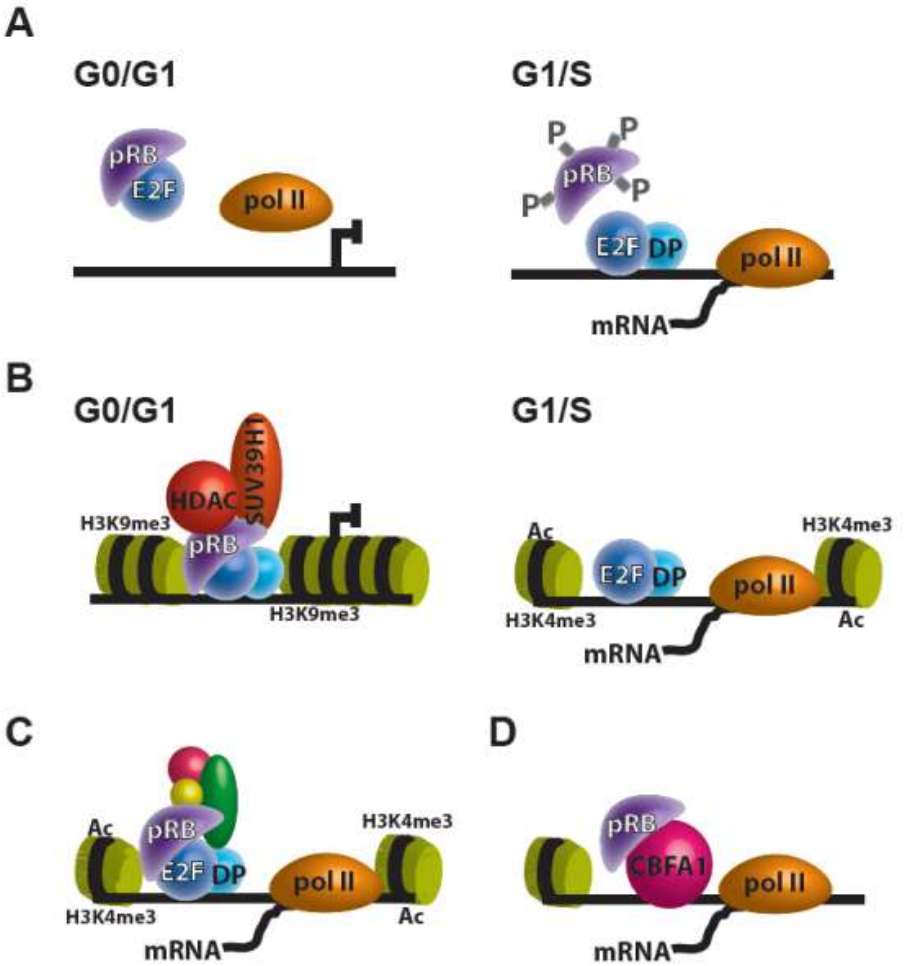
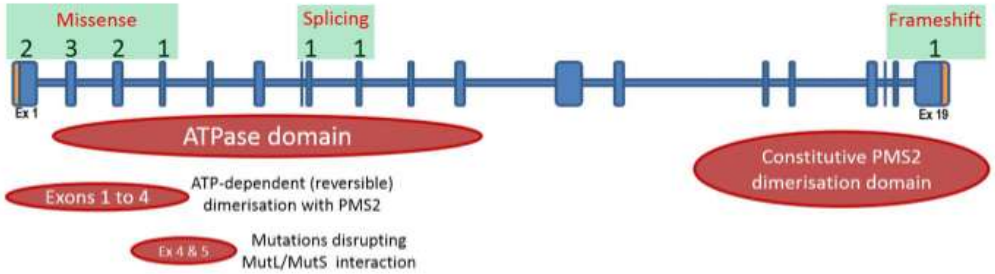


Figure 1. Transcriptional regulation by pRB. (**A–C**) The pRB can regulate E2F targets in at least three different mechanisms: (**A**) direct pRB repression on E2F transcription; (**B**) pRB recruitment of transcriptional corepressors, like HDACs and histone methyltransferases (e.g., SUV39H1) to E2F targets; and (**C**) association of the pRB-E2F complex with transcriptional coactivators, which results in increased expression of E2F targets. (**D**) pRB can regulate transcription through its interaction with other transcription factors (e.g., CBFA1).



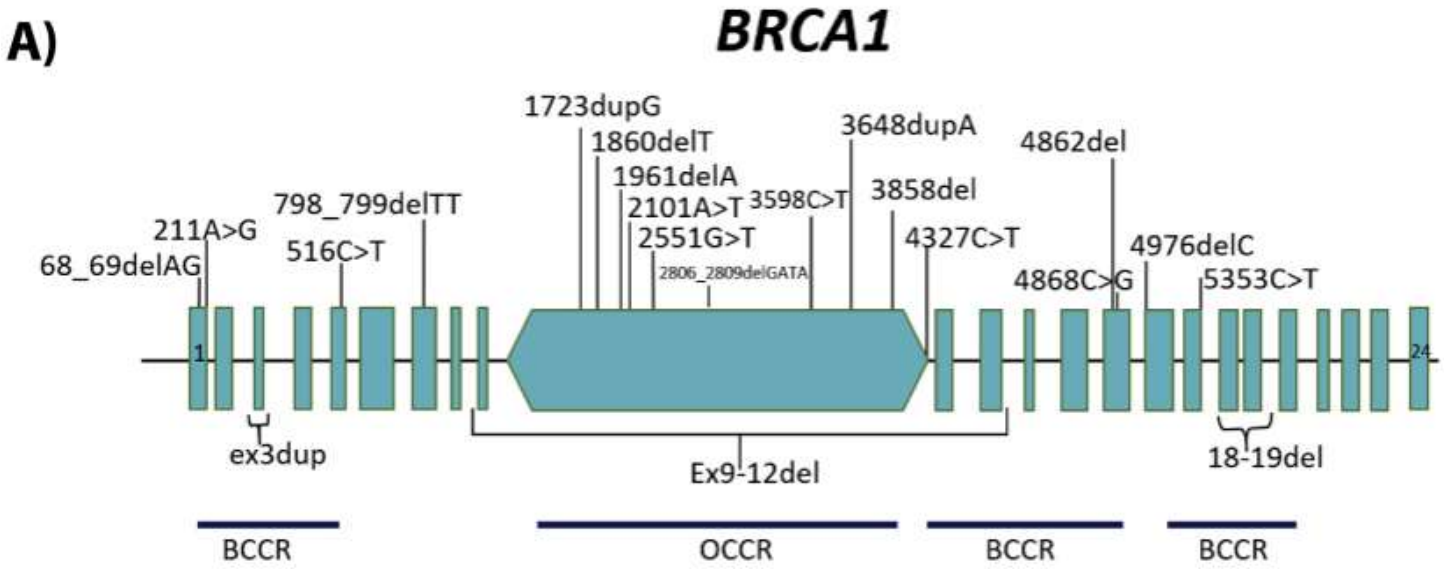
***MLH1 (*DNA mismatch repair protein)** *3p22.2*

Table 1 Clinicopathological features of the 10 patients with no proven transmission of their epimutation

Patient no.	Gender	Tumor type	Age at diagnosis (yr)	MSI status	MMR protein expression
P1	F	Endometrial adenocarcinoma	48	MSI	MLH1/PMS2 loss
		Right colon adenocarcinoma	49	MSI	MLH1/PMS2 loss
P2	F	Ovarian adenocarcinoma	51	MSI	MLH1/PMS2 loss
P3	F	Transverse colon carcinoma	36	MSI	MLH1/PMS2 loss
		Sigmoid tubulovillous adenoma	40	NI	MLH1/PMS2 loss
P4	F	Colon adenocarcinoma	56	MSI	MLH1 loss (PMS2 NI)
P5	F	Right colon adenocarcinoma	49	MSI	MLH1/PMS2 loss
		Endometrial adenocarcinoma	52	ND	ND
P6	M	Rectal adenocarcinoma	29	MSI	MLH1/PMS2 loss
P7	F	Right colon and rectal adenocarcinomas	52	MSI	MLH1/PMS2 loss
P8	F	Cecal adenocarcinoma	49	MSI	MLH1/PMS2 loss
P9	M	Colon adenocarcinoma	29	MSI	MLH1 loss (PMS2 ND)
P10	M	Left colon adenocarcinoma	35	MSI	MLH1 NI (PMS2 loss)

F, female; M, male; MMR, mismatch repair; MSI, microsatellite instability; ND, not determined; NI, noninterpretable.

BRCA1 (Breast Cancer gene 1) 17q21



Hipermetilación de Islas CpG

- Biomarcador

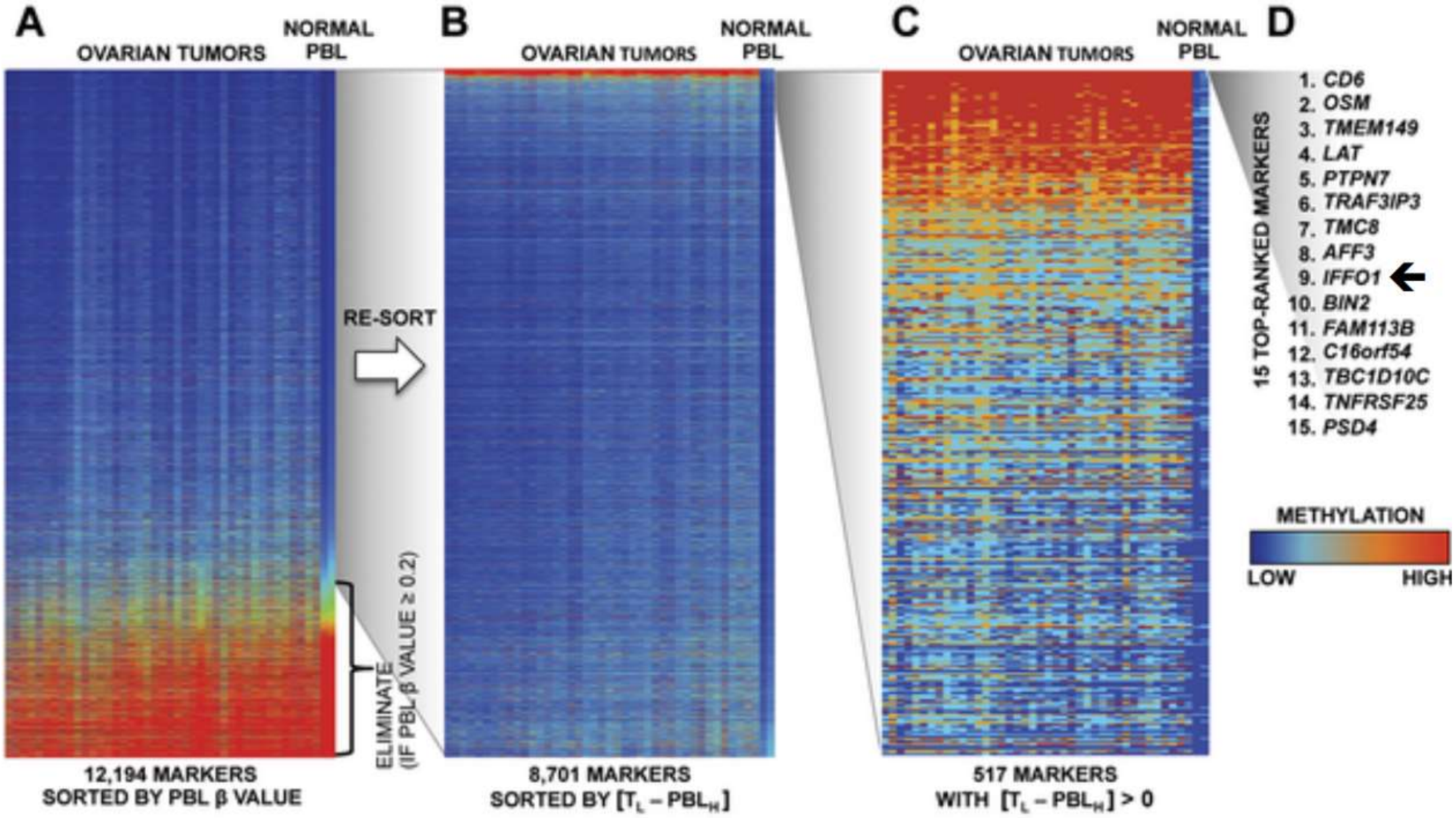
– Permite distinguir células normales de células cancerígenas.

- Ejm. Células tumorales vs células benignas de la piel, próstata.

- Ejm. En la sangre: Células tumorales, ADN libre de células tumorales.

– Identificación de características específicas

- La detección de hipermetilación es más sensible que el análisis de ARN.


A
OVARIAN TUMORS
NORMAL PBL
RE-SORT
ELIMINATE (IF PBL β VALUE ≥ 0.2)
12,194 MARKERS SORTED BY PBL β VALUE
B
OVARIAN TUMORS
NORMAL PBL
8,701 MARKERS SORTED BY [T_L – PBL_H]
C
OVARIAN TUMORS
NORMAL PBL
517 MARKERS WITH [T_L – PBL_H] > 0
D
15 TOP-RANKED MARKERS
1. CD6
2. OSM
3. TMEM149
4. LAT
5. PTPN7
6. TRAF3IP3
7. TMC8
8. AFF3
9. IFFO1
10. BIN2
11. FAM113B
12. C16orf54
13. TBC1D10C
14. TNFRSF25
15. PSD4
METHYLATION
LOW
HIGH

Hipermetilación de Islas CpG

1. **Diagnóstico**

- Ejm. *GSTP1* se encuentra hipermetilado en cáncer de próstata y no metilado en hiperplasia benigna.

2. **Pronóstico**

- Ejm. La hipermetilación de miR-34b/c está asociado con metastasis.

3. **Tratamiento**

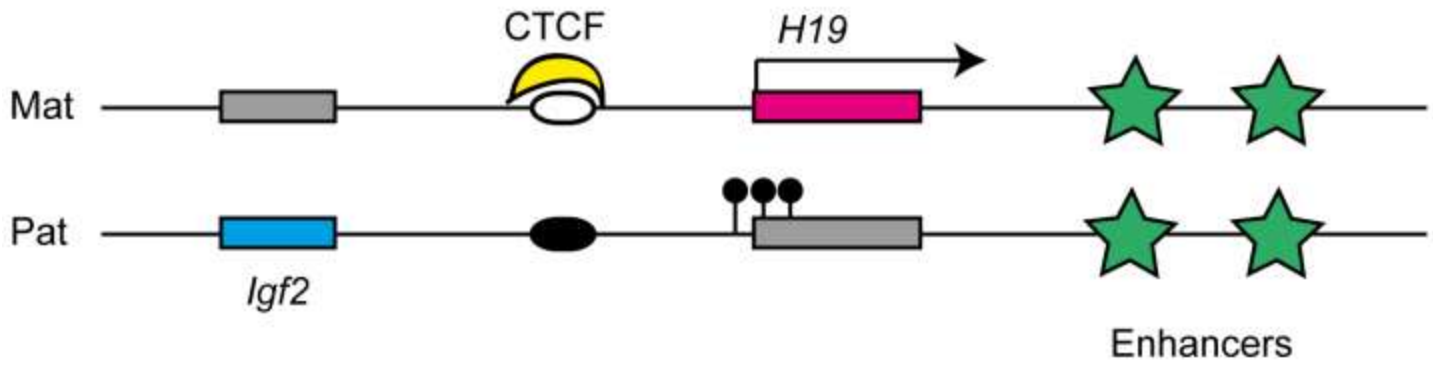
Ejm. La hipermetilación de *MGMT* (glioma) sugiere que el paciente responderá bien a la quimioterapia con temozolomida (agente alquilante), *MGMT* normalmente repara lesiones alquil-guanina en el ADN.

Hipermetilación de ICRs (Imprinting Control Regions)

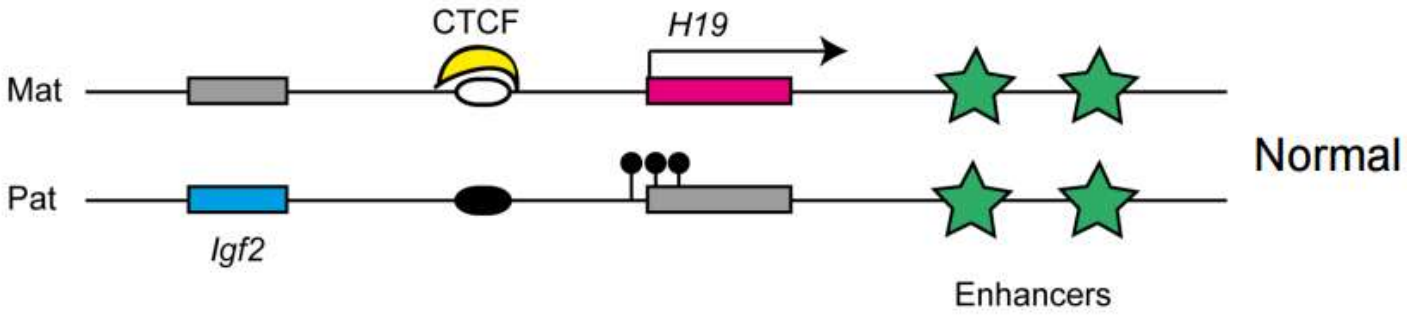
- Alteración de la metilación de ICRs pueden resultar en aumento o sobre expresión de genes promotores del crecimiento celular.

- Es un evento común de neoplasias en sus etapas iniciales.

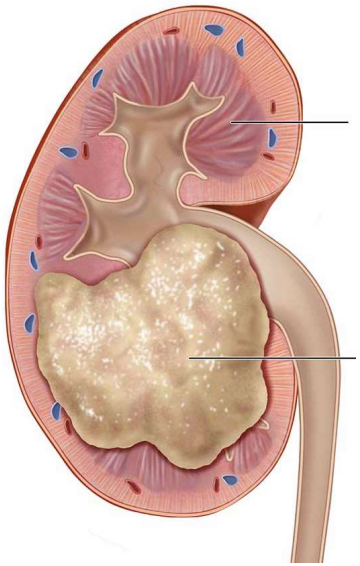
Ejm. Hipermetilación del ICR, genera aumento en la expresión de Igf2 en el tumor de Wilm.

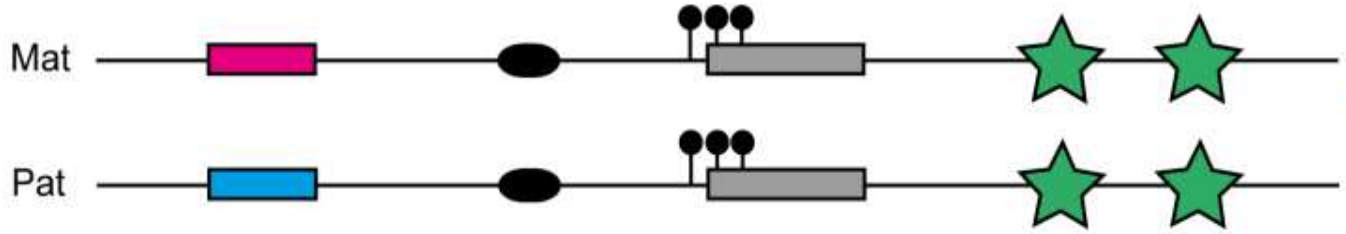


Hipermetilación de ICRs (Imprinting Control Regions)



Normal





Wilm's tumour

Hipometilación global

Fue la primera alteración epigenética encontrada en células tumorales.

• Se observa en diferente grado en la mayoría de los tumores, progresa con la gravedad (similar a la hipermetilación de las Islas CpG).

• Sus consecuencias dependen de la localización:

- Elementos repetidos/Regions intergénicas: generan inestabilidad genómica.

- Hipometilación de CpG en promoters: activación de oncogenes.

Hipometilación e Inestabilidad genómica

• Modelos de ratón: deleción de *Dnmt1* en tejidos específicos genera hipometilación / inestabilidad genómica.

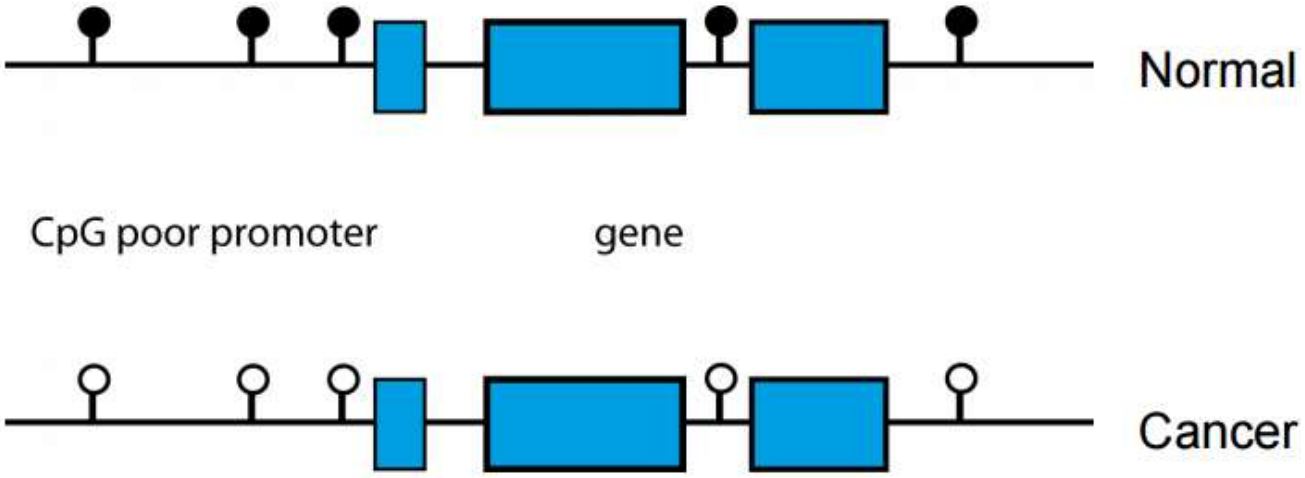
• Humanos: mutaciones en *DNMT3B* en el síndrome ICF *(Immunodeficiency, Centromere instability and Facial anomalies syndrome*), donde la inestabilidad genómica es una característica principal.

• En la mayoría de los cánceres.

Hipometilación de promotores con pocas CpGs

- Menos común que la hipometilación de los elementos repetidos.
- Puede resultar en activación de los genes:

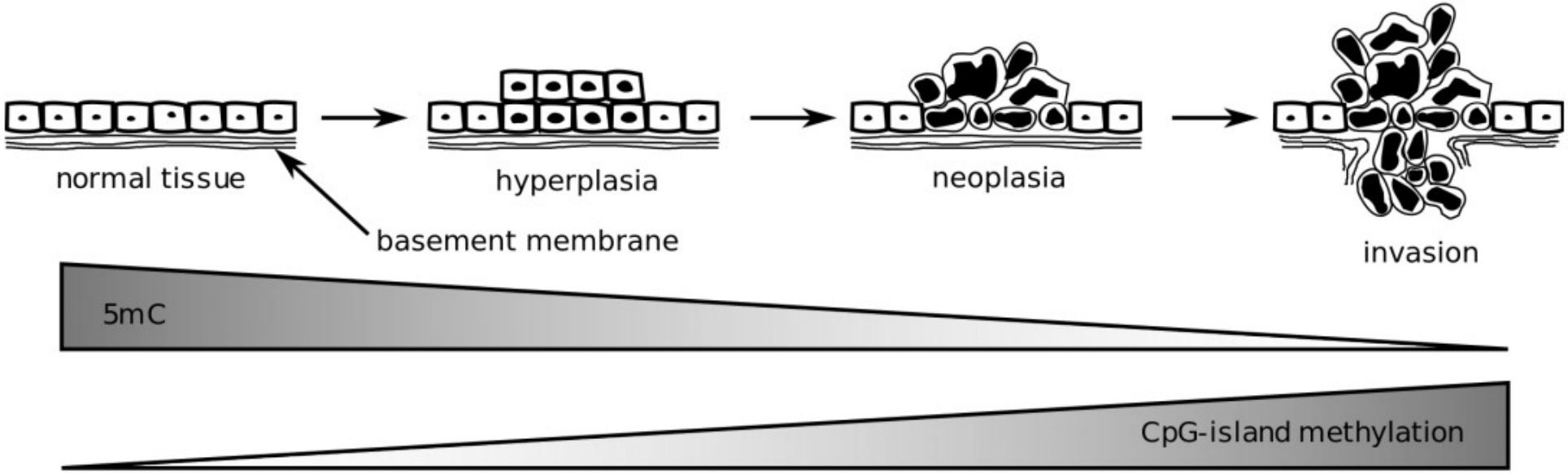
- Ejm: R-RAS en cáncer gástrico, microRNA (miR21) que inactiva a PTEN (supresor de tumor) en glioma.



Contribución de la metilación en el cáncer

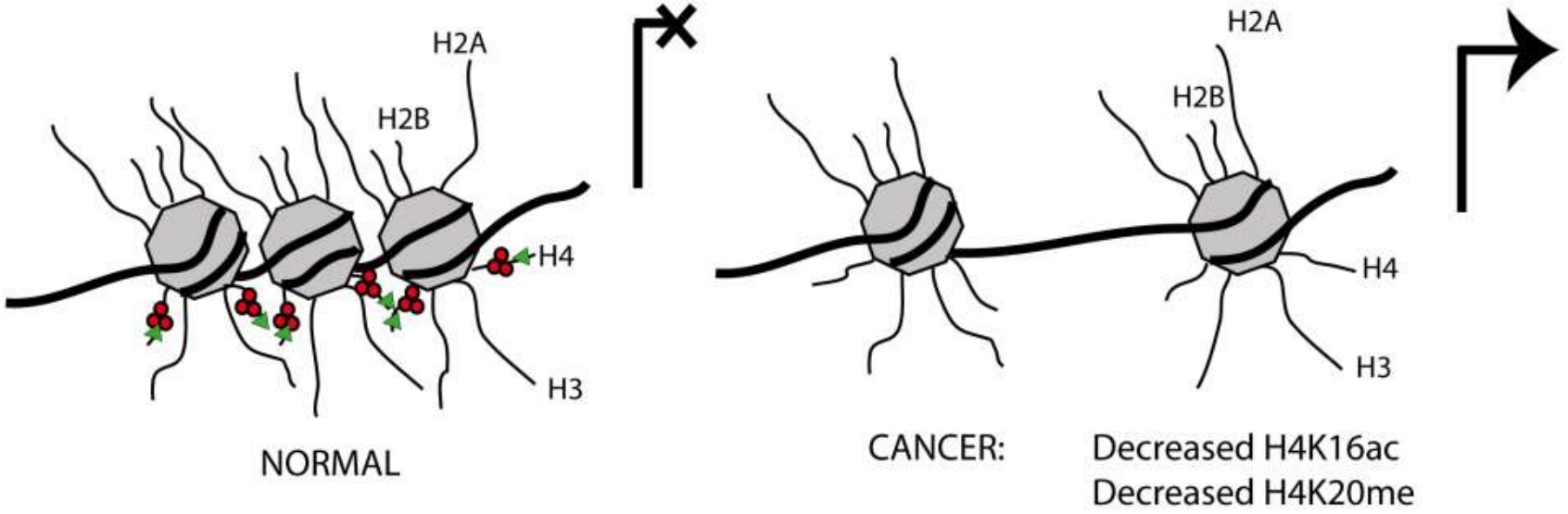
- Hipometilación global.

- Hipermetilación de genes supresores de tumor.



Modificaciones postraduccionales de histonas en el cáncer

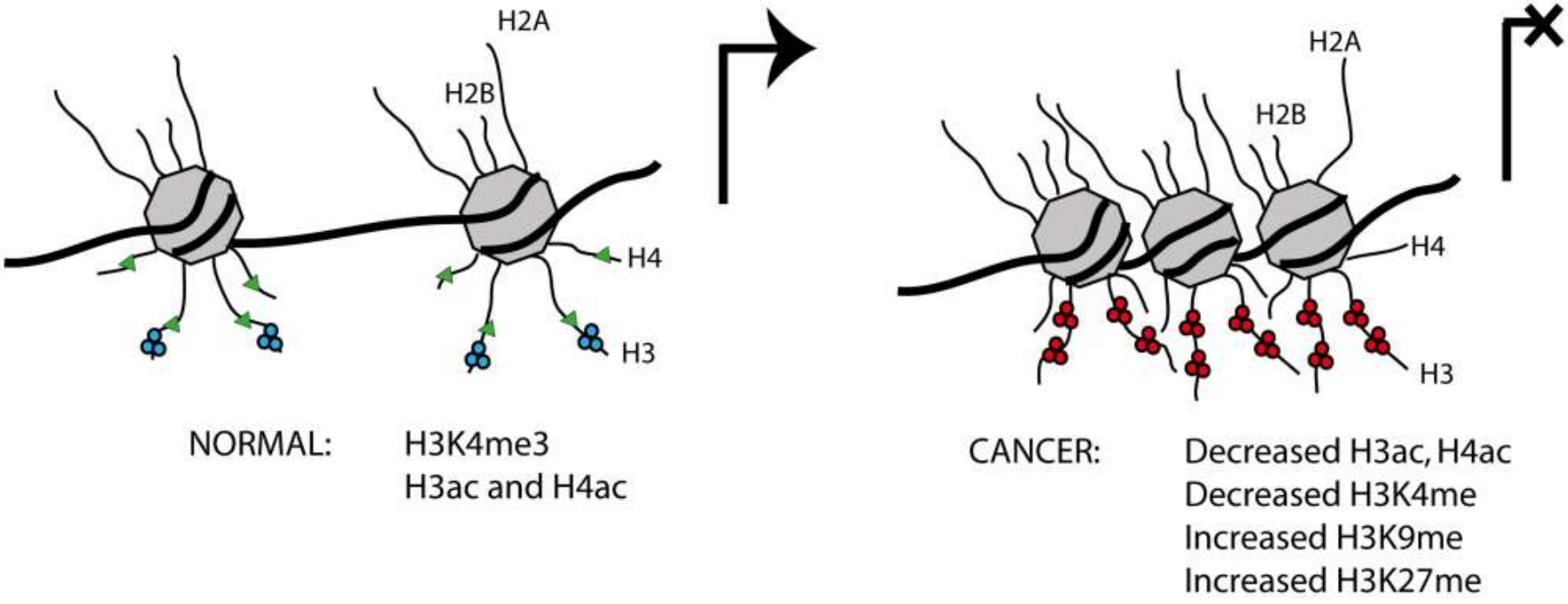
Elementos repetitivos, a nivel global.



Modificaciones postraduccionales de histonas en el cáncer

En CGIs hipermetiladas.

Genes enriquecidos de targets para PRC2 (H3K27me).



Mutaciones en las histonas y el cáncer

Mutaciones en H3.1 (H3 canónica) y en la variante de histona H3.3 se observó en niños con glioma de grado severo.

– Mutación K27 a M

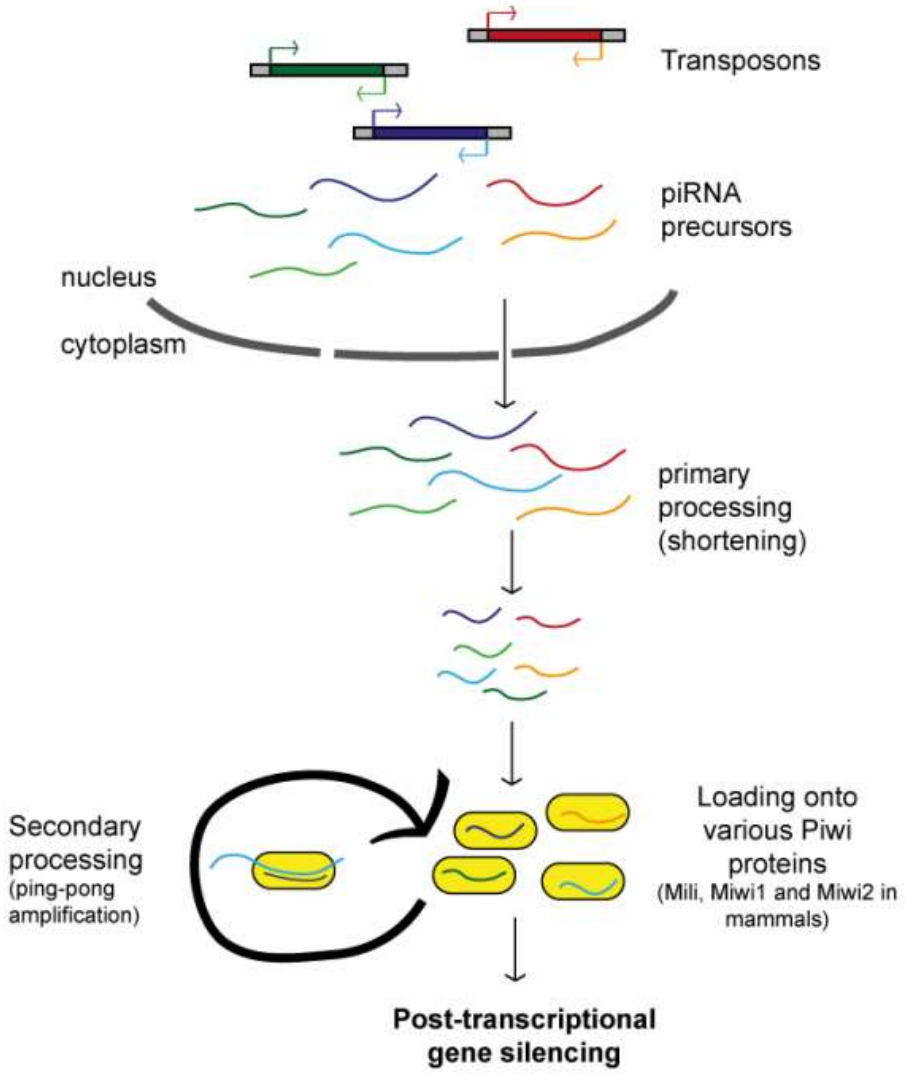
- Esta histona no puede ser acetilada o metilada
- Pudiera mimetizar la metilación.

– La mutación en H3.1, G34 to V, altera la capacidad de metilar K36 (marca activa).

ARNs no codificantes y el cáncer

Expresión de piRNA está alterada en células tumorales.

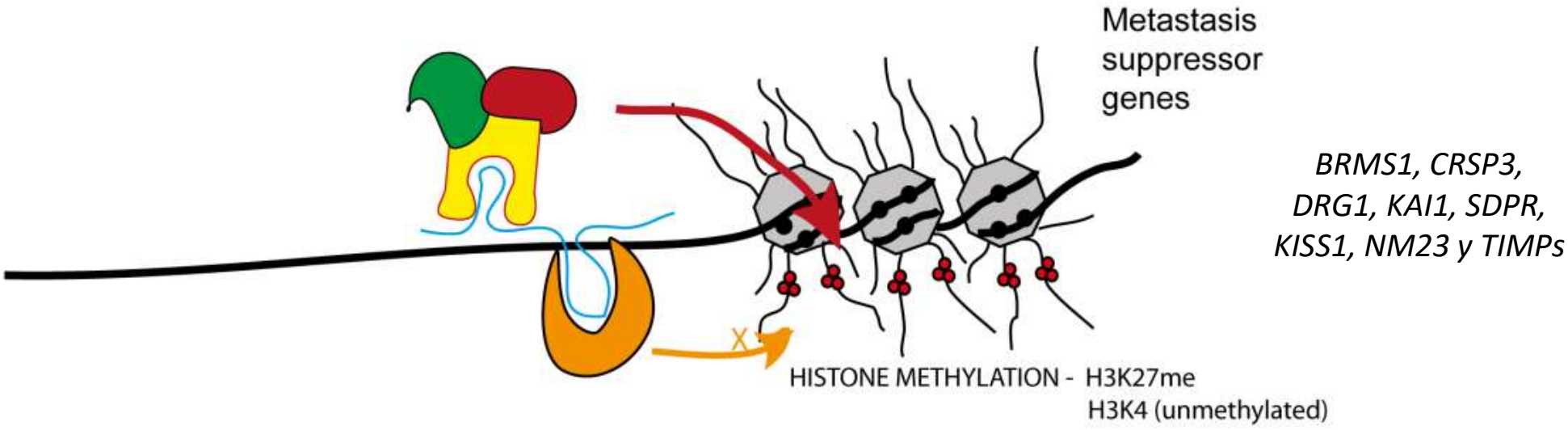
– Relacionado a la hipometilación de los elementos repetidos.



lncRNAs y el cáncer

Existe evidencia de alteración en la expresión de LncRNAs en el cáncer.

- Se ha relacionado con mal o favorable pronóstico dependiendo del tipo de cáncer.
- HOTAIR cuando su expresión está aumentada en el cáncer de mama se asocia con metástasis.
- HOTAIR es indicador de mal pronóstico en cáncer de esófago, y se observa aumentado en cáncer de colon e hígado.



BRMS1, CRSP3, DRG1, KAI1, SDPR, KISS1, NM23 y TIMPs

Contribución ambiental a la alteración en las modificaciones de histonas

• Carcinógeno ⟹ mutagénico o no-mutagénico

• Los metales pesados, pueden alterar la actividad de enzimas modificadoras de las histonas.

⟶ El ambiente puede afectar?

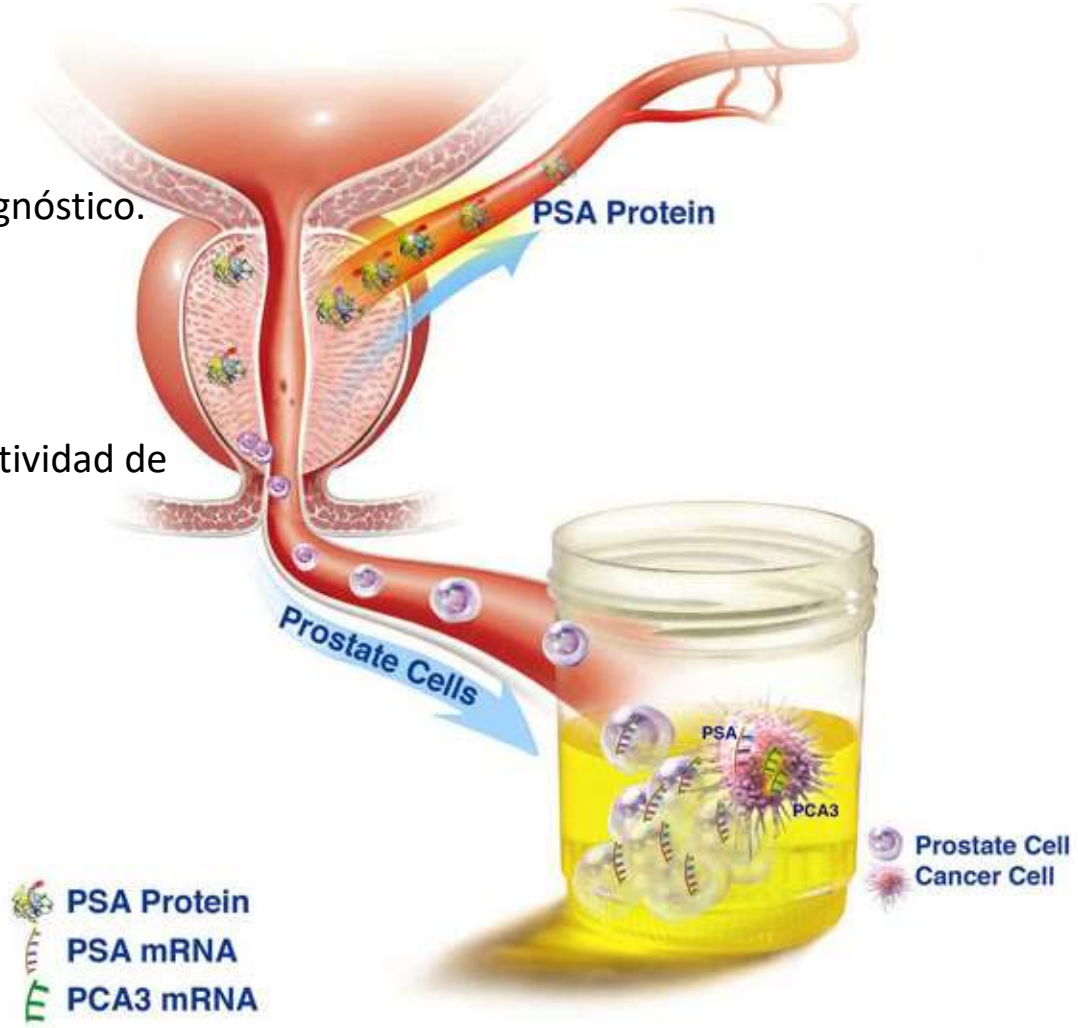
⟶ No necesariamente ocurren en periodos embriológicamente sensibles, y pueden generar cáncer a partir de una sola célula.

lncRNAs y el cáncer

• Diagnóstico – Expresión de LncRNA puede ser usado para diagnóstico.

– Ej. PCA3 en cáncer de próstata en orina.

• Terapéutica – lncRNAs pueden ser usados para bloquear la actividad de oncogenes.



lncRNAs y el cáncer

Table 1. Dysregulated ncRNAs in cancer.

Variable	ncRNA	Mechanism	Dysregulated in	Functions in Cancers	Ref.
lncRNA	HOTAIR	Oncogene	Endometrial, lung, ovarian, prostate, thyroid	Interacts with PRC2 to methylate and silence tumor suppressor genes	[70–72]
	MALAT1	Oncogene + tumor suppressor	Breast, endometrial, lung, ovarian, prostate, thyroid	Alternative splicing, metastasis	[71,73,74]
	MEG3	Tumor suppressor	Breast, colorectal, gastric, liver, lung, ovarian, prostate	Regulates proliferation, angiogenesis, epithelial-to-mesenchymal transition, drug sensitivity	[71,75,76]
	H19	Oncogene + tumor suppressor	Bladder, breast, colorectal, endometrial, ovarian, prostate	Induces cell survival pathways in response to stress, epithelial-to-mesenchymal transition (primary site) and mesenchymal-to-epithelial transition (secondary site)	[77]
	BRAFP1	Oncogene	Lymphoma	Activates BRAF	[78]
	NANOG	Oncogene	Breast, colorectal, hepatocellular, leukemia, lung, pancreatic, prostate	Sustains cell-renewal and confers stem cell-like properties. Involved with proliferation, migration, invasion, drug resistance	[79]
	OCT4	Oncogene	Liver, lung, pancreas	Sustains cell-renewal and confers stem cell-like properties. Involved with proliferation, migration, invasion, drug resistance	[80]
	PTENP1	Tumor suppressor	Breast, gastric, prostate, renal	Sponges microRNAs that target PTEN	[55,71,81–84]
	circPRKCI	Oncogene	Glioma, lung	Promotes proliferation and migration by sponging tumor suppressing miRNAs (e.g., miR-545)	[85,86]
	circHIPK3	Oncogene	Breast, colorectal, gallbladder, gastric, ovarian	Promotes cancer growth and metastasis by sponging tumor suppressing miRNAs (e.g., miR-7, miR-193a)	[87,88]
piRNA	piR-651	Oncogene	Lung	Enhances cell viability and metastasis	[89]
	piR-823	Oncogene + tumor suppressor	Colorectal, esophageal, gastric	Affects cell growth, metastasis, DNA methylation, apoptosis, transcriptional activity	[90–92]
	piR-932	Oncogene	Breast	Epithelial-to-mesenchymal transition	[93]
miRNA	miR-15/16	Tumor suppressor	Chronic lymphocytic leukemia (CLL), prostate cancer, colorectal, pleural mesothelioma	Enhances apoptosis, reduces tumor size and metastasis, and regulates immunological response	[94–97]
	miR-29	Tumor suppressor	Breast, head and neck, pancreatic, prostate, liver, lung, pancreas	Induces senescence and apoptosis. Mitigates against cancer metabolism proliferation, migration, and invasion	[98–105]

cancers MDPI

Review

Non-Coding RNAs in Cancer Diagnosis and Therapy: Focus on Lung Cancer

Patricia Le, Giulia Romano, Patrick Nana-Sinkam and Mario Acunzo *

Division of Pulmonary Diseases and Critical Care Medicine, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA 23298, USA; patricia.le@vcuhealth.org (P.L.); giulia.romano@vcuhealth.org (G.R.); patrick.nana-sinkam@vcuhealth.org (P.N.-S.)
* Correspondence: mario.acunzo@vcuhealth.org

Simple Summary: Researchers have spent nearly two decades unraveling the roles of non-coding RNAs in cancer biology. In recent years, deep transcriptomic profiling of tissue and circulating non-coding RNAs in cancer patients have elucidated non-coding RNAs as potential biomarkers that can inform cancer diagnosis and prognosis. Clinical trials have also begun examining non-coding RNA-based drugs as adjuncts to traditional chemotherapeutics. Overall, our review is structured to provide an overview of non-coding RNAs in cancer biology, diagnostics, and therapeutics, focusing on lung cancer.

lncRNAs y el cáncer

cancers

MDPI

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Table 3. Current clinical trials with ncRNA-based therapeutics.

Clinical Trial ID	Stage	Disease	Therapeutic
NCT03608631	Phase I	Pancreatic cancer	**iExosomes** derived mesenchymal stromal cells with KRAS G12D siRNA
NCT01591356	Phase I	Advanced or recurrent solid tumors	**EphA2-targeting** DOPC-encapsulated siRNA
NCT00938574	Phase I	Advanced solid tumors	**Atu027** (siRNA targeting PKN3)
NCT00882180 + NCT01158079	Phase I	Advanced solid tumors with liver involvement	**ALN-VSP02** (lipid nanoparticle with siRNA targeting VEGF-A + KSP)
NCT03087591 + NCT02166255	Phase I	Metastatic solid neoplasms	**APN401** (peripheral blood mononuclear cells transfected with cbl-b siRNA)
NCT02369198	Phase I	Pleural mesothelioma, NSCLC	**TargomiRs** (miR-16 mimic)
NCT00689065	Phase I (terminated)	Solid tumors	**CALAA-01** (siRNA targeting RRM2)
NCT01829971 + NCT02862145	Phase I (terminated)	Solid tumors, liver cancer	**MRX34** (miR-34 mimic)
NCT01188785 + NCT01676259	Phase I + II	Pancreatic cancer	**siG12D-LODER** (siRNA targeting KRAS G12D)
NCT01437007	Phase I/II	Primary/secondary liver cancer	**TKM-080301** (siRNA targeting PLK1)
NCT02110563 + NCT02314052	Phase I/II (terminated)	Solid tumor, multiple myeloma, lymphoma	**DCR-MYC** (siRNA targeting MYC)
NCT03713320 + NCT03837457	Phase II (terminated)	Cutaneous T-Cell Lymphoma/Mycosis Fungoides	**Cobomarsen/MRG-106** (oligonucleotide inhibitor of miR-155)

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Table 2. ncRNA biomarkers in lung cancer.

	Biomarker	Sample	Clinical Information	Ref.
Disease/ Diagnostic	Seven paired miRNA panel	Plasma	Distinguishes early-stage LUAD + benign disease from control	[222]
	Five paired miRNA panel	Plasma	Distinguishes early-stage LUAD from benign disease	[222]
	Ten paired miRNA panel	Plasma	Distinguishes NSCLC (LUAD + LUSC) from controls (healthy/endobronchitis patients)	[223]
	SNHG1 + RMRP	Plasma	Distinguishes NSCLC from cancer-free controls	[224]
	Let-7b-5p, let-7e-5p, miR-24-5p, and miR-21-5p	Exosome	Distinguishes stage-I NSCLC patients from healthy controls	[225]
	miR-181-5p + miR-361-5p	Exosome	Can discern LUAD from other NSCLC histologies	[225]
	miR-320b + miR-10b-5p	Exosome	Can discern LUSC from other NSCLC histologies	[225]
	circRNA-0001073 + circRNA-0001495	Tissue	Differentiate LUAD and LUSC	[226]
	miR-126	Exosome	Distinguishes early-stage NSCLC patients from healthy controls	[227]
	RNA panels including ncRNAs	Tumor-educated platelets	Early- and late-stage NSCLC detection	[228]
	Edited miR-411-5p	Tissue + Exosomes	Distinguishes late-stage NSCLC from controls	[229]
	Edited miR-99a-5p	Tissue	Distinguishes LUAD from controls	[230]
Prognostic/ Treatment	Edited miR-99a-5p	Tissue	Informs of shorter overall survival and recurrence-free survival after resection of LUAD	[230]
	miR-17-3p miR-1268b + miR-6075	Plasma	Predicts resectable lung cancers regardless of histology and staging	[231]
	Let-7	Tissue	Informs of poor prognosis following tumor resection	[176]
	Let-7a + miR-155	Tissue	Informs of overall survival	[103]
	MALAT1	Tissue	Informs of poor prognosis for LUSC patients	[232]

RESUMEN DE LAS ALTERACIONES EPIGENÉTICAS EN EL CÁNCER

Metilación del ADN

– Hipometilación global.

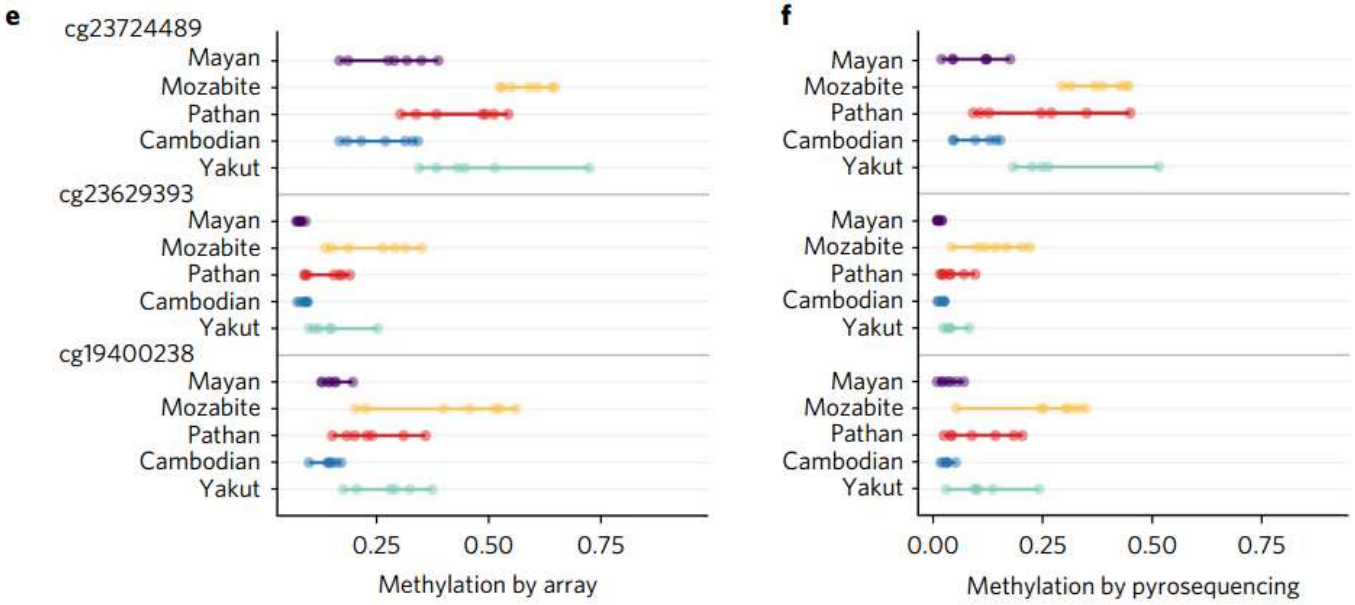
– Hipermetilación de genes supresores de tumor.

- **Modificaciones de Histonas**

– A nivel global, aumento en las marcas epigenéticas de silenciamiento y pérdida de marcas de activación en Islas CpG.

- **Expresión alterada de ARNs no codificantes**

DIVERSIDAD EPIGENÉTICA EN POBLACIONES HUMANAS



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ARTICLES

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Worldwide patterns of human epigenetic variation

Oana Carja[1,5*], Julia L. MacIsaac[2,3], Sarah M. Mah[2,3], Brenna M. Henn[4], Michael S. Kobor[2,3], Marcus W. Feldman[1] and Hunter B. Fraser[1]

DNA methylation is an epigenetic modification, influenced by both genetic and environmental variation, that plays a key role in transcriptional regulation and many organismal phenotypes. Although patterns of DNA methylation have been shown to differ between human populations, it remains to be determined how epigenetic diversity relates to the patterns of genetic and gene expression variation at a global scale. Here we measured DNA methylation at 485,000 CpG sites in five diverse human populations, and analysed these data together with genome-wide genotype and gene expression data. We found that population-specific DNA methylation mirrors genetic variation, and has greater local genetic control than mRNA levels. We estimated the rate of epigenetic divergence between populations, which indicates far greater evolutionary stability of DNA methylation in humans than has been observed in plants. This study provides a deeper understanding of worldwide patterns of human epigenetic diversity, as well as initial estimates of the rate of epigenetic divergence in recent human evolution.

DIVERSIDAD EPIGENÉTICA EN POBLACIONES HUMANAS

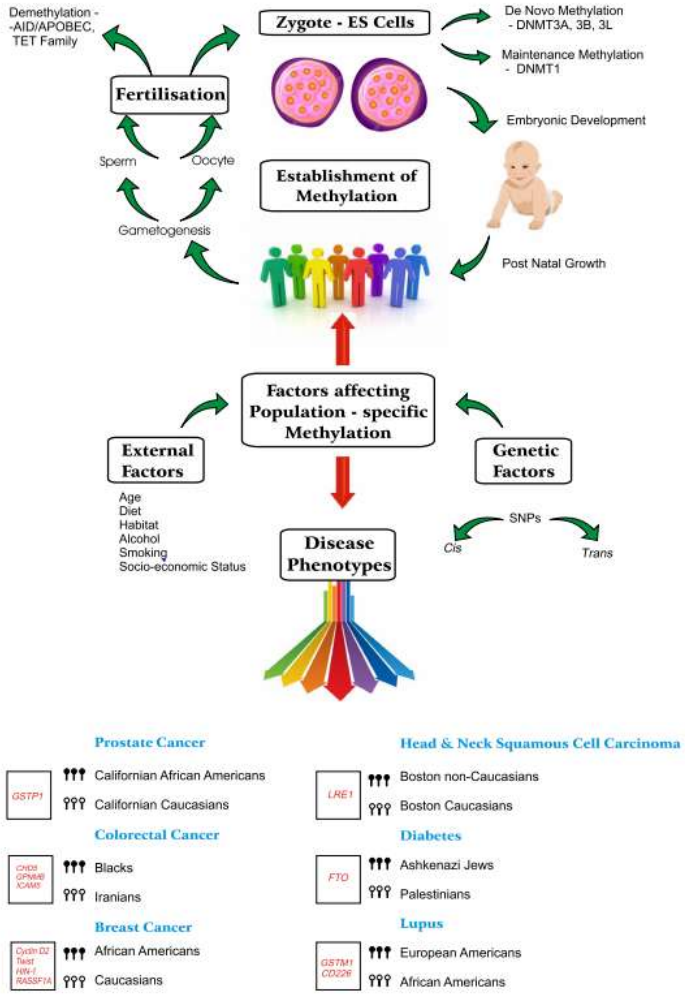

Fig. 1 Factors that shape the human methylome set their mark during early embryonic development and lead to differential methylation patterns in populations. Establishment of methylation is mediated by DNMT1, DNMT3A, DNMT3B, and DNMT3L. Demethylation of the gametes (oocyte and sperm) in the zygote occur immediately after fertilization, mediated by spontaneous cytosine deamination by AID/APOBEC enzymes or the TET family of oxygenases that catalyse oxidation of 5mC to 5-hydroxy-mC. DNA methylation differences among populations are due to varying environmental and genetic factors. These factors may lead to disease phenotypes which are shown to differ between populations (represented by various *colours*). The figure represents an example of one study of each disease discussed in text. Prostate cancer (Enokida et al. 2005); colorectal cancer (Mokarram et al. 2009); breast cancer (Mehrotra et al. 2004); head and neck squamous cell carcinoma (Hsiung et al. 2007); diabetes (Toperoff et al. 2015); lupus (Coit et al. 2013). *Dark lollipops* indicate high methylation levels of the disease-associated gene in that particular population/ethnic group, whereas *light lollipops* indicate low methylation levels (colour figure online)

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DOI 10.1007/s00438-016-1264-2

REVIEW

DNA methylation-based variation between human populations

Farzeen Kader[1] · **Meenu Ghai**[1]

Received: 12 February 2016 / Accepted: 25 October 2016

Abstract Several studies have proved that DNA methylation affects regulation of gene expression and development. Epigenome-wide studies have reported variation in methyl-

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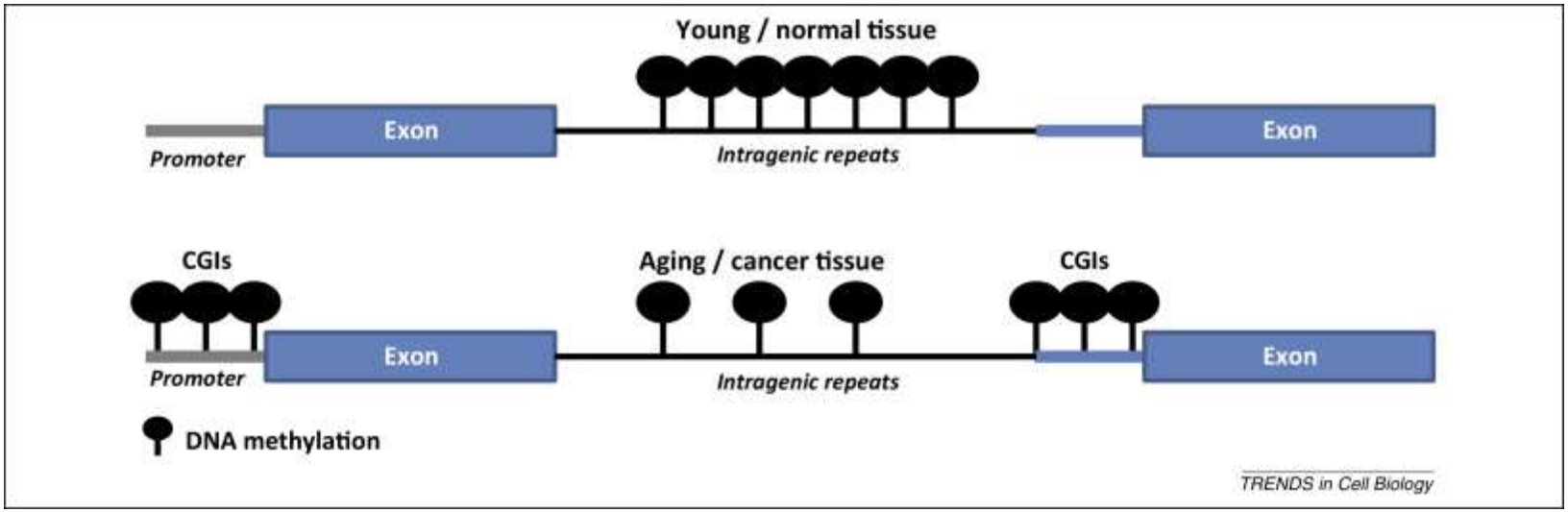
Table 1 Summary of disease-associated variations of DNA methylation patterns between populations

Disease/illness	Target gene	Region of gene/site of interest	Hypomethylation (*n* participants)	Hypermethylation (*n* participants)	References
Malignant mesothelioma	IGTBP-3	Promoter	USA (40)	Japan (16)	Tomii et al. (2006)
Head and neck squamous cell carcinoma	LRE1	160 bp region; i.e. restriction products of *Tas*I (63 and 97 bp)	Boston Caucasians (258)	Boston non-Caucasians (20)	Hsiung et al. (2007)
Prostate cancer	*GSTP1*	Promoter	Caucasians (77) Asians (170)	African Americans (44)	Enokida et al. (2005)
Prostate cancer	*GSTP1, AR, RARβ2, SPARC, TIMP3, NKX2-5*	Promoters of all stated genes	Caucasians (12–40)	African Americans (40)	Kwabi-Addo et al. (2010)
Colorectal cancer	*ICAM5, GPNMB, CHD5*	Promoters of all stated genes	Iranians (51)	Blacks (51)	Mokarram et al. (2009)
Breast cancer	*HIN-1, Twist, Cyclin D2, RASSF1A*	Promoters of all stated genes	Caucasian women	African American women	Mehrotra et al. (2004)
Diabetes	FTO	CpG site located within intron Chr 16:53809231-2; hg19	Palestinians (929)	Israeli Jews (629)	Toperoff et al. (2015)
Diabetes	*TXNIP*	cg19693031 (Chr 1:145441552)	Europeans (7066)	Indian Asians (13,535)	Chambers et al. (2015)
	ABCG1	cg06500161 (Chr 21:43656587)			
	SOCS3	cg18181703 (Chr17:76354621)			
	PHOSPHO1	cg02650017 (Chr17:47301614)			
	SREBF1	cg11024682 (Chr17:17730094)			
Lupus	*IL32*	cg08978665 (Chr 16:3115707)	African Americans (21 healthy; 21 patients)	European Americans (45 healthy; 42 patients)	Coit et al. (2013)
		cg00471190 (Chr 16:3115809)			
		cg00239353 (Chr 16:3115133)			
		cg23813257 (Chr 16:3115286)			
	CD226	cg20768743 (Chr 18:67624846)			
	CDKN1A	cg24425727 (Chr 6:36645648)			
	GSTM1	cg18938907 (Chr 1:110230456)			
		cg11680055 (Chr 1:110230252)			
		cg24506221 (Chr 1:110230401)			
		cg10950028 (Chr 1:110230633)			
	PTPRN2	cg22216157 (Chr 7:157643037)			

EPIGENÉTICA Y ENVEJECIMIENTO



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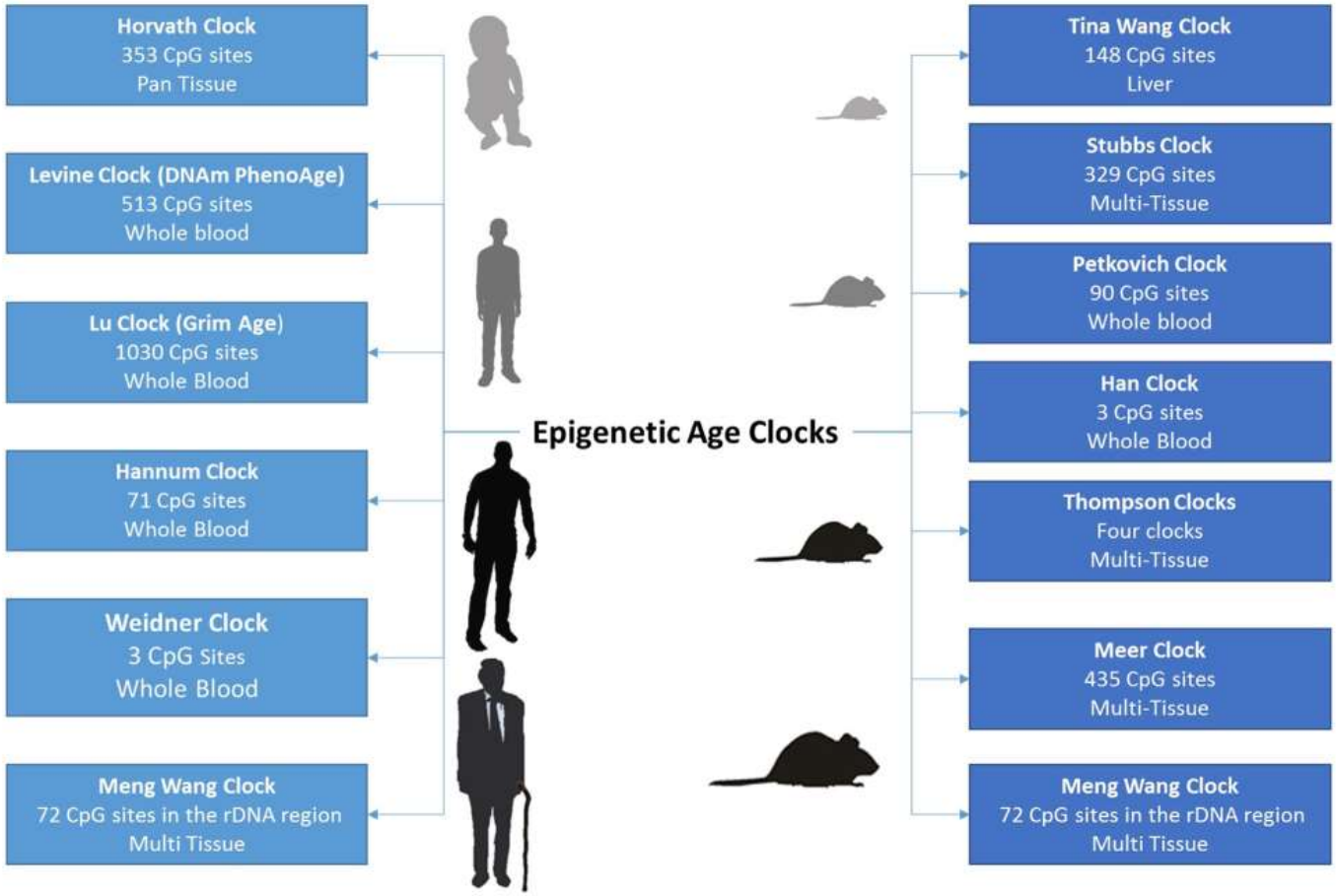

FIGURE 1 | The growing number of epigenetic age clocks developed for both humans and mice, including the number of CpG sites comprising the age-prediction model, as well as the tissues in which age can be estimated.

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REVIEW
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DNA Methylation Biomarkers in Aging and Age-Related Diseases

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Recent research efforts provided compelling evidence of genome-wide DNA methylation alterations in aging and age-related disease. It is currently well established that DNA methylation biomarkers can determine biological age of any tissue across the entire human lifespan, even during development. There is growing evidence suggesting epigenetic age acceleration to be strongly linked to common diseases or occurring in response to various environmental factors. DNA methylation based clocks are proposed as biomarkers of early disease risk as well as predictors of life expectancy and mortality. In this review, we will summarize key advances in epigenetic clocks and their potential application in precision health. We will also provide an overview of progresses in epigenetic biomarker discovery in Alzheimer's, type 2 diabetes, and cardiovascular disease. Furthermore, we will highlight the importance of prospective study designs to identify and confirm epigenetic biomarkers of disease.

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7a Clase

EPIGENÉTICA

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