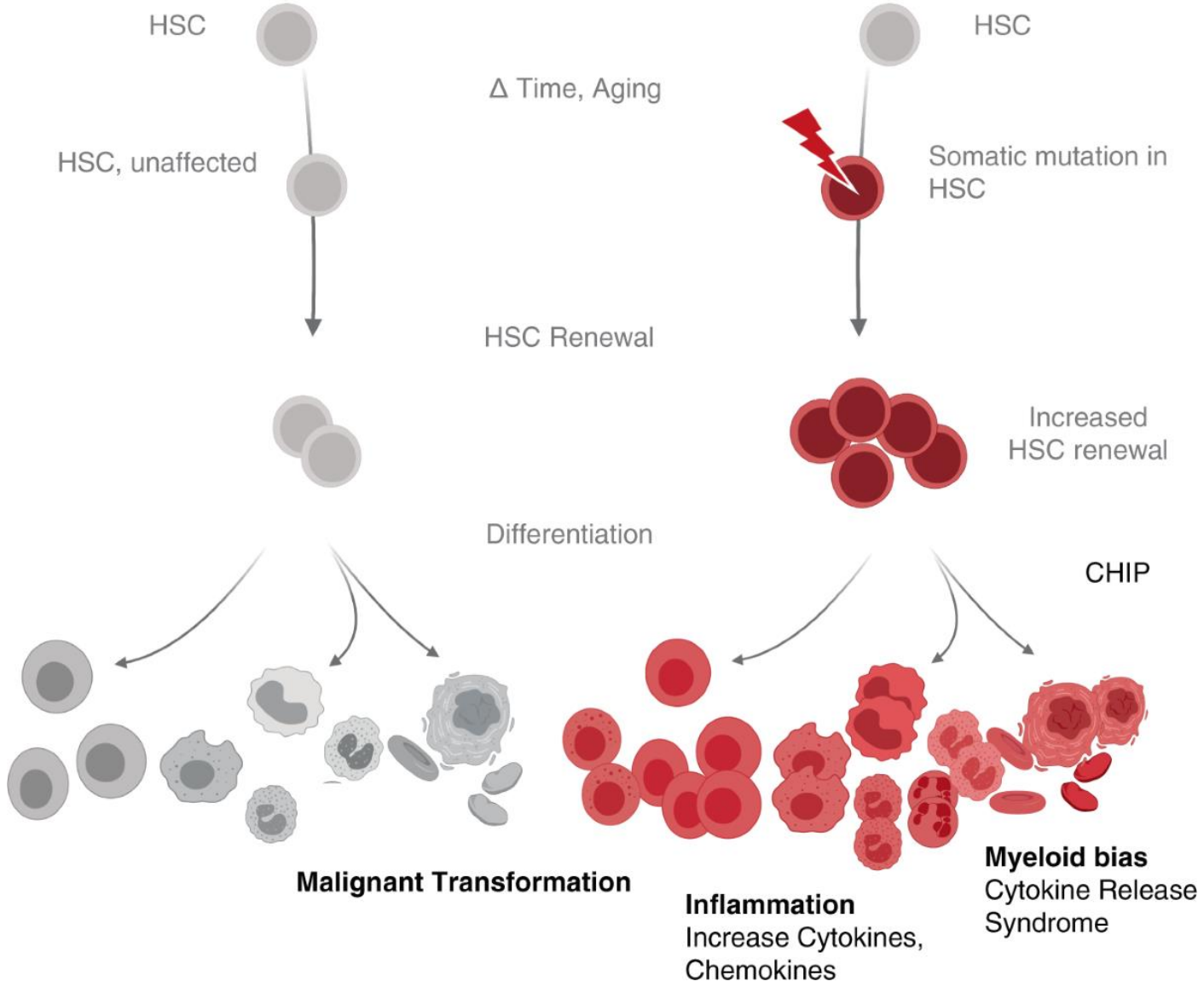
Unraveling Epigenetic and Transcriptomic Trajectories in Hematopoiesis during Aging

Bled, 2025, Atakan Ayden

Aging reprograms hematopoietic stem cells and reshapes blood cell production



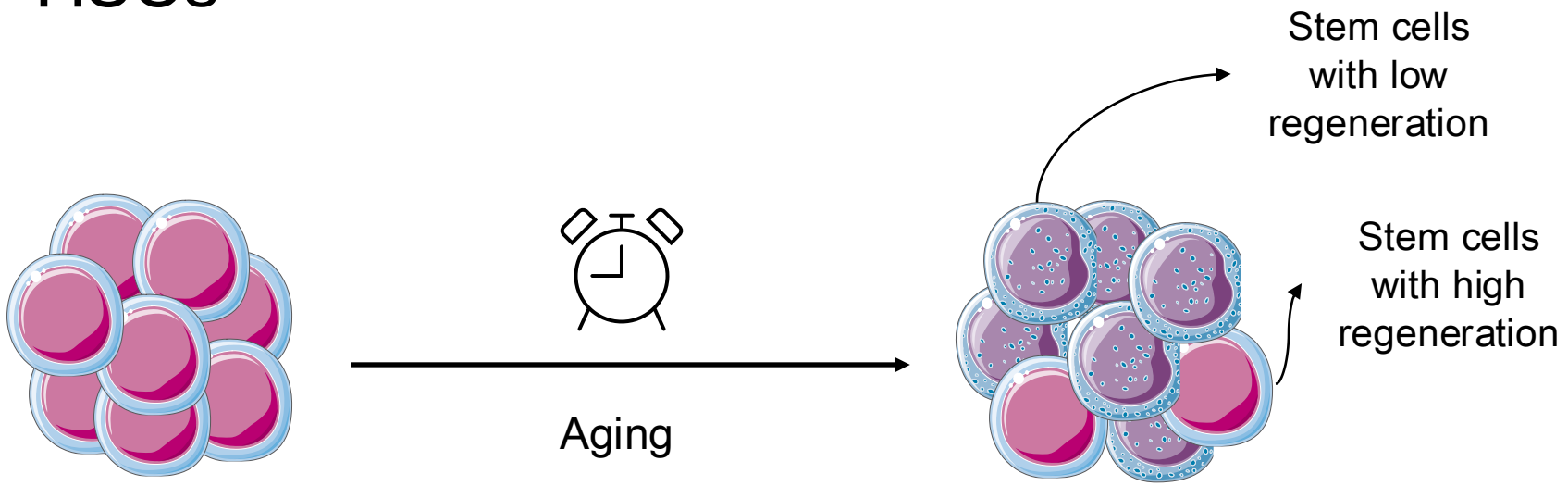
Young HSCs

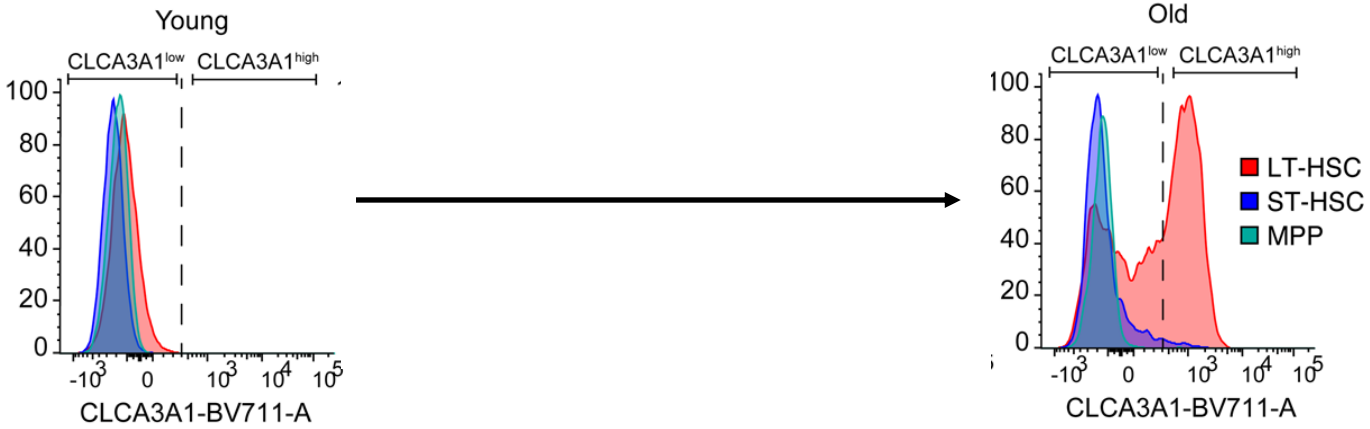
- High self-renewal capacity
- Balanced lineage output

Old HSCs

- Decline in regeneration capacity
- Decreased red blood cells, B and T lymphocytes
- Increased myeloid cells & susceptibility to AML

The aging marker Clca3a1 distinguishes between old and young-like HSCs

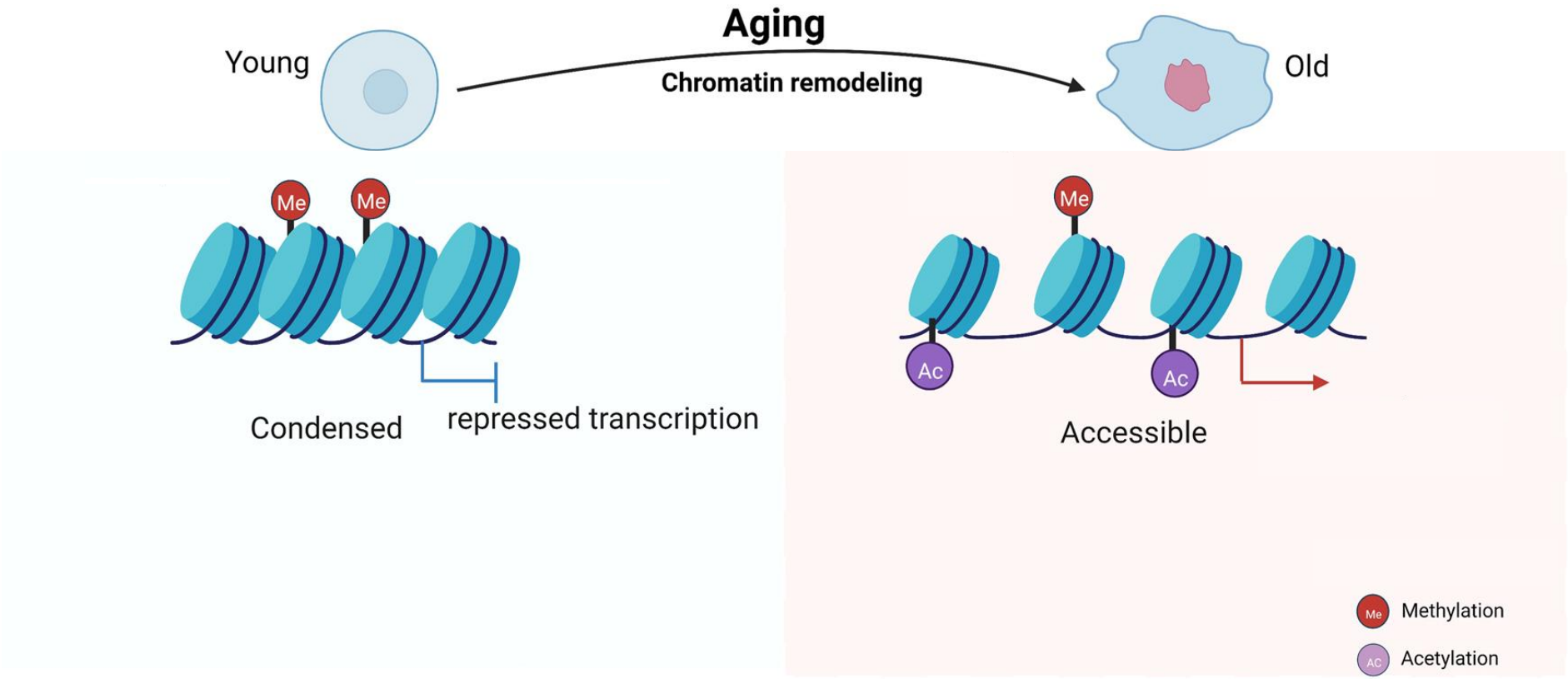




- During aging, blood cells are derived from fewer and fewer stem cells
- Clca3a1 is highly expressed on the surface of cells with lower regeneration.

"Taz protects hematopoietic stem cells from an aging-dependent decrease in PU.1 activity", Nature Communications, 2022

Aging transforms our genome through coordinated chromatin remodeling

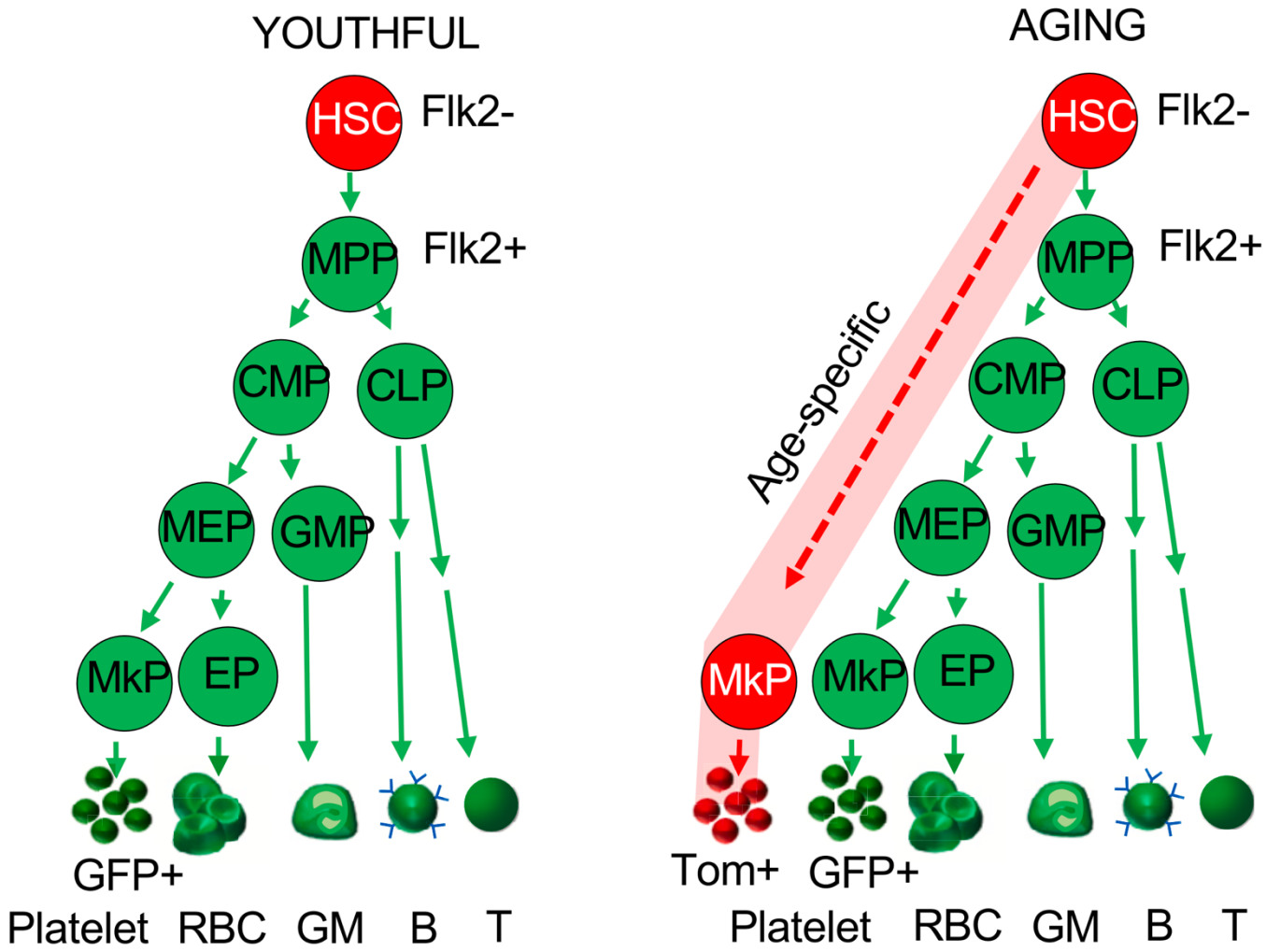


- Trend is activation of genes in aged cells
- But there is also locus specific changes.

Wang, K., Liu, H., Hu, Q. *et al*. (2022)

Aging-induced shortcut megakaryopoiesis

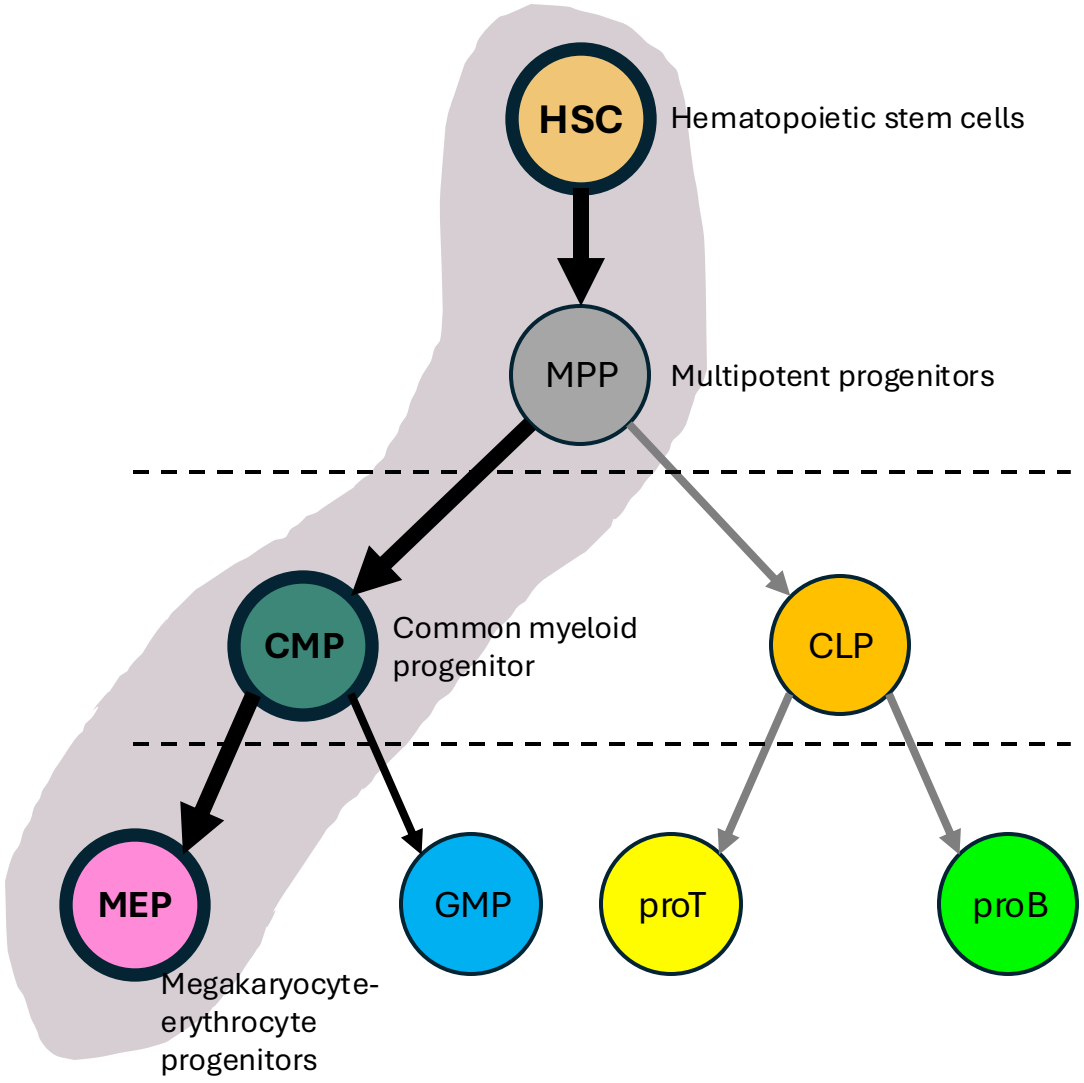
- Two distinct pathways for platelet production
- Shortcut pathway driven by megakaryocyte progenitors
- Aging-induced pathway contributes increased platelet reactivity



An age-progressive platelet differentiation path from hematopoietic stem cells causes exacerbated thrombosis", Cell, 2024

Aim of the project

- Transcriptome changes in high (old) and low (young-like) cells in three cell types (HSCs, CMPs, and MEPs)
- Epigenetic changes in HSCs in high (old) and low (young-like) cells
- **Are genes changed during aging in CMPs and MEPs epigenetically primed in HSCs?**



Method – Three Layers: CUT&TAG, scATAC-seq, RNA-seq

Cell isolation from bone marrow

HSC

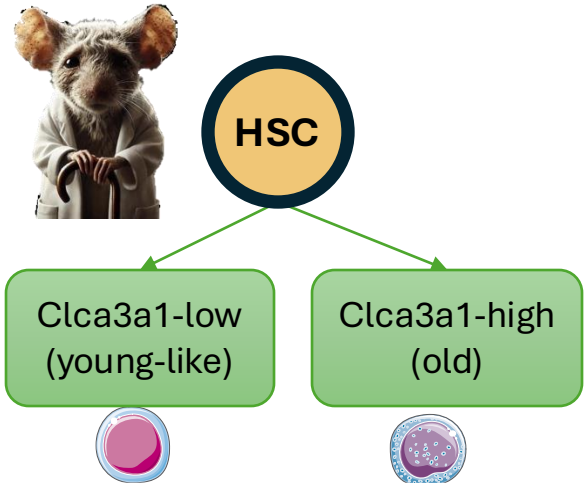
CMP

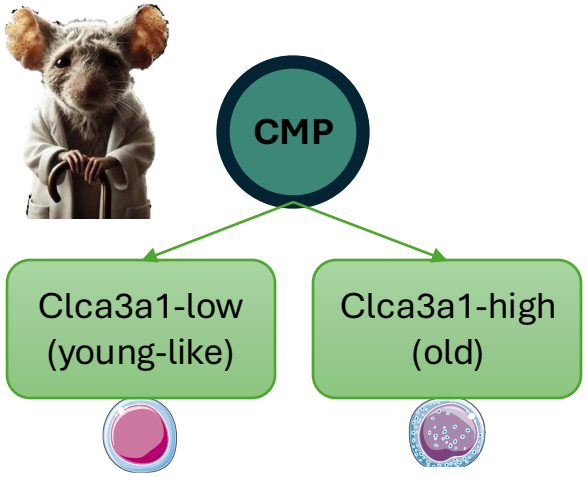
MEP

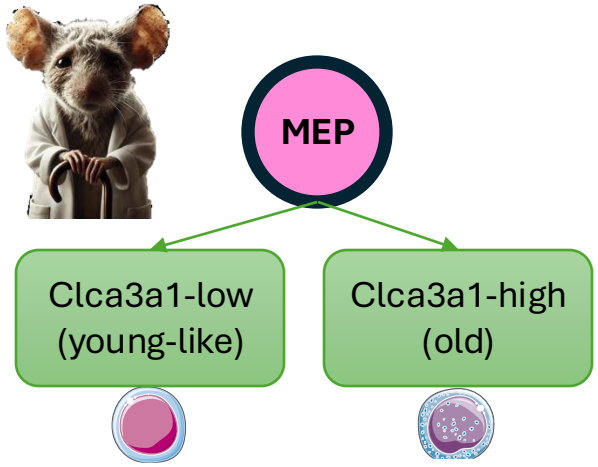
Method – Three Layers: CUT&TAG, scATAC-seq, RNA-seq

Cell isolation from bone marrow

FACS sorting





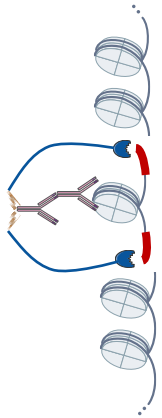


Method – Three Layers: CUT&TAG, scATAC-seq, RNA-seq

Cell isolation from bone marrow

FACS sorting

Sequencing



HSC

Clca3a1-low (young-like)

Clca3a1-high (old)

RNA-seq

CUT&TAG

H3K27me3

H3K27ac

H3K4me1

scATAC-seq

CMP

Clca3a1-low (young-like)

Clca3a1-high (old)

RNA-seq

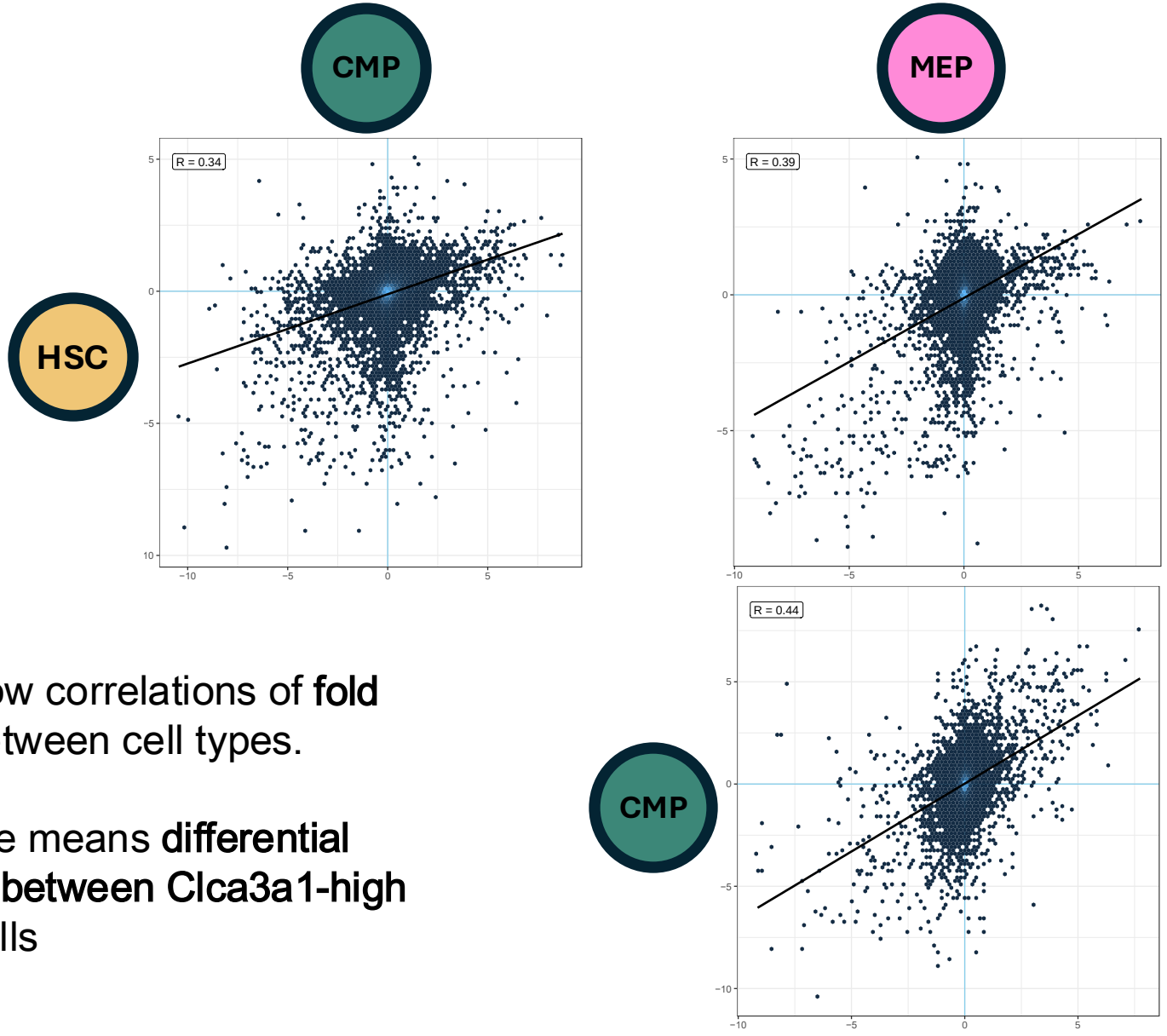
MEP

Clca3a1-low (young-like)

Clca3a1-high (old)

RNA-seq

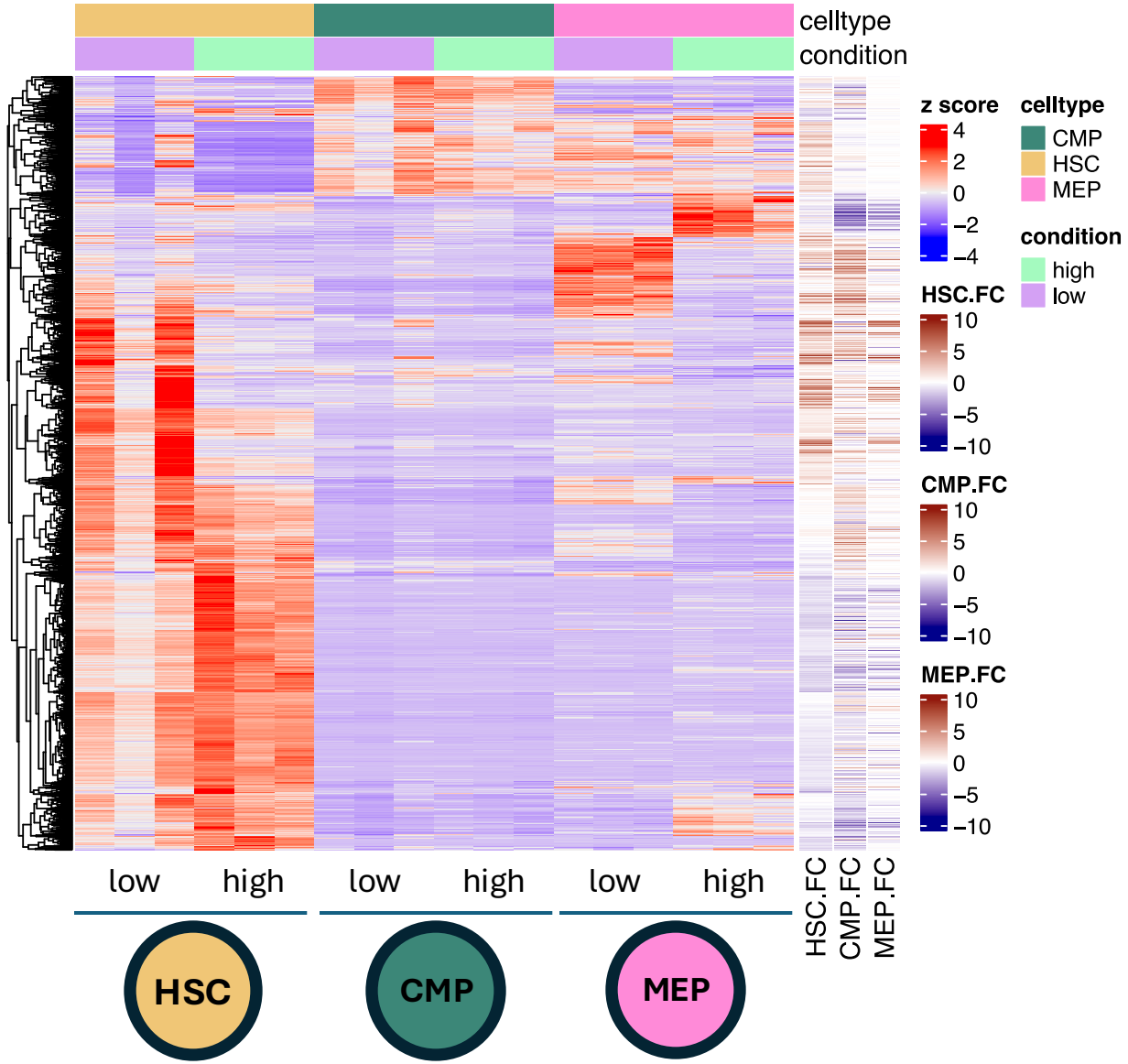
Correlations of fold changes between cell types



- Figures show correlations of **fold changes** between cell types.
- Fold change means **differential expression between Clca3a1-high and -low** cells

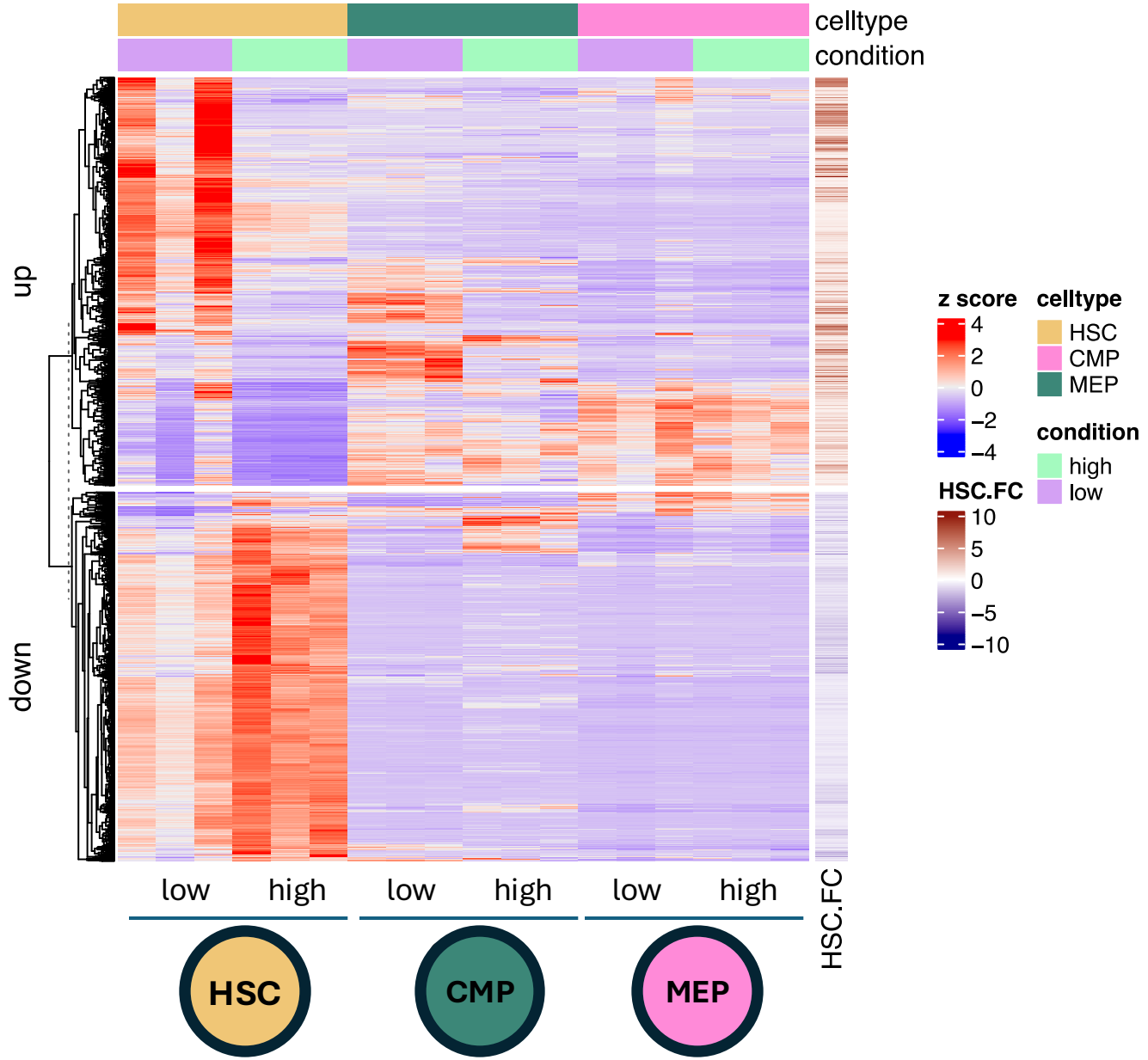
DE genes expression values in three cell types

- Heatmap shows every gene which is significantly expresssed in every cell type
- DE genes shows almost same regulation in both HSCs and CMPs



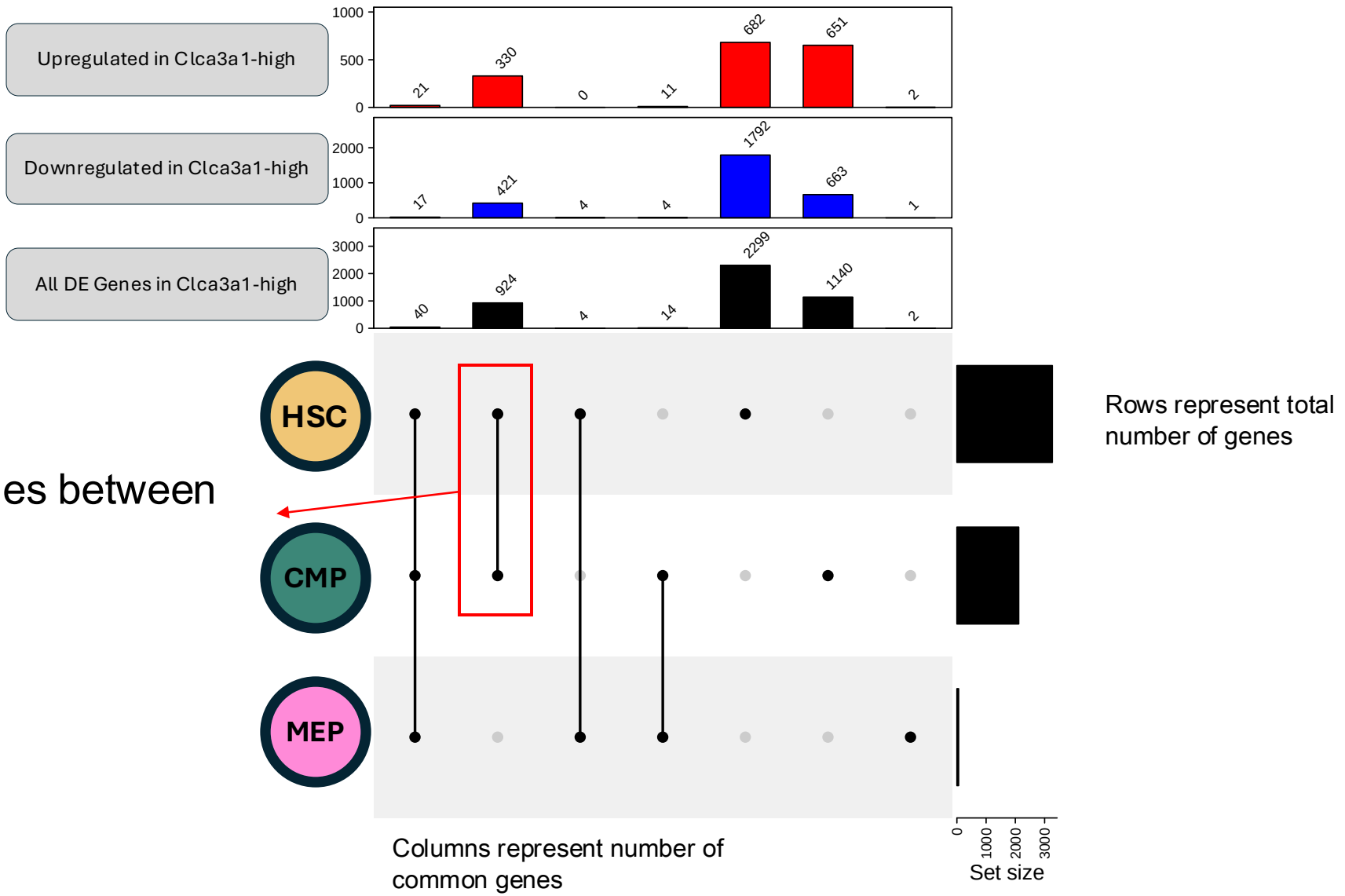
DE genes in HSCs

- Many genes do not show significant change in other cell types (CMPs and MEPs)
- Those genes changing during aging show different pattern in cell types



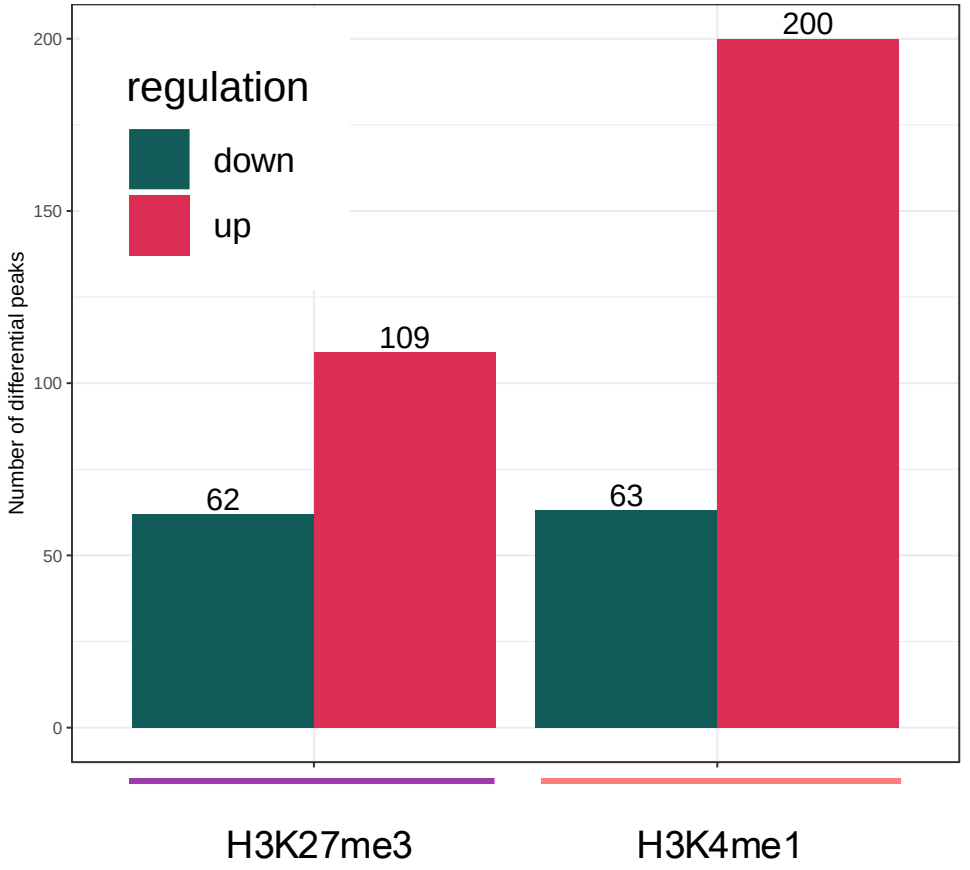
Common DE genes between cell types

- overlapped genes between **HSC** and **CMP**

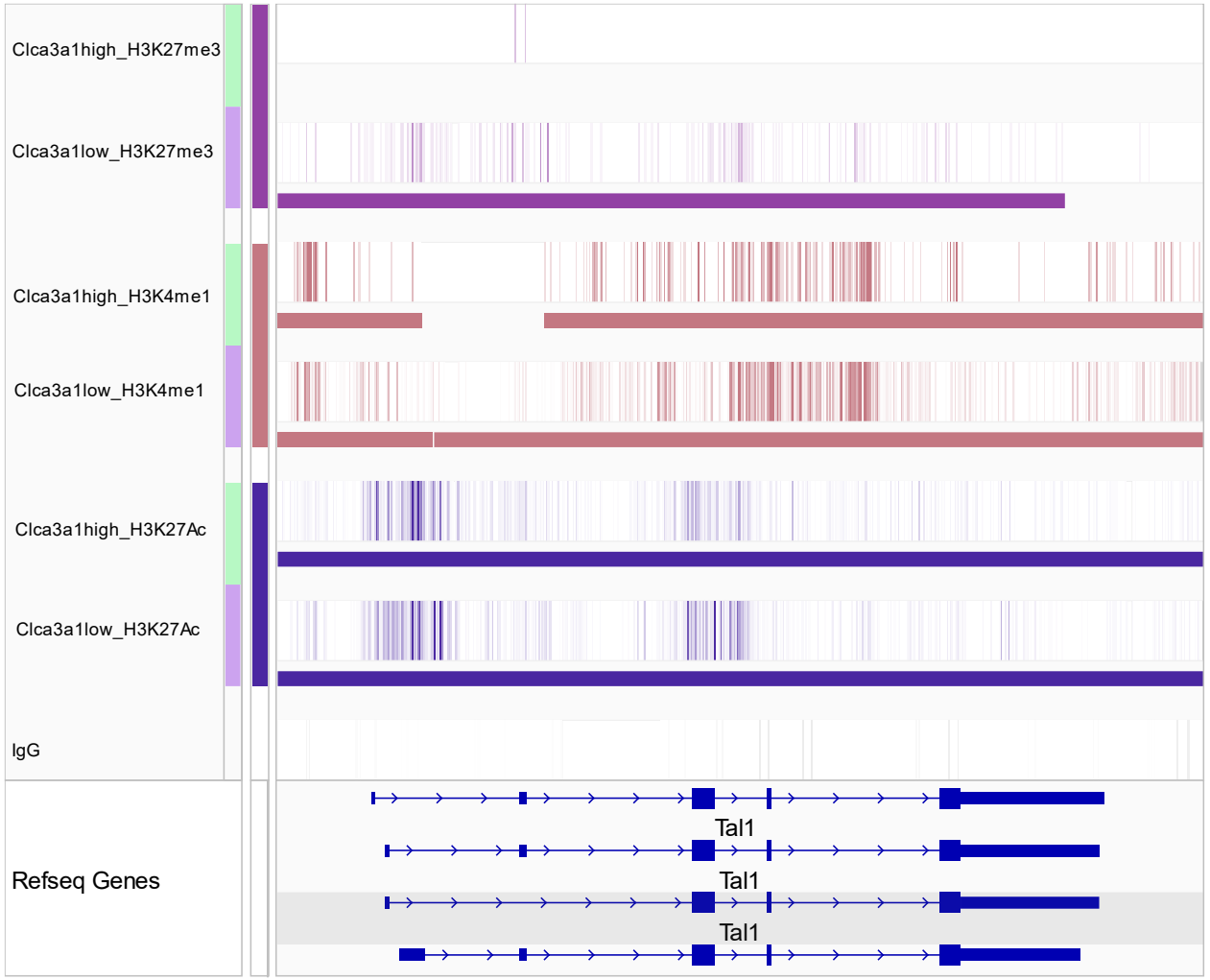


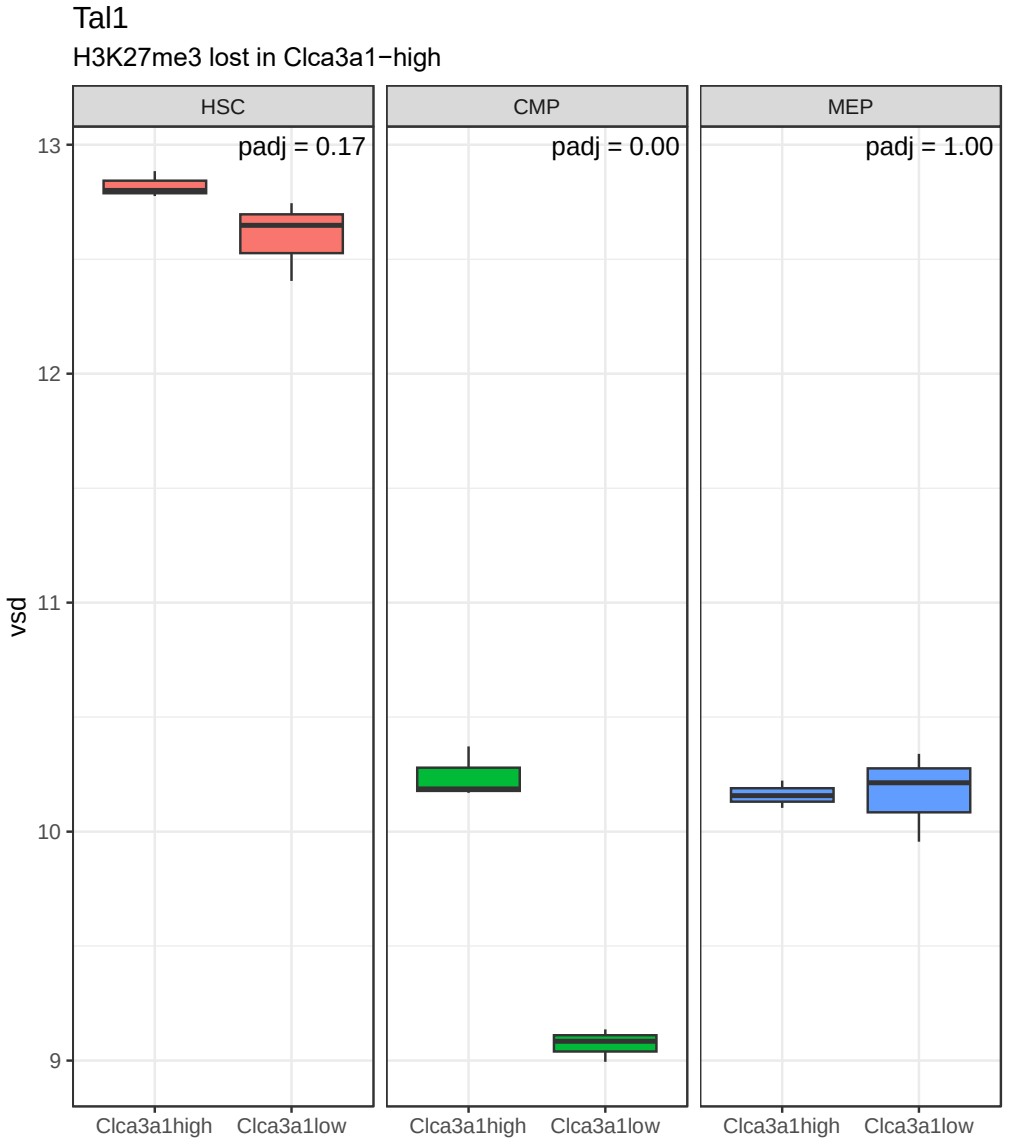
Epigenetic priming in HSCs with DE in differentiated cell types

- Overlap of differential histone modification peaks in HSCs and DE genes in CMPs and MEPs
- Filtered significant histone modification peaks in promoters and plot gene expression in cell types
- For instance:
  - H3K27me3 upregulated in high -> gene downregulation in high

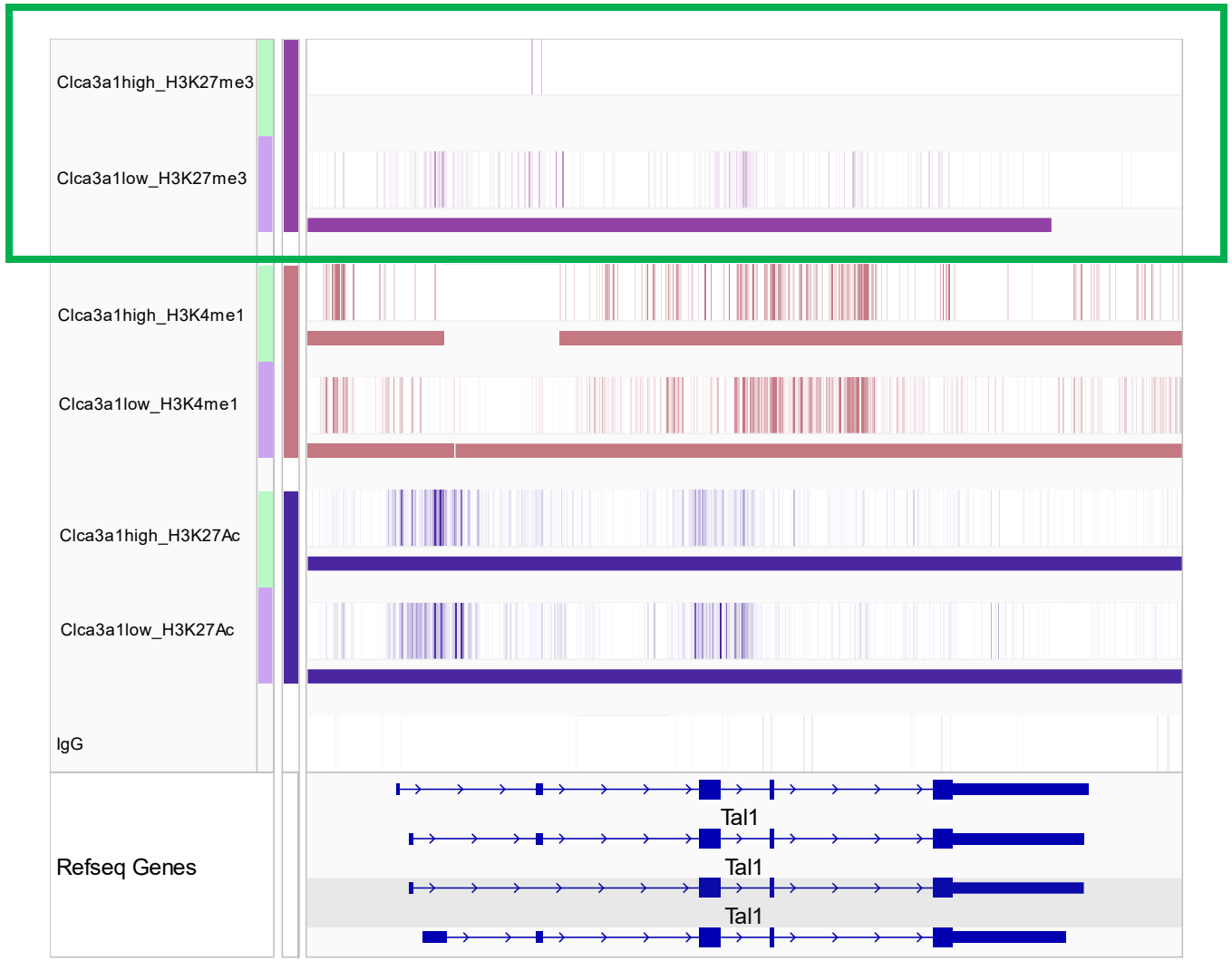


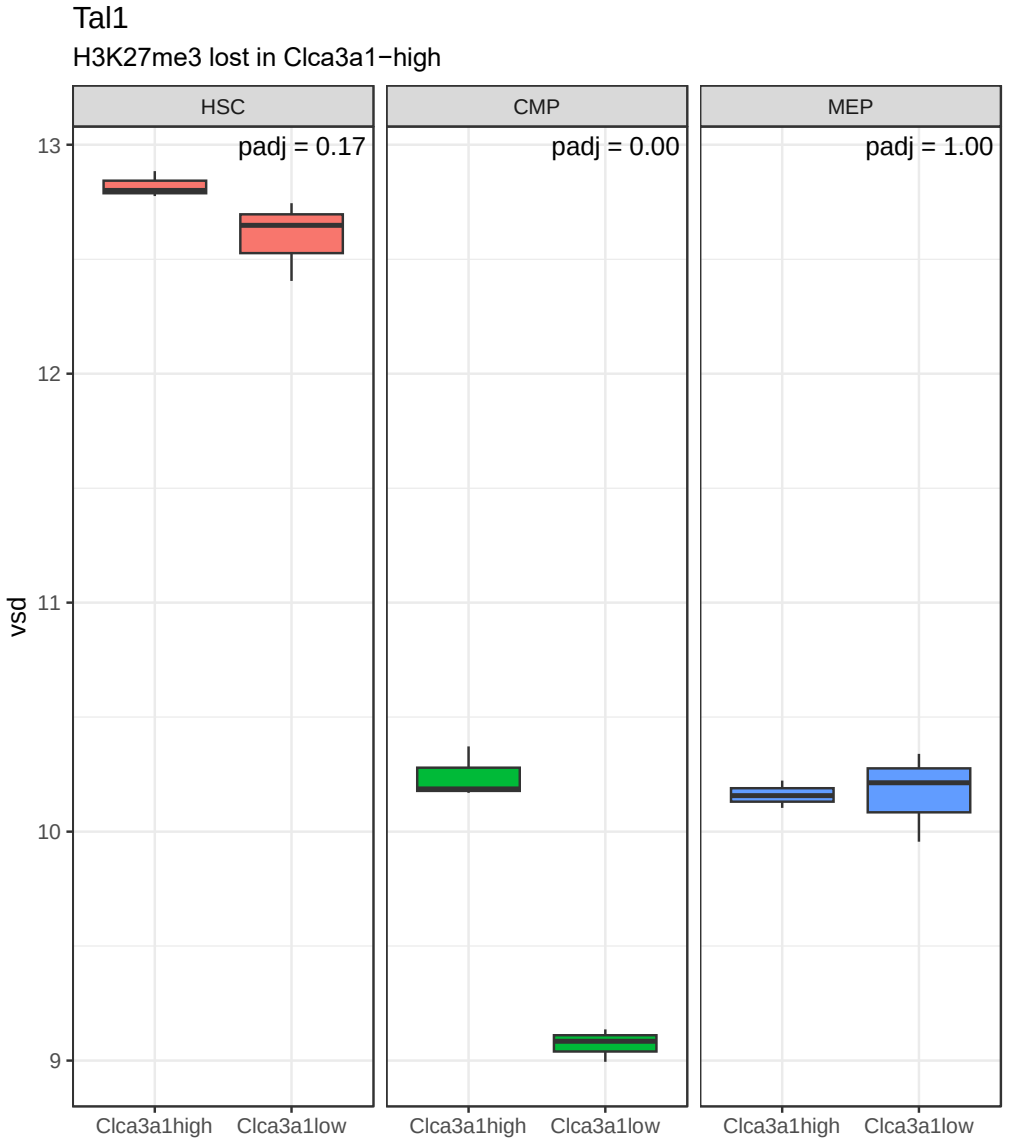
H3K27me3 in Tal1 gene body



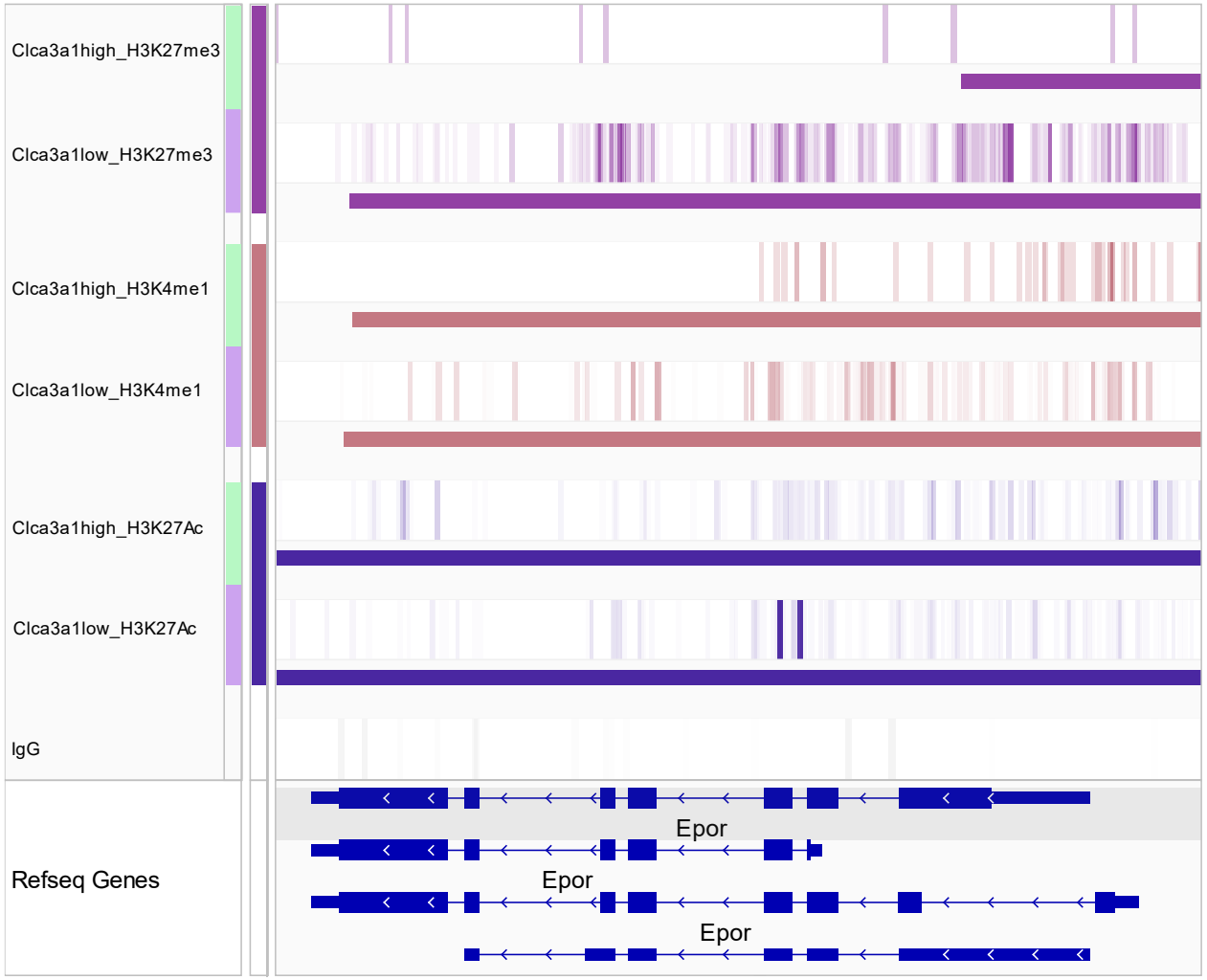


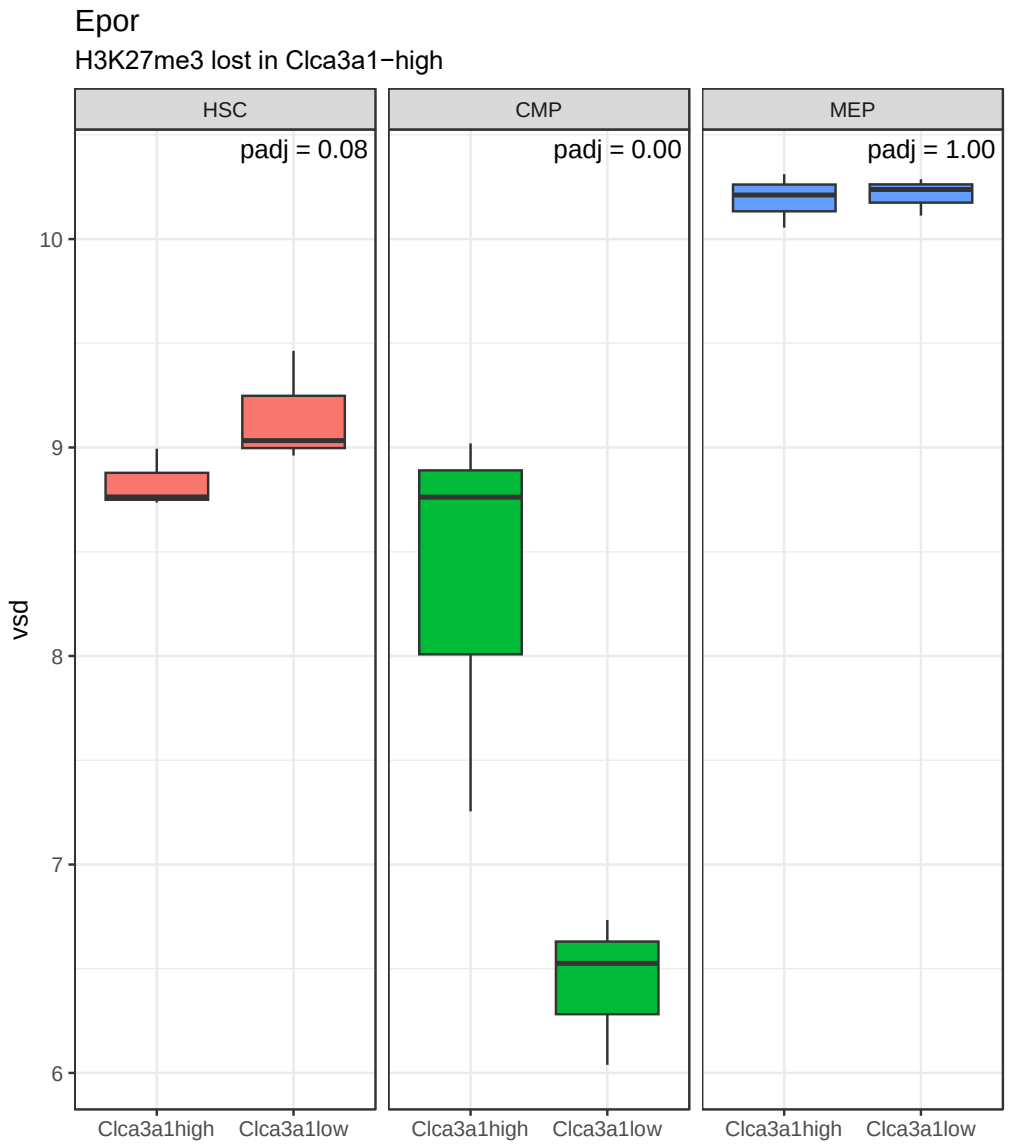
H3K27me3 in Tal1 gene body



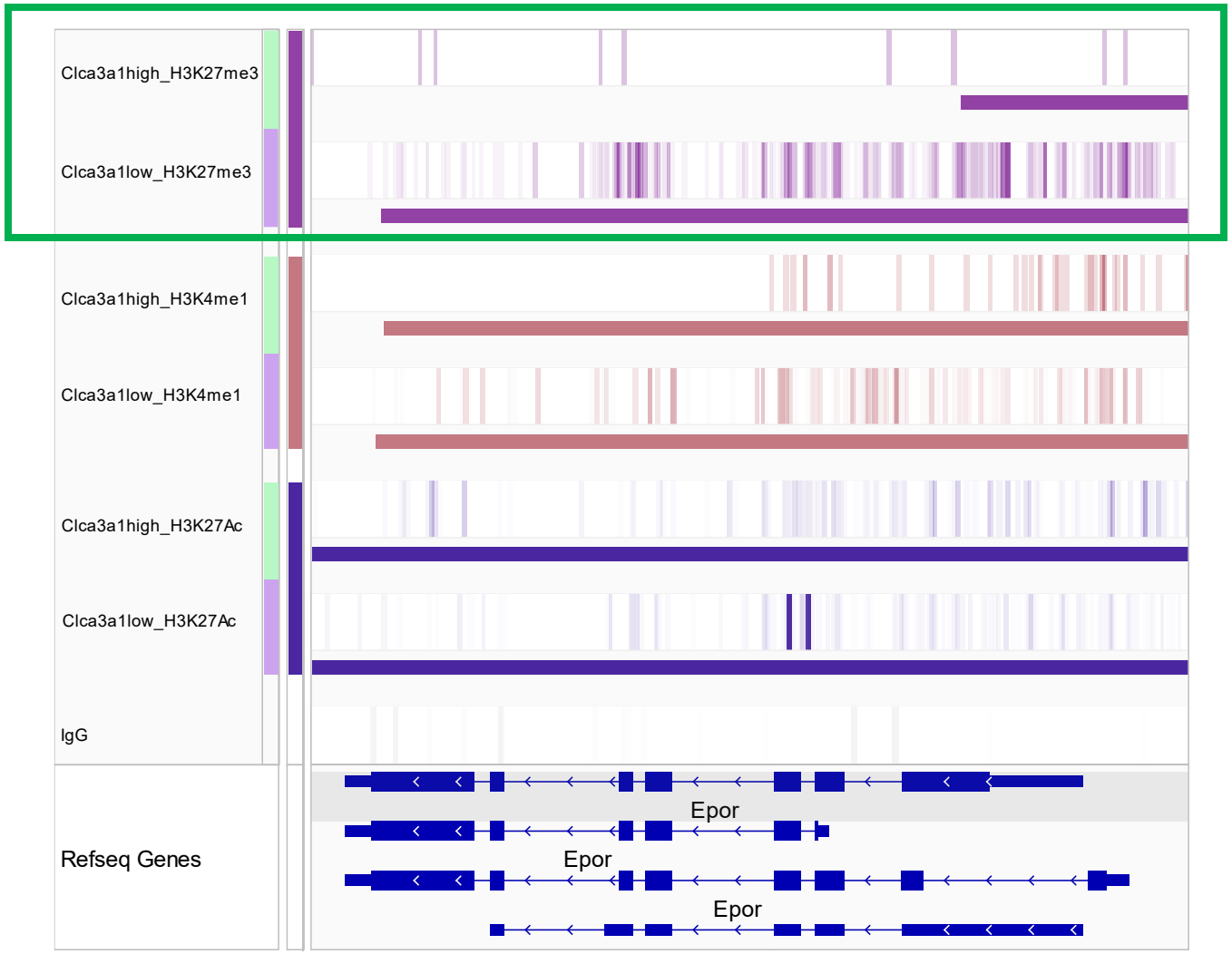


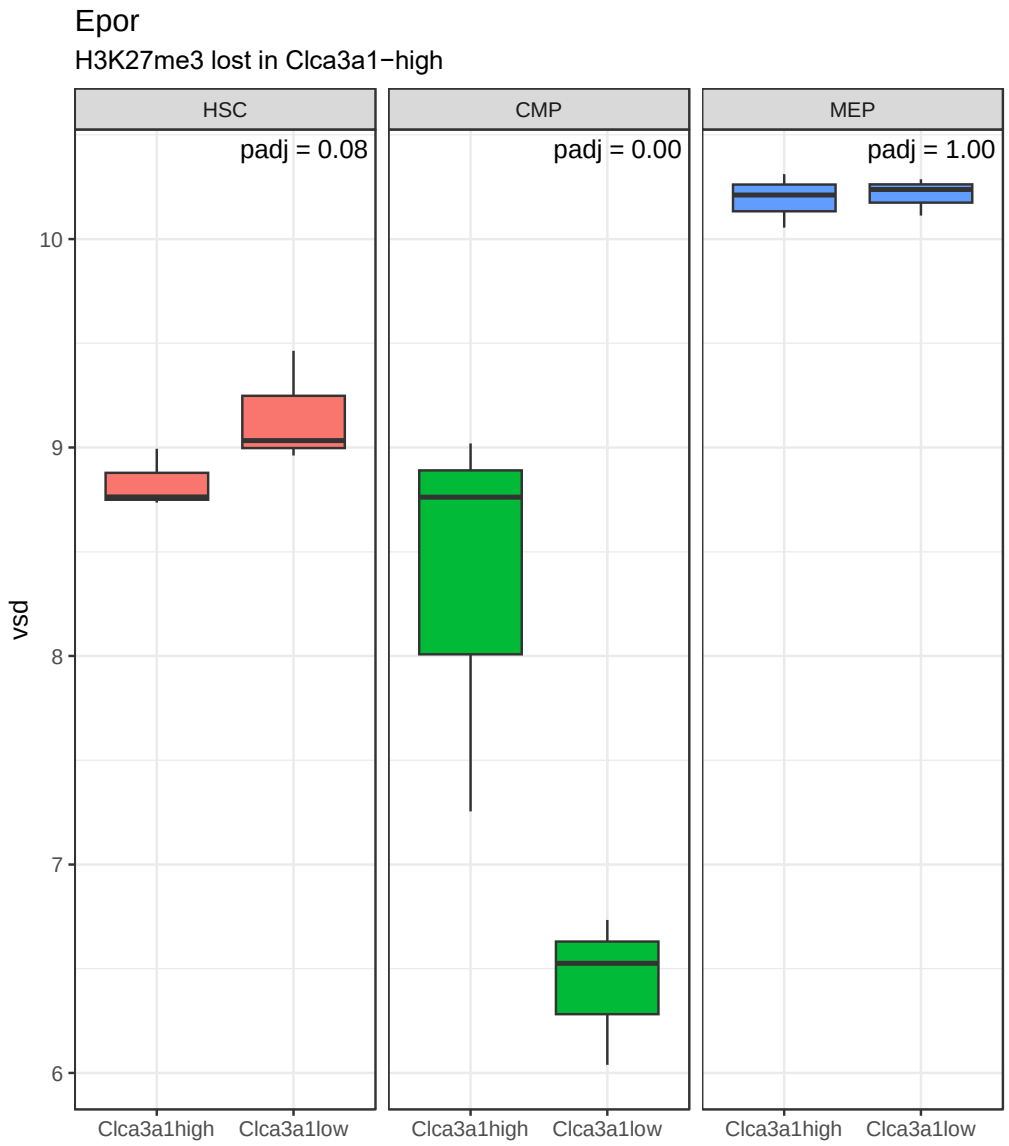
H3K27me3 in Epor promoter



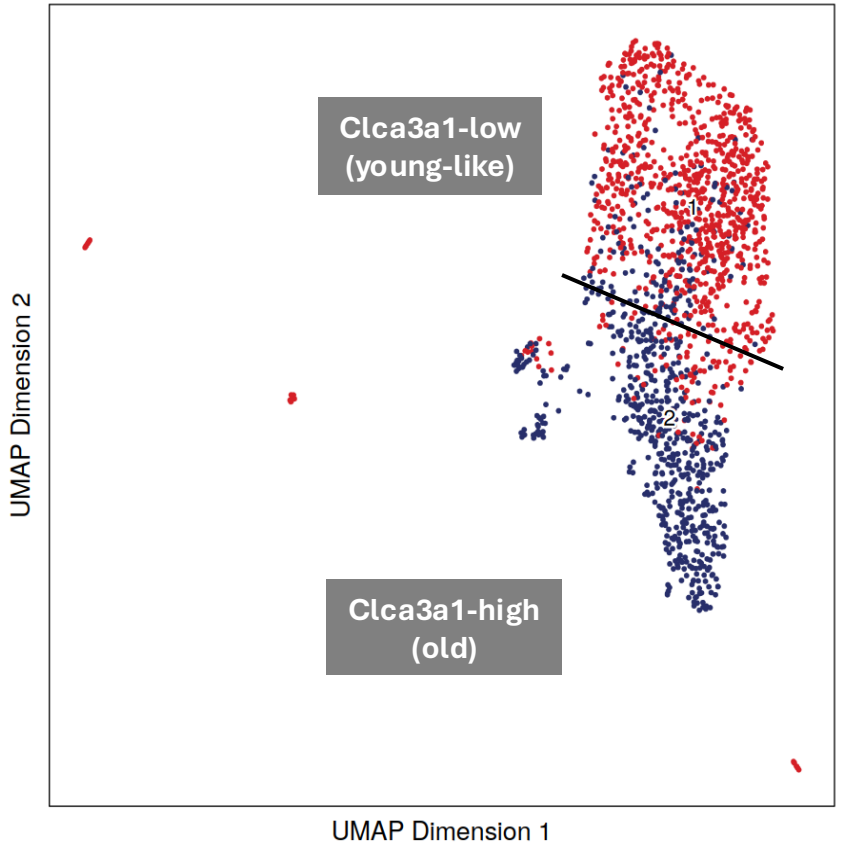


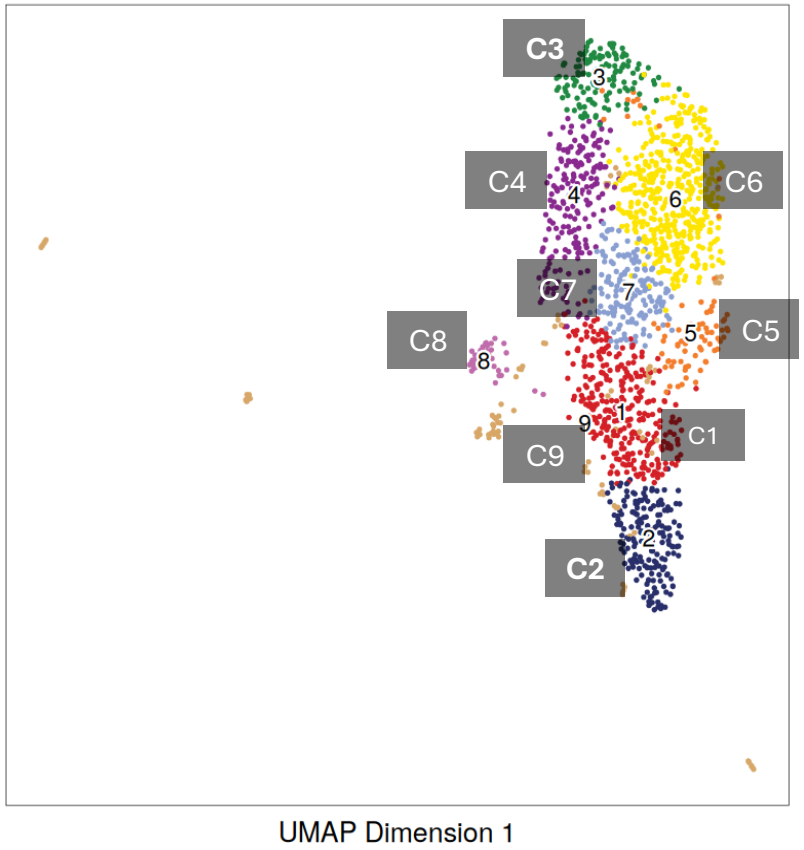
H3K27me3 in Epor promoter

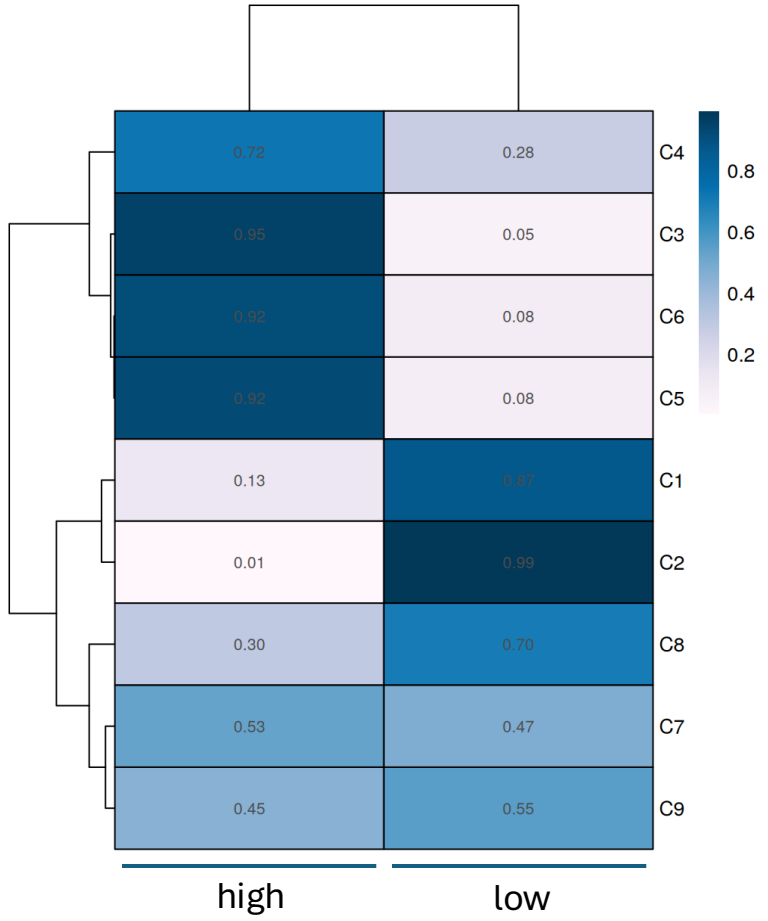




Open chromatin in single cell level in HSCs

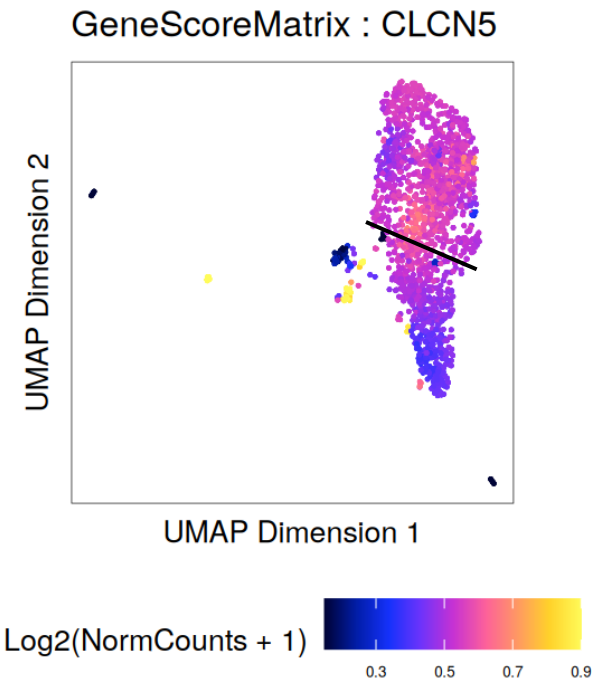


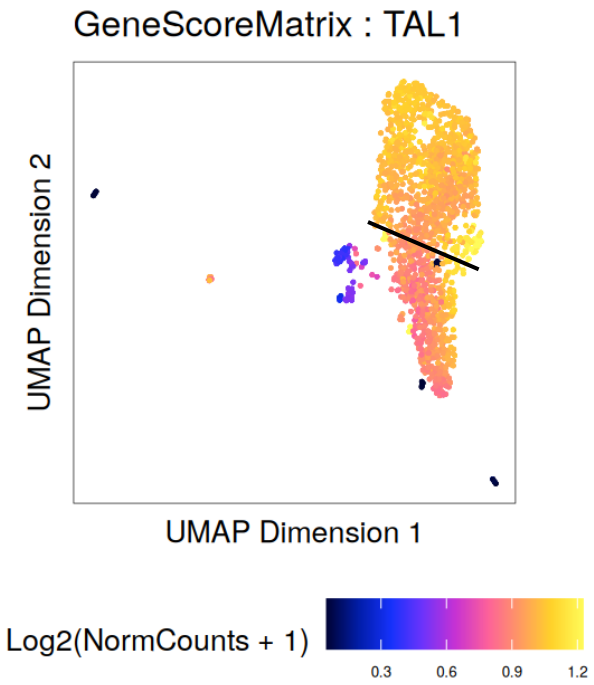


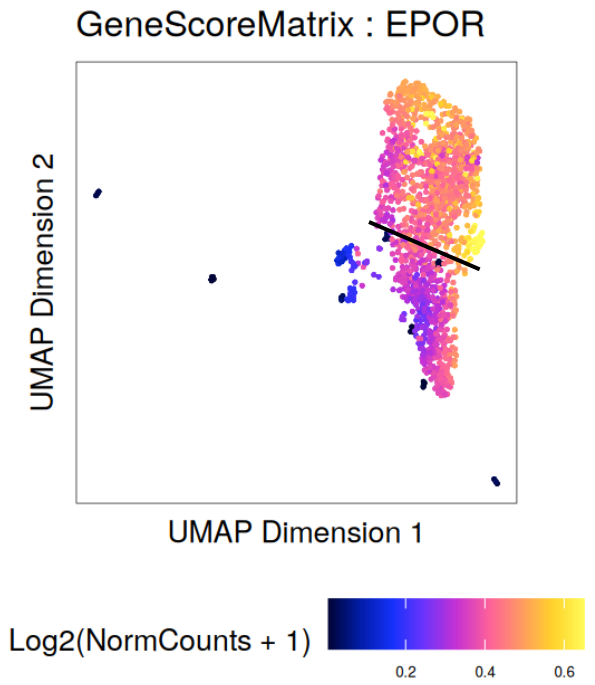


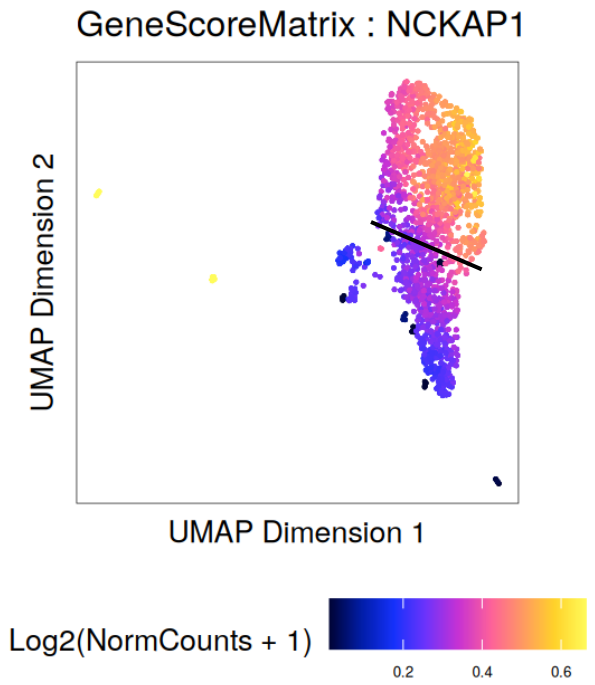
Similarity between clusters based on ATAC signal

ATAC signals of differentially bound H3K27me3 peaks



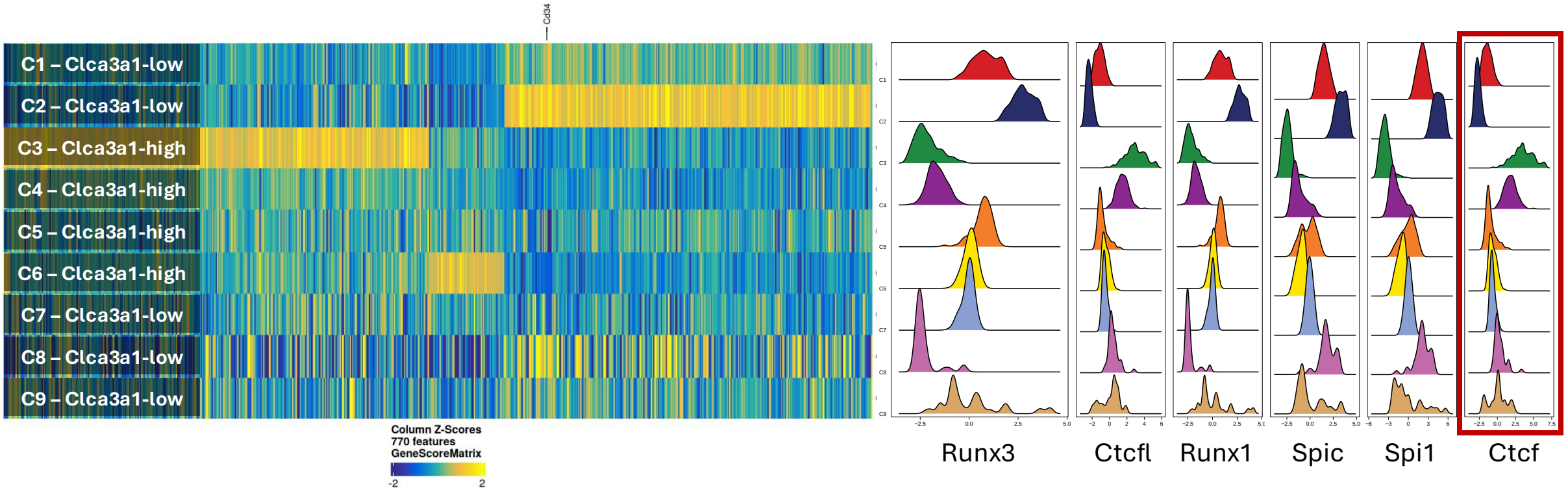




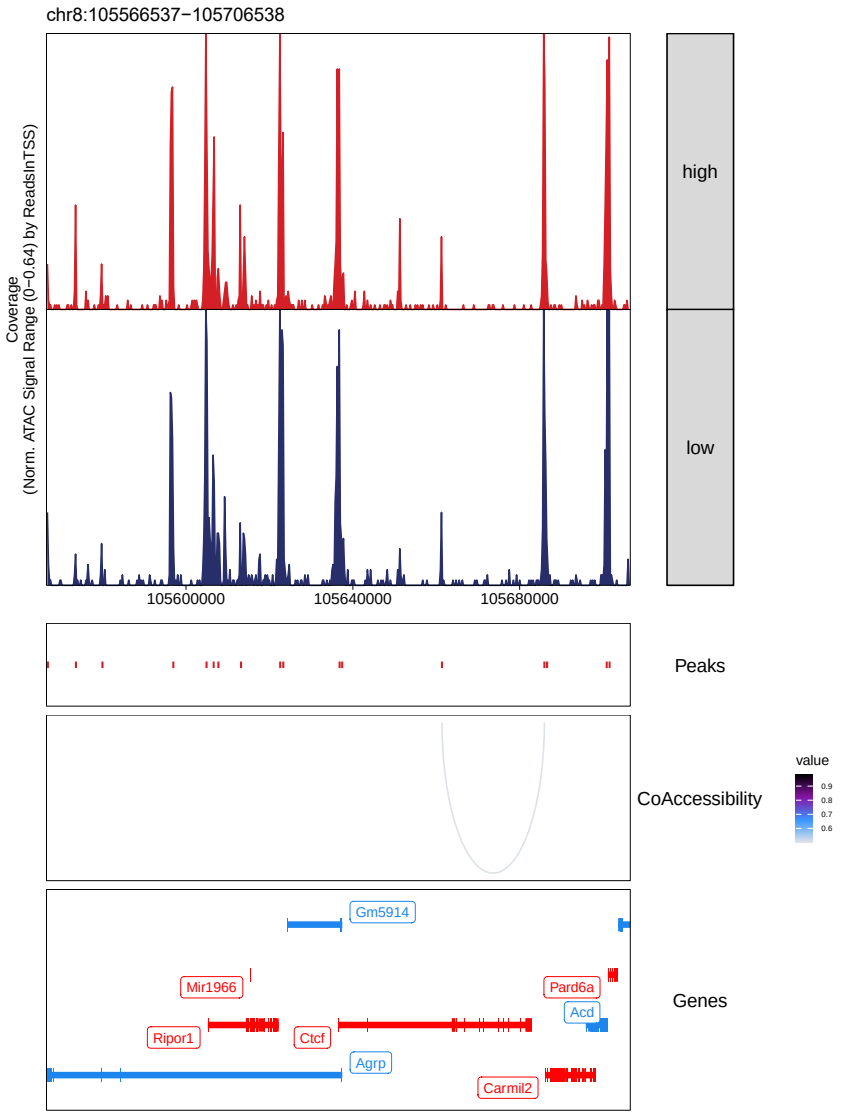


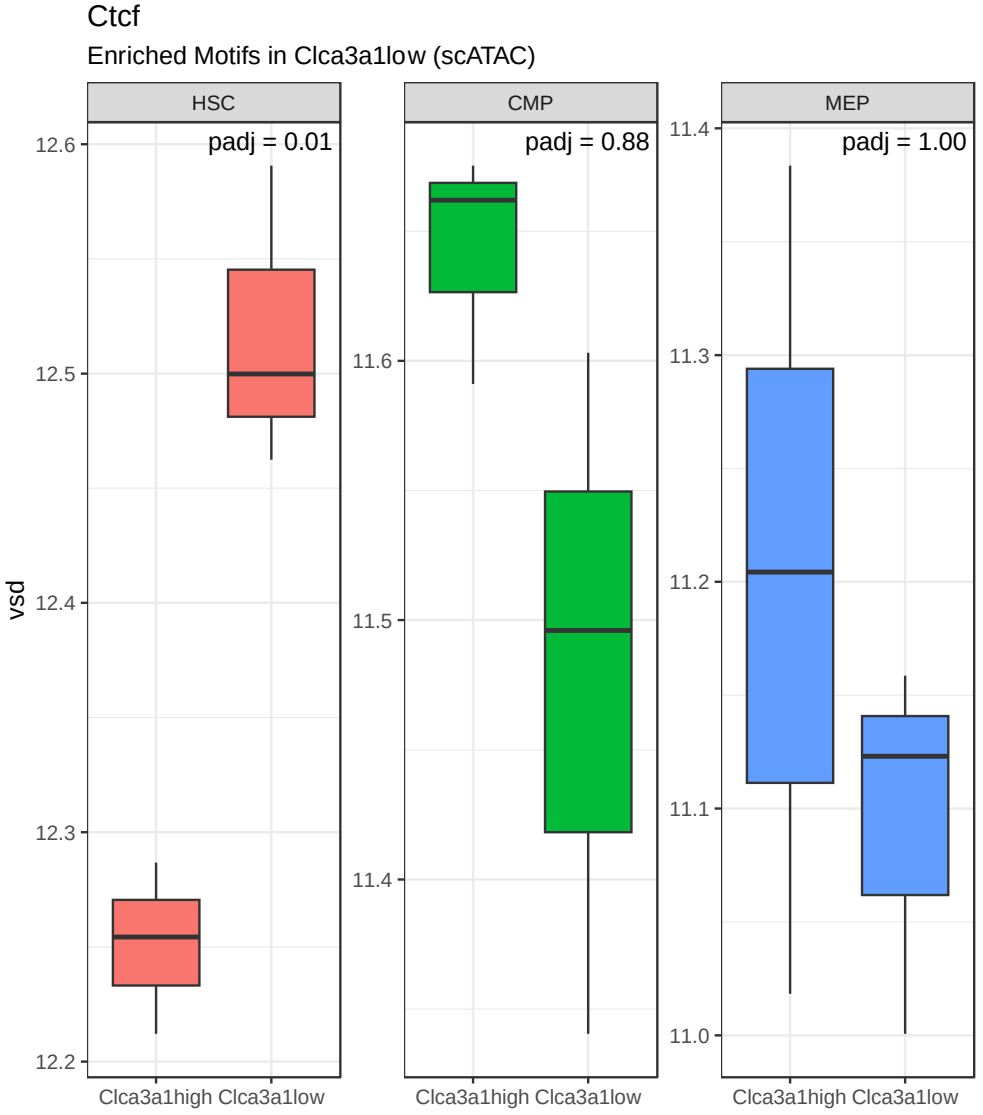
Marker genes of clusters and predicted motif binding deviations

- Clusters C2 (low) and C3 (high) have distinct marker genes.
- Based on predicted motif binding of Ctcf, clusters C3 and C4 (both high) are distinct



Ctcf Expression in Cell Types and Track in ATAC





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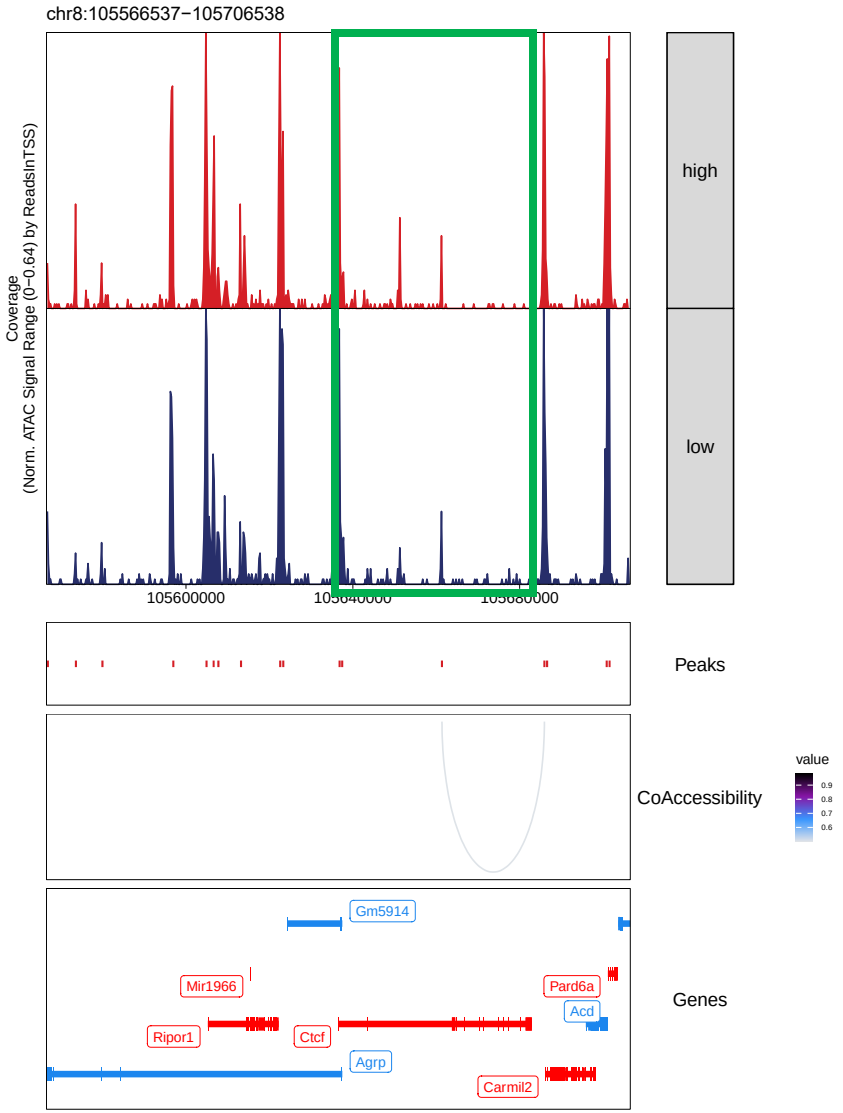
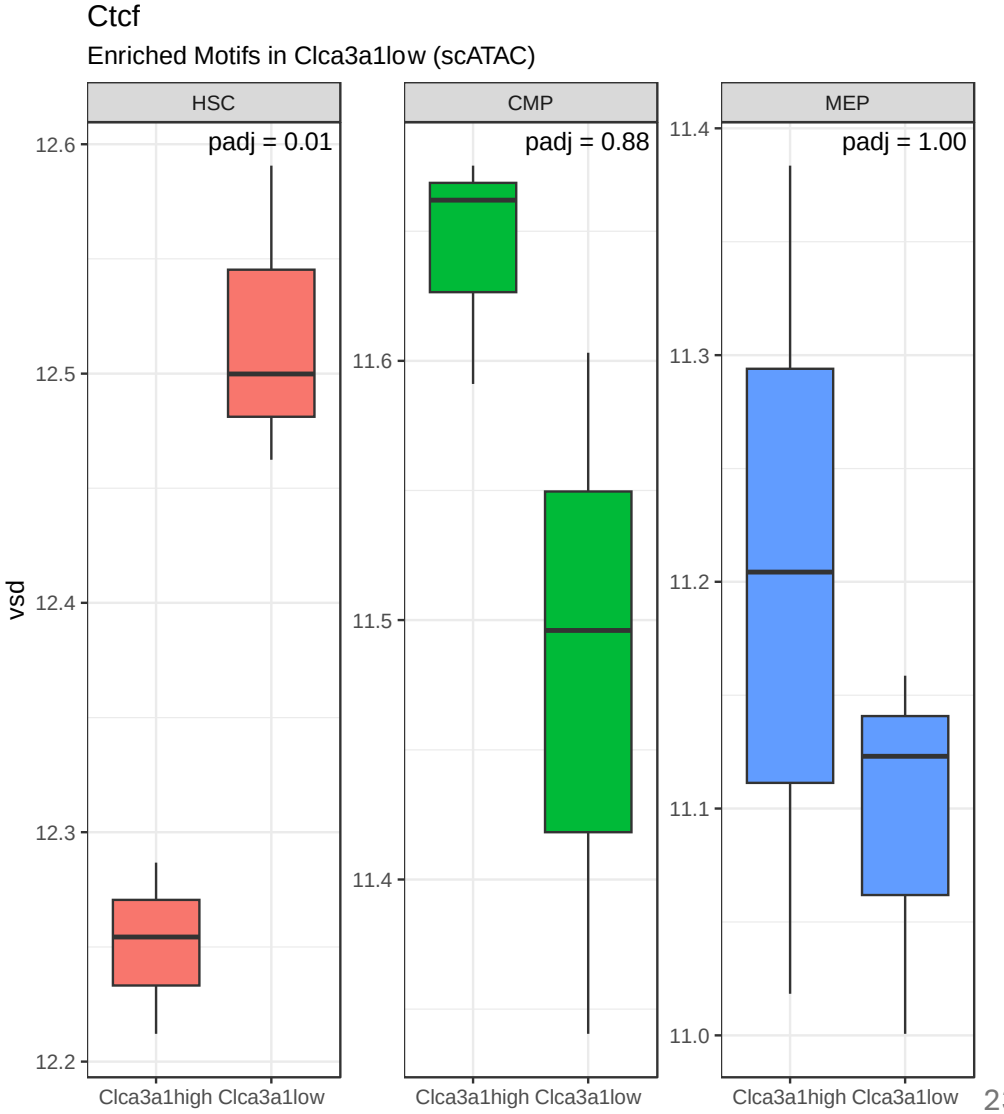
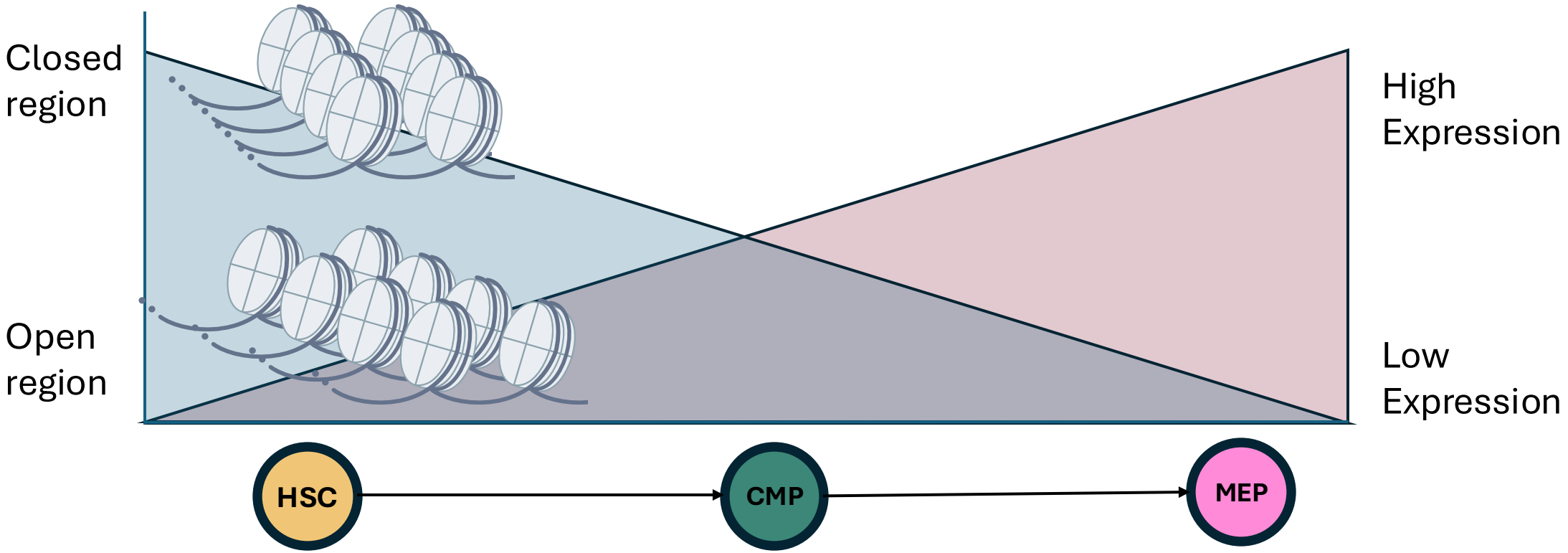


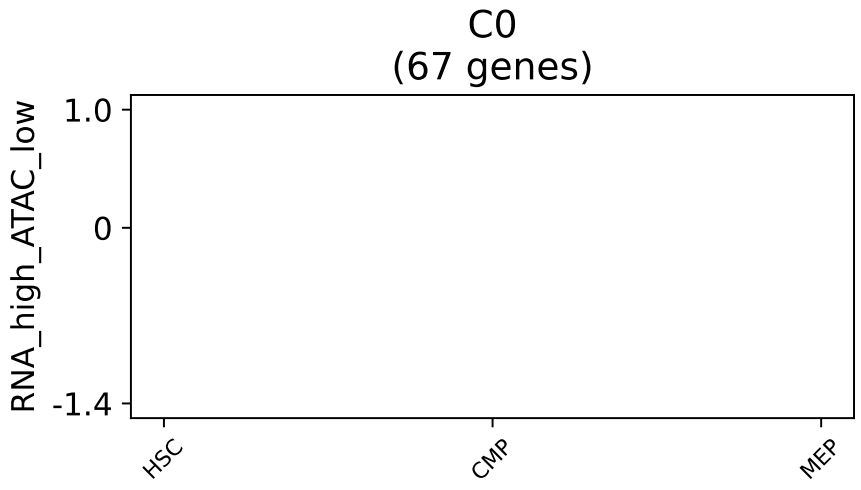


Gene expression trajectories of primed genes

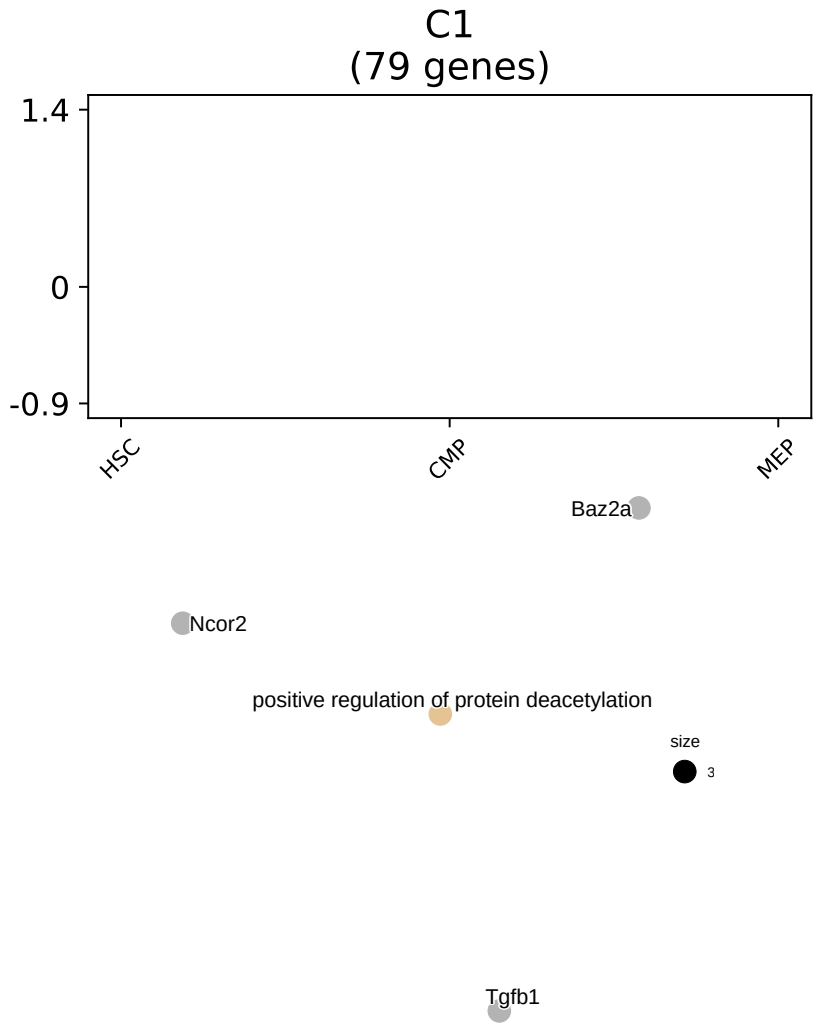
- Selecting Differential genes (RNA) and Marker Peaks (ATAC)



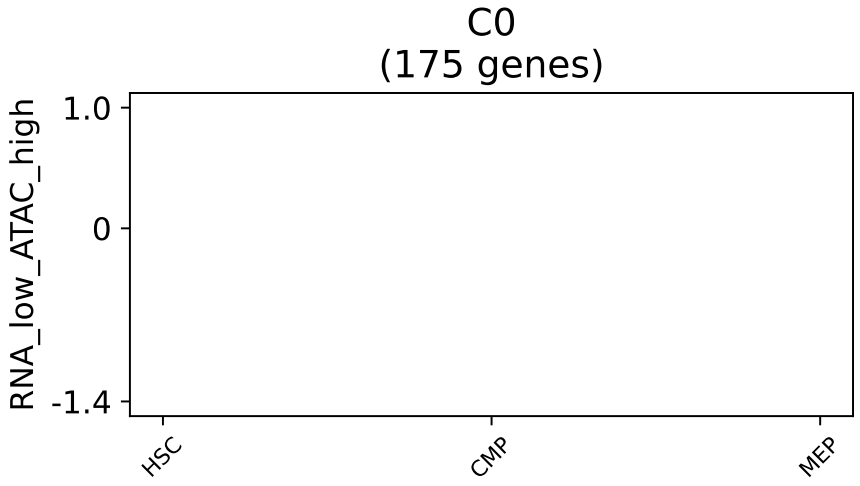
Clustering of DEGs – up in RNA, down in ATAC in Clca3a1high cells



No enriched
GO terms



Clustering of DEGs – down in RNA, up in ATAC in Clca3a1high genes



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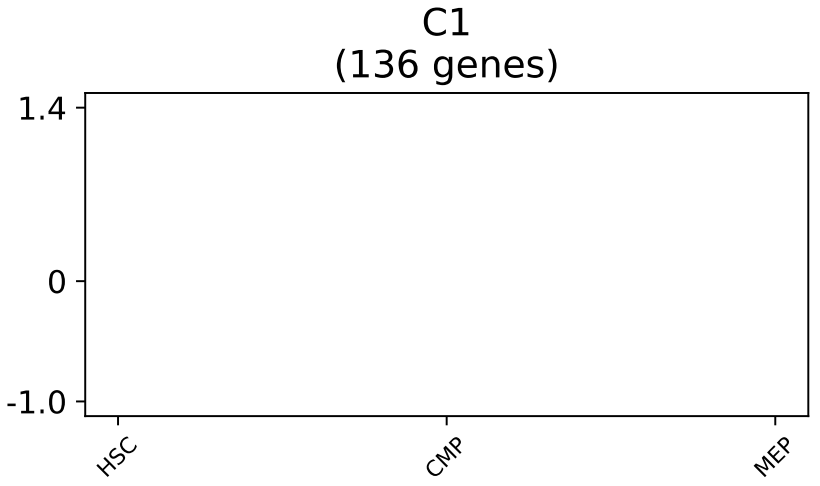

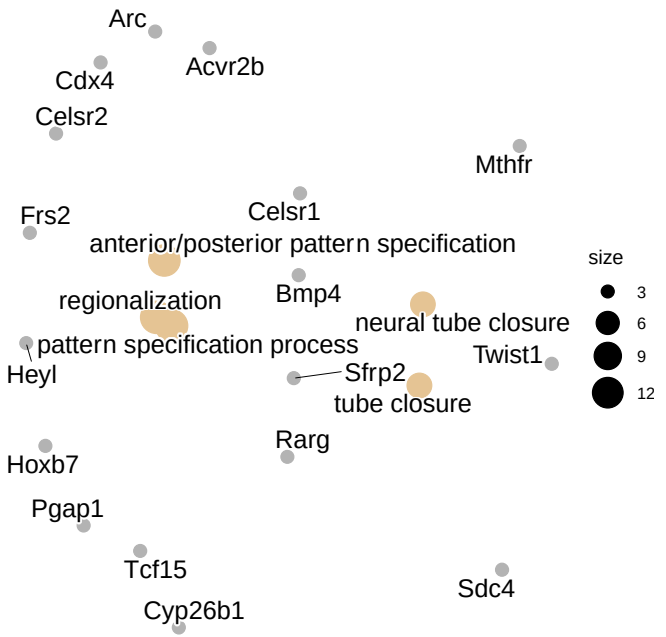

Summary and future remarks

What we want

Find out epigenetically primed genes between Clca3a1-high (old) and Clca3a1-low (young-like) cells

What we achieved

We characterized epigenetics of high and low cells find which genes are primed and expressed through differentiation

What has to be done

Matched scATAC and scRNA multiome sequencing to track changes through differentiation

Thanks

- **Special Thanks to**
- **Hoffmann Group**
  - Steve Hoffmann
  - Alena van Bommel
  - Konstantin Riege
  - And other wonderful group members
- **Björn von Eyß. (TickTock Consortium)**
- **Peter Stadler**

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