PARALLEL SINGLE-CELL SEQUENCING LINKS TRANSCRIPTIONAL AND EPIGENETIC HETEROGENEITY

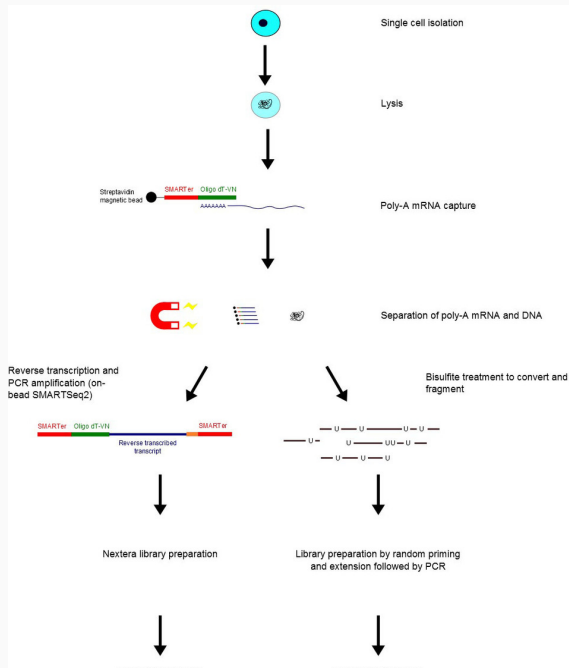Angermueller et al., Nature Methods, January 11, 2016. doi:10.1038/nmeth.3728.

Saket Choudhary

February 11, 2016

BISC 542

scM&T-seq: Parallel single-cell genome-wide
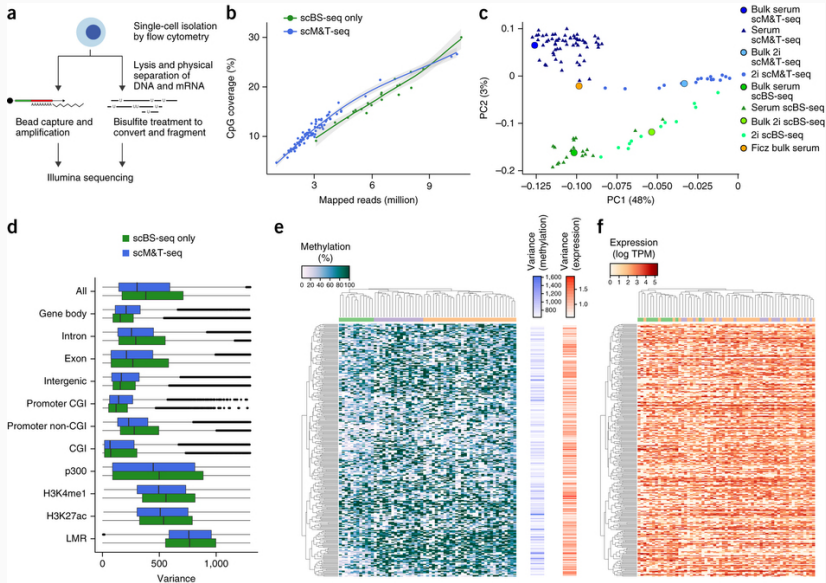methylation & transcriptome seq
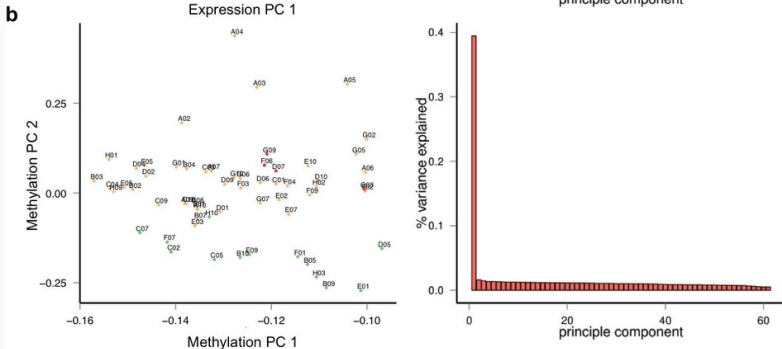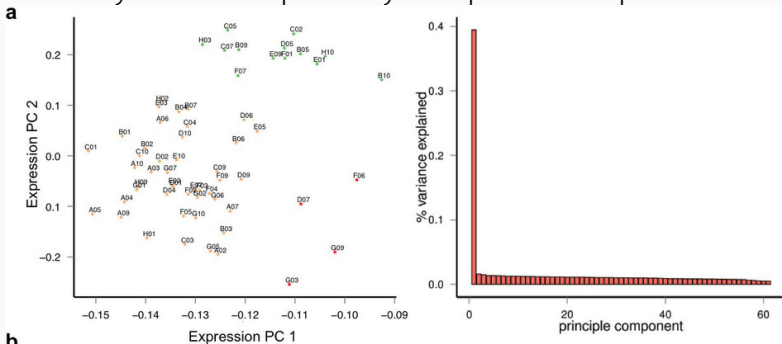$\implies$ Coupled/Uncoupled?

Protocol

Data:

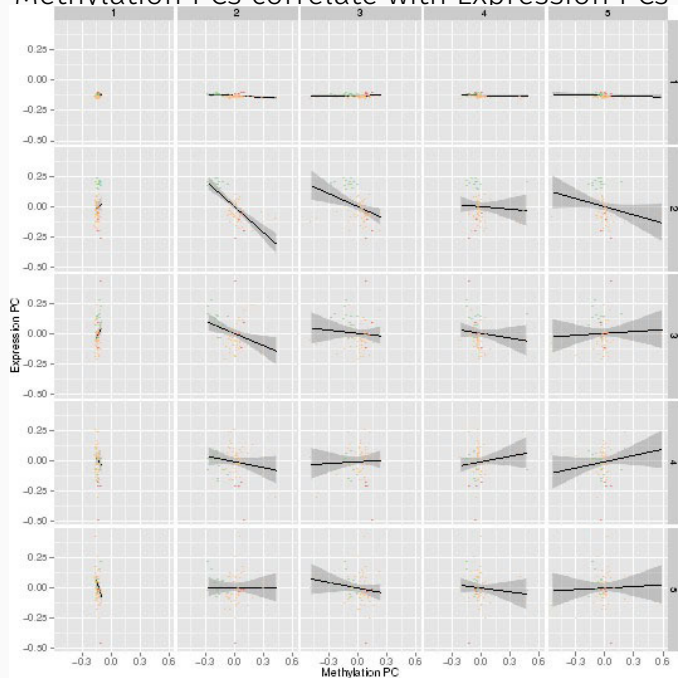76 individual serum ESC + 16 ESCc in '2i'[induces hypomethylation]

Variation in methylation levels are explained by cell type

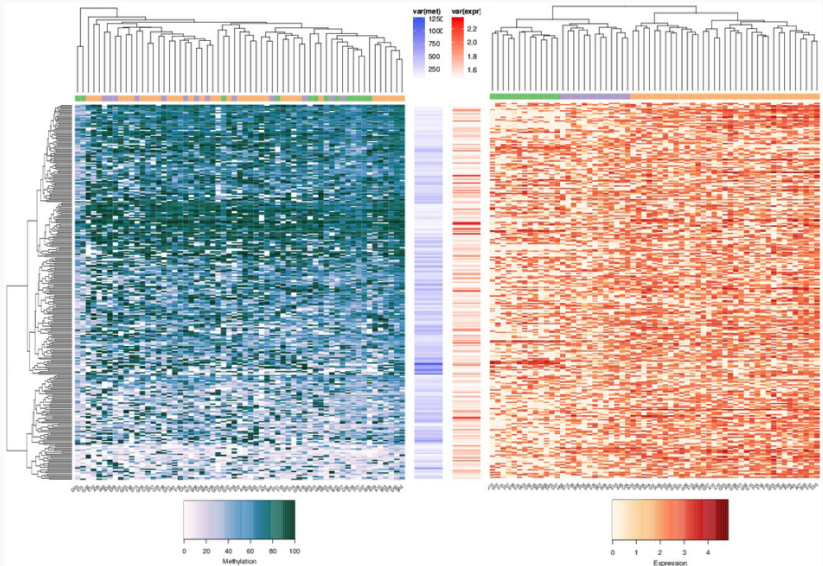# Methylation PCs partially recapitulate expression

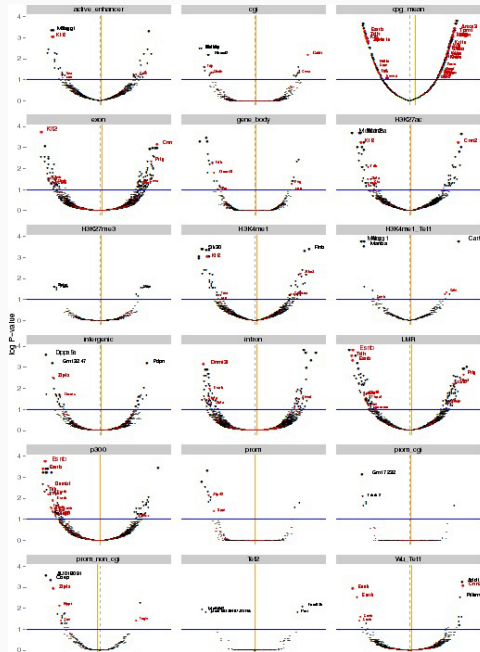# Methylation PCs correlate with Expression PCs

6

Global methylome and transcriptome profiles are complementary

Association between expression levels and methylation : BOTH negative and positive $\implies$ Interactions are Complex!

Correlation coefficients in alternative genomic context:

Validates with bulk RNA-seq and BS-seq[Oranges]
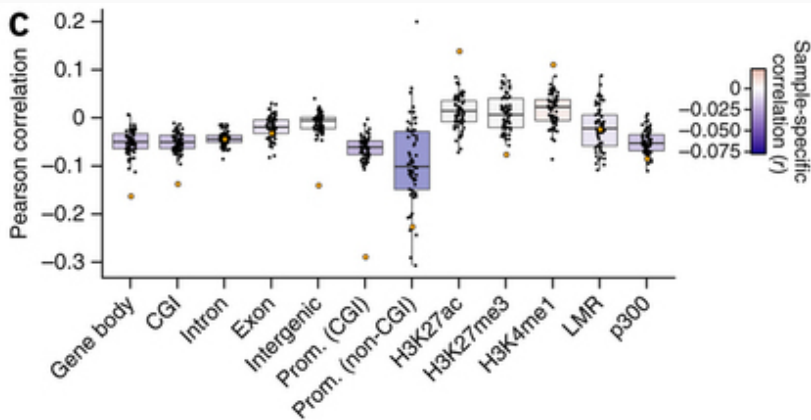
Insights

Transcriptome and Methylome can be
uncoupled

Insights

Association with transcription:

- v/s methylation at non-CpG island promoters : negative (known)
- v/s methylation at distal regulatory elements : both

Summary

- Parallel methylome & transcriptome profiling: feasbile
- Associations can be quantified at single-cell level
- Fluctuating pluripotency in serum ESC ≅ Epigenetic heterogenity

Ideas

- Spearman Correlation? for individual CpGs or regions to observe trend
- Infer cell state from data?[Complementary]
- CA instead of PCA to reveal transcriptome-methylome clusters. See Fellenberg et al.

Academic Valentine

http://tinyurl.com/acadvalentines

References

· Seisenberger, Stefanie, et al. "The dynamics of genome-wide DNA methylation reprogramming in mouse primordial germ cells." Molecular cell 48.6 (2012): 849-862.

· Han, Han, et al. "DNA methylation directly silences genes with non-CpG island promoters and establishes a nucleosome occupied promoter." Human molecular genetics (2011): ddr356.

· Ficz, Gabriella, et al. "Dynamic regulation of 5-hydroxymethylcytosine in mouse ES cells and during differentiation." Nature 473.7347 (2011): 398-402.

· Macaulay, Iain C., et al. "G&T-seq: parallel sequencing of single-cell genomes and transcriptomes." Nature methods 12.6 (2015): 519-522.

· Smallwood, Sébastien A., et al. "Single-cell genome-wide bisulfite sequencing for assessing epigenetic heterogeneity." Nature methods 11.8 (2014): 817-820.

· Yang, Xiaojing, et al. "Gene body methylation can alter gene expression and is a therapeutic target in cancer." Cancer cell 26.4 (2014): 577-590.

· Bogdanović, Ozren, et al. "Temporal uncoupling of the DNA methylome and transcriptional repression during embryogenesis." Genome research 21.8 (2011): 1313-1327.

· Fellenberg, Kurt, et al. "Correspondence analysis applied to microarray data." Proceedings of the National Academy of Sciences 98.19 (2001): 10781-10786.