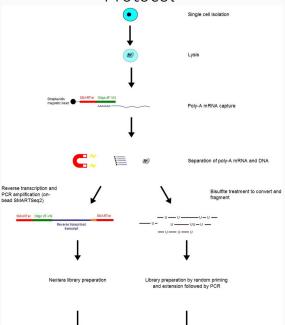
PARALLEL SINGLE-CELL SEQUENCING LINKS TRANSCRIPTIONAL AND EPIGENETIC HETEROGENEITY

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 ⇒ Coupled/Uncoupled?

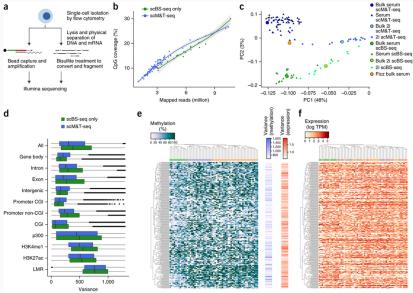
Protocol



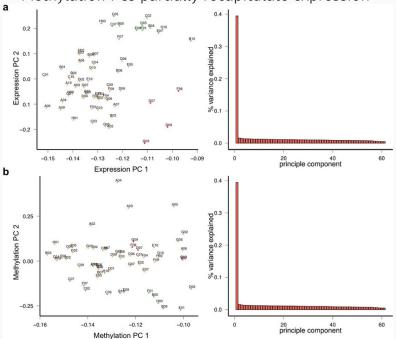
Data:

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

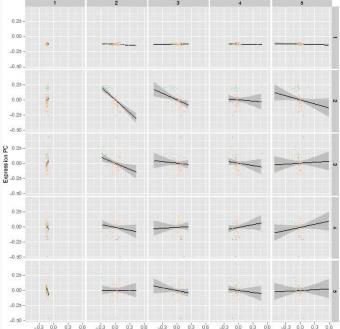
Variation in methylation levels are explained by cell type



Methylation PCs partially recapitulate expression

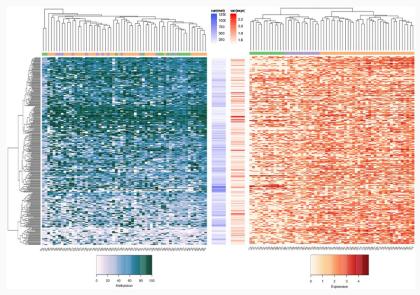


Methylation PCs correlate with Expression PCs



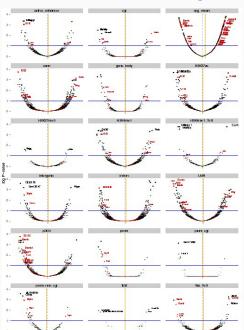
Methylation PC

Global methylome and transcriptome profiles are complementary

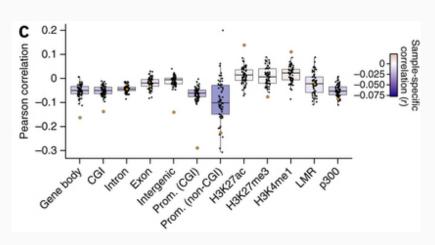


Association between expression levels and methylation : BOTH negative and positive \implies Interactions are Complex!

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

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.