

# Genomic and transcriptomic landscapes of acute promyelocytic leukemia

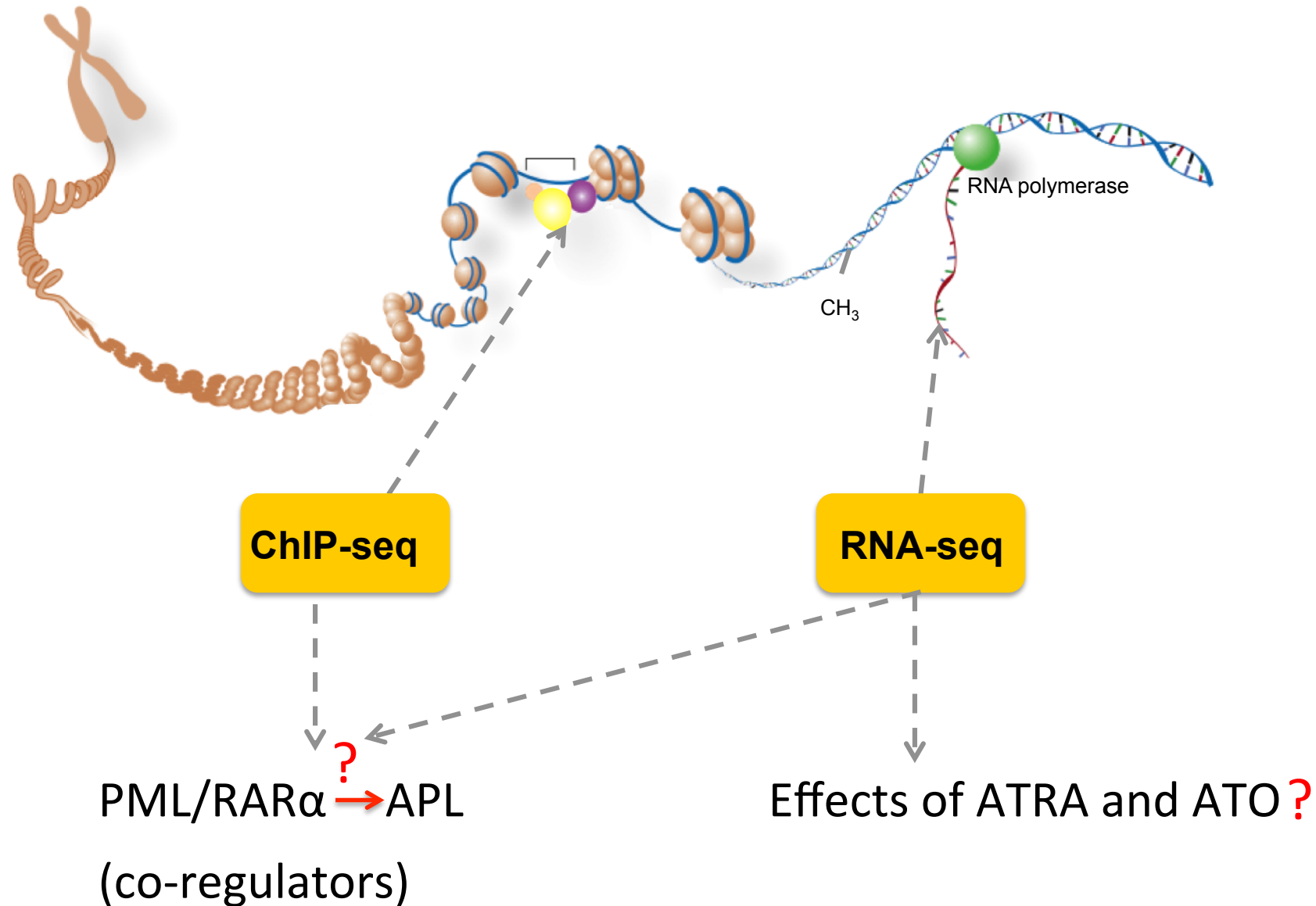
Kankan Wang

State Key Laboratory of Medical Genomics

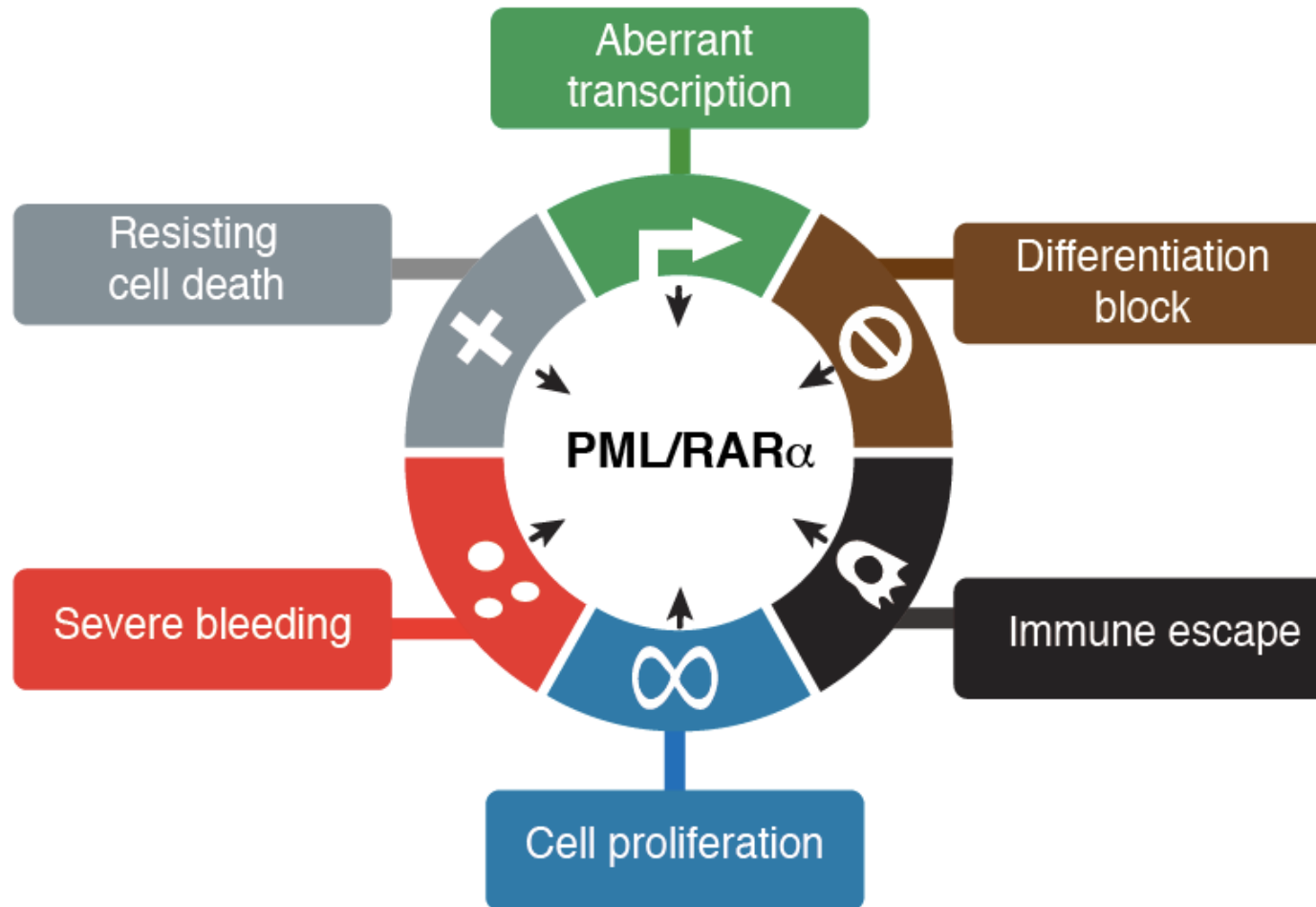
Rui-Jin Hospital

Shanghai Jiaotong University School of Medicine

# Understanding the pathogenesis and treatment of APL using high-throughput technologies

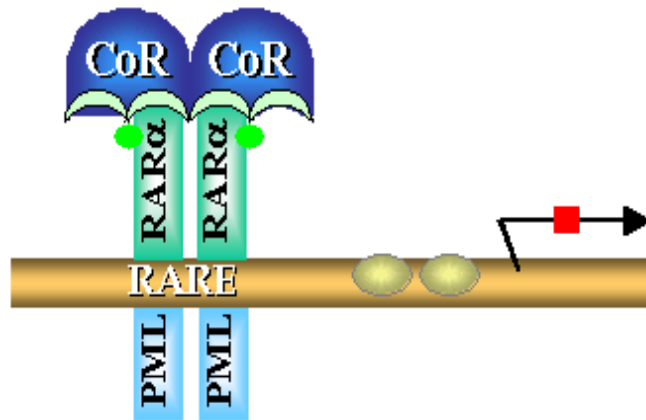


# Hallmarks of acute promyelocytic leukemia

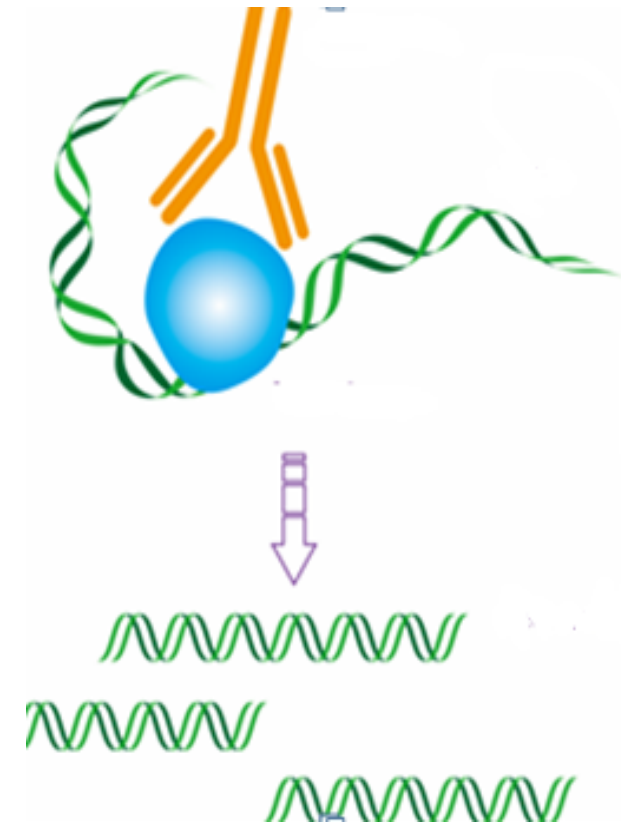


**How does PML/RAR $\alpha$  drive the development of APL?**

# Genome-wide PML/RAR $\alpha$ binding sites

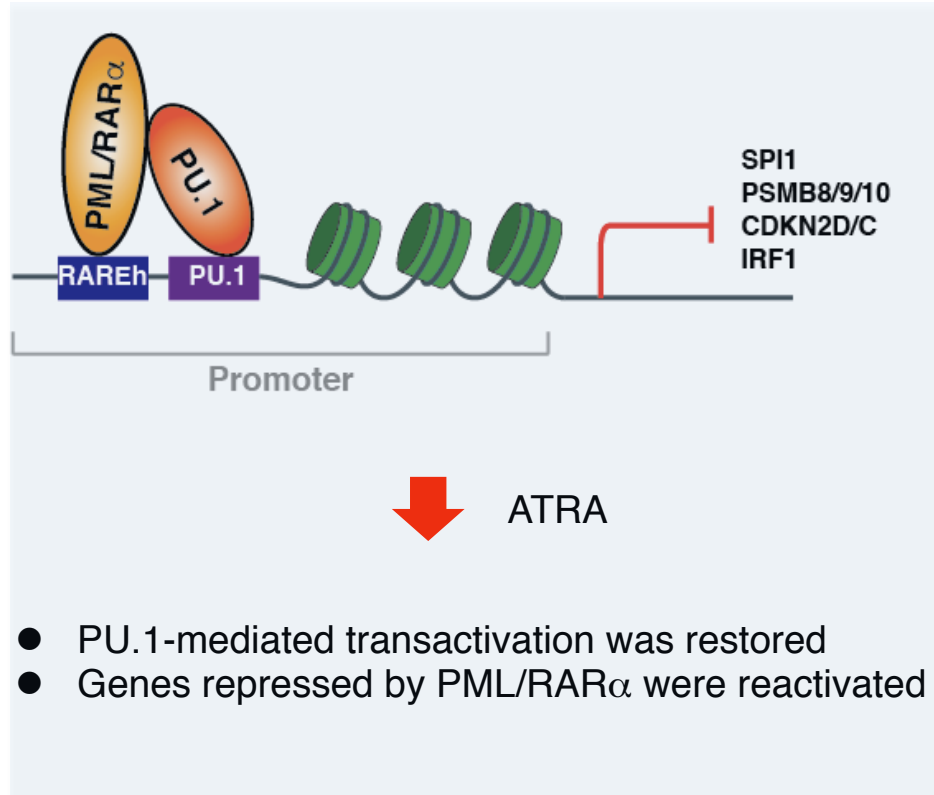


- PML/RAR $\alpha$  retains the DNA binding domain of wild-type RAR $\alpha$ .
- PML/RAR $\alpha$  acts as a strong transcriptional repressor.
- Myeloid commitment is hardly affected in various RAR-deficient mice.

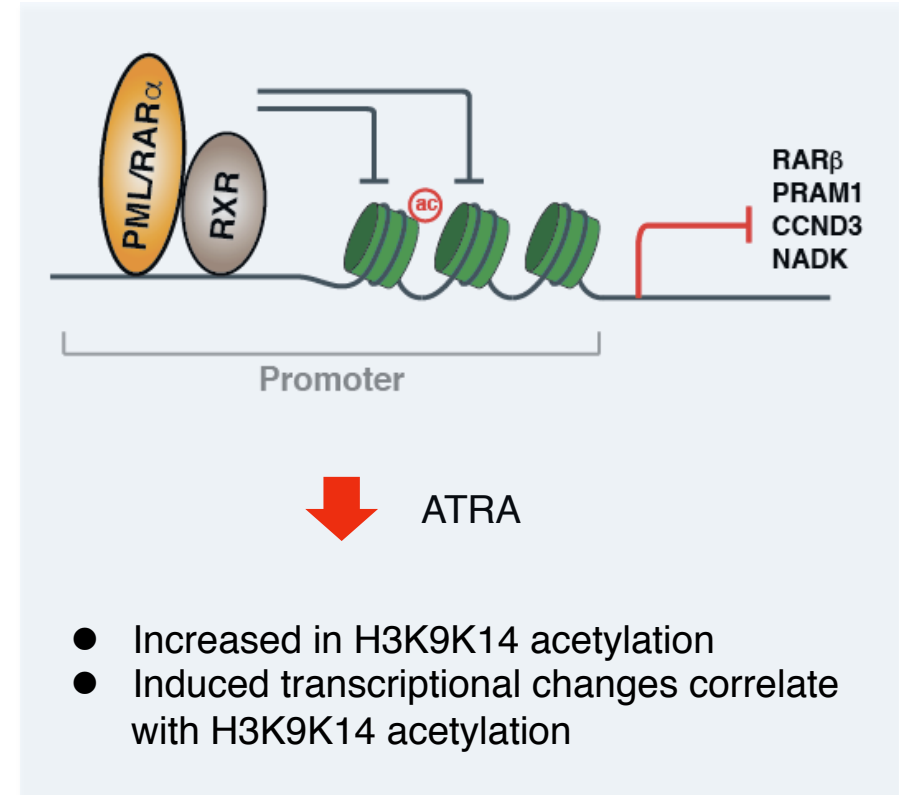


ChIP-chip/ChIP-seq

# Genome-wide binding pictures of PML/RAR $\alpha$



Wang et al. Cancer Cell 2010



Martens et al. Cancer Cell 2010

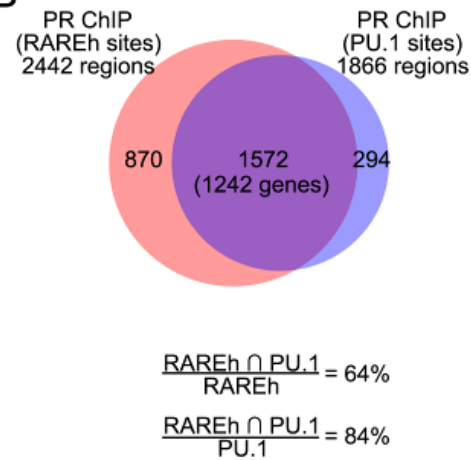
# PU.1 and RARE half sites are the most significant motifs in the PML/RAR $\alpha$ CHIP regions

A

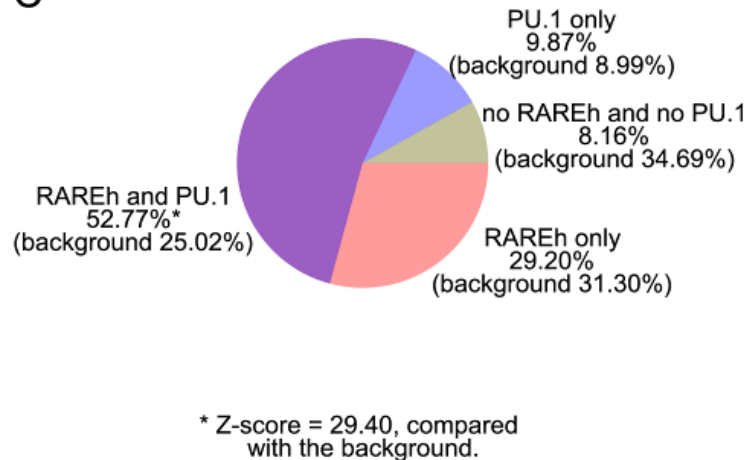
	Identified Motif	Description	# Regions	% Regions	Z-score
I. <i>De novo</i>	AGGAAG	ETS family	1893	63.54%	27.43
	RSRGGAA	PU.1	1871	62.81%	22.16
	GTGACTCA	AP1	193	6.48%	13.73
II. TRANSFAC	V\$ETS_Q6	ETS family	2200	73.85%	30.26
	V\$PU1_Q6	PU.1	1866	62.64%	24.77
	V\$AP1_C	AP1	525	17.62%	15.63
III. Consensus scanning	RGKTCA	RARE half	2442	81.97%	18.23
	RGKTCA(n) <sub>2,5</sub> RGKTCA*	DR2, DR5	395	13.26%	9.82

\* One mismatch was allowed.

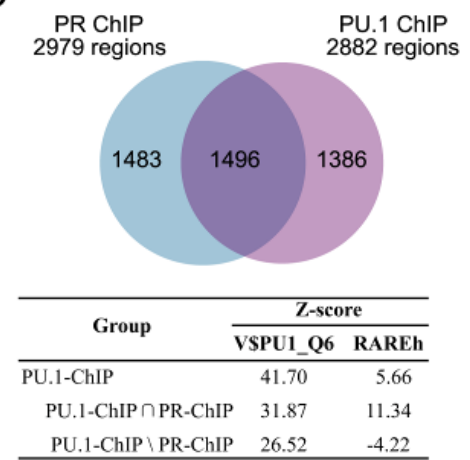
B



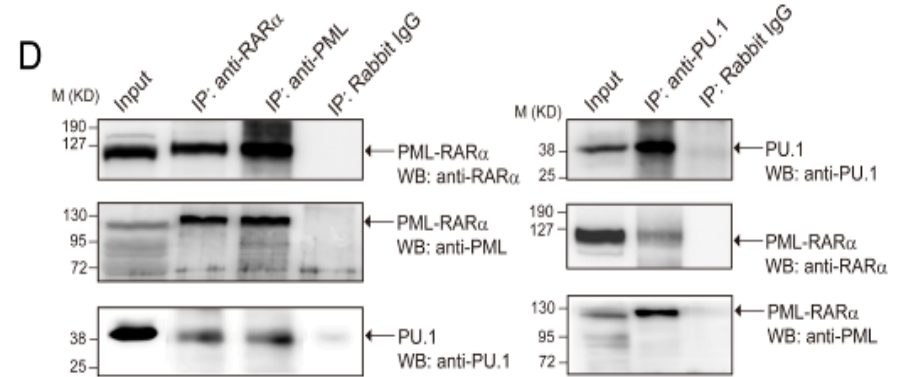
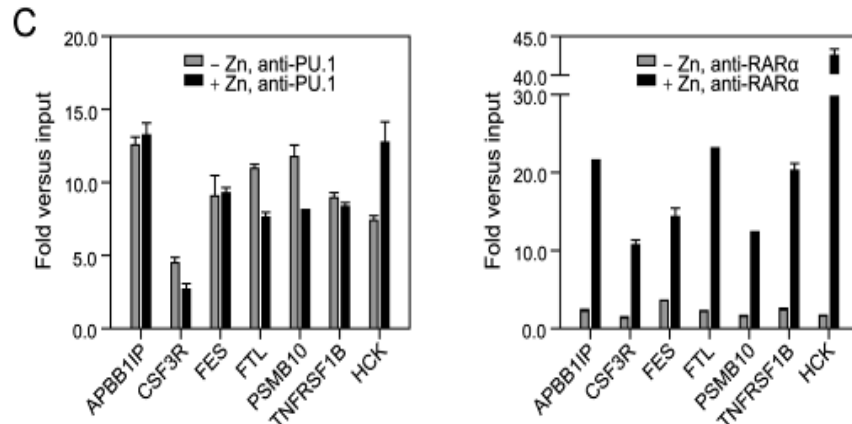
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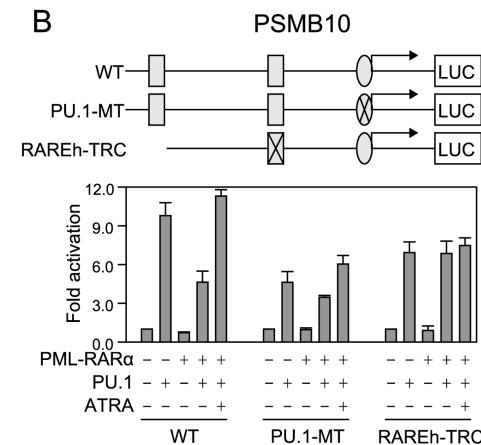
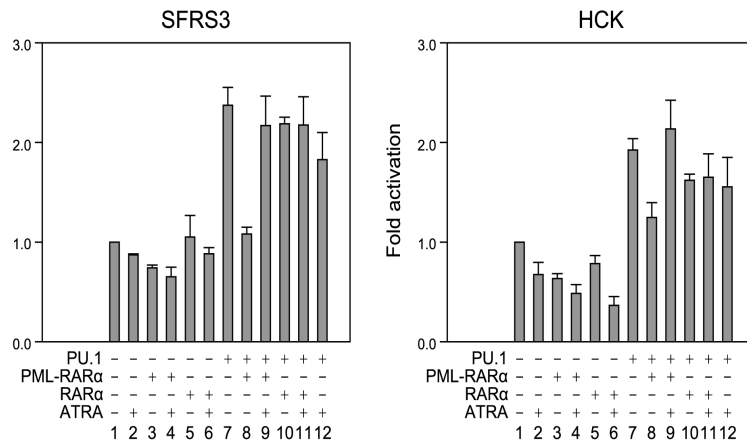
D



# PML/RAR $\alpha$ predominantly represses PU.1-regulated genes

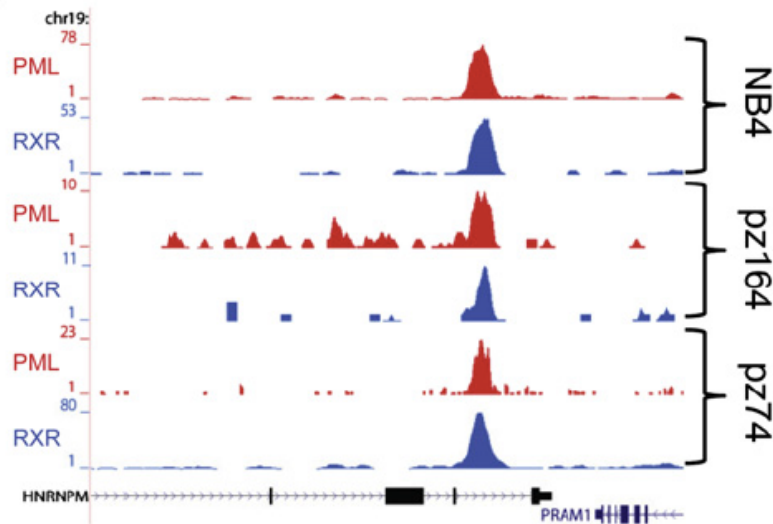


Recruitment of PML/RAR $\alpha$  to chromatin pre-bound by PU.1

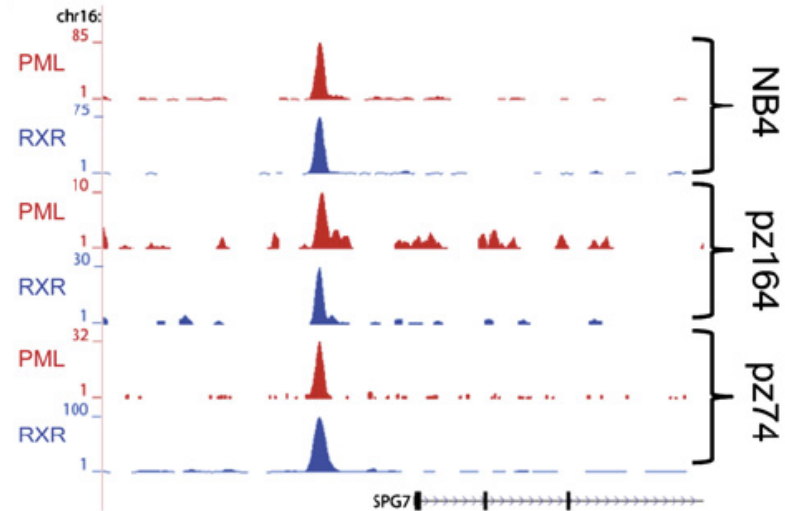


Repression of PU.1-dependent transactivation through both PU.1 and RARE half sites

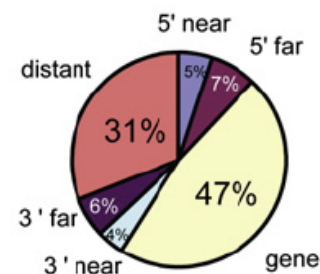
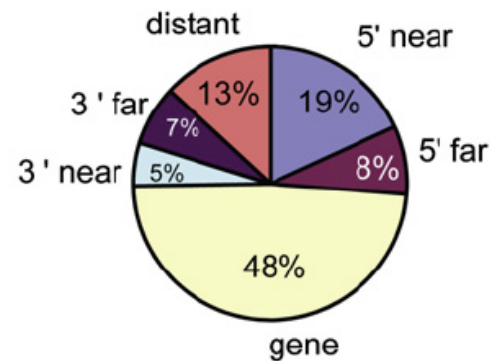
# PML/RAR $\alpha$ tends to colocalize with RXR preferentially on promoter regions



PML-RAR $\alpha$

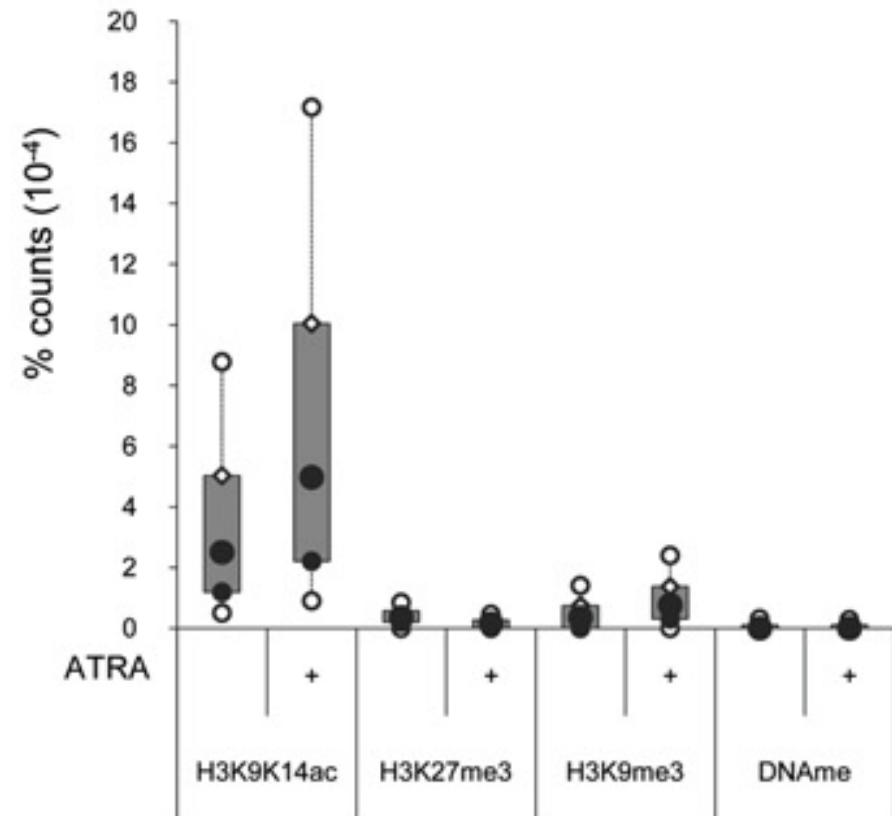
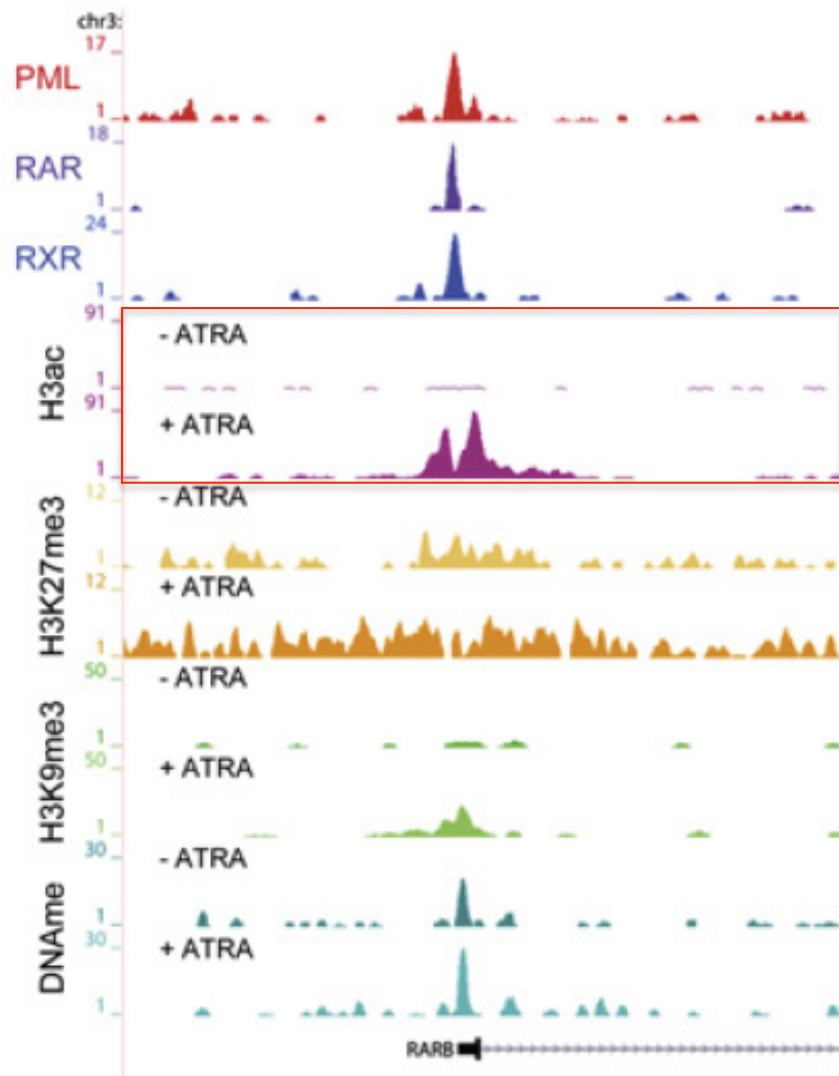


genomic DNA





# ATRA treatment increases the level of H3K9K14ac but not H3K9me3 and H3K27me3

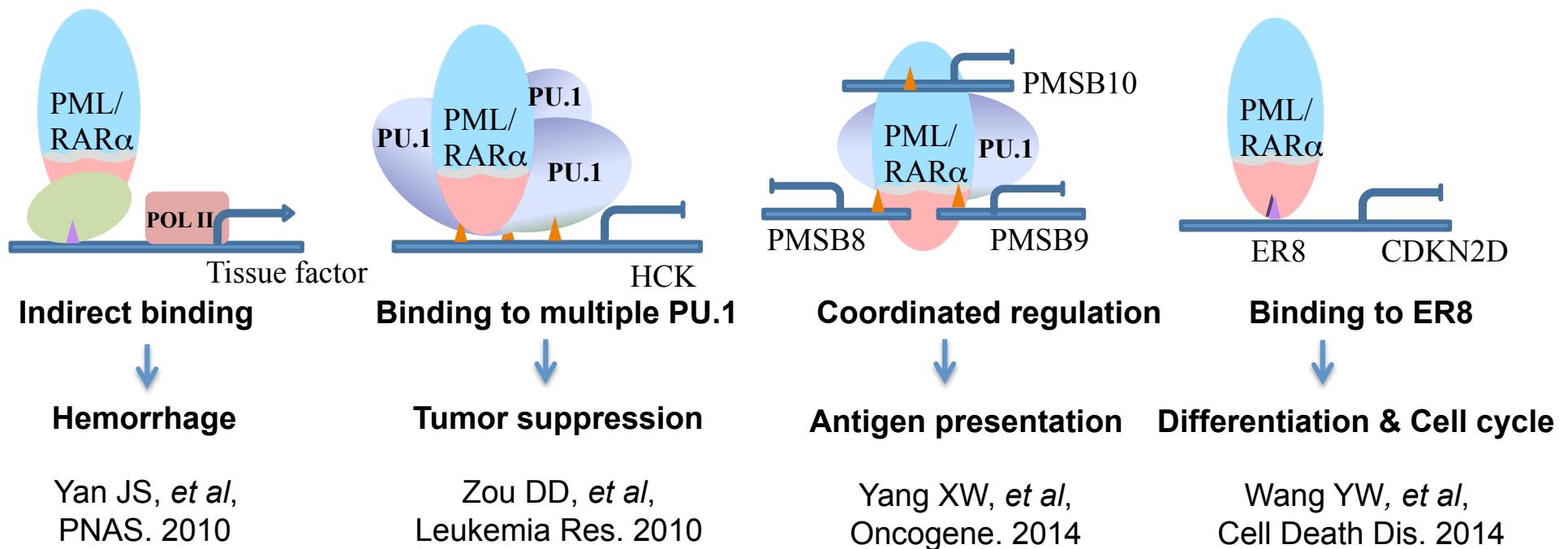


Martens et al. Cancer Cell 2010

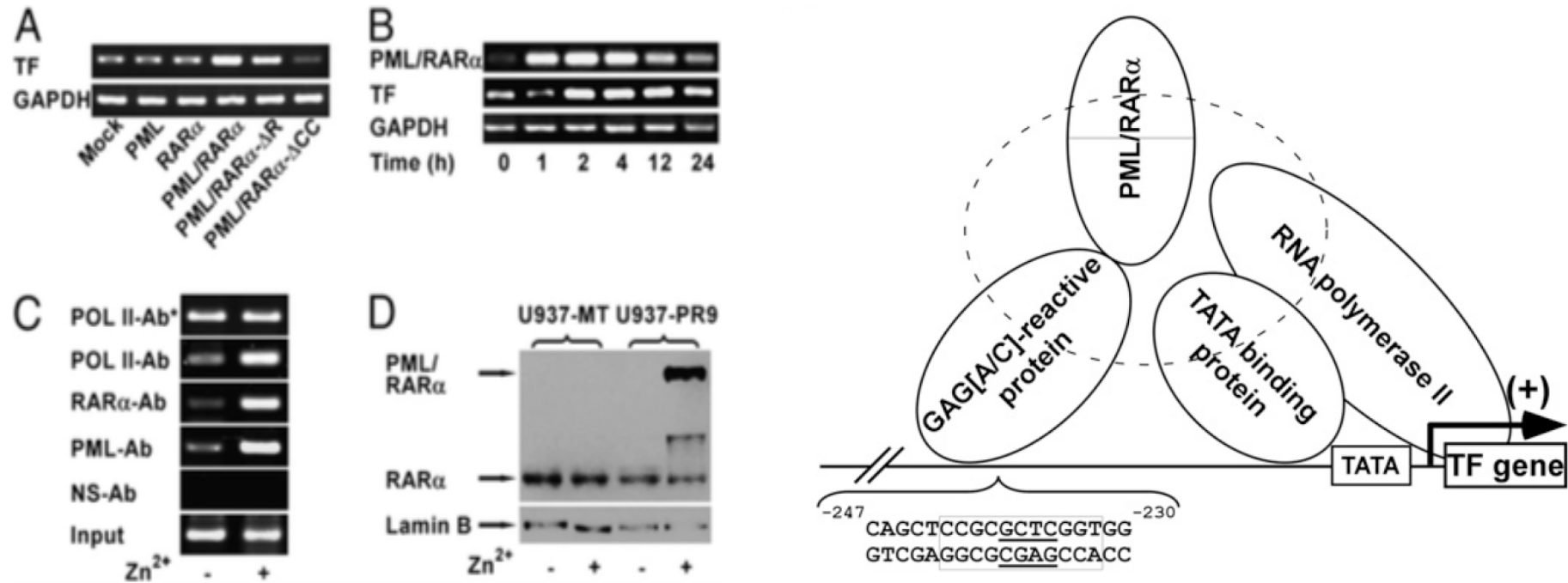
# Regulatory features and functions of PML/RAR $\alpha$ key targets in APL

Genome-wide PML/RAR $\alpha$  binding

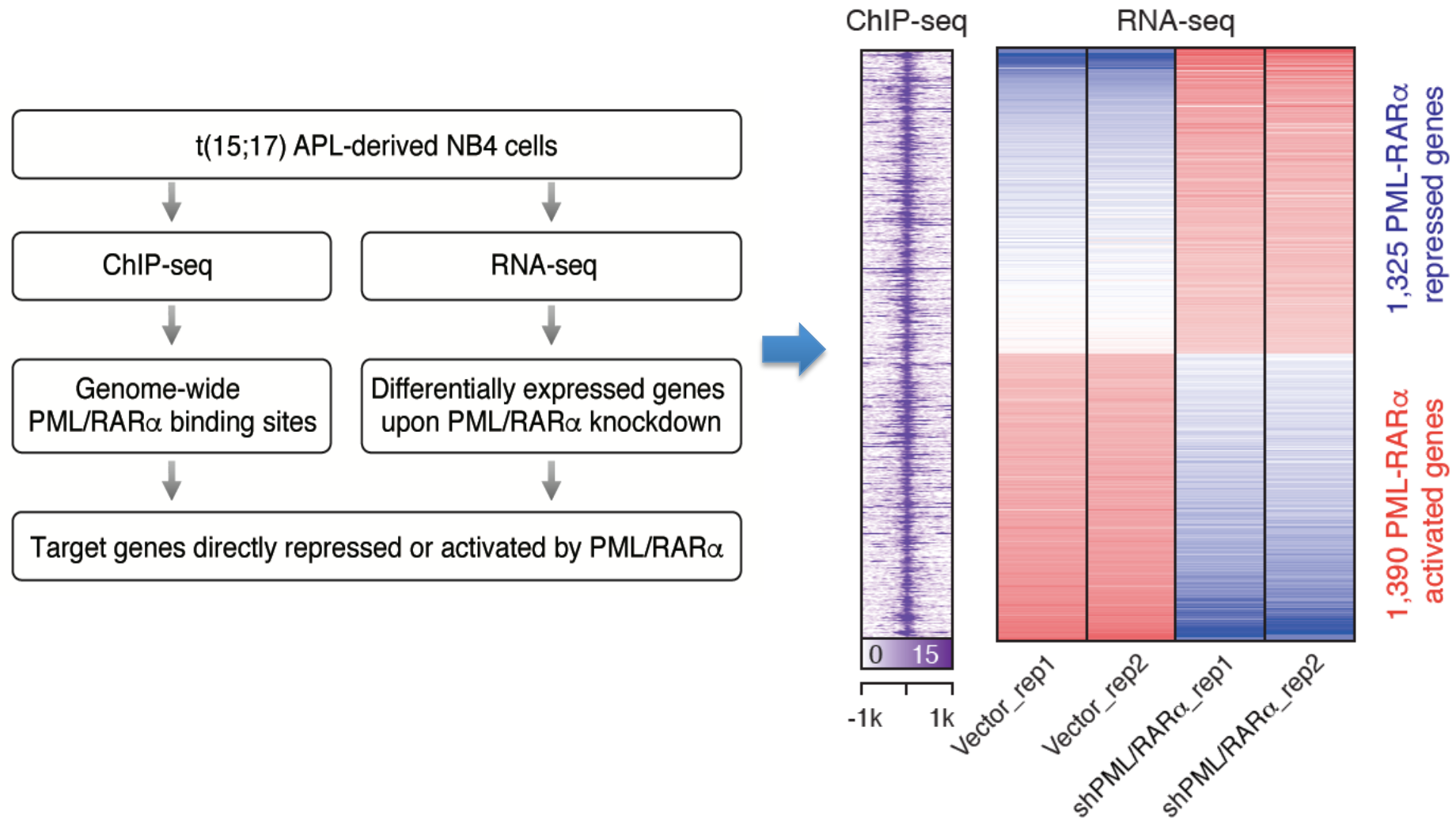
Detailed analysis of key targets



# PML/RAR $\alpha$ transactivates the tissue factor promoter through an indirect interaction

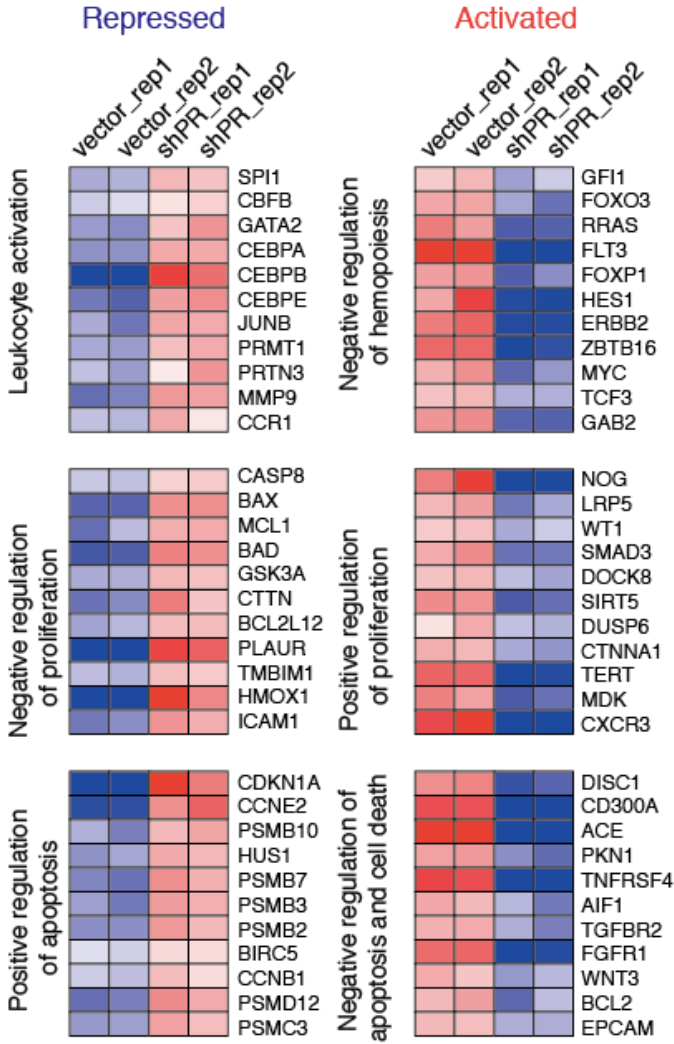
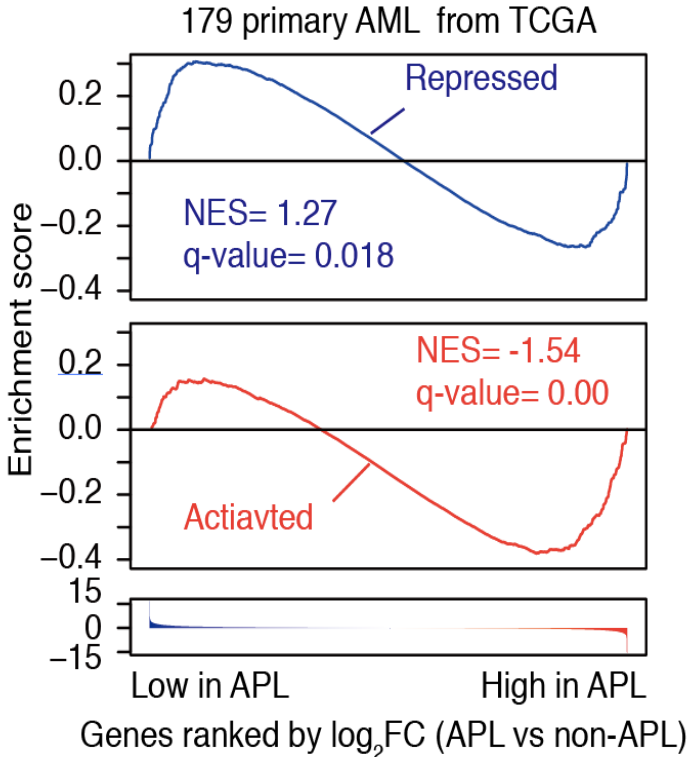


# PML/RAR $\alpha$ exerted both repressive and activating functions



Unpublished data





# Functionally importance of both PML/RAR $\alpha$ -repressed and -activated targets







Unpublished data

# Repression was associated with RAR $\alpha$ , whereas activation was independent of RAR $\alpha$

**a**

Motif	Description	p-value
	PU.1	1.23e-21
	AML1	3.65e-9
	DR5	0.28
	DR2	0.85

**b**

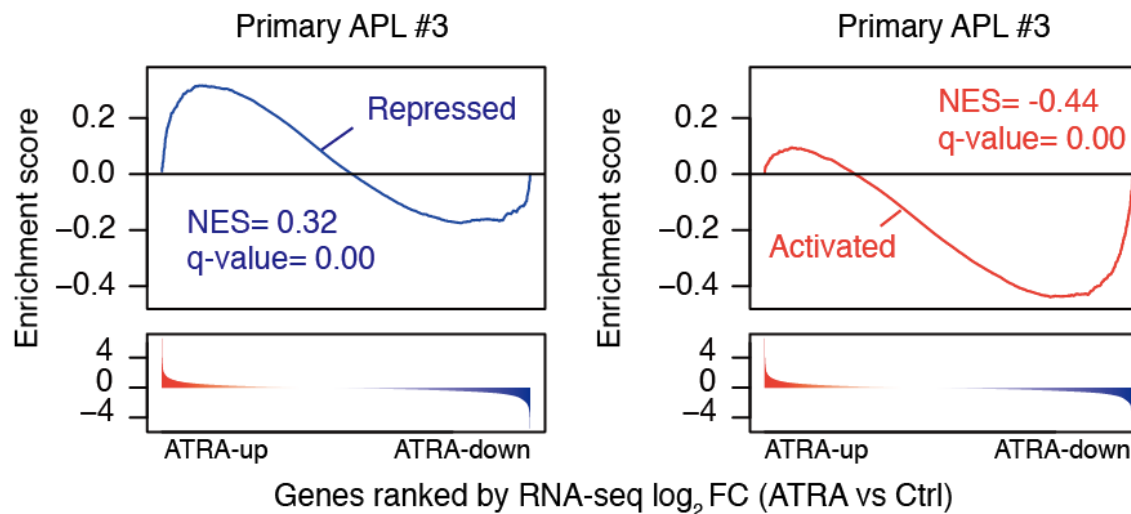
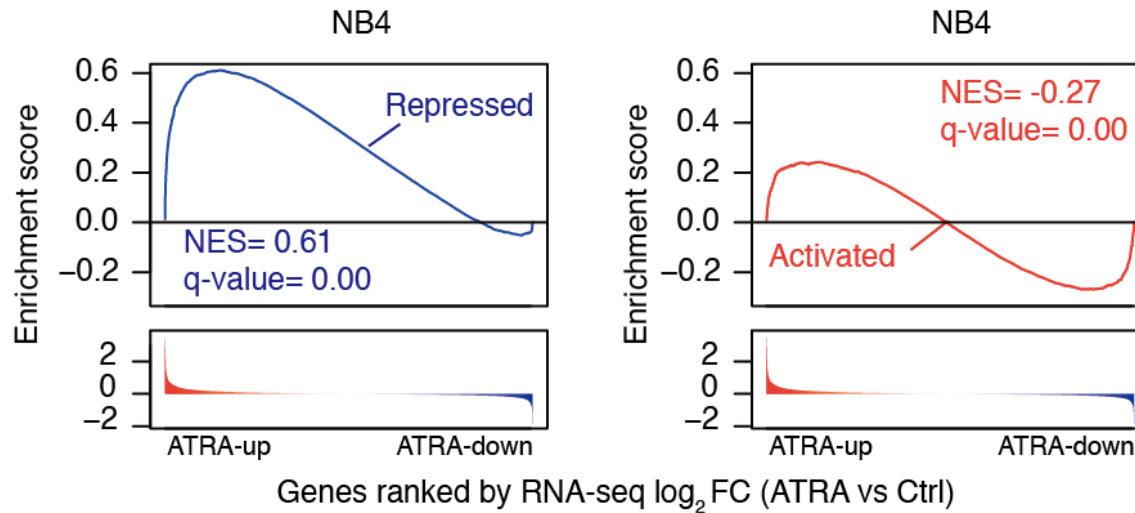
Motif	Description	p-value
	DR5	5.95e-12
	DR2	4.32e-8
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	DR5	0.15
	DR2	0.22

Repressed

Activated

Unpublished data

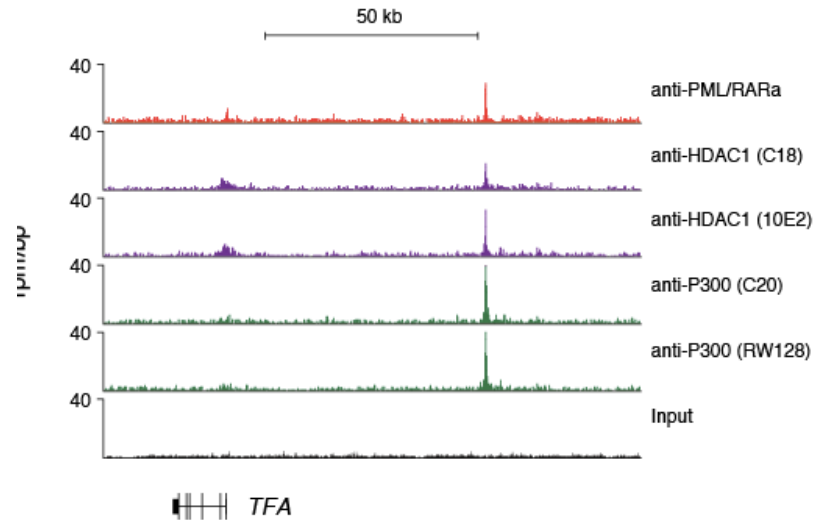
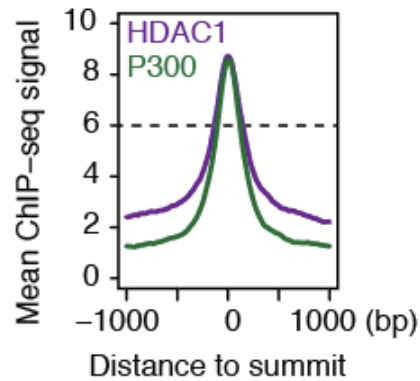
# Distinct ATRA effects on PML/RAR $\alpha$ -activated and -repressed genes



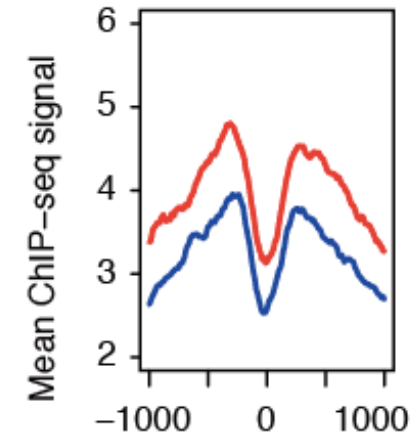
Unpublished data

# PML/RAR $\alpha$ preferentially existed within super-enhancer regions

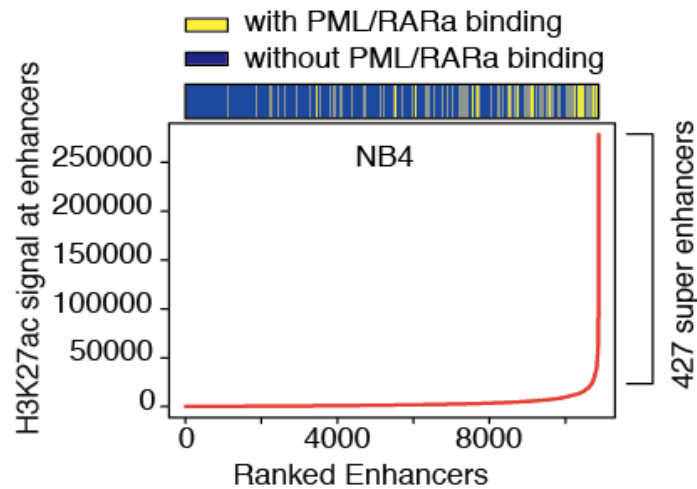
Activated-targets



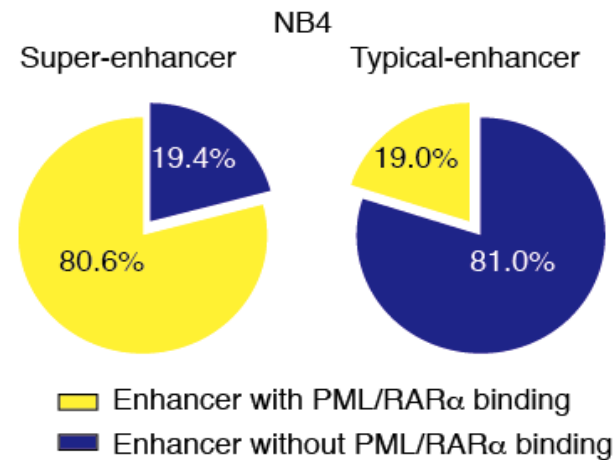
H3K27ac



**b**



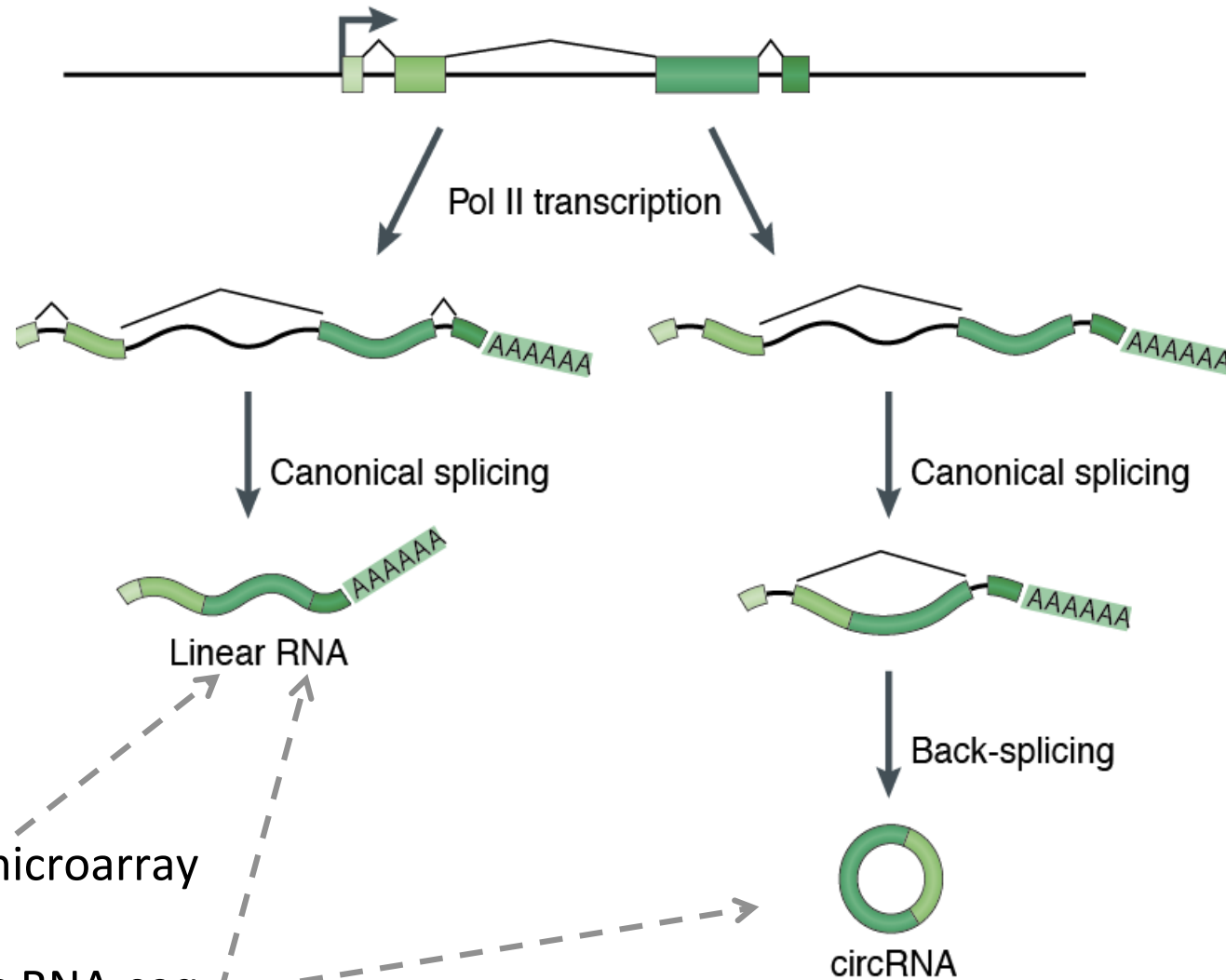
**c**



Unpublished data

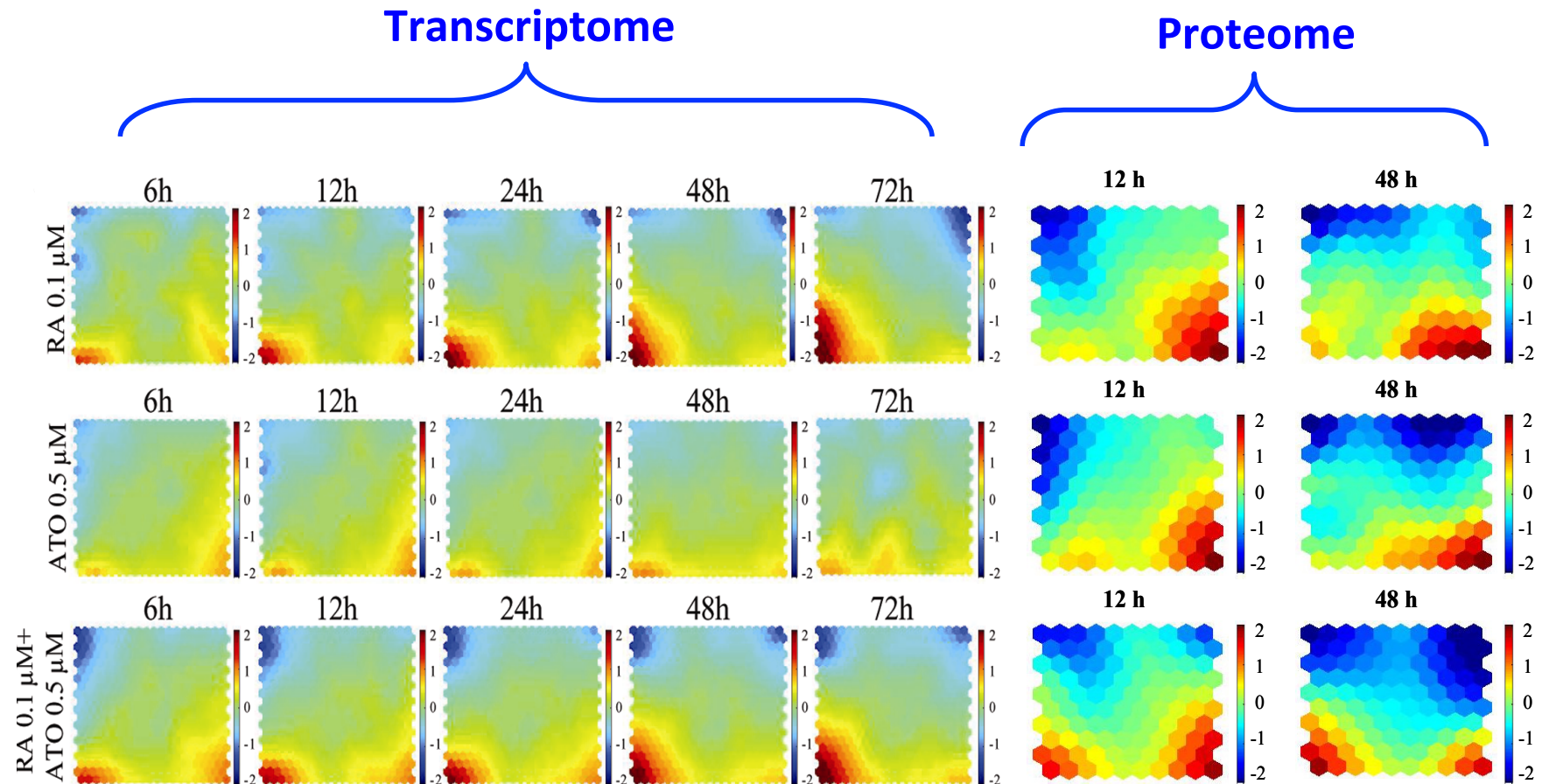


# Transcriptome analysis of the mechanism of ATRA action

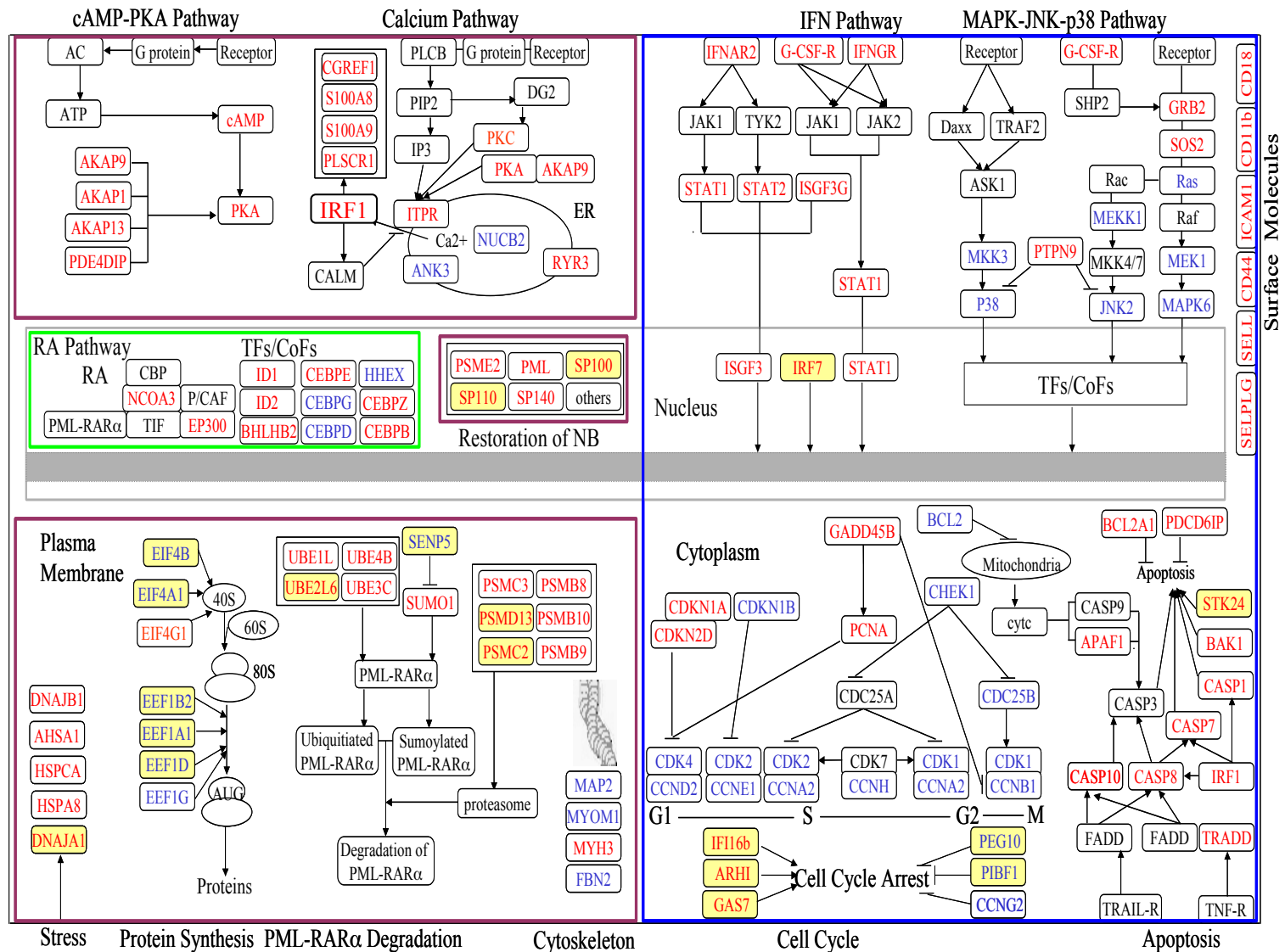


- RNA-seq/microarray
- Ribo-minus RNA-seq

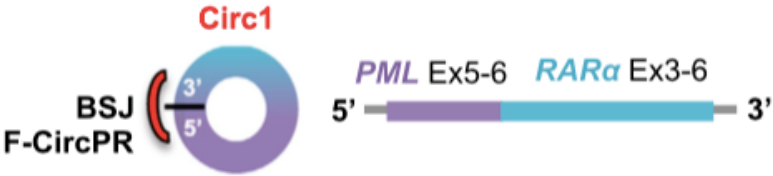
# ATRA regulates gene expression at the transcriptomic level, whereas ATO functions at the proteomic level



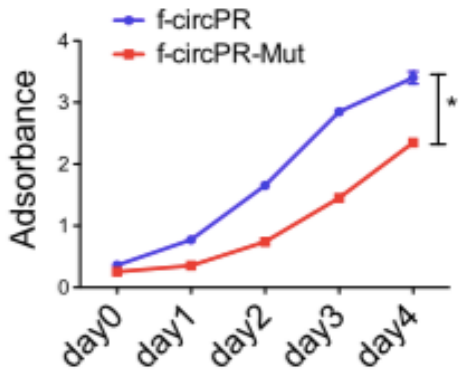
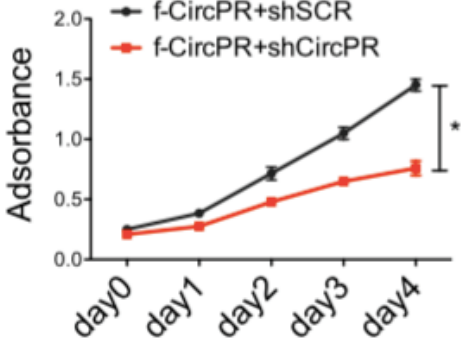
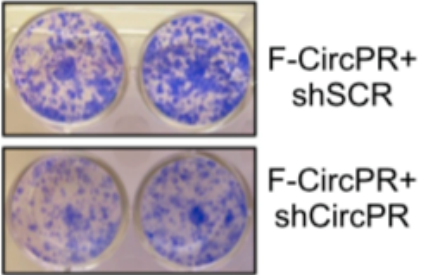
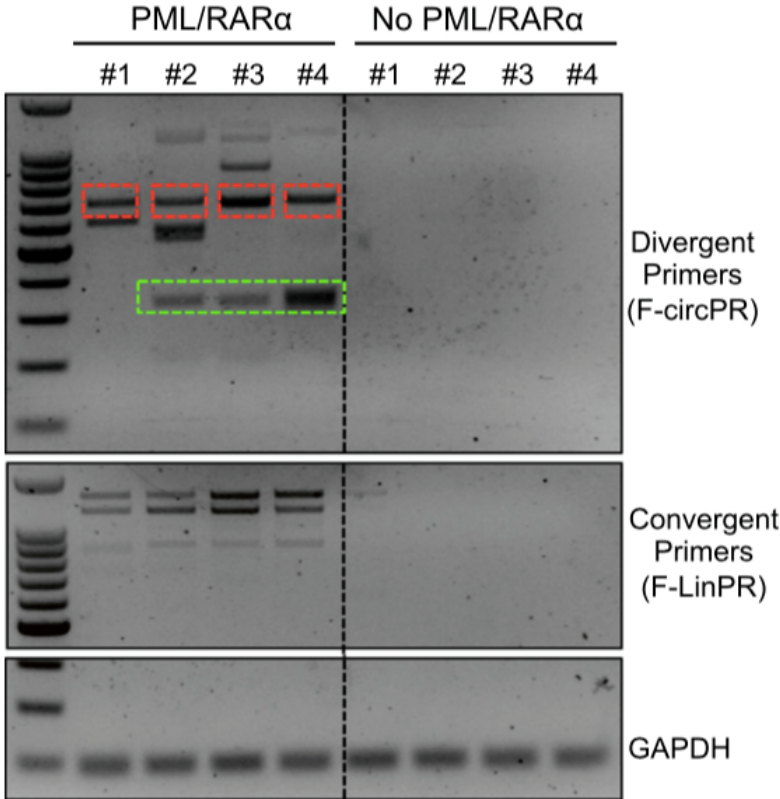
# Molecular networks underlying the combination of ATRA and ATO in NB4 cells



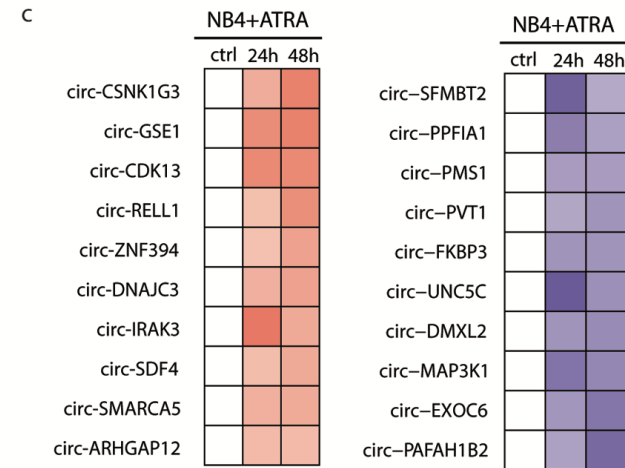
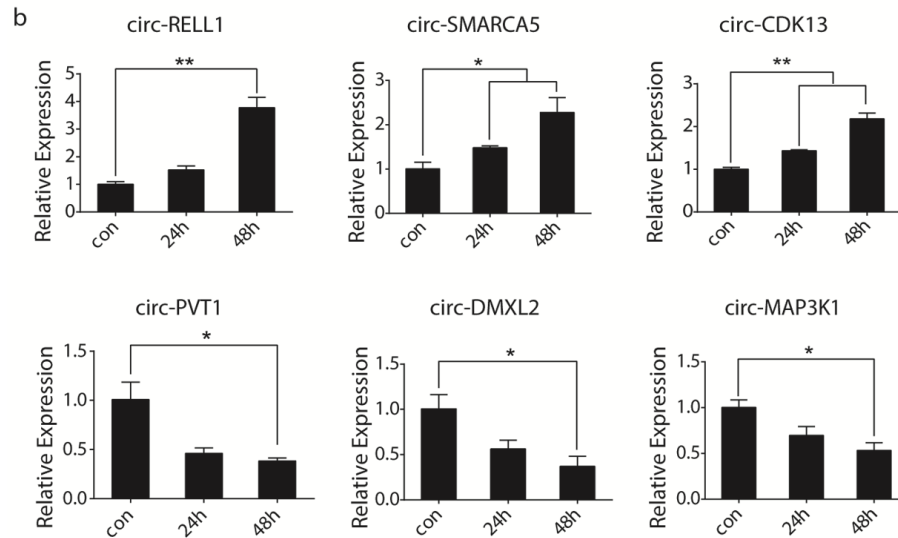
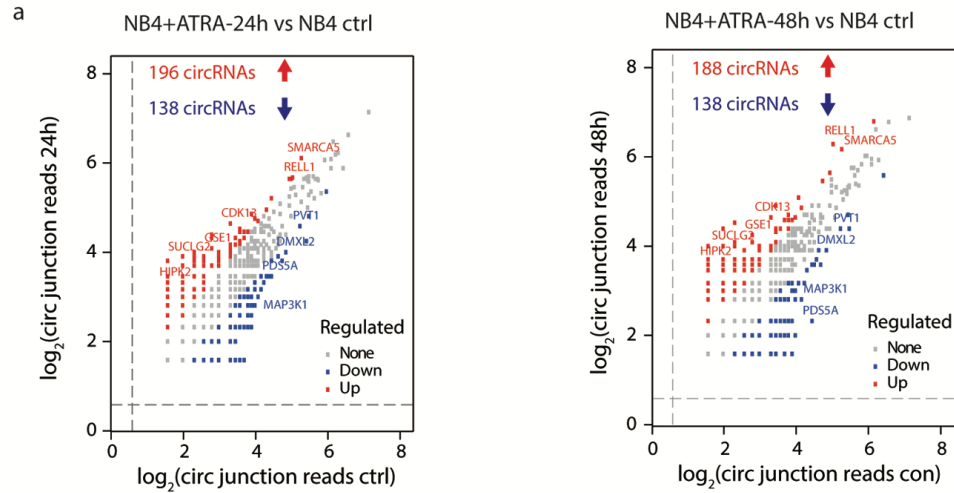
# Circular RNA generating from the fusion site of PML/RAR $\alpha$ is oncogenic and contributes to cellular transformation



BSJ: back-splicing junctions

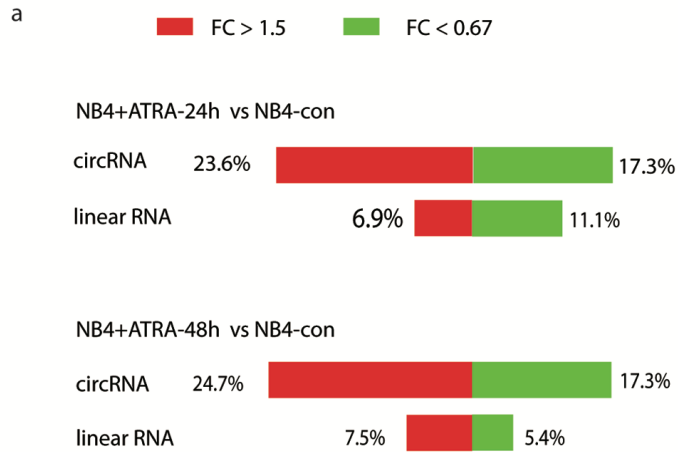


# Dynamic regulated circRNA profiling upon ATRA treatment of APL cells



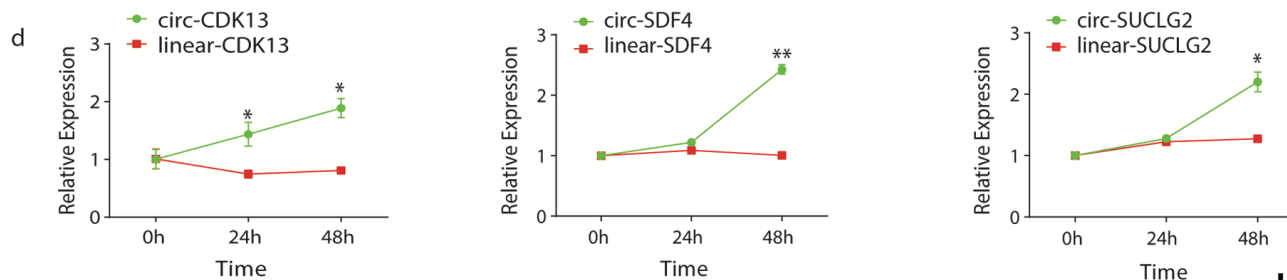
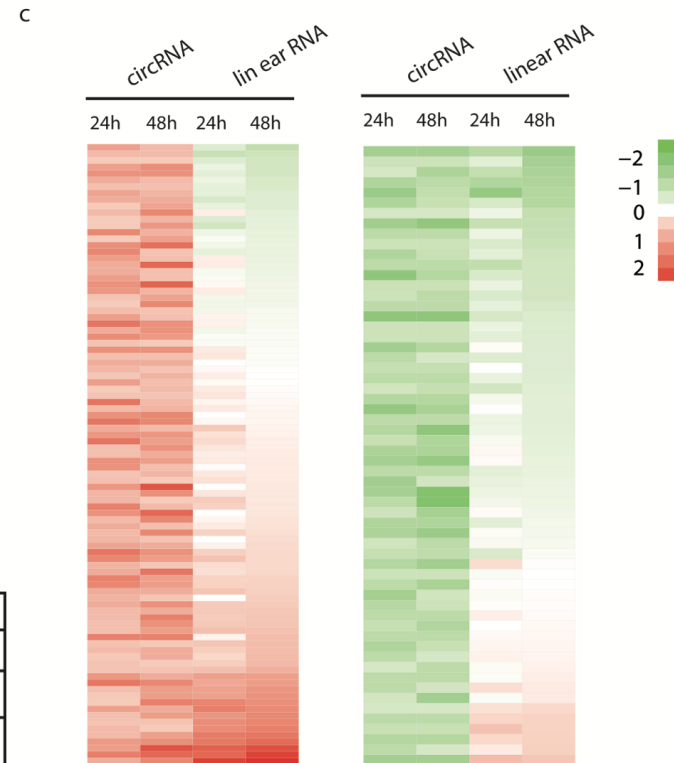
Unpublished data

# circRNA regulation independent of their host linear mRNA



b

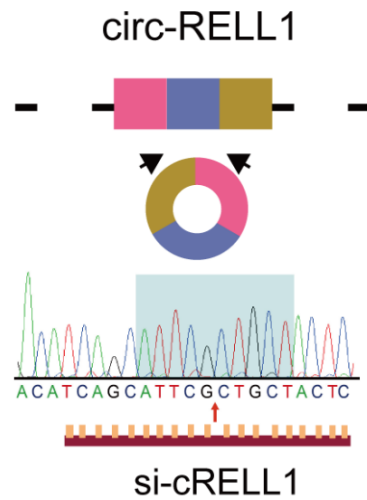
circRNA expression	linear RNA expression			Sum
	↑	→	↓	
↑	19	75	1	95
↓	1	53	6	60



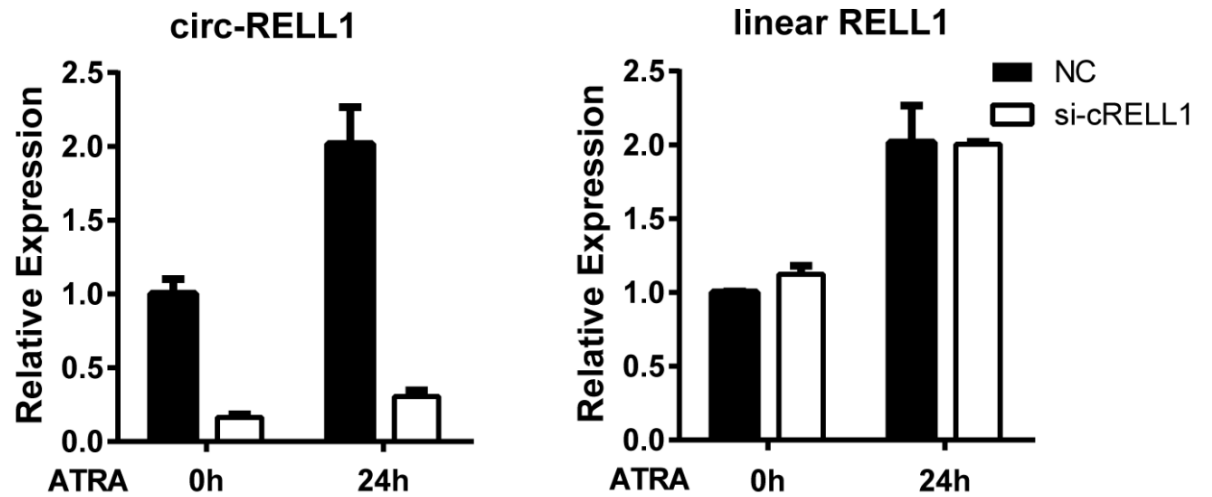
Unpublished data

# Requirement of circ-RELL1 in ATRA-induced differentiation of APL cells

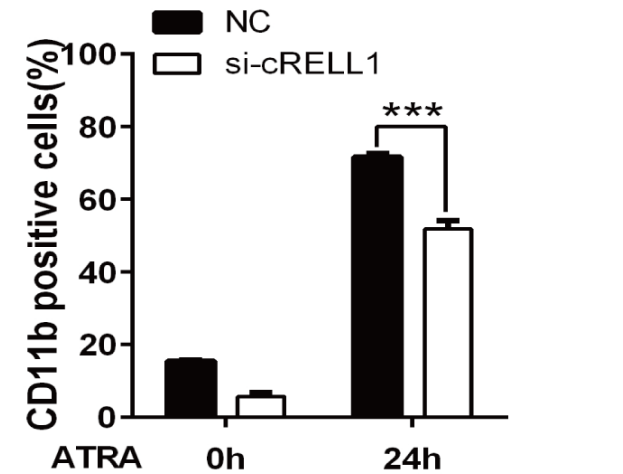
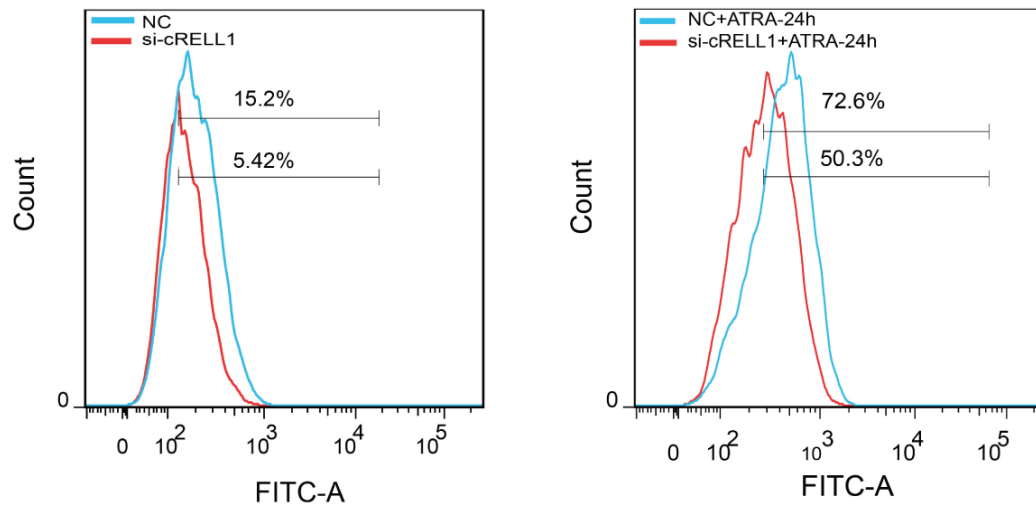
c



d



e



Unpublished data

# Summary

- Genome-wide binding pictures of PML/RAR $\alpha$ 
  - PML/RAR $\alpha$  selectively targets PU.1-regulated genes.
  - PML/RAR $\alpha$  is colocalized with RXR on chromatin.
  - PML/RAR $\alpha$  exerts both activation and repression roles of in driving APL.
- Regulatory features and functions of key targets of PML/RAR $\alpha$ .
- Transcriptomic view of the mechanism of ATRA action
  - ATRA induces transcriptional remodeling and a series of signaling pathways in APL cells.
  - ATRA dynamically regulates a number of circRNAs upon ATRA treatment.



# Acknowledgements

## Omics platforms

Yun Tan

Ping Wang

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Xuehua Zhu



## Functional studies

Wen Jin

Xianwen Yang

Xuefei Ma

Yewei Wang



## Bioinformatics analysis

Hai Fang

Ming Zhao

Jiantao Shi

Huanwei Wang