XXV Congreso de la SEAP-IAP, Zaragoza, 2011

Reunión del Club de Patologia Urológica

Alteraciones Epigenéticas en el Cancer de Próstata

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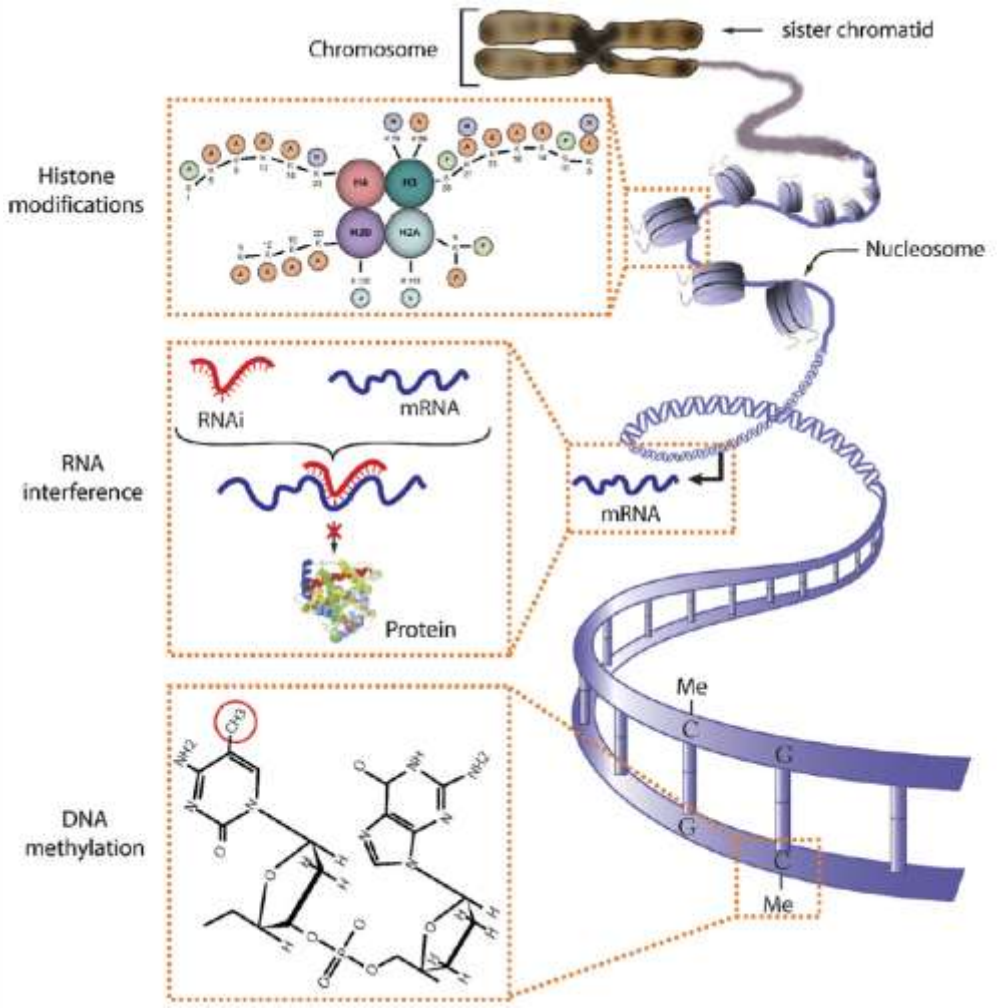
Portugal

Epigenetic alterations in Prostate cancer: overview

- Epigenetic mechanisms and Cancer
  - DNA methylation
  - Histone modifications / chromatin remodeling
  - microRNAs
- Epigenetic alterations in Prostate cancer
- Crosstalk between genetic and epigenetic mechanism in Prostate cancer
- Epigenetic biomarkers for Prostate cancer management

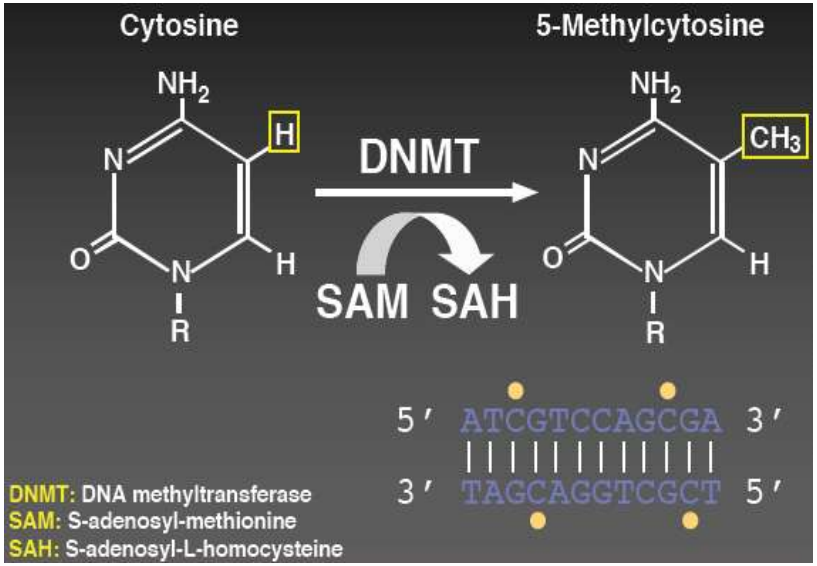
Epigenetic mechanisms and Cancer

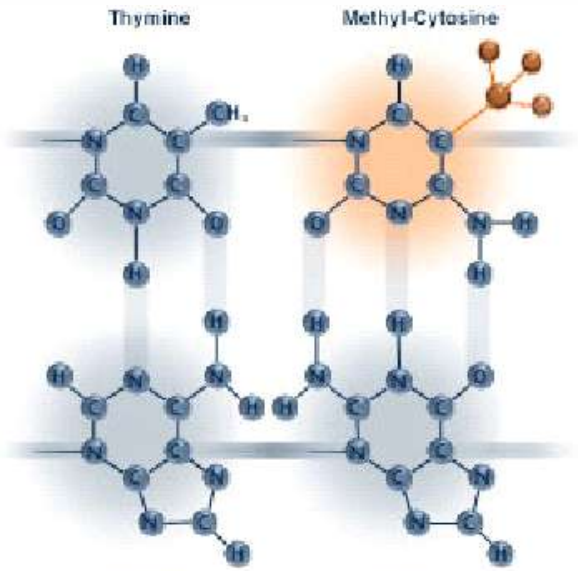
Epigenetics: heritable changes in gene expression and chromatin organization that are not encoded in the genomic DNA itself.

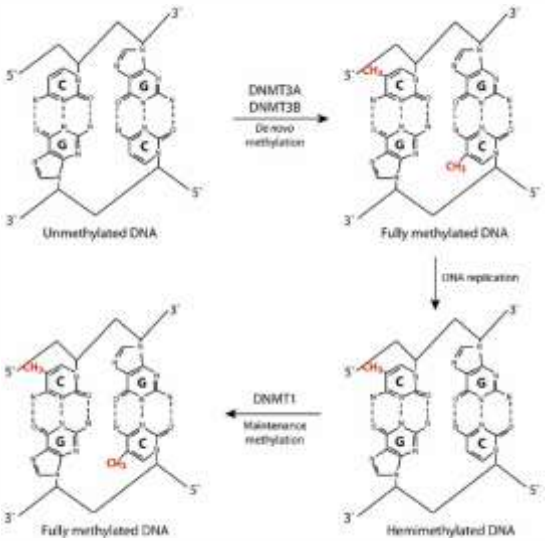


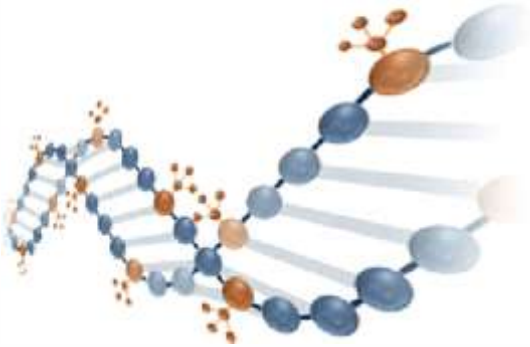
DNA methylation

Cytosine methylation in ***CpG:*** *Cytosine phosphate Guanine*









DNA methylation

CpG islands

• Cluster of CpG dinucleotides in small stretches of DNA (0.5- 4 kb in length), usually > 60% GC content.

  • 80 % of CpG in genome are not associated with CpG islands

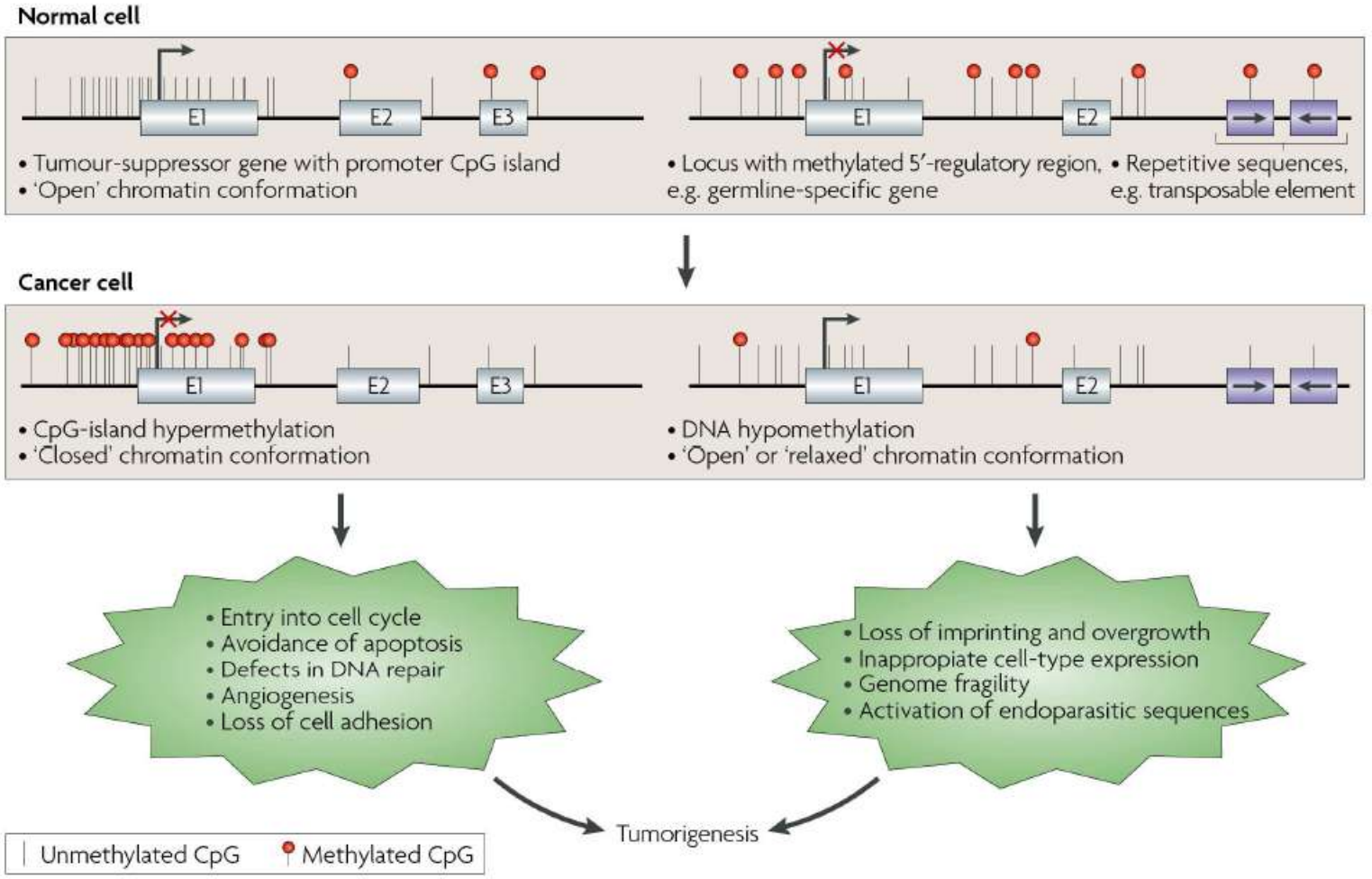
• According to computer prediction by bioinformatics, there are at least 20,000 CpG islands:

  ~ 60 % in promoter region,

  ~ 30 % in coding sequences,

  ~ 10 % in other region.

DNA methylation and Cancer



DNA methylation and Cancer

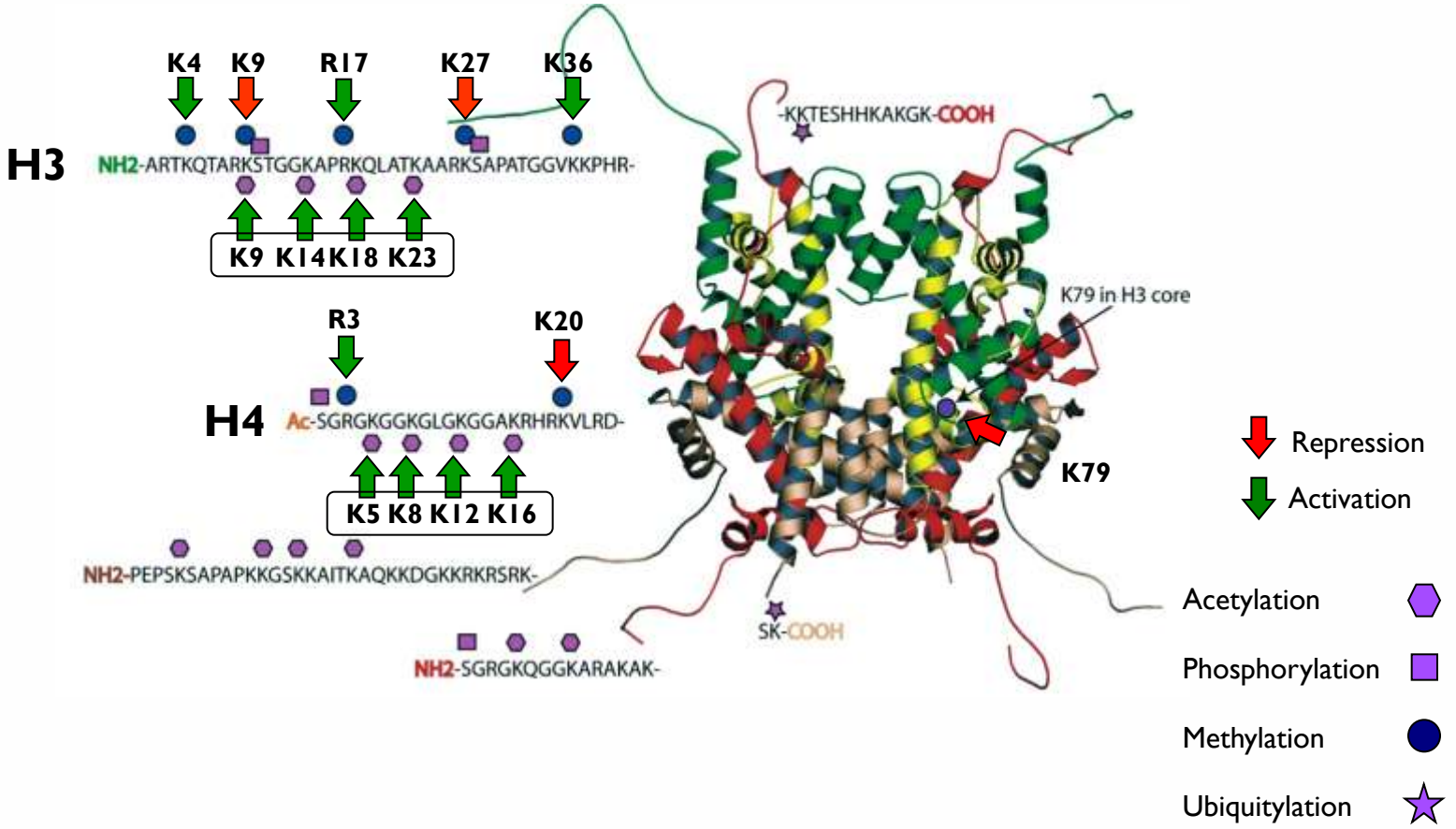
IPOPORTO
INSTITUTO PORTUGUÊS DE ONCOLOGIA DO PORTO FG, EPE

Table 2.4 Cellular pathways disrupted by promoter CpG hypermethylation of tumor suppressor genes

Pathways	Representative hypermethylated genes
DNA repair	MLH1, MGMT, WRN, BRCA1
Hormone response	Estrogen, progesterone, androgen, prolactin and tyroid-stimulating hormone receptors
Vitamin response	RARβ2, CRBP1
Ras signaling	RASSF1A, NOREIA
Cell cycle	p16INK4a, p15INK4b, Rb
P53 network	p14ARF, p73, HIC-1
Cell adherence and invasion	E-cadherin, H-cadherin, FAT cadherin, EXT-1, SLIT2, EMP3
Apoptosis	TMS1, DAPK, WIF-1, SFRP1
Wnt signalling	APC, DKK-1, IGFBP-3
Tyrosine Kinase cascades	SOCS-1, SOCS-3, SYC
Transcription factors	GATA-4, GATA-5, ID4
Homeobox genes	PAX6, HOXA9
Other pathways	GSTP1, LKB1/STK11, THBS-14, COX-2, SRBC, RIZ1, TPEF/HPP1, SLC5A8, Lamin A/C
microRNAs	miR-127 (targeting BCL6), miR-124a (targeting CDK6)

Esteller, 2007

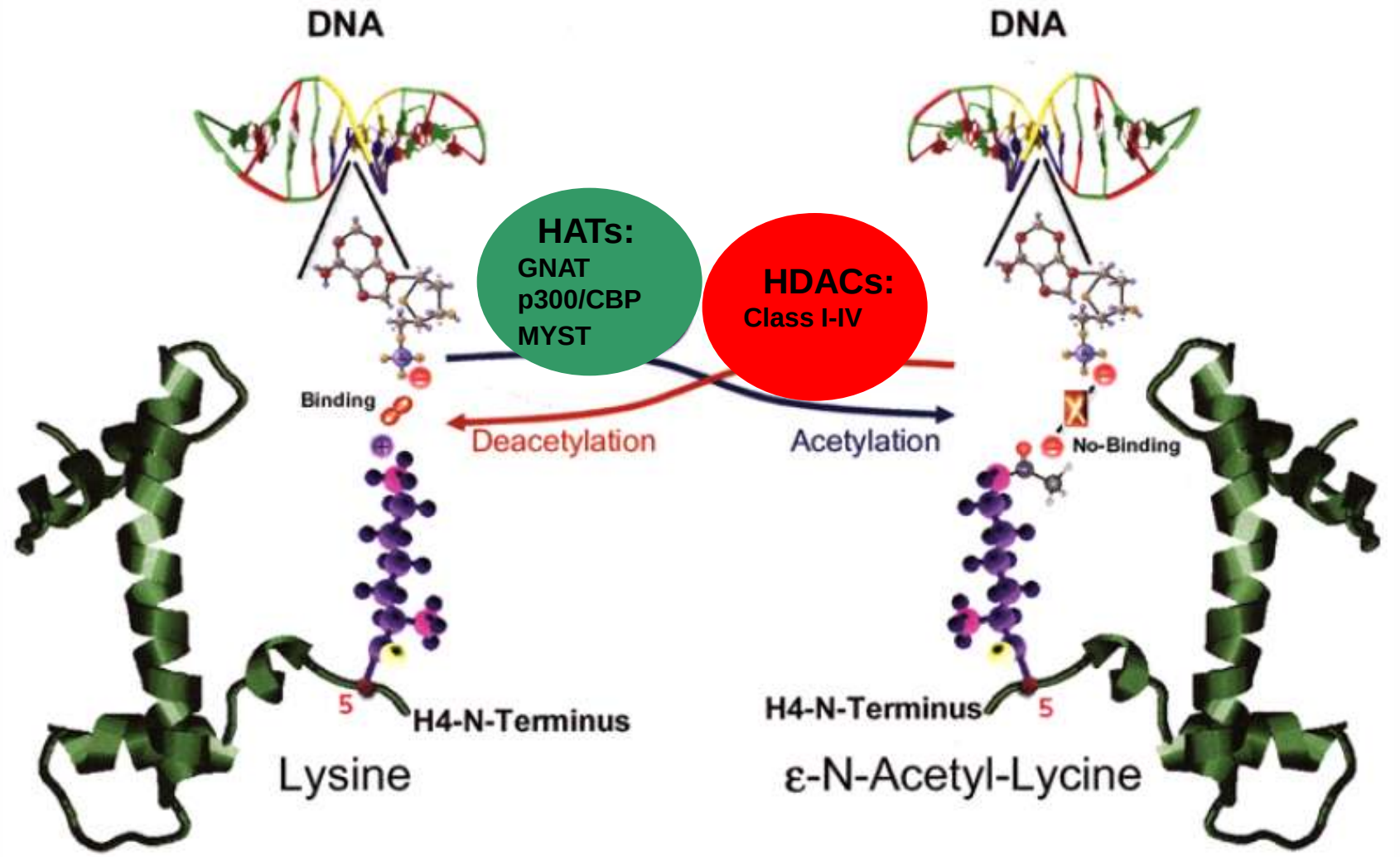
Histone Modifications



"The histone code," acts as a layer of epigenetic regulation of gene expression affecting chromatin structure and remodeling

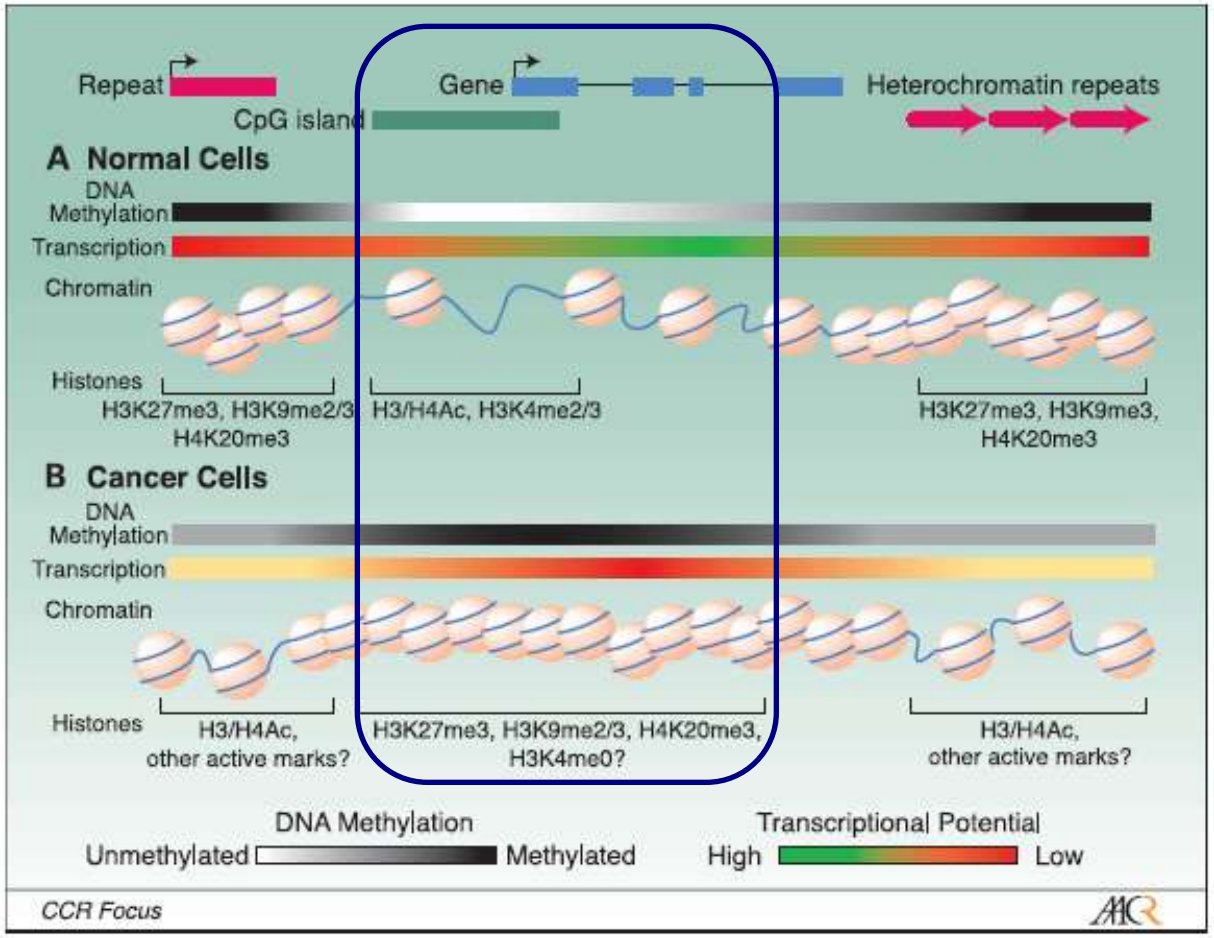
Histone Modifications

Inactive / Active



Herranz & Esteller, 2007

DNA methylation & histone modification patterns are altered in Cancer

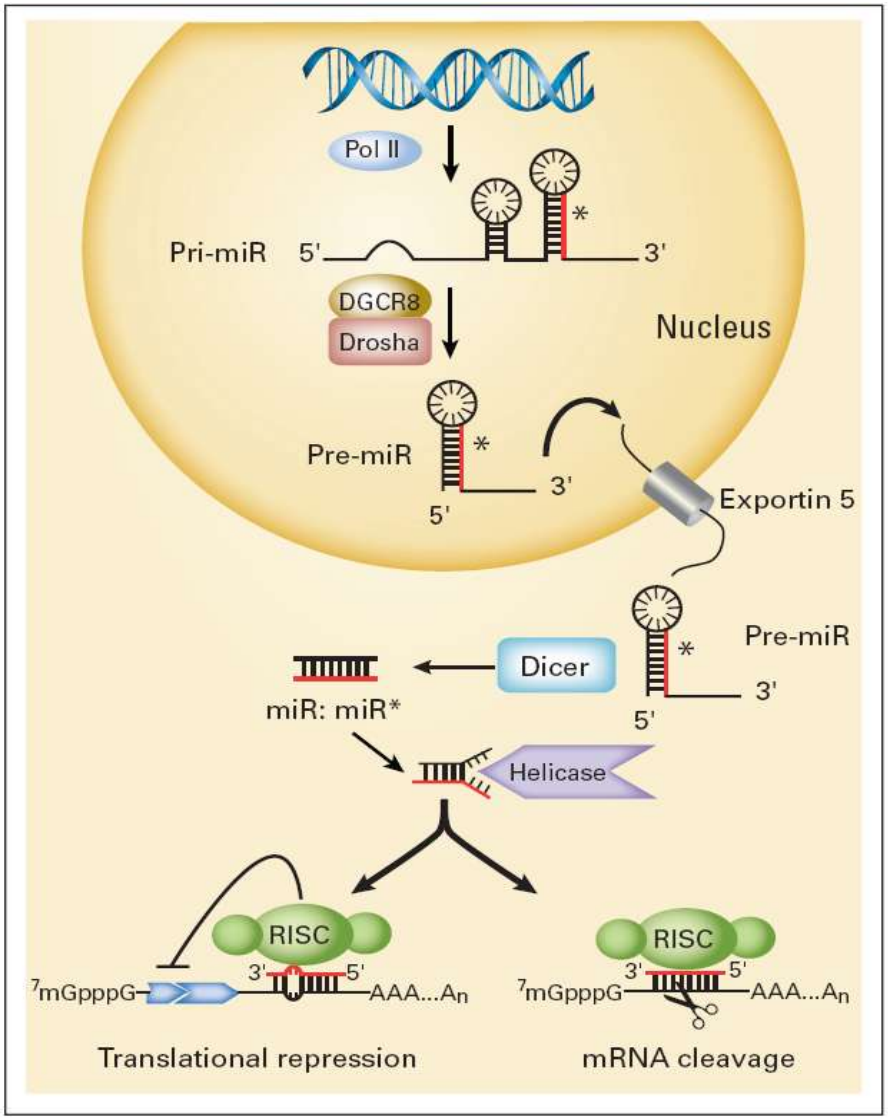


McCabe et al., 2009

microRNAs (miRs)

- MicroRNAs (miRNAs) are a family of 21–25 nucleotide non-coding RNAs

- They negatively regulate gene expression at the post-transcriptional level in a sequence-specific manner:
  - Translational repression
  - mRNA cleavage



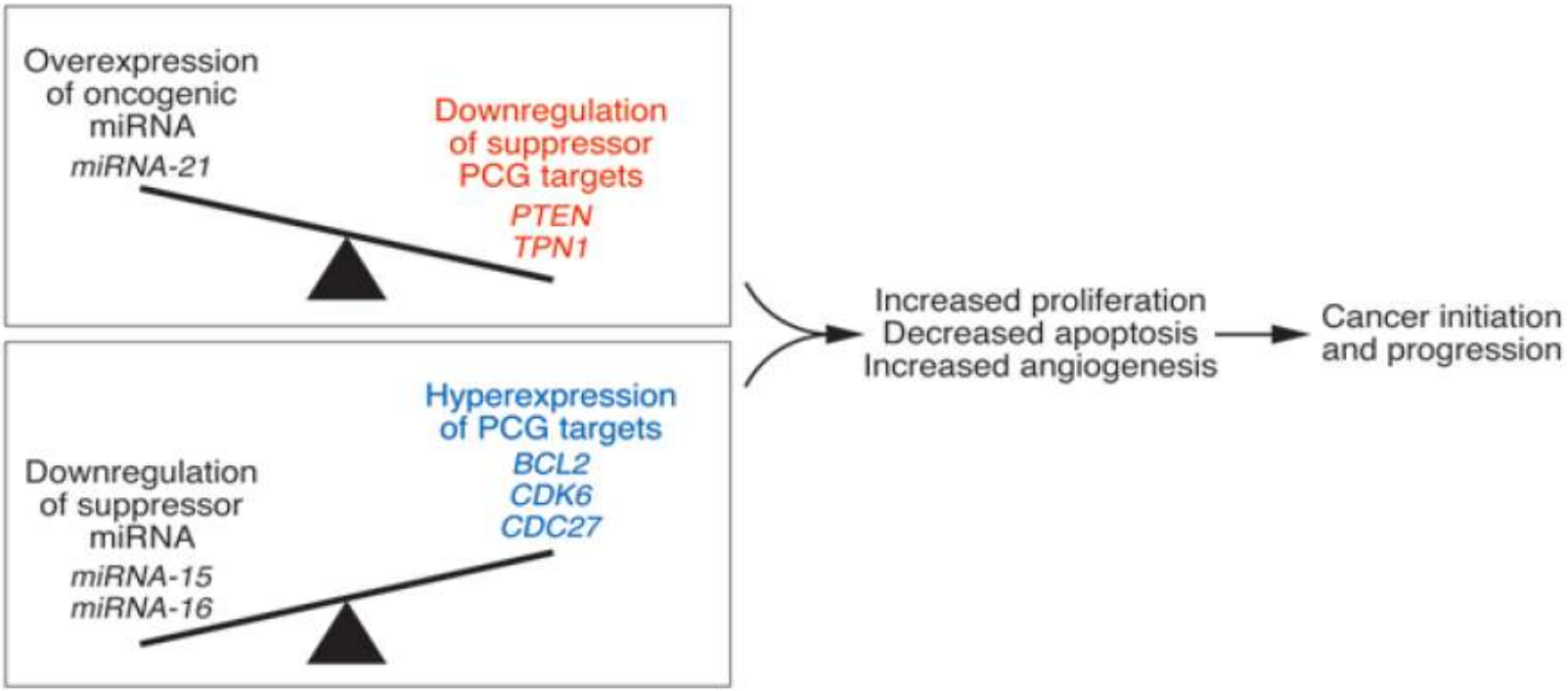
Ivorio et al., 2009

microRNAs (miRs)

- ~ 700 miR discovered in humans
- miRNA may be located either within the introns or exons of protein-coding genes (70%) or in intergenic areas (30%)
- ~ 30% of human genes are regulated by miRNA
- A single miRNA can regulate dozens of transcripts
- A transcript may be a target of several miR

microRNAs & Cancer

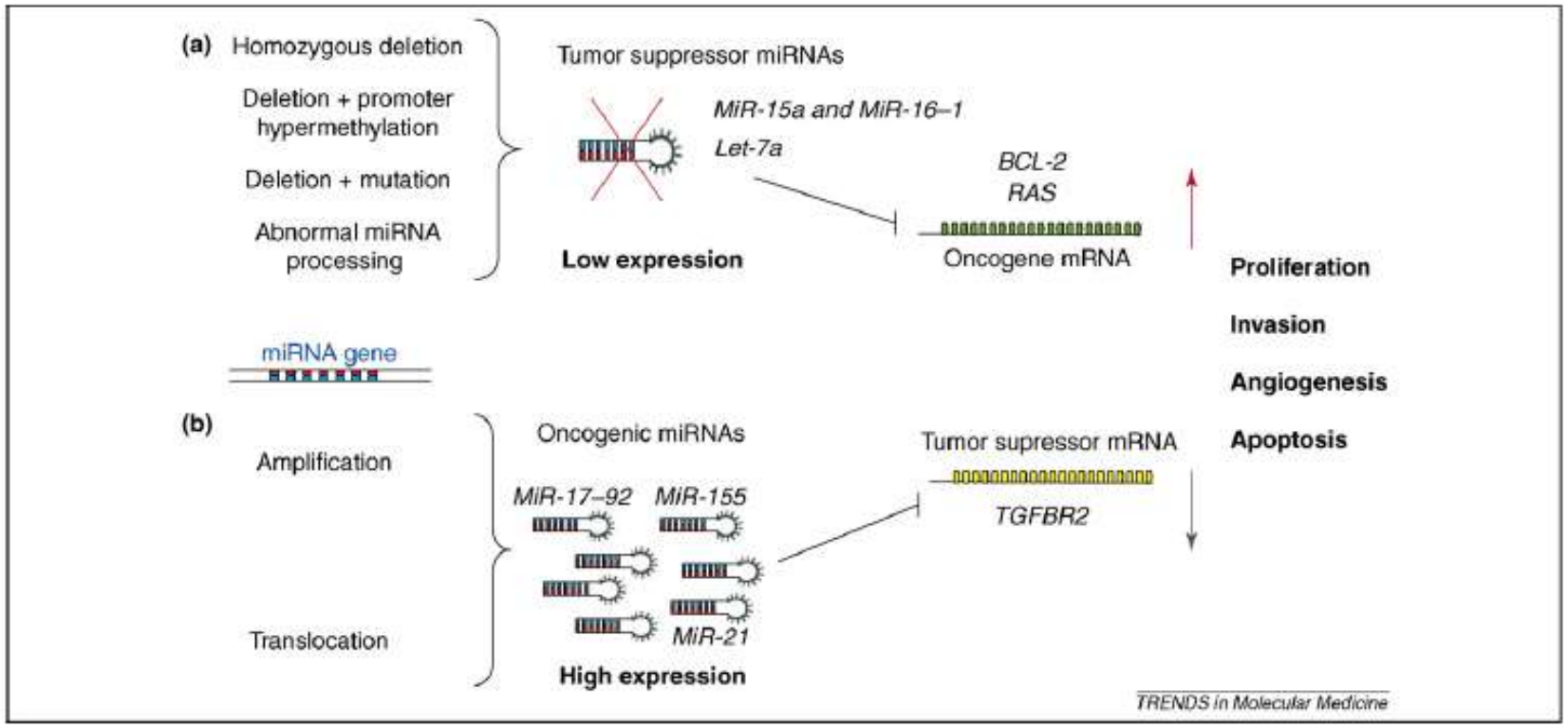
- Role of miRNAs in carcinogenesis



Calin et al., 2007

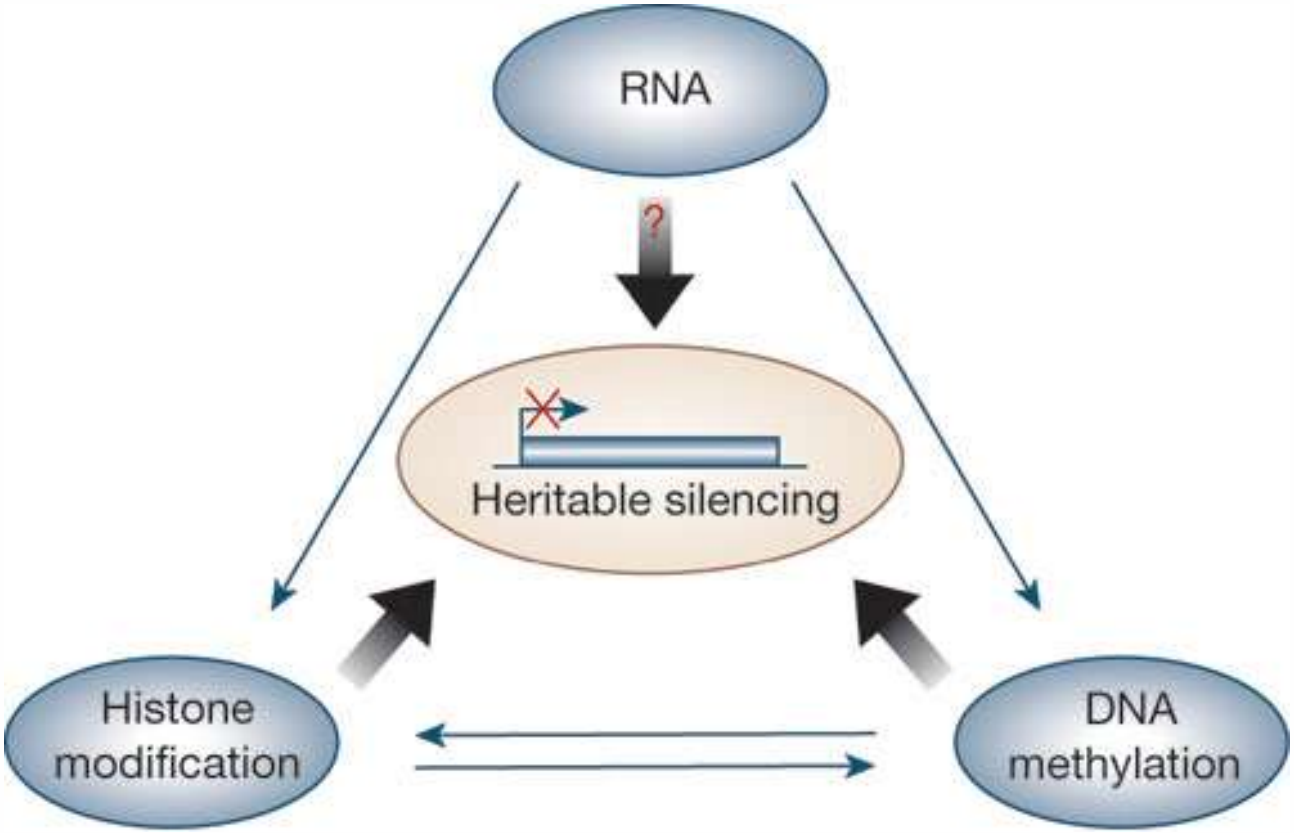
microRNAs & Cancer

- Mechanisms of miRNAs deregulation



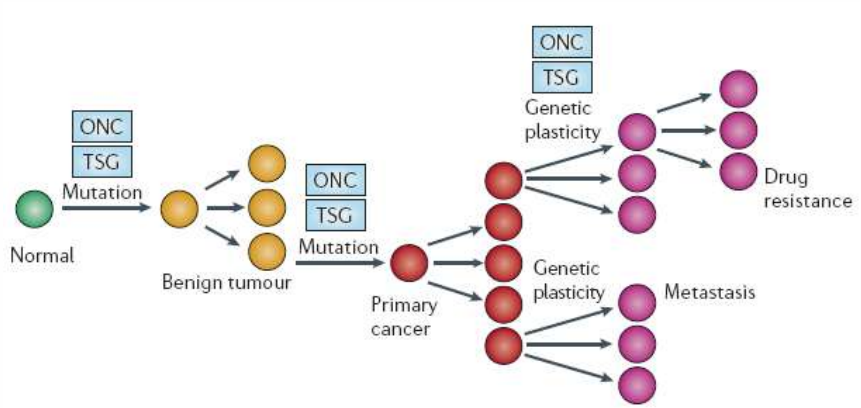
Garzon et al., 2006

Genetics and Epigenetics

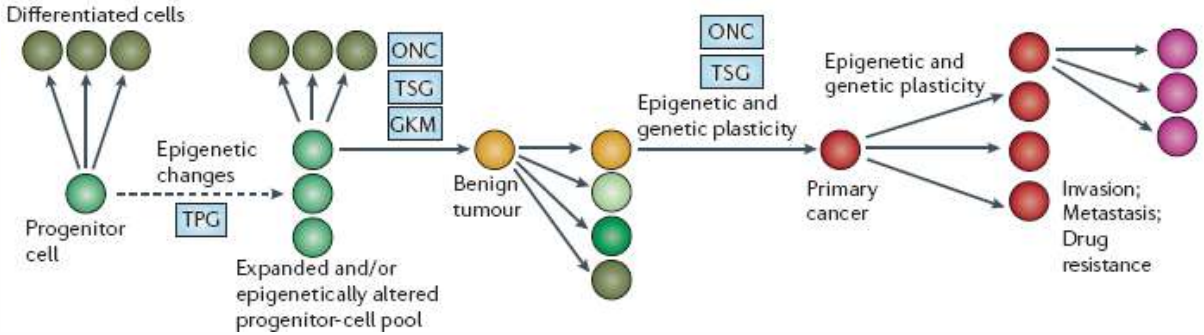


Genetics and Epigenetics

The clonal genetic model of cancer



The epigenetic progenitor model of cancer



Epigenetic alterations in Prostate cancer: DNA methylation

Table 1. Genes affected by epigenetic aberrations in prostate cancer

Epigenetic aberration	Gene symbol[1]	References
DNA hypermethylation		
Hormonal response	AR, ESR1, ESR2, RARB, RARRES1	12, 14, 19-21, 35, 36, 39, 58, 78, 184
Cell cycle control	CCND2, CDKN2A, CDKN1A, SFN	52, 56, 58, 59, 61-63, 78, 242
Tumor cell invasion/tumor architecture	APC, CAV1, CD44, CDH1, CDH13, LAMA3, LAMB3, LAMC2	55, 58, 66, 69, 70, 72-76, 78-80, 243
Repair of DNA damage	GSTP1, MGMT	85, 86, 84, 87, 88, 90, 203-205, 208, 244, 21, 70, 78, 206, 210, 245, 55, 57, 58, 243, 246
Signal transduction	DAB2IP, DAPK1, EDNRB, RASSF1	55, 58, 71, 78, 98, 103, 247, 248
Inflammatory response	PTGS2	58
Others	ALDH1A2, HIC1, MDR1, PXMP4	21, 58, 243, 249-251
DNA hypomethylation	CAGE, HPSE, PLAU, XIST	131, 133, 135, 136
Histone hypoacetylation	CAR, CPA3, RARB, VDR	172, 179, 184, 252, 253
Histone methylation	DAB2IP, GSTP1, PSA	10, 167, 170, 191

[1] Genes are listed alphabetically in each category

Li and Dahiya, 2007

DNA methylation as a Prostate cancer biomarker

Advantages of DNA methylation as a Cancer biomarker:

- **Easy to screen**, because it is localized in a particular region of the gene
- It is a **positive signal that is less likely to be masked** through contaminant normal DNA
- More stable and more easily manipulated than RNA
- Requires **very small amounts of DNA**
- It requires low amounts of DNA, suitable for **several types of biological fluids** and biopsy samples as **serum/plasma**, **urine**, bronchoalveolar lavage fluid, saliva, sputum, ductal lavage fluid and fine-needle aspirates

DNA methylation as a Prostate cancer biomarker

Journal of the National Cancer Institute, Vol. 93, No. 22, November 21, 2001

Quantitation of GSTP1 Methylation in Non-neoplastic Prostatic Tissue and Organ-Confined Prostate Adenocarcinoma

Carmen Jerónimo, Henning Usadel, Rui Henrique, Jorge Oliveira, Carlos Lopes, William G. Nelson, David Sidransky

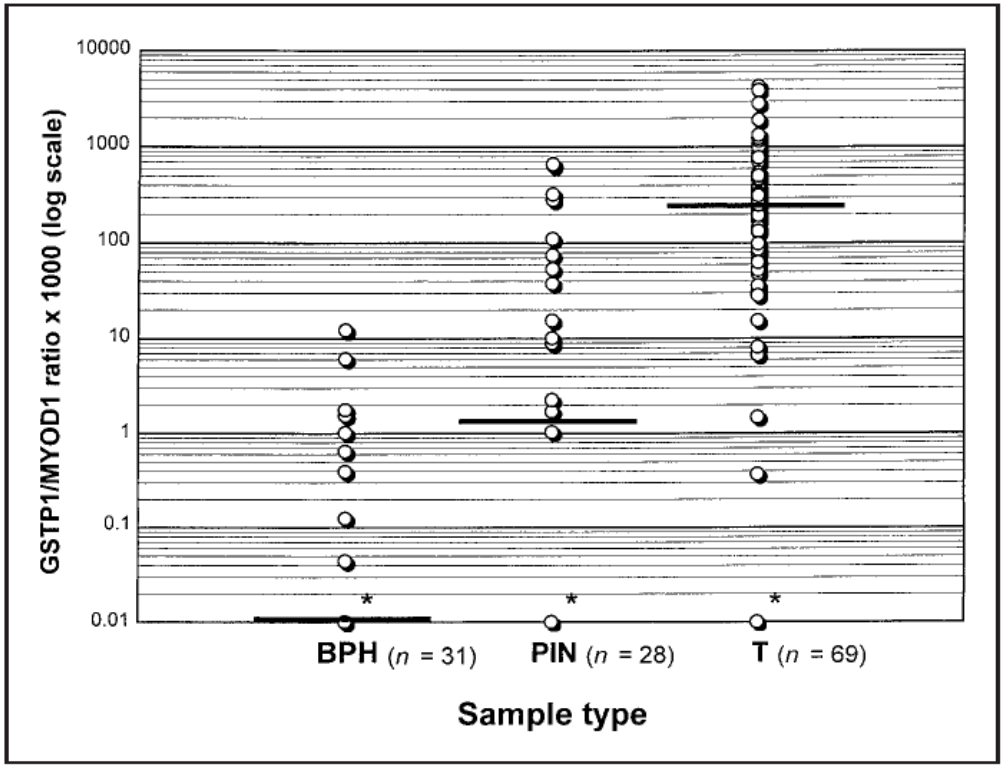


Fig. 1. Distribution of GSTP1 methylation levels in prostate tissues displaying benign prostatic hyperplasia (BPH), prostate intraepithelial neoplasia (PIN), and clinically localized prostate adenocarcinoma (T). Nine (29.0%) of 31 patients with BPH, 63 (91.3%) of 69 patients with T, and 15 (53.6%) of the 28 paired PIN lesions harbored methylated GSTP1 promoter DNA as determined by real-time methylation-specific polymerase chain reaction. Each **circle** represents a different tissue sample. The **solid horizontal bar** indicates the median ratio of methylated GSTP1/MYOD1 (×1000) within a group of patients. The median ratio of methylated GSTP1/MYOD1 differed statistically significantly between BHP and PIN ($P = .014$), between BPH and T ($P<.001$), and between PIN and T ($P = 1 \times 10^{-5}$). **Asterisks** indicate the samples (n = 22 for BPH; n = 13 for PIN; n = 6 for T) that had a median ratio of methylated GSTP1/MYOD1 equal to 0, which

DNA methylation as a Prostate cancer biomarker

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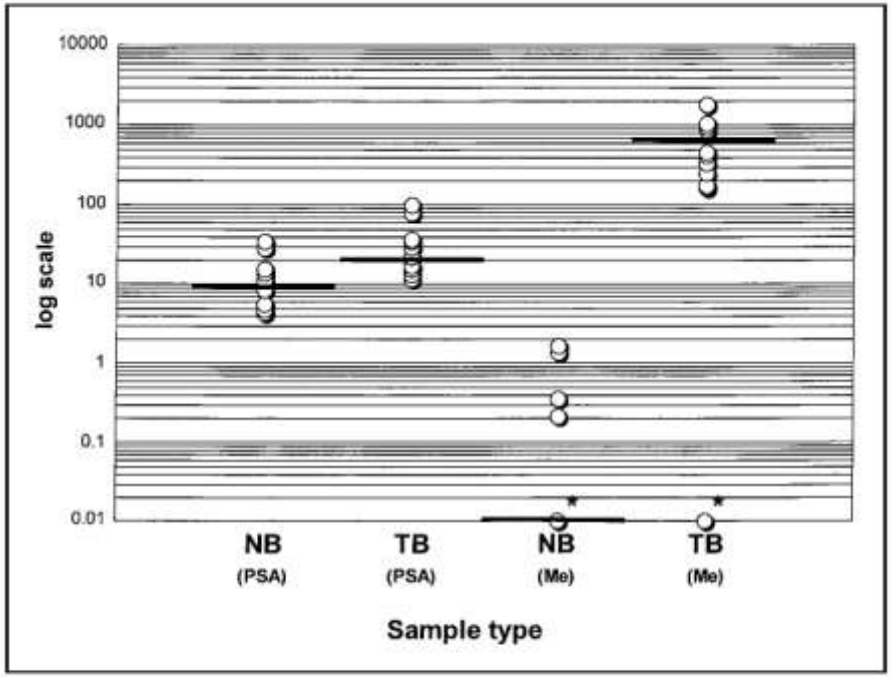


Fig. 2. Distribution of the levels of serum prostate-specific antigen (PSA) and GSTP1 methylation (log scale) in prostate sextant biopsy samples from patients without (NB = normal biopsy; n = 10) and with a histologic diagnosis of prostate cancer (TB = tumor biopsy; n = 11). The *y*-axis represents the GSTP1/MYOD1 ratio × 1000 (Me) or PSA values. Four (40.0%) of 10 patients with methylated NB had a GSTP1/MYOD1 ratio (×1000) less than 10, and 10 (90.9%) of 11 patients with TB had a GSTP1/MYOD1 ratio (×1000) greater than 10 in their biopsy specimens (Me = methylation level of GSTP1). **Asterisks** indicatethe samples (n = 6 for NB and n = 1 for TB) that had a median ratio of methylated GSTP1/MYOD1 equal to 0, which cannot be plotted on a log scale. The **solid horizontal bar** indicates the median ratio of either serum PSA or methylated GSTP1/MYOD1×1000 within a group of patients. The median serum PSA levels differed statistically significantly between NB and TB (P = .014). The difference between the medians of methylated GSTP1/MYOD1 in NB and TB was also statistically significant (P = .0007).

DNA methylation as a Prostate cancer biomarker

Journal of the National Cancer Institute, Vol. 95, No. 21, November 5, 2003

Quantitative GSTP1 Methylation and the Detection of Prostate Adenocarcinoma in Sextant Biopsies

Susan V. Harden, Harriette Sanderson, Steven N. Goodman, Alan A. W. Partin, Patrick C. Walsh, Jonathan I. Epstein, David Sidransky

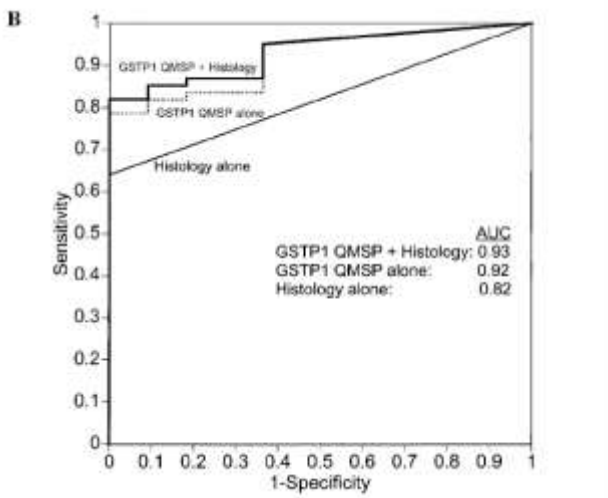


Table 1. Sensitivity and specificity of histology and the gene encoding glutathione *S*-transferase π (GSTP1) quantitative methylation-specific polymerase chain reaction (QMSP) assay in prostate cancer detection*

	Patients with prostate cancer					Patients without prostate cancer	
	Histology alone or GSTP1 QMSP combined with histology			GSTP1 QMSP alone		Histology alone or GSTP1 QMSP combined with histology	
Test (threshold)	No. test-positive/ No. true-positive	% sensitivity (95% CI)	Sensitivity increment† (95% CI)	No. test-positive/ No. true-positive	% Sensitivity (95% CI)	No. test-negative/ No. true-negative	% specificity (95% CI)
Histology	39/61	64 (51 to 76)	NA	NA	NA	11/11	100 (72 to 100)
GSTP1 QMSP (>10)	46/61	75 (63 to 86)	11 (5 to 22)	43/61	70 (57 to 81)	11/11	100 (72 to 100)
GSTP1 QMSP (>5)	48/61	79 (68 to 89)	15 (7 to 26)	46/61	75 (63 to 86)	11/11	100 (72 to 100)
GSTP1 QMSP (>2)	52/61	85 (74 to 93)	21 (12 to 34)	50/61	82 (70 to 91)	10/11	91 (58 to 99)
GSTP1 QMSP (>1)	54/61	89 (78 to 95)	25 (15 to 37)	54/61	89 (78 to 95)	7/11	64 (31 to 89)

19 *GSTP1* Hypermethylation for Prostate Cancer Detection

Rui Henrique and Carmen Jerónimo

Table 1
Performance of *GSTP1* Hypermethylation for Detection of Prostate Cancer in Urine and Plasma/Serum

Sample type, study (ref.)	*Method*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Urine					
Goessl et al. (2000) *(28)*	CMSP	34.4	100	100	58.8
Goessl et al. (2001) *(29)*	CMSP	72.5	97.6	96.7	78.8
Cairns et al. (2001) *(30)*	CMSP	21.4	ND	ND	ND
Jerónimo et al. (2002) *(31)*	CMSP	30.4	96.8	95.5	34.1
	QMSP	18.8	96.8	92.9	34.9
Gonzalgo et al. (2003) *(32)*	CMSP	38.9	ND	ND	ND
Hoque et al. (2005) *(33)*	QMSP	48.1	100	100	77.1
Rouprêt et al. (2007) *(34)*	QMSP	83.2	86.8	94.0	67.3
Plasma/serum					
Goessl et al. (2000) *(28)*	CMSP	71.9	100	100	71.0
Jerónimo et al. (2002) *(31)*	CMSP	36.2	100	100	41.3
	QMSP	13.0	100	100	34.1

PPV, positive predictive value; NPV, negative predictive value; CMSP, conventional methylation-specific PCR; QMSP, quantitative methylation-specific PCR; ND, not determined.

To be useful for prostate cancer screening, testing for *GSTP1* hypermethylation must be feasible in body fluids (urine & plasma/serum)

From: *Current Clinical Urology: Prostate Cancer Screening*, Edited by: D. P. Ankerst et al.
DOI 10.1007/978-1-60327-281-0_19 © Humana Press, a part of Springer Science+Business Media, LLC 2009

19 *GSTP1* Hypermethylation for Prostate Cancer Detection

Rui Henrique and Carmen Jerónimo

Table 2
Diagnostic Information Provided by Hypermethylation Analysis of the Combination of *GSTP1* with Other *Loci*, in Tissue Samples and Urine

Sample type, study (ref.)	*Method*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Prostate tissue					
Yegnasubramanian et al. (2004) *(37)*	QMSP				
GSTP1/MDR1		97.3	100	100	92.6
GSTP1/MDR1/APC		98.6	96.0	98.6	96.0
GSTP1/MDR1/APC/PTGS2		100	92.0	97.3	100
GSTP1/MDR1/APC/PTGS2/RASSF1A		100	92.0	97.3	100
Tokumaru et al. (2004) *(38)*	QMSP				
GSTP1/TIG1		88.5	100	100	61.1
GSTP1/APC		85.2	100	100	55.0
GSTP1/RARB2		90.2	100	100	64.7
GSTP1/TIG1/APC/RARB2		96.7	100	100	93.8
Jerónimo et al. (2004) *(39)*	QMSP				
GSTP1/APC		98.3	100	100	93.8
Bastian et al. (2005) *(40)*	QMSP				
GSTP1/PTGS2		96.2	100	100	87.5
GSTP1/APC		96.2	92.9	98.1	86.7
GSTP1/RASSF1A		98.1	71.4	92.9	90.9
GSTP1/APC/PTGS2		98.1	92.9	98.1	92.9
Enokida et al. (2005) *(41)*	CMSP				
GSTP1/APC/MDR1		75.9	84.1	92.1	58.6
Urine					
Hoque et al. (2005) *(33)*	QMSP				
GSTP1/ARF/CDNK2A/MGMT		86.5	100	100	92.9
Rouprêt et al. (2007) *(34)*	QMSP				
GSTP1/APC/RASSF1A/RARB2		86.3	89.5	95.3	72.3

PPV, positive predictive value; NPV, negative predictive value; CMSP, conventional methylation-specific PCR; QMSP, quantitative methylation-specific PCR.

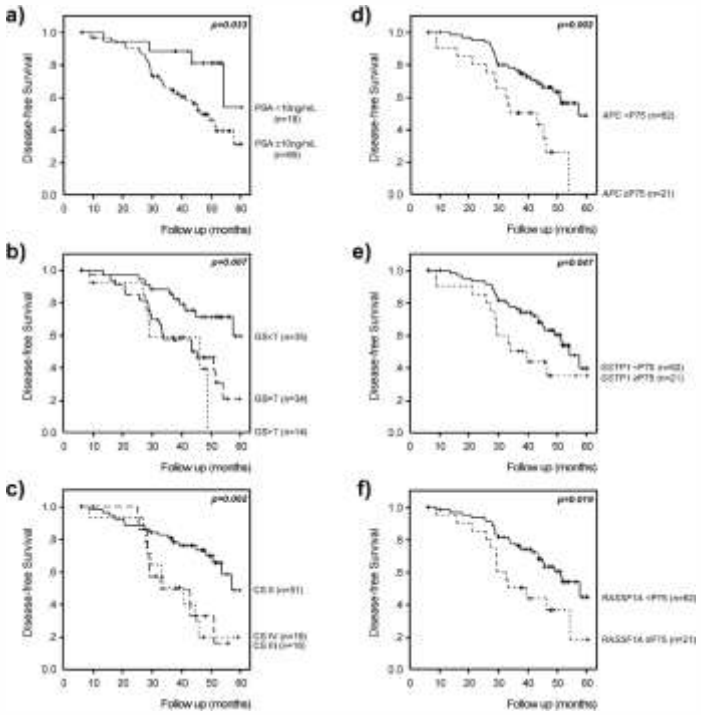
Multigene methylation analysis enhances the rate of cancer detection, maintaining high specificity and positive predictive value, and increases the negative predictive value of the assay

DNA methylation as a Prostate cancer biomarker

Clin Cancer Res 2007;13(20) October 15, 2007

High Promoter Methylation Levels of *APC* Predict Poor Prognosis in Sextant Biopsies from Prostate Cancer Patients

Rui Henrique,[1,5] Franclim R. Ribeiro,[2] Daniel Fonseca,[3] Mohammad O. Hoque,[7] André L. Carvalho,[7] Vera L. Costa,[2] Mafalda Pinto,[2] Jorge Oliveira,[4] Manuel R. Teixeira,[2,5] David Sidransky,[7] and Carmen Jerónimo[2,5,6]



Disease-free survival
- Clinical stage
- Serum PSA levels
- Gleason score
-**High-methylation levels of *APC*, *GSTP1*, and *RASSF1A***

Disease-specific survival
- Clinical stage
- High-methylation levels of *APC*

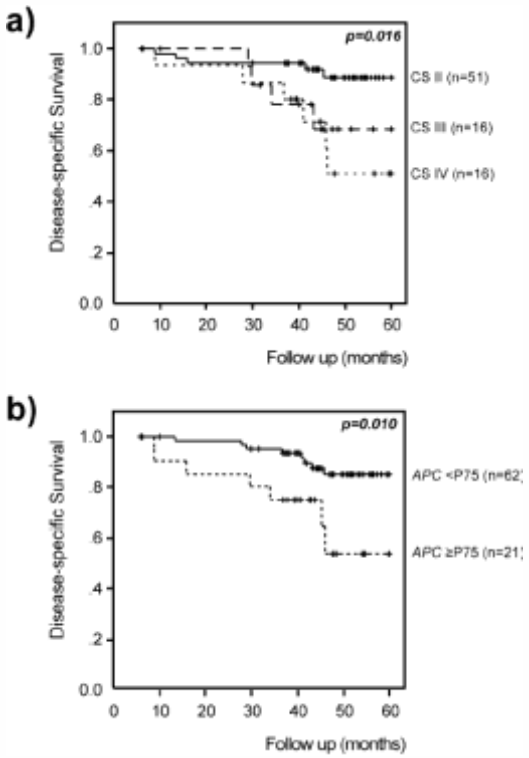


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Table 3. Cox regression models assessing the potential of clinical and epigenetic variables in the prediction of disease-specific or disease-free survival for 83 PCa patients

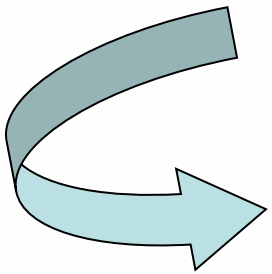
Model tested	Variables*	OR	95% CI for OR	*P*
Disease-specific survival	CS = IV versus CS = II	5.03	1.53-16.51	0.008
	APC methylation ≥ P75	3.51	1.23-9.96	0.018
Disease-free survival	CS = III versus CS = II	2.66	1.19-5.94	0.017
	CS = IV versus CS = II	3.09	1.40-6.82	0.005
	APC methylation ≥ P75	2.58	1.29-5.16	0.008

Abbreviations: OR, odds ratio; CS, clinical stage; CI, confidence interval; P75, percentile 75 for methylation level.
*Only variables displaying independent prognostic information in the final step of each model (forward conditional setting) are displayed.

Clinical stage and *APC* high-methylation levels are independent predictors of outcome

Epigenetic alterations in Prostate cancer: Histone modifications

- Overexpression of enzymes involved in the modification of histone tails:
  - HDAC1 (histone deacetylase 1)
    - Global deacetylation
  - EZH2 (enhancer of zeste homolog 2)
    - Histone-lysine N-methyltransferase (H3K27me3)
    - Member of the Polycomb group family
  - LSD1(lysine-specific demethylase 1)
    - Removes methyl groups from H3K4



Associated with aggressive forms of Prostate cancer

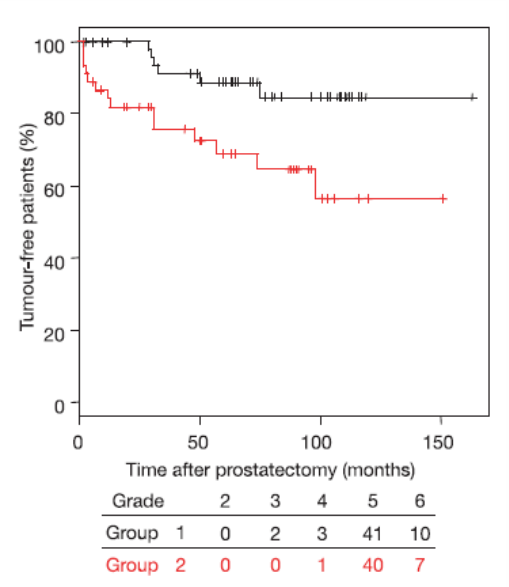
Epigenetic alterations in Prostate cancer: Histone modifications

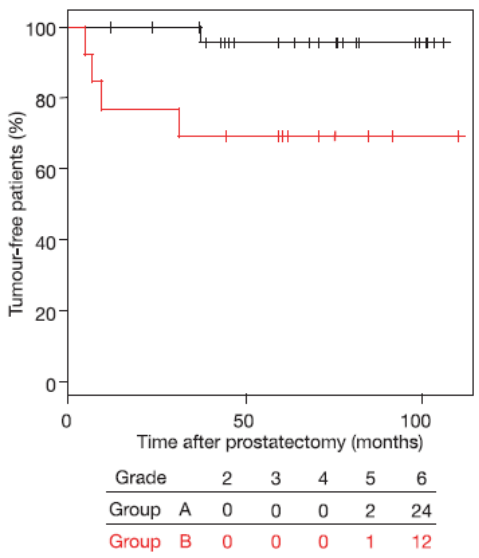
nature
LETTERS

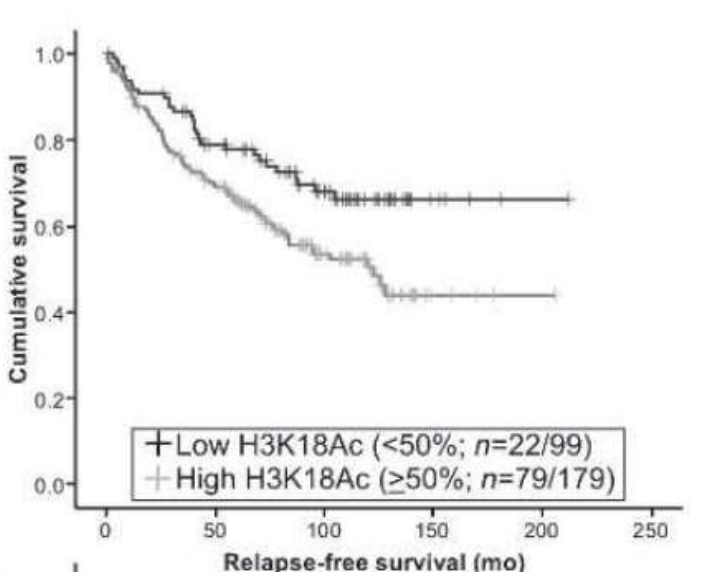
Global histone modification patterns predict risk of prostate cancer recurrence

Research Article
Cancer Epidemiology, Biomarkers & Prevention

Global Levels of Specific Histone Modifications and an Epigenetic Gene Signature Predict Prostate Cancer Progression and Development



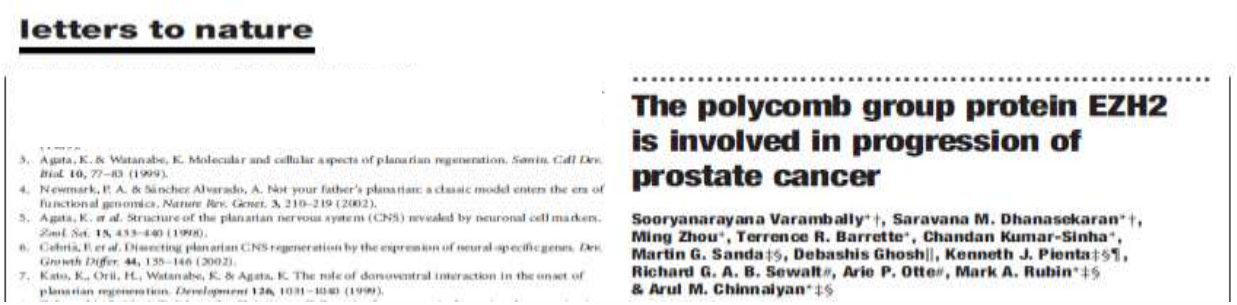




- **Prognostic value of histone modifications, especially H3K18Ac, were largely confined to less-aggressive or early-stage cancers, including low Gleason score prostate cancer**

- **H3K18Ac was associated with relapse-free survival**
- **H3K18Ac levels were independent predictors of PSA relapse**

Epigenetic alterations in Prostate cancer: Histone modifications



letters to nature

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The polycomb group protein EZH2 is involved in progression of prostate cancer

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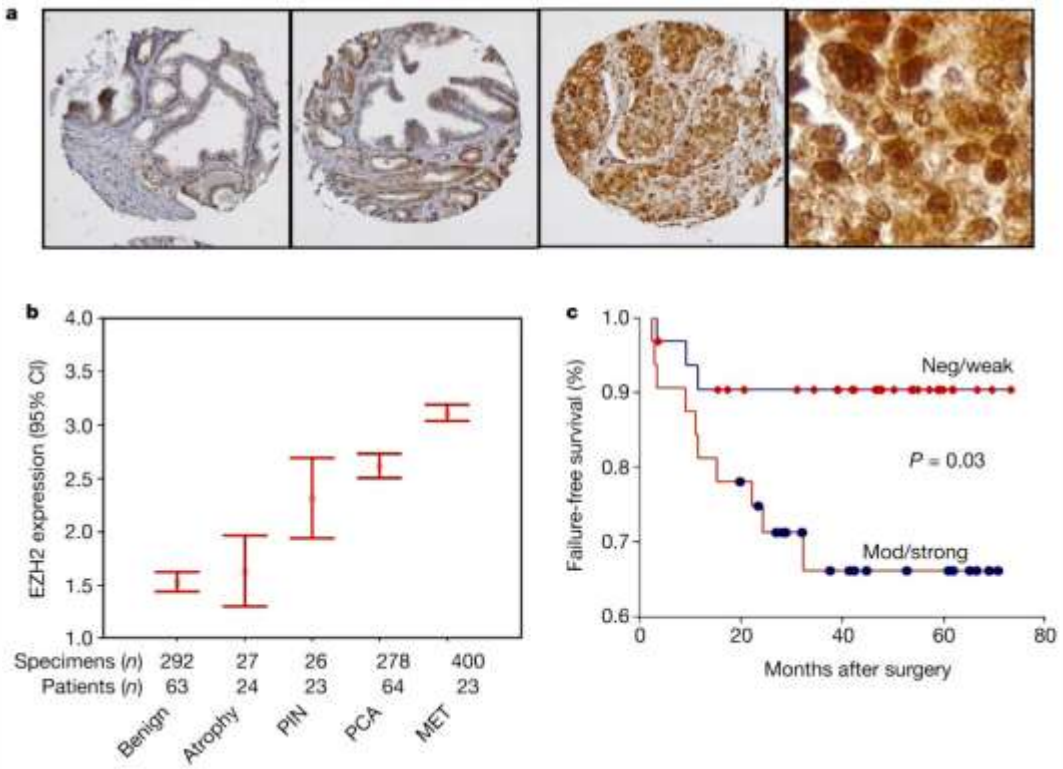
n = 1023

- EZH2 mRNA and protein are increased in metastatic prostate cancer

- Clinically localized prostate cancers that express higher levels of EZH2 have a poorer prognosis



Epigenetic alterations in Prostate cancer: Histone modifications

Int. J. Cancer: **122**, 595–602 (2008)
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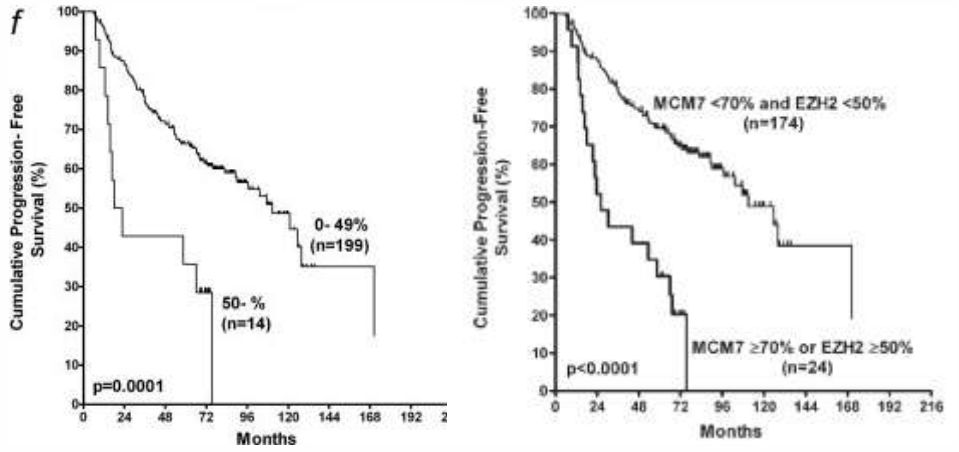
EZH2, Ki-67 and MCM7 are prognostic markers in prostatectomy treated patients

Sari Laitinen[1], Paula M. Martikainen[2], Teemu Tolonen[2], Jorma Isola[1], Teuvo L.J. Tammela[3] and Tapio Visakorpi[1]*



Variable	EZH2, *n* (%)		
	0-49%	50%	*p*-value
Gleason score			
<7	76/81 (94)	5/81 (6)	
7	98/101 (97)	3/101 (3)	
>7	20/26 (77)	6/26 (23)	0.0012
pT-score			
pT2	135/143 (94)	8/143 (6)	
pT3	63/69 (91)	6/69 (9)	0.3943
PSA			
Mean	15.8	34.5	
SD	12.9	65.3	0.0017
Age			
Mean	63.3	62.2	
SD	4.8	5.0	0.4055

- Increased EZH2 was significantly associated with a higher Gleason score and a shorter progression-free survival

- EZH2 is a potential prognostic biomarker in PCa patients submitted to radical prostatectomy

Epigenetic alterations in Prostate cancer: miRNAs

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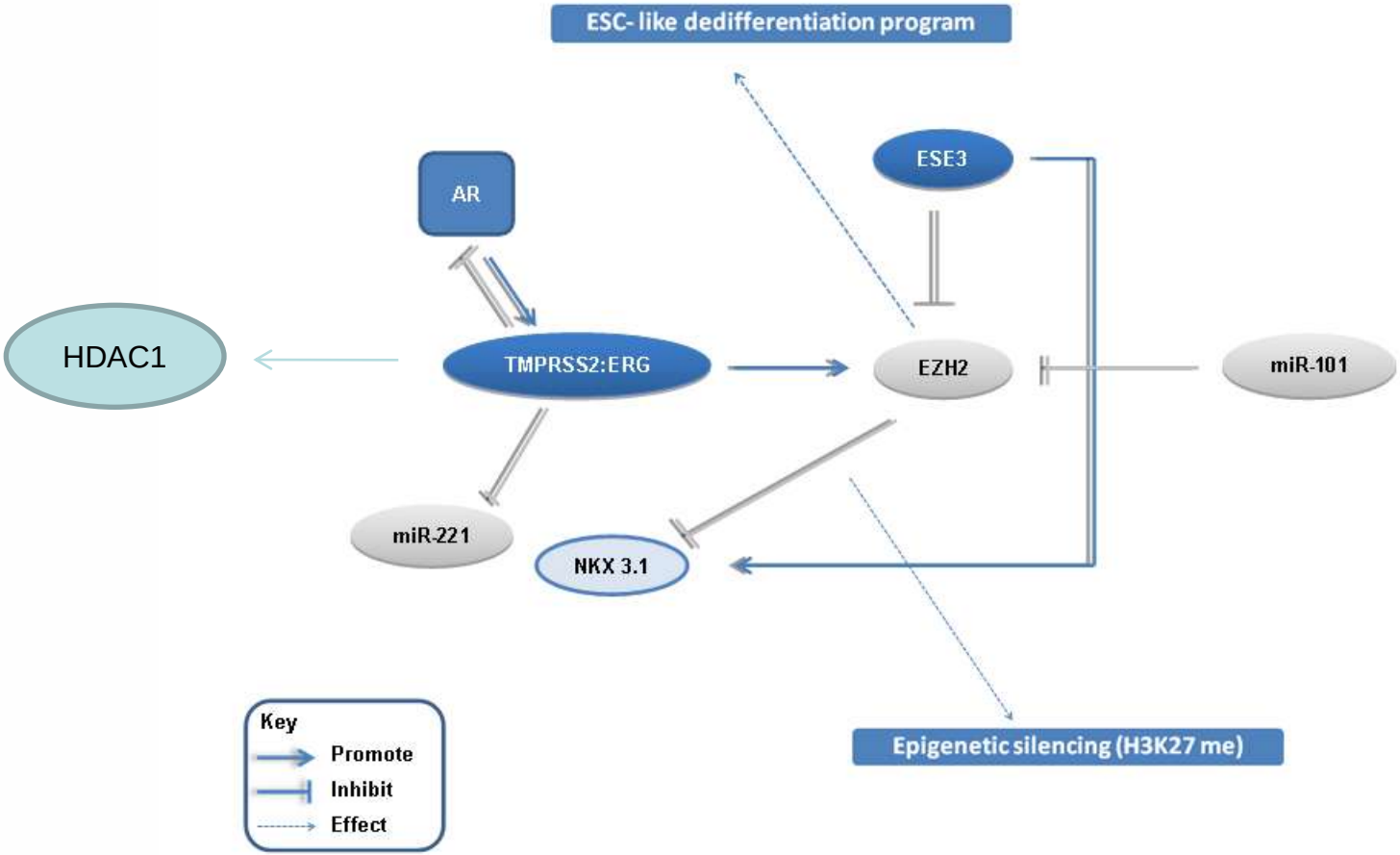
Table 1 – MicroRNA (miRNA) expression in prostate cancer. A summary of miRNAs with altered expression, including their targeted messenger RNAs and pathways

MiRNA	Expression	MRNA target	Pathway	Reference
PCa:				
miR-20a	Up	E2F1-3	Apoptosis	[22]
miR-21	Up	PTEN, AKT, androgen pathway	Apoptosis, mTOR pathway, androgen independence	[23,35]
miR-24	Up	FAF1	Apoptosis	[77]
miR-32	Up	BCL2L11(Bim)	Apoptosis	[16]
miR-106b	Up	P21, E2F1	Cell cycle control/apoptosis and proliferation	[16,78]
miR-125b	Up	P53, BBC3(Puma), BAK1	Apoptosis	[34]
miR-148a	Up	CAND1	Cell cycle control	[79]
miR-221	Up	p27(kip1)	Cell cycle control and androgen independence	[29,39]
miR-222	Up	p27(kip1)	Cell cycle control and androgen independence	[29,39]
miR-521	Up	Cockayne syndrome protein A	DNA repair	[31]
miR-1	Down	Exportin-6, tyrosine kinase 9	Gene expression	[16]
miR-7	Down	ERBB-2 (EGFR, HER2)	Signal transduction	[80]
miR-15a-16 cluster	Down	CCND1 and WNT3a	Cell cycle regulation, apoptosis and proliferation	[30]
miR-34a	Down	HuR/Bcl2/SIRT1->p53/p21/BBC3	Apoptosis and drug resistance	[6,27]
miR-34c	Down	E2F3, bcl2	Apoptosis and proliferation	[28]
miR-101	Down	EZH2	Gene expression	[13]
miR-107	Down	Granulin	Proliferation	[81]
miR-143	Down	MYO6, ERK5	Cell migration, proliferation	[82,83]
miR-145	Down	MYO6, BNIP3L->AIFM1, CCNA2, TNFSF10	Cell migration, apoptosis, cell cycle control	[75,82]
miR-146a	Down	ROCK1	–	[36]
miR-148a	Down	MSK1	Proliferation, stress response and drug resistance	[84]
miR-205	Down	IL-24 and IL-32, Cepsilon	Cell growth and invasion, EMT	[23,85]
miR-331-3P	Down	ERBB-2, CDCA5, KIF23	Signal transduction, cell cycle control	[41,42]
miR-449a	Down	HDAC-1	Gene expression	[86]
miR-1296	Down	MCM family	DNA replication	[87]
Let-7a	Down	E2F2 and CCND2	Cell cycle control and proliferation	[88]

MiRNA = microRNA; mRNA = messenger RNA; PCa = prostate cancer; PTEN = phosphatase and tensin homologue; mTOR = mammalian target of rapamycin; IL = interleukin; EMT = epithelial-to-mesenchymal transition.

Catto et al., 2011

ETS - Polycomb group proteins and ETS - miRNA crosstalk



Jerónimo et al., 2011 (in press)

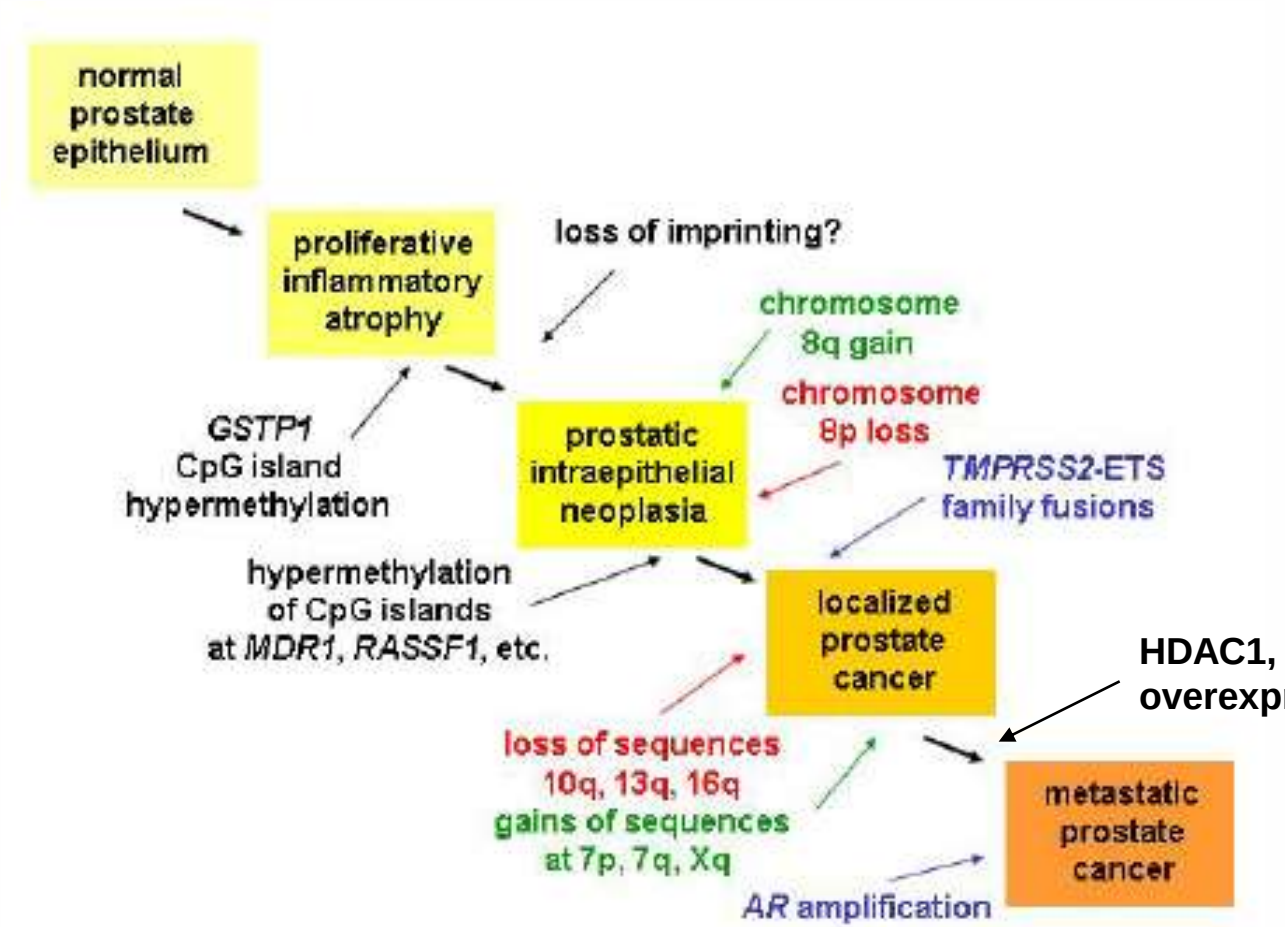
Interplay among epigenetic mechanisms

- miRNAs downregulated due to hypermethylation:
  - miR21, miR34a, miR126, miR145, miR193b, miR191b, miR205
- miRNAs upregulated due to hypomethylation:
  - miR615

- Up to a third of transcriptionally deregulated miRNA loci display a concordant pattern of DNA methylation and H3K9 acetylation

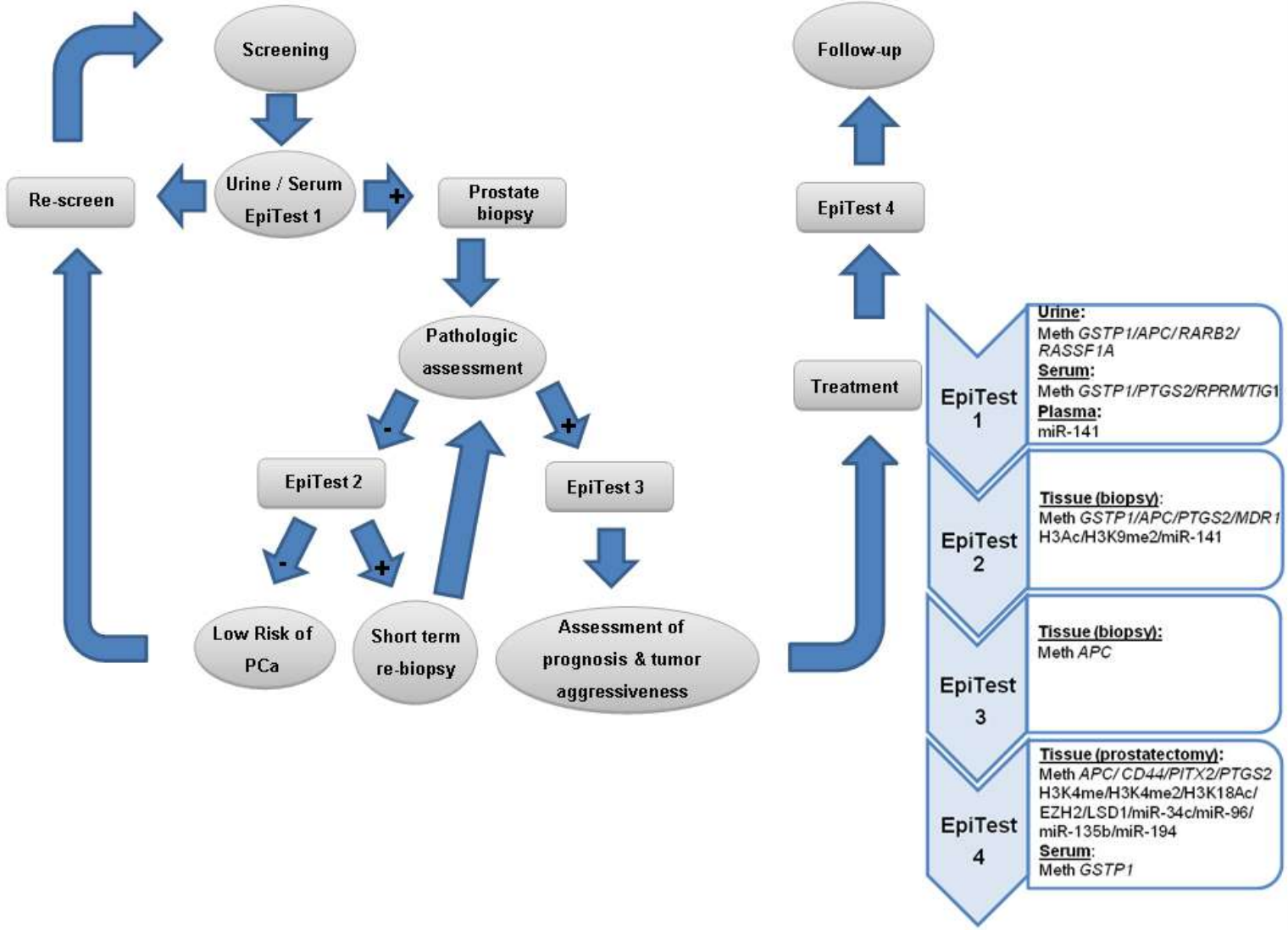
- miRNAs targeting genes that encode for histone modifying enzymes:
  - miR449a (target: HDAC1) and miR101 (target: EZH2) are downregulated in prostate cancer

An integrated progression model for Prostate cancer



Nelson et al., 2007

Epigenetic biomarkers for Prostate cancer management



Jerónimo et al., 2011 (in press)

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XXV Congreso de la SEAP-IAP, Zaragoza, 2011

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Muchas gracias!