

ELMER 2.0

An R/Bioconductor package to reconstruct gene regulatory networks from DNA methylation and transcriptome profiles

Tiago Chedraoui Silva
RECOMB-CBB

University of São Paulo / Cedar-Sinai

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- 3 Methods: Algorithms and tools
- 4 Analysis
- 5 Conclusion

Enhancer Linking by Methylation/Expression Relationship

ELMER 2.0

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Bioinformatics

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Systems Biology



Systems Biology

ELMER 2.0: An R/Bioconductor package to reconstruct gene regulatory networks from DNA methylation and transcriptome profiles

Tiago Chedraoui Silva ^{1,2}, Simon G Coetzee ², Lijing Yao ³, Nicole Yeager ², Dennis J Hazelett ², Houtan Noushmehr ⁵, De-Chen Lin ^{4,*}, Benjamin P Berman ^{2,4,*}

¹Department of Genetics, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil.

²Center for Bioinformatics and Functional Genomics, Cedars-Sinai Medical Center, Los Angeles, CA USA

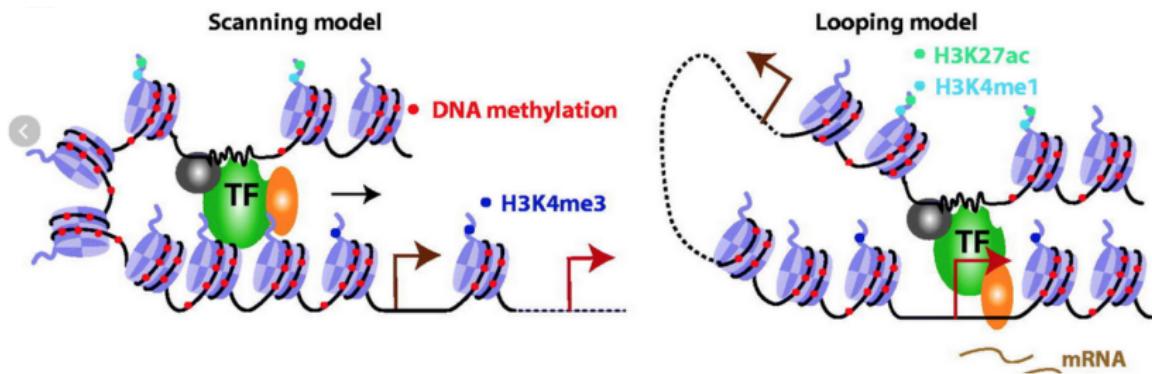
³ BioTech Sequencing Solutions, Belmont, CA, USA.

⁴ Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA and

⁵ Department of Neurosurgery, Henry Ford Hospital, Detroit, MI, USA

* To whom correspondence should be addressed.

Enhancer-mediated gene regulation

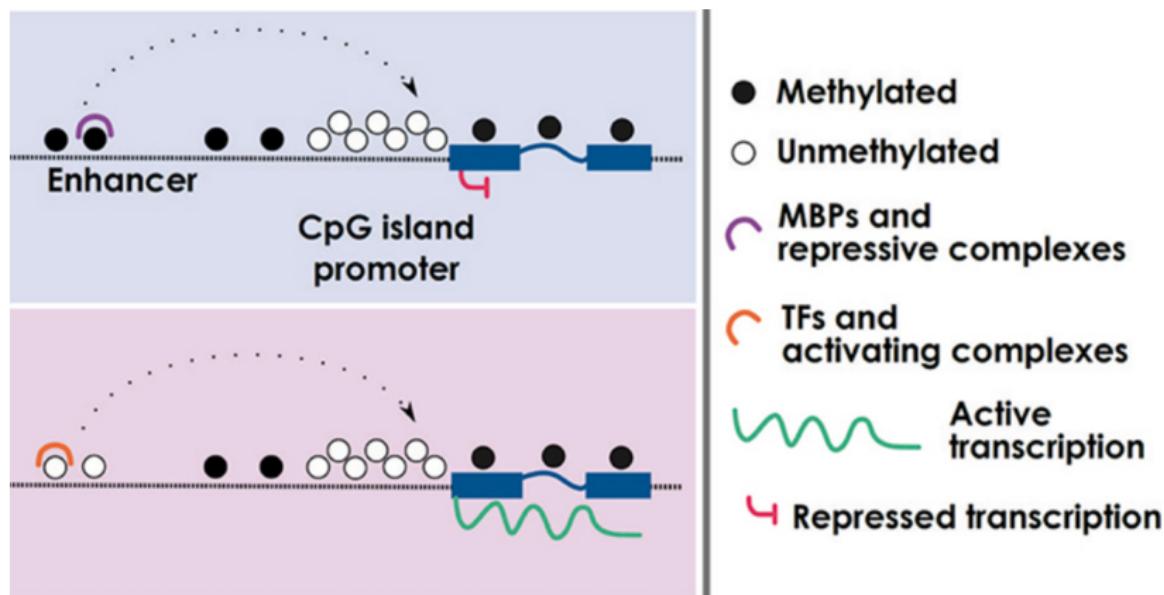


Source: Yao et al. Genome Biology (2015)

Enhancer-mediated gene regulation

- 73% of the tested distal elements do not link to the nearest gene (Sanyal et al., 2012)
 - 40% of the enhancers involved in loops do not interact with the TSS of the nearest gene (Li et al., 2012),
 - one-third of the distal interactions were not directed to the promoter of the nearest gene (Mifsud et al., 2015),
 - 85% of tumor-specific enhancers that could be linked to the expression of a nearby gene skipped the nearest gene (Yao et al., 2015).

Enhancer-mediated gene regulation



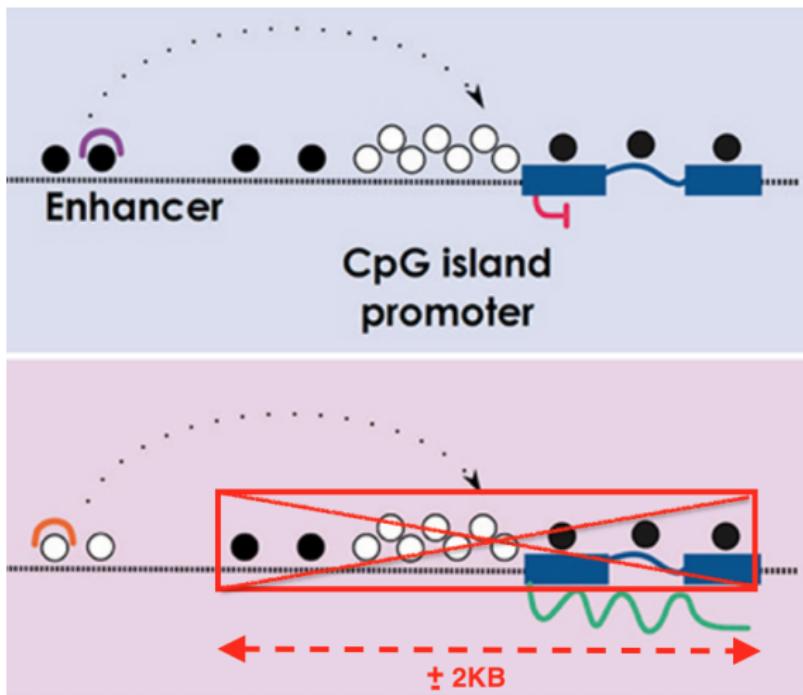
Source: Carrio et al. Frontiers in aging neuroscience (2015)

Algorithm

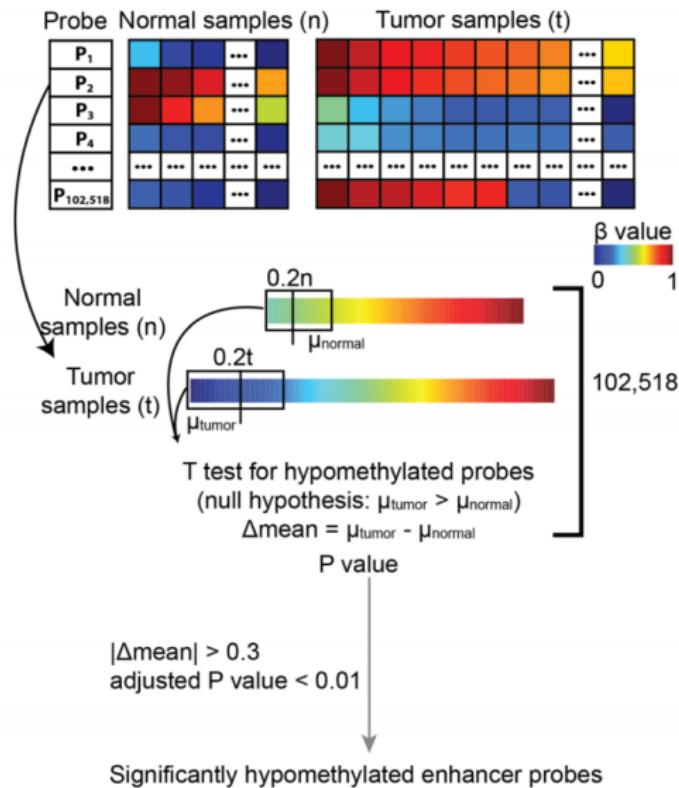
Steps

- ① Identify distal probes on HM450K/EPIC.
 - ② Identify distal probes with significantly different DNA methylation level in group 1 compared to group 2.
 - ③ Identify putative target genes for differentially methylated distal enhancer probes.
 - ④ Identify enriched motifs for the distal probes which are significantly differentially methylated and linked to a putative target gene.
 - ⑤ Identify regulatory TFs whose expression associate with DNA methylation at motifs.

Step 1: Identify distal probes

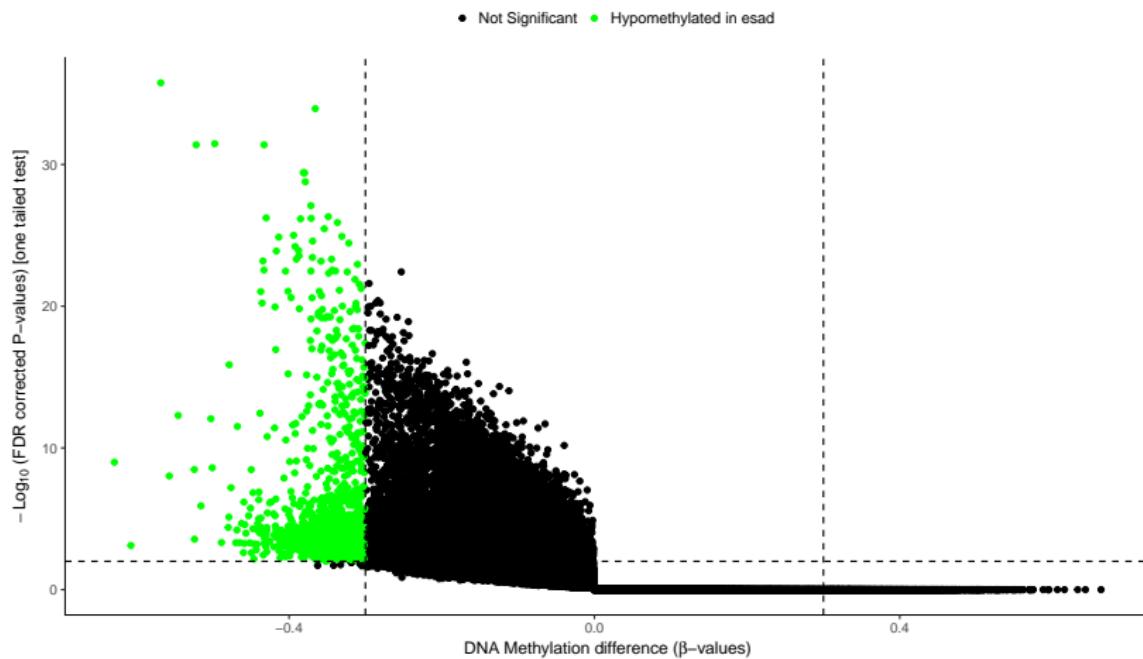


Step 2: Differentially methylated distal probes

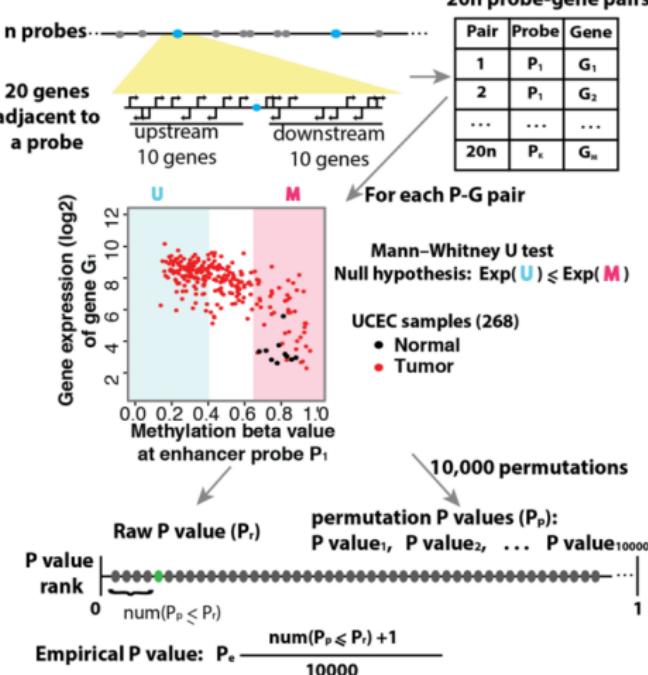
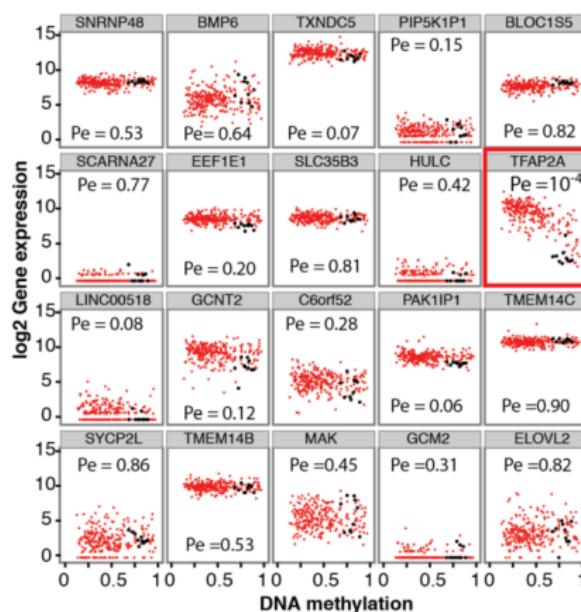


Step 2: Differentially methylated distal probes

Volcano plot – Probes hypomethylated in esad vs normal



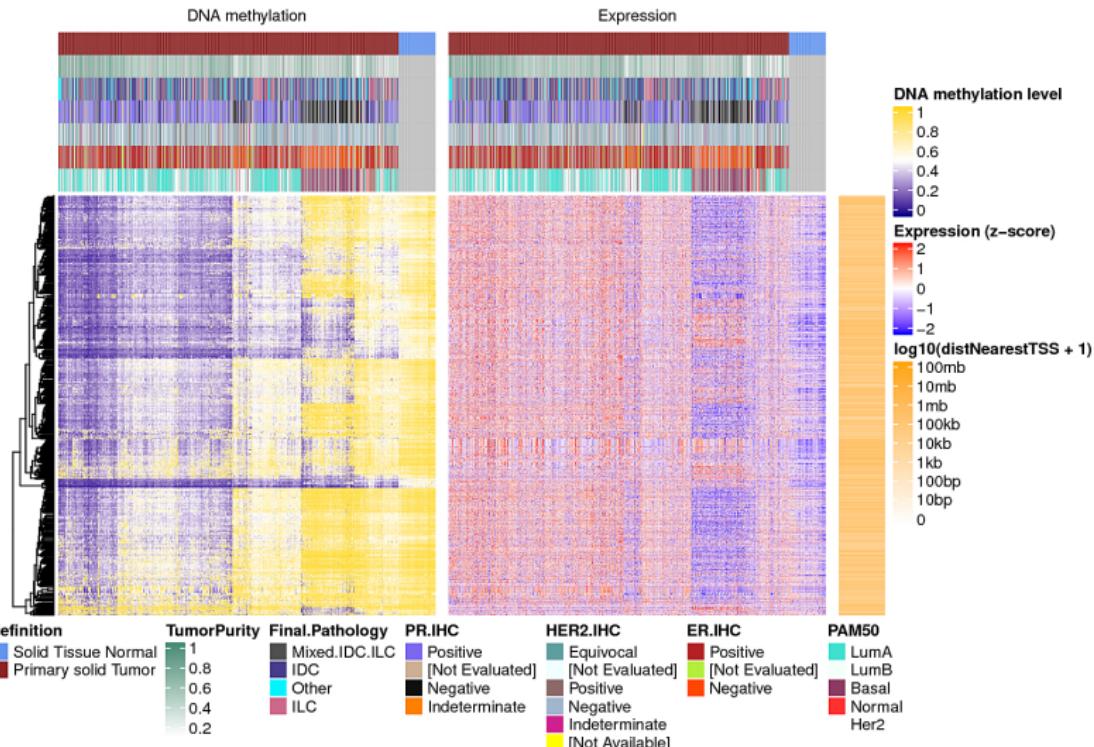
Step 3: Identification of putative target gene(s)

A**B**

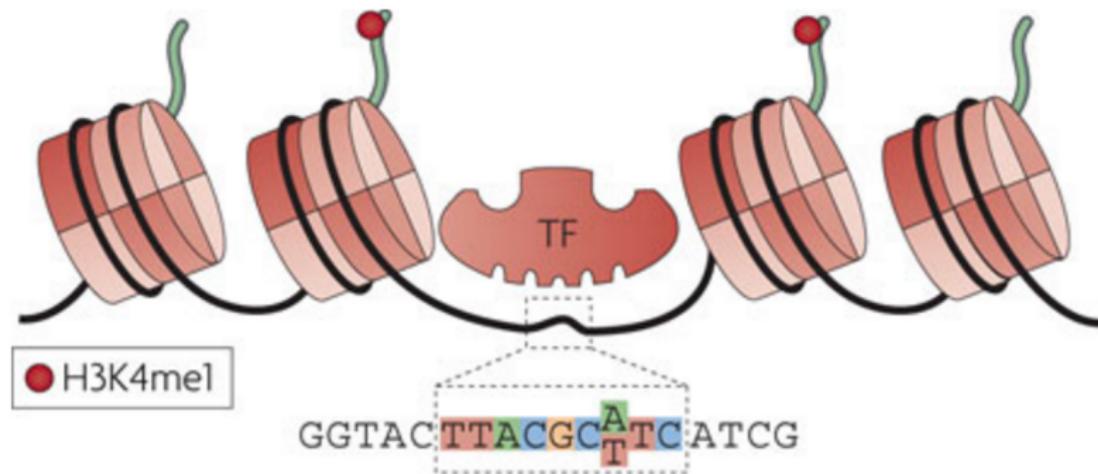
Source: Yao et al. Genome Biology (2015)

Step 3: Probe-target gene pairs inferred

Correspondence between probe DNA methylation and distal gene expression



Step 4: Motif enrichment analysis



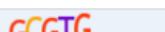
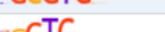
Nature Reviews | Genetics

Hawkins RD, et al. Next-generation genomics: an integrative approach. Nature Reviews Genetics (2010)

Step 4: TF motifs source

HOCOMOCO Home Human TFs Mouse TFs Tools Downloads Help

Switch to CORE collection Reset Select Columns Get CSV HUMAN_mono_motifs.tsv PWMs for HUMAN transcription factors (full)

Model	LOGO	Transcription factor	Quality	TF family	TF subfamily
ASCL1_HUMAN.H11MO.0.A		ASCL1 (GeneCards)	A	MyoD / ASC-related factors[1.2.2]	Achaete-Scute-like factors[1.2.2.2]
ASCL2_HUMAN.H11MO.0.D		ASCL2 (GeneCards)	D	MyoD / ASC-related factors[1.2.2]	Achaete-Scute-like factors[1.2.2.2]
AHR_HUMAN.H11MO.0.B		AHR (GeneCards)	B	PAS domain factors[1.2.5]	Ahr-like factors[1.2.5.1]
EPAS1_HUMAN.H11MO.0.B		EPAS1 (GeneCards)	B	PAS domain factors[1.2.5]	Ahr-like factors[1.2.5.1]
HIF1A_HUMAN.H11MO.0.C		HIF1A (GeneCards)	C	PAS domain factors[1.2.5]	Ahr-like factors[1.2.5.1]
AIRE_HUMAN.H11MO.0.C		AIRE (GeneCards)	C	AIRE[5.3.1]	AIRE[5.3.1.0.1]
ALX1_HUMAN.H11MO.0.B		ALX1 (GeneCards)	B	Paired-related HD factors[3.1.3]	ALX[3.1.3.1]
ALX3_HUMAN.H11MO.0.D		ALX3 (GeneCards)	D	Paired-related HD factors[3.1.3]	ALX[3.1.3.1]
ALX4_HUMAN.H11MO.0.D		ALX4 (GeneCards)	D	Paired-related HD factors[3.1.3]	ALX[3.1.3.1]
AP2A_HUMAN.H11MO.0.A		TFAP2A (GeneCards)	A	AP-2[1.3.1]	AP-2alpha[1.3.1.0.1]
AP2B_HUMAN.H11MO.0.B		TFAP2B (GeneCards)	B	AP-2[1.3.1]	AP-2beta[1.3.1.0.2]
AP2D_HUMAN.H11MO.0.D		TFAP2D (GeneCards)	D	AP-2[1.3.1]	AP-2delta[1.3.1.0.4]
AP2C_HUMAN.H11MO.0.A		TFAP2C (GeneCards)	A	AP-2[1.3.1]	AP-2gamma[1.3.1.0.3]

Step 4: Motif enrichment analysis

Objective

Evaluate the enrichment of transcription factors in certain genomic regions.

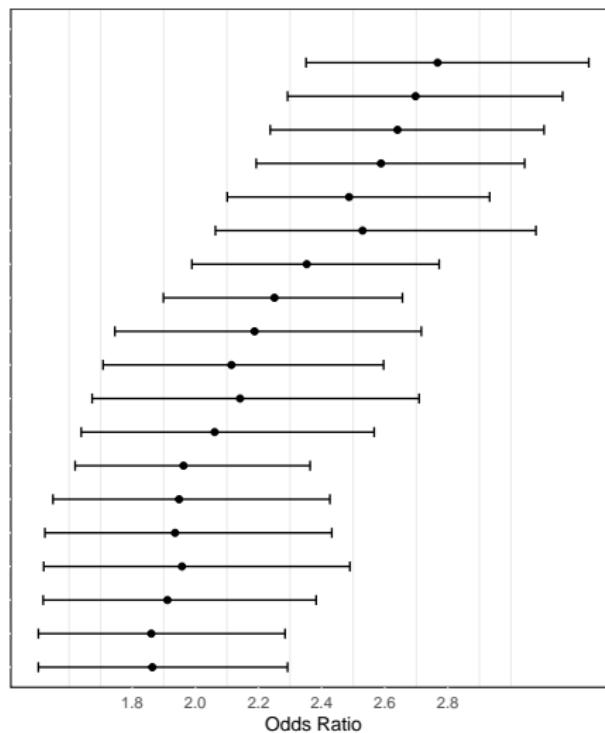
- ① Perform motif matching of transcription factors in probes regions (window $\pm 250\text{bp}$). Performed using HOMER (Hypergeometric Optimization of Motif EnRichment) with HOCOMOCO motifs.
- ② Evaluate which transcription factors are more likely to occur in those regions than in background regions using Fisher's exact test with FDR correction.

Fisher's exact test

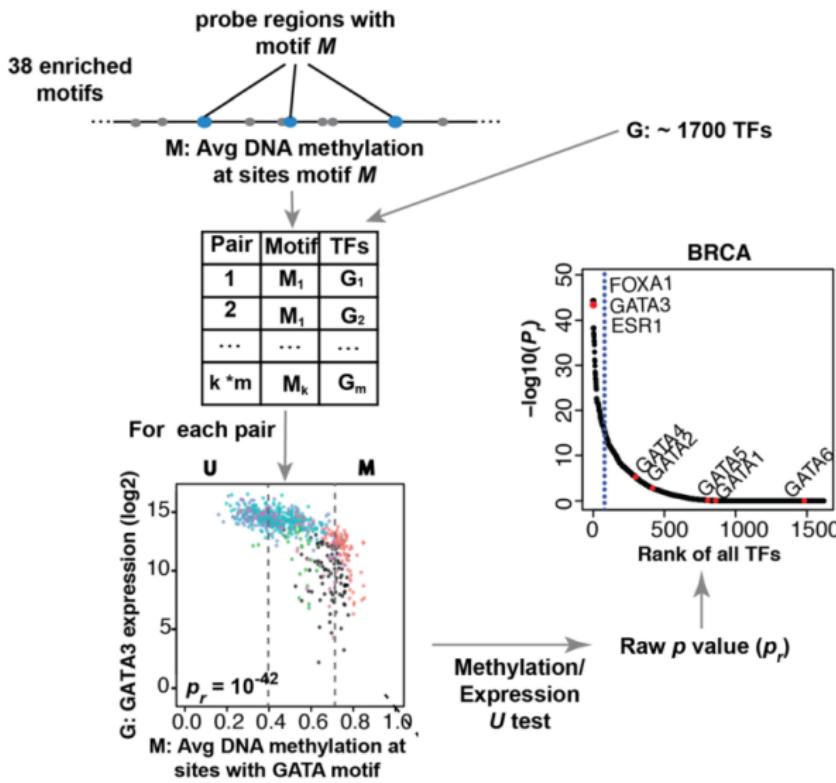
- a: nb of input regions with a match for TF motif.
- b: nb of input regions with no match for TF motif.
- c: nb of background regions with a match for TF motif.
- d: nb of background regions with no match for TF motif.

Step 4: Motif enrichment analysis

Motif	Odds ratio (95% CI)	# probes (% of paired)
FOSL2	2.77 (2.35–3.25)	201 (0.23%)
FOSL1	2.7 (2.29–3.16)	202 (0.23%)
FOSB	2.64 (2.24–3.1)	193 (0.22%)
FOS	2.59 (2.19–3.04)	193 (0.22%)
JUN	2.49 (2.1–2.93)	184 (0.21%)
BATF	2.53 (2.06–3.08)	118 (0.13%)
JUND	2.35 (1.99–2.77)	186 (0.21%)
JUNB	2.25 (1.9–2.66)	181 (0.2%)
HXB13	2.19 (1.74–2.72)	94 (0.11%)
PIT1	2.11 (1.71–2.6)	106 (0.12%)
PRRX1	2.14 (1.67–2.71)	78 (0.09%)
CDX1	2.06 (1.64–2.57)	91 (0.1%)
LMX1A	1.96 (1.62–2.36)	134 (0.15%)
BATF	1.95 (1.55–2.43)	91 (0.1%)
NKX32	1.94 (1.52–2.43)	83 (0.09%)
HME1	1.96 (1.52–2.49)	74 (0.08%)
IRX3	1.91 (1.52–2.38)	90 (0.1%)
PO4F3	1.86 (1.5–2.28)	106 (0.12%)
PO4F1	1.86 (1.5–2.29)	104 (0.12%)



Step 5: Identification of master regulator TF



Source: Yao et al. *Genome Biology* (2015).

Step 5: Master Regulator TF table

motif	OR	top.potential.TF.family	pvalue.TF.family	top.potential.TF.subfamily	pvalue.TF.subfamily
All		All	All	All	All
HXB13_HUMAN.H11MO.0.A	2.19	HOXB7	6.39e-7	HOXA13	0.00000105
CDX1_HUMAN.H11MO.0.C	2.06	HOXB7	6.39e-7	CDX2	8.20e-7
HXD9_HUMAN.H11MO.0.D	1.98	HOXB7	6.39e-7	HOXA13	0.00000105
PDX1_HUMAN.H11MO.1.A	1.89	HOXB7	6.39e-7	PDX1	0.0000355
HXC11_HUMAN.H11MO.0.D	1.84	HOXB7	6.39e-7	HOXA13	0.00000105
HXB6_HUMAN.H11MO.0.D	1.84	HOXB7	6.39e-7	HOXB7	6.39e-7
HXD8_HUMAN.H11MO.0.D	1.84	HOXB7	6.39e-7	HOXC8	0.00000134
CDX2_HUMAN.H11MO.0.A	1.83	HOXB7	6.39e-7	CDX2	8.20e-7
HXD12_HUMAN.H11MO.0.D	1.77	HOXB7	6.39e-7	HOXA13	0.00000105
HXC9_HUMAN.H11MO.0.C	1.74	HOXB7	6.39e-7	HOXA13	0.00000105

Showing 1 to 10 of 31 entries

Previous

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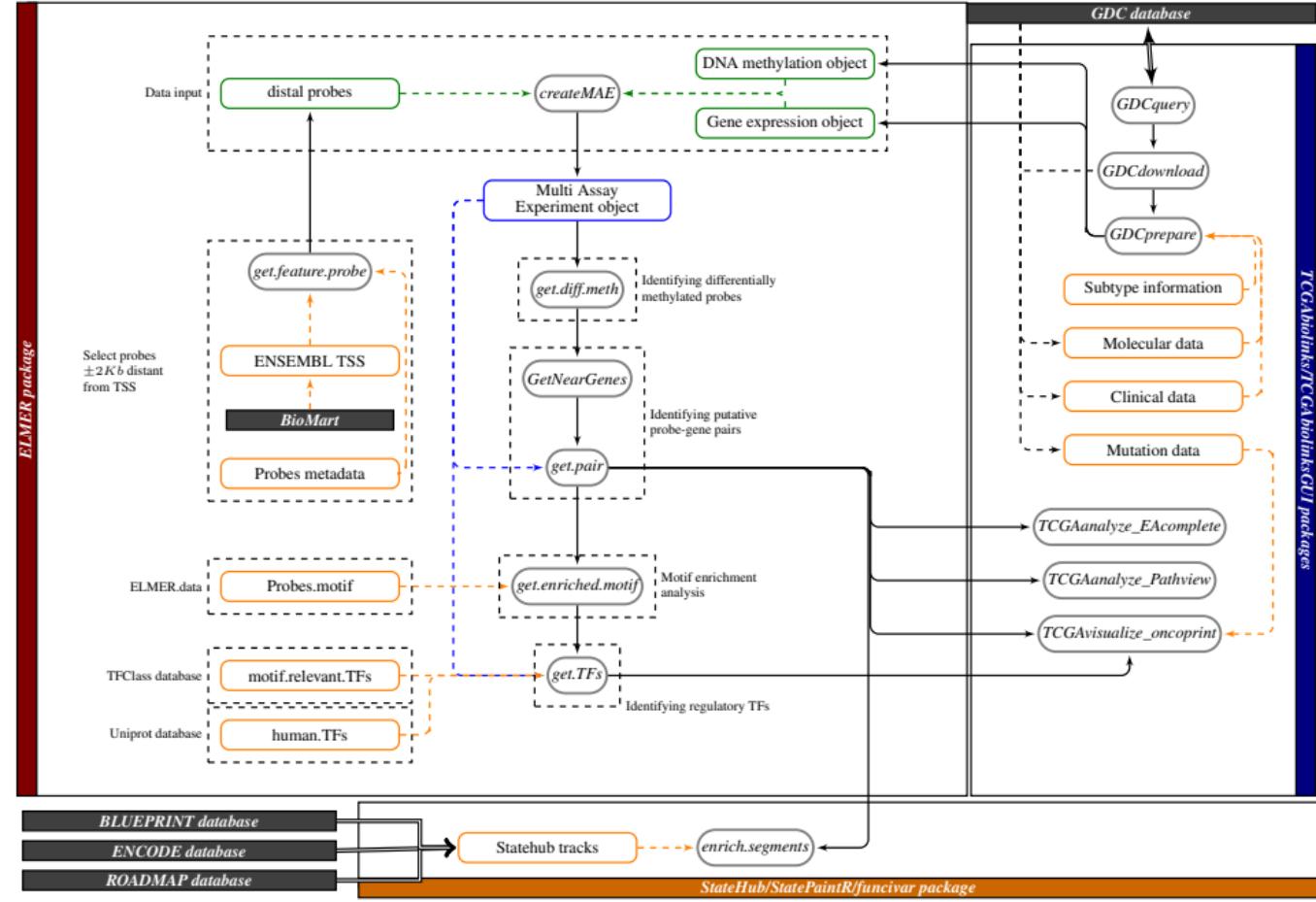
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Next

Main differences between ELMER old version (v.1) and the new version (v.2)

Features	ELMER Version 1	ELMER Version 2
Primary data structure	mee object (custom data structure)	MAE object (Bioconductor data structure)
Auxiliary data	Manually created	Programmatically created
Number of human TFs	1,982	2,014 (UniProt database)
Number of TF motifs	91	771 (HOCOMOCO v11 database)
TF classification	78 families	82 families and 331 subfamilies (TFClass database, HOCOMOCO)
Analysis performed	Normal vs tumor samples	Group 1 vs group 2
Statistical grouping	Unsupervised only	Unsupervised or supervised using labeled groups
TCGA data source	The Cancer Genome Atlas (TCGA)	The NCI's Genomic Data Commons (GDC)
Genome of reference	GRCh37 (hg19)	GRCh37 (hg19)/GRCh38 (hg38)
DNA methylation platforms	HM450	EPIC and HM450
Graphical User Interface (GUI)	None	TCGAbiolinksGUI
Automatic report	None	HTML summarizing results
Annotations	None	StateHub



Difference of groups U and M definition in supervised and unsupervised mode

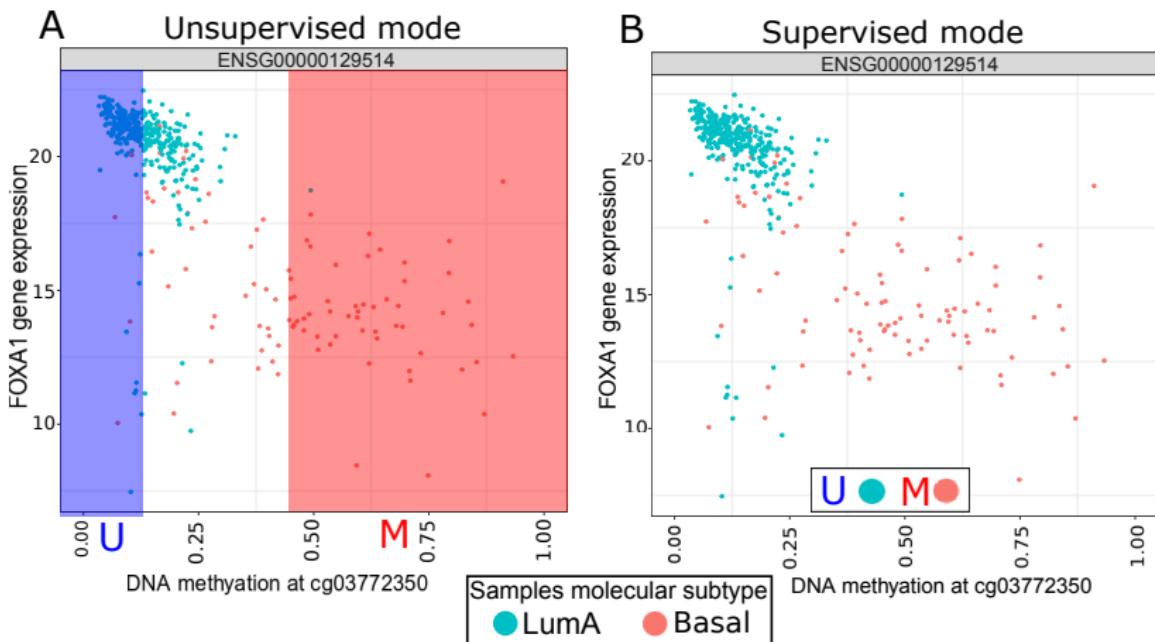


Figure: A: *unsupervised* mode; when minSubgroupFrac argument is set to 40%, the methylated group is defined as the highest quintile and the unmethylated group as the lowest quintile; B: *supervised* mode; methylated and unmethylated group are defined as one of the known molecular subtypes.

Case study: TCGA Breast Invasive Carcinoma (BRCA)

Table: Summary of the available samples in TCGA for BRCA

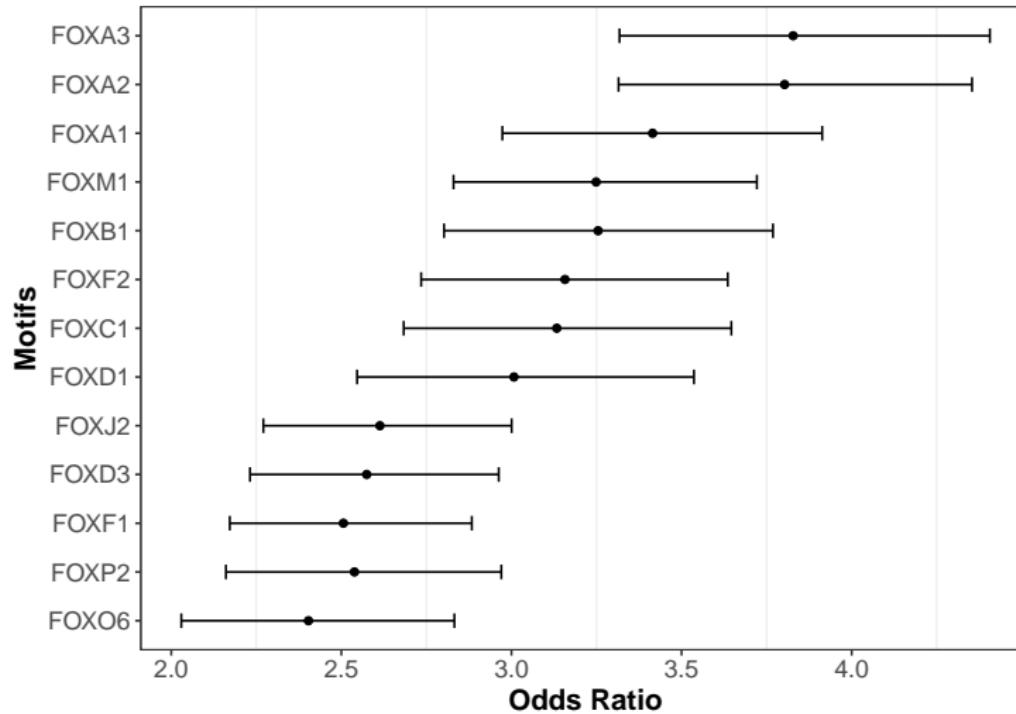
Group	Samples w/ methylation (450K)	Samples w/ gene ex- pression (FPKM-UQ)	Samples w/ both
Primary solid Tumor	791	1102	778
Solid Tissue Normal	96	113	83

Table: Results supervised mode

Inferred gene-probe pairs	2167
Enriched motifs	312
Master Regulator TF	17

Top enriched motifs

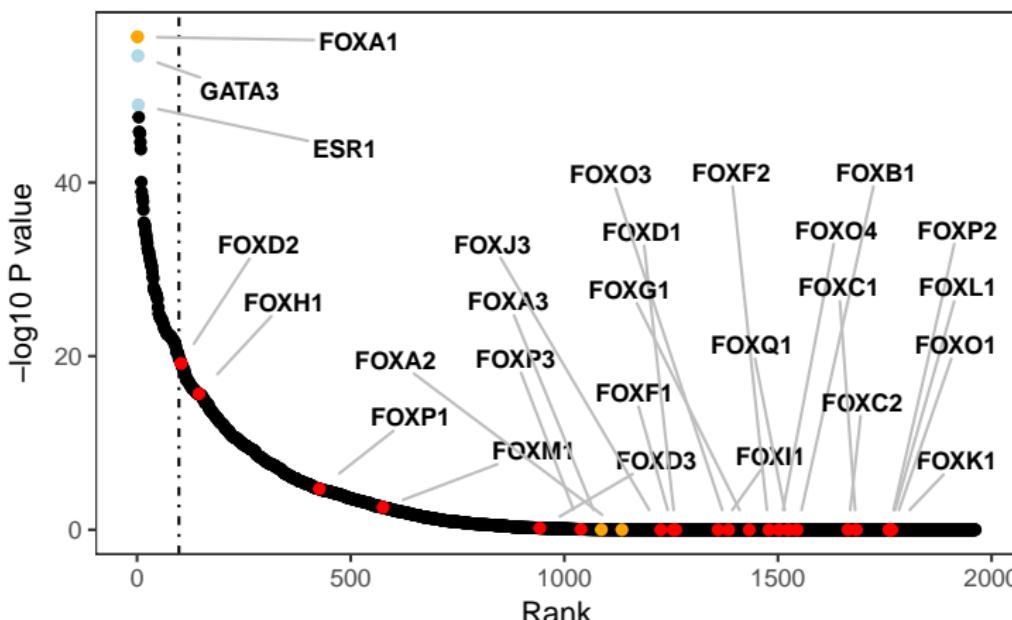
Probes hypomethylated in Primary solid Tumor vs Solid Tissue Normal



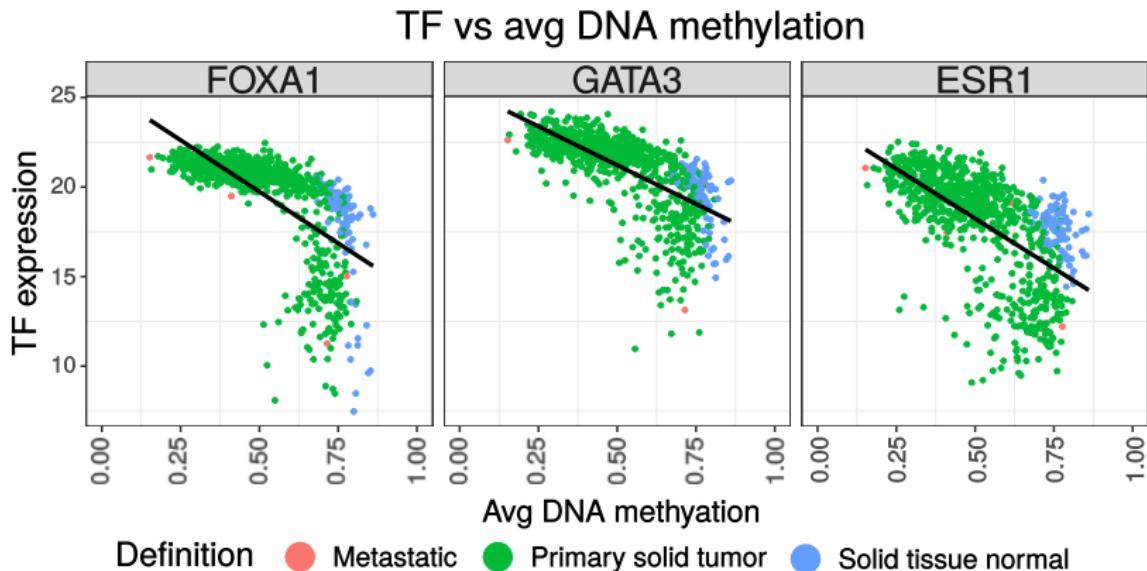
TF ranking plot - FOXA3 motif

Motif: FOXA3

TF classification • None • Same family • Same subfamily • Top 3



DNA methylation at motifs vs TF expression





Candidate master regulator TF

RESEARCH ARTICLE | OPEN ACCESS

Expression of FOXA1 and GATA-3 in breast cancer: the prognostic significance in hormone receptor-negative tumours

André Albergaria, Joana Paredes, Bárbara Sousa, Fernanda Milanezi, Vítor Carneiro, Joana Bastos, Sandra Costa, Daniella Vieira, Nair Lopes, Eric W Lam, Nuno Lunet and Fernando Schmitt

Breast Cancer Research 2009 11:R40 | DOI: 10.1186/bcr2327 | © Albergaria et al.; licensee BioMed Central Ltd. 2009

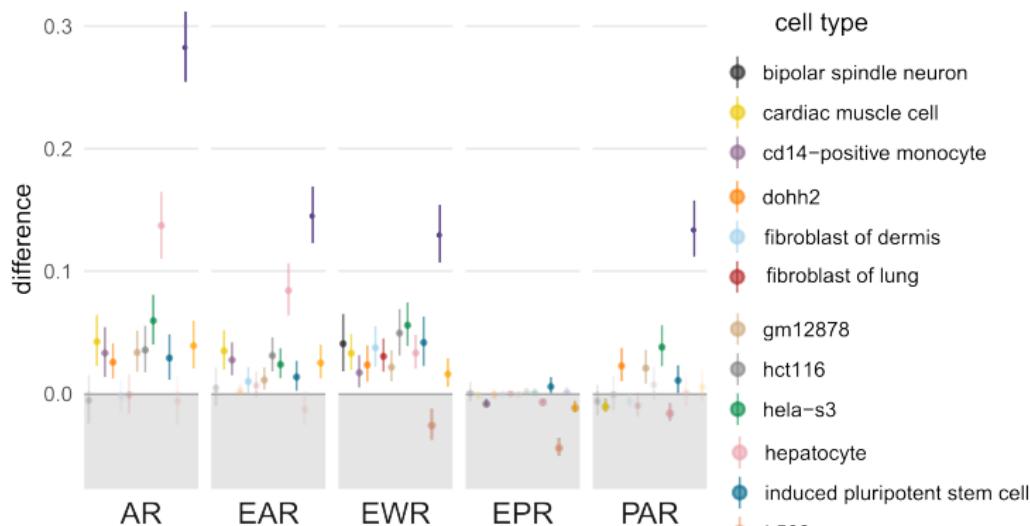
Received: 5 January 2009 | Accepted: 23 June 2009 | Published: 23 June 2009

Article | [OPEN](#)

Retinoic acid receptor alpha is associated with tamoxifen resistance in breast cancer

Henrik J. Johansson, Betzabe C. Sanchez, Filip Mundt, Jenny Forshed, Aniko Kovacs, Elena Panizza, Lina Hultin-Rosenberg, Bo Lundgren, Ulf Martens, Gyöngyvér Máthé, Zohar Yakhini, Khalil Helou, Kamilla Krawiec, Lena Kanter, Anders Hjerpe, Olle Stål, Barbro K. Linderholm & Janne Lehtio

Characterization of chromatin state context of enriched probes using FunciVar



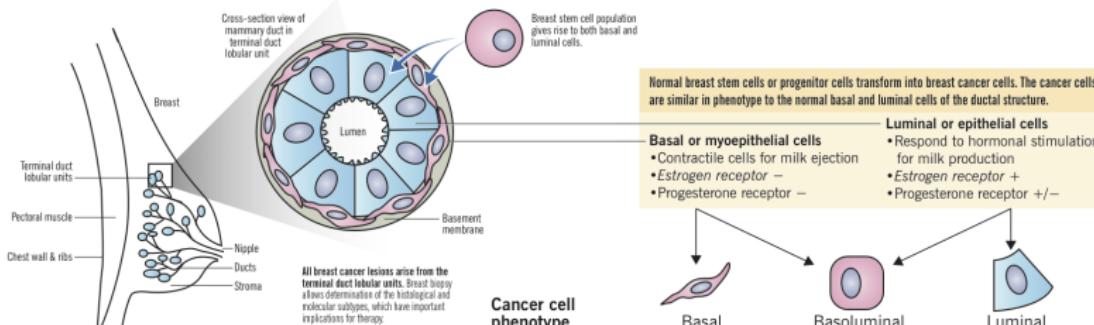
Acronyms

- AR: Active region
EAR: active enhancer
EWR: Weak Enhancer
EPR: poised enhancer
PAR: active promoter

Supervised analysis: BRCA molecular subtypes

Breast cancer pathogenesis and histologic vs. molecular subtypes

Eric Wong and Jemma Rebello



Histological subtypes	Ductal	Lobular	Cancer cell phenotype	Molecular subtypes
Preinvasive cancer 25% Cells limited to basement membrane	Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cadherin loss 1% progress per year Can be bilateral		Triple negative ER-, PR-, HER2- HER2+ Luminal B Luminal A
Invasive cancer 75% Extension beyond the basement membrane	Invasive ductal carcinoma (IDC) 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	Invasive lobular carcinoma (ILC) 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+	% of breast cancers Receptor expression Histologic grade Level of cell differentiation Prognosis Correlates to histologic grade Response to medical therapy	15-20% 10-15% 20% 40% HER2 High (grade III) Low (grade I) Poor Good Chemotherapy Trastuzumab Endocrine

Curr Treat Options Oncol. 2000 Aug;1(3):199-209.
Clin Transl Oncol. 2008 Dec;10(12):777-85.

Nat Clin Pract Oncol. 2007 Sep;4(9):516-25.
Rostami BE

Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

Supervised analysis: Candidate regulatory TFs

TF	LumA (vs basal)	LumB (vs basal)	LumA (vs normal)	LumB (vs normal)	Basal (vs LumA)	Basal (vs LumB)	Basal (vs HER2)	HER2 (vs Basal)
AR	x	x	x					
BCL11A					x	x	x	
CEBPB					x	x	x	
E2F3					x		x	
EMX1	x	x	x					
ESR1	x	x	x	x				
ETV6					x	x	x	
FOXA1	x	x	x	x				x
FOXP1	x	x						x
GATA3	x	x	x	x				x
HOXB1	x	x						
HOXB2	x	x						x
HOXB3								x
HOXC10								x
KLF5						x	x	
LMX1B	x	x	x					
MNX1								x
MYB	x			x				
NFIL3					x	x		
PBX1		x		x		x		
RARA	x	x	x					
RUNX3					x	x		
SOX8						x		
SOX9						x		
SOX11					x	x		
ZNF467	x	x	x			x		
ZIC1					x	x	x	

TF master regulator: Basal

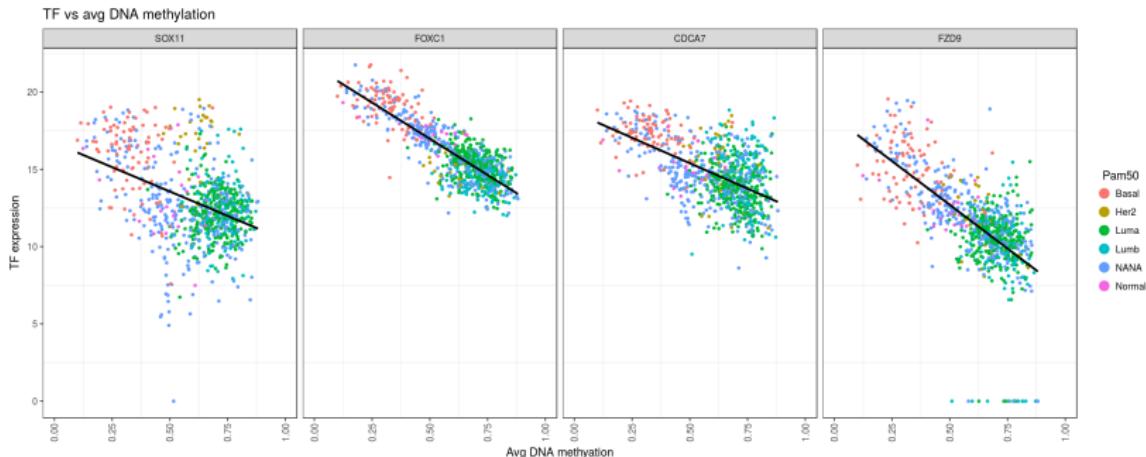


Figure: SOX11 and top3 TF expression vs avg DNA methylation of paired enriched probes for SOX10 - Probes hypermethylated in LumA vs Basal

Master regulator TF: molecular known subtypes

The SOX11 transcription factor is a critical regulator of basal-like breast cancer growth, invasion, and basal-like gene expression

Jonathan H. Shepherd^{1,3}, Ivan P. Uray³, Abhijit Mazumdar³, Anna Tsimelzon², Michelle Savage³, Susan G. Hilsenbeck², Powell H. Brown^{1,3}

FOXA1 repression is associated with loss of BRCA1 and increased promoter methylation and chromatin silencing in breast cancer

C Gong,^{1,2,6} K Fujino,^{1,3,6} L J Monteiro,¹ A R Gomes,¹ R Drost,⁴ H Davidson-Smith,⁵ S Takeda,³ U S Khoo,² J Jonkers,⁴ D Sproul,⁵ and E W-F Lam^{1,*}

negative breast cancer cell lines to regain hormonal sensitivity.⁴¹ In addition to promoting mammary luminal phenotype, FOXA1 might also have a more direct role in repressing the basal breast cancer phenotype. It has been shown that FOXA1 also inhibits the transcription of basal-type associated genes such as *CD58*, *ANXA1*, *JAG1* and *SOX9*, whereas the loss of FOXA1 leads to the derepression of these basal genes.¹³ These findings together highlight a critical role of FOXA1 in maintaining the luminal and

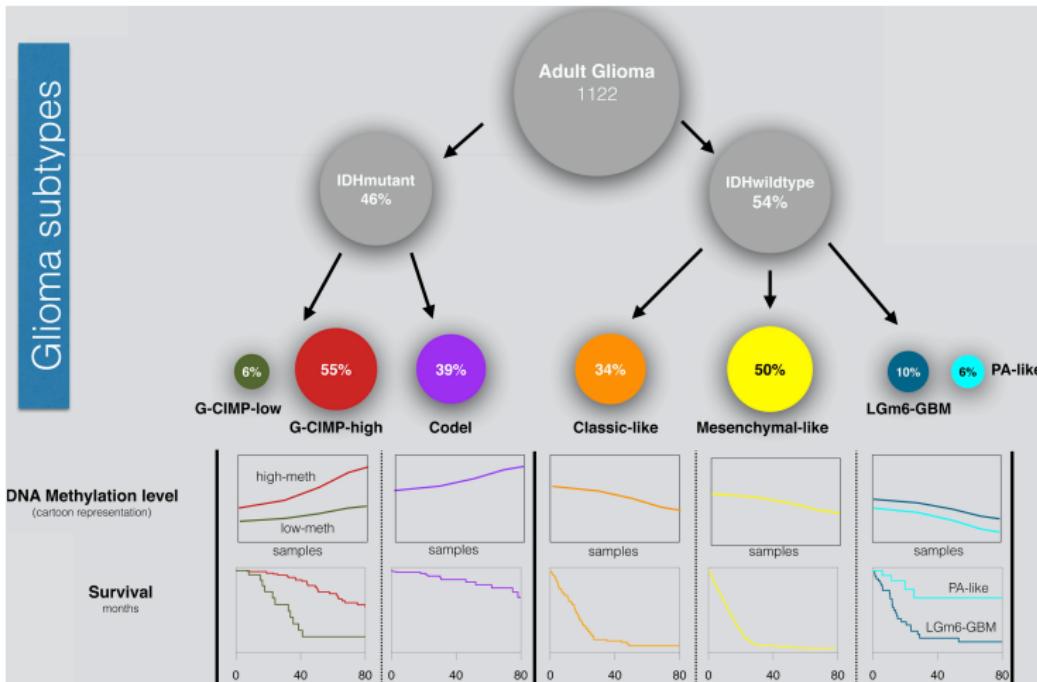
GATA-3 maintains the differentiation of the luminal cell fate in the mammary gland.

Kouros-Mehr H¹, Slorach EM, Sternlicht MD, Werb Z.

Author information

GATA3 acts upstream of FOXA1 in mediating ESR1 binding by shaping enhancer accessibility

Glioma analysis: glioma subgroups



Source: Ceccarelli M, et al. Cell (2016)

Candidate master regulator Transcription Factors (TF)

Top TFs

- HOXD13
 - HMX3
 - ZSCAN16
 - SOX11
 - PAX3
 - FOXM1

HOXD13

DNA methylation profiles of long- and short-term glioblastoma survivors

Thoria Shinawi,¹ Victoria K. Hill,¹ Dietmar Krex,² Gabriele Schackert,² Dean Gentle,¹ Mark R. Morris,³ Wenbin Wei,⁴ Garth Cruickshank,⁵ Fionnán R. Maher¹ and Farida Latifi.*

¹Centre for Rare Diseases and Personalized Medicine; Department of Medical & Molecular Genetics; School of Clinical and Experimental Medicine; University of Birmingham College of Medical and Dental Sciences; Birmingham, UK; ²Department of Neurosurgery; University Hospital Dresden; Dresden, Germany; ³School of Applied Sciences; University of Wolverhampton; Wolverhampton, UK; ⁴School of Cancer Sciences; University of Birmingham; Birmingham, UK; ⁵Department of Neurosurgery; University of Birmingham; Queen Elizabeth Hospital; Birmingham, UK

Keywords: DNA methylation, gliomas, IDH1, long-term survivors, short-term survivors

Glioblastoma (GBM) is the most common and malignant type of primary brain tumor in adults and prognosis of most GBM patients is poor. However, a small percentage of patients show a long term survival of 36 mo or longer after diagnosis. Epigenetic profiles can provide molecular markers for patient prognosis: recently, a G-CIMP positive phenotype associated with *IDH1* mutations has been described for GBMs with good prognosis. In the present analysis we performed genome-wide DNA methylation profiling of short-term survivors (STS; overall survival < 1 y) and long-term survivors (LTS; overall survival > 3 y) by utilizing the HumanMethylation450K BeadChips to assess quantitative methylation at > 480,000 CpG sites. Cluster analysis has shown that a subset of LTS showed a G-CIMP positive phenotype that was tightly associated with *IDH1* mutation status and was confirmed by analysis of the G-CIMP signature genes. Using high stringency criteria for differential hypermethylation between non-cancer brain and tumor samples, we identified 2,638 hypermethylated CpG loci (890 genes) in STS GBMs, 3,101 hypermethylated CpG loci (1,062 genes) in LTS (wild type *IDH1*) and 11,293 hypermethylated CpG loci in LTS (mutated for *IDH1*), reflecting the CIMP positive phenotype. The location of differentially hypermethylated CpG loci with respect to CpG content, neighborhood context and functional genomic distribution was similar in our sample set, with the majority of CpG loci residing in CpG islands and in gene promoters. Our preliminary study also identified a set of CpG loci differentially hypermethylated between STS and LTS cases, including members of the homeobox gene family (*HOXD8*, *HOXD13* and *HOXC4*), the transcription factors *NR2F2* and *TFAP2A*, and *Dickkopf2*, a negative regulator of the wnt/β-catenin signaling pathway.



FOXM1 and PAX3

FoxM1: a potential drug target for glioma

Yu Li¹, Sicong Zhang¹, and Suyun Huang^{1,2}

¹Department of Neurosurgery, the University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Abstract

Malignant glioma is an aggressive disease and there is no effective therapy. Recently, with the elucidation of mechanisms for glioma formation and progression, the critical molecules involved in the process are considered as therapeutic targets and numerous of drugs against these targets are ongoing for evaluation in clinic trial. FoxM1 has been recognized as one of the common pathways in cancer cells including glioma cells. FoxM1 signal network is reported to be critical in glioma by promoting cell proliferation, invasion, angiogenesis and cancer stem cell self-renewal. FoxM1 may represent a novel therapeutic target and FoxM1 inhibitors may provide a new therapeutic strategy against glioma.

Keywords

FoxM1; glioma; proliferation; invasion; angiogenesis; self-renewal; drug target

PAX3 is overexpressed in human glioblastomas and critically regulates the tumorigenicity of glioma cells.

Xia L¹, Huang Q, Nie D, Shi J, Gong M, Wu B, Gong P, Zhao L, Zuo H, Ju S, Chen J, Shi W.

✉ Author information

Abstract

Paired box 3 (PAX3) is overexpressed in glioma tissues compared to normal brain tissues, however, the pathogenic role of PAX3 in human glioma cells remains to be elucidated. In this study, we selected the human glioma cell lines U251, U87, SHG-44, and the normal human astrocytes, 1800, which have differential PAX3 expression depending upon the person. siRNA targeting PAX3 and PAX3 overexpression vectors were transfected into U87 and SHG-44 glioma cell lines, and cell proliferation, invasion, apoptosis, and differentiation were examined by CCK-8 assays, transwell chamber assays, tunnel staining, Annexin V/PI analysis, and Western blotting, respectively. In addition, we used subcutaneous tumor models to study the effect of PAX3 on the growth of glioma cells in vivo. We found that PAX3 was upregulated in the three glioma cell lines. PAX3 knockdown inhibited cell proliferation and invasion, and induced apoptosis in the U87MG glioblastoma cell line, whereas PAX3 upregulation promoted proliferation, inhibited apoptosis, and increased invasion in the SHG-44 glioma cell line. Moreover, we found that targeting PAX3 expression in glioma cell lines together with chemotherapeutic treatment could increase glioma cell susceptibility to

SOX11

Highly specific overexpression of the transcription factor SOX11 in human malignant gliomas

Weigle B¹, Ebner B, Temme A, Schwind S, Schmitz M, Kiessling A, Rieger MA, Schackert G, Schackert HK, Rieber EP

Author information

Abstract

Malignant glioma comprises the majority of primary human brain tumors with 16,800 new cases reported each year in the USA. Its prognosis remains dismal despite numerous attempts to improve conventional therapeutic modalities. Therefore, much effort is devoted to the exploration of alternative forms of treatment such as immunotherapy. The identification of potential target structures highly overexpressed in brain tumors is a crucial prerequisite for the activation of the immune defense against malignant glioma cells. By screening an expression database for genes highly expressed in glioblastoma multiforme (GBM), we identified the Pit-Oct-Unc (POU) cooperating transcription factor SOX11 that is known to be crucially involved in brain development. Analysis of the expression pattern of SOX11 in different normal adult and fetal tissues by multiple tissue dot blot and by a highly sensitive quantitative PCR assay confirmed the selective overexpression of SOX11 in fetal brain tissue. Examination of tissue specimens obtained from malignant gliomas and from normal brain by quantitative real-time PCR (Q-RT-PCR) revealed upregulation of SOX11 in almost all tumor samples (15/16) as compared to the pooled normal brain. Seventy-five percent of the tumor samples (12/16) showed a 5- to more than 600-fold overexpression. We conclude that, after downregulation of SOX11 in the adult brain, its expression is reactivated during tumorigenesis and that SOX11 therefore represents a promising novel molecular target for adjuvant therapy of malignant gliomas.

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Next steps: TF knockdown

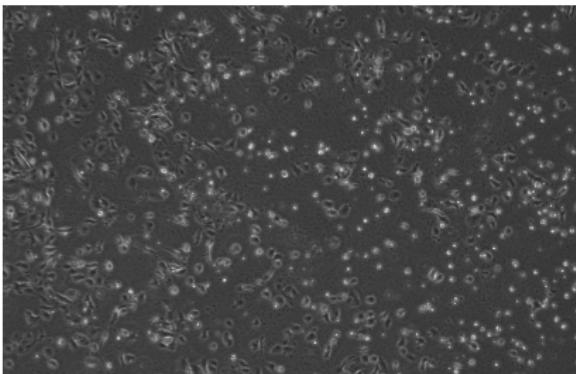
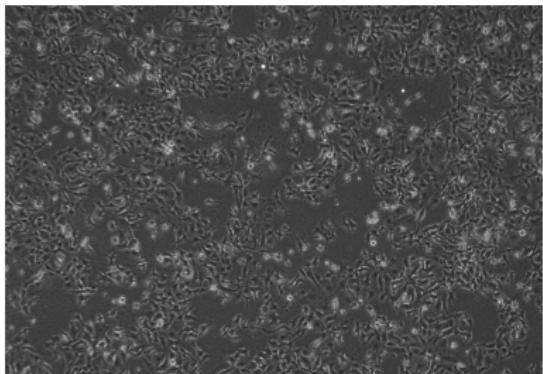


Figure: Candidate master regulator Transcription Factors (TF) knockdown in the SKGT4 human esophageal adenocarcinoma cell line. Figure produced by Dr. Dechen Lin.