Robust gene expression programs underlie recurrent cell states and phenotype switching in melanoma

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Melanoma cell states

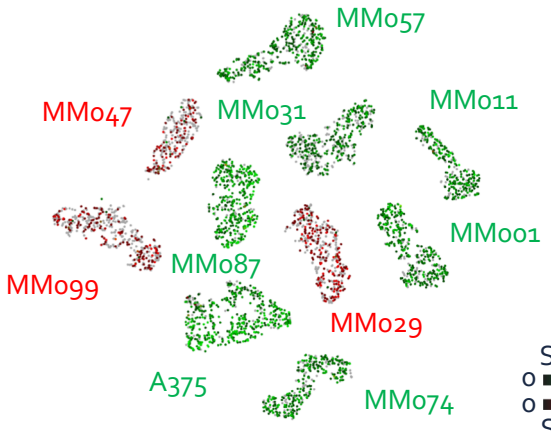
Melanoma shows particularly high regulatory heterogeneity, showing highly plastic regulatory states. We have previously laid out gene regulatory networks (GRNs) and master regulators underlying two commonly found states, the *melanocytic* (MEL) and the *mesenchymal-like* (MES) state. However, the dynamics of the transition between states remain poorly characterized. Recently, scattered evidence illustrates the existence of additional, intermediate state(s). To decipher the gene expression programs in baseline cultures and during cancer state switching, we performed single cell RNA-seq at baseline and at different stages after induction of the switch by SOX10-KD. We profiled more than 35,000 single cells across 10 cultures at 14 time points (from 0 to 72h).

In addition we profiled the chromatin landscape using ATAC-seq, at baseline and 24-48-72h after SOX10KD, to pinpoint the epigenomic determinants.

SCIENCE MEETS LIFE

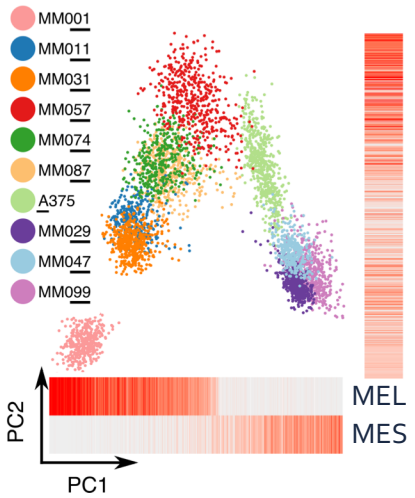
A) Melanoma cultures exhibit distinct cell states

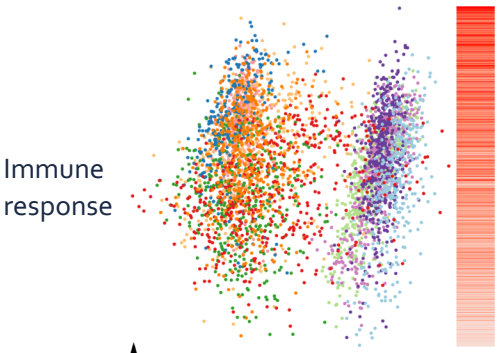
SOX9 – SOX10
(Log CPM expression)



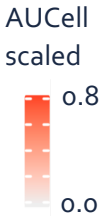
Two main transcriptional states:
MEL and MES

PCA





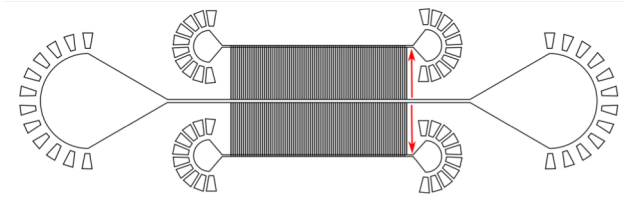
CCA



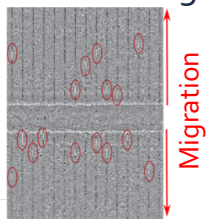
Two subtypes of MEL cell states, with varying mesenchymal-like (PC1) and immune-response-like (PC2) properties, and heterogeneity

B) Transcriptional state predicts single-cell migration

Layout microfluidic migration device

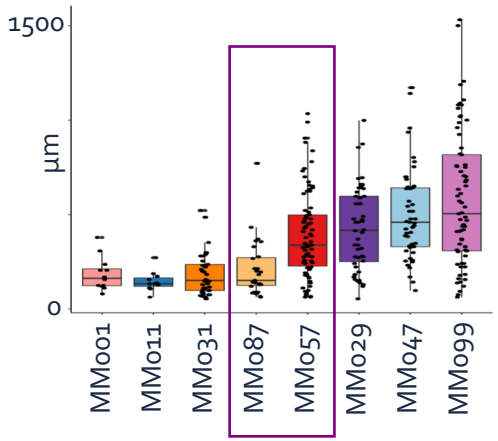


Lens-free imaging

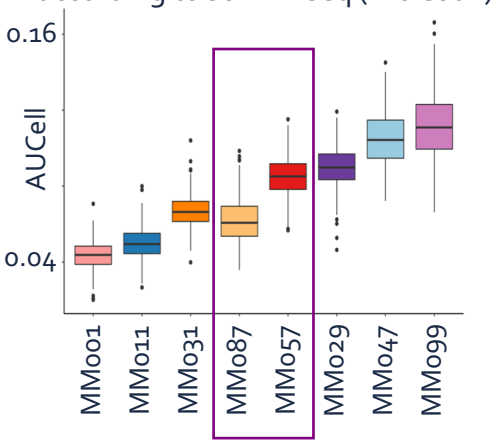


MES cultures are the most migratory

Maximal distance travelled

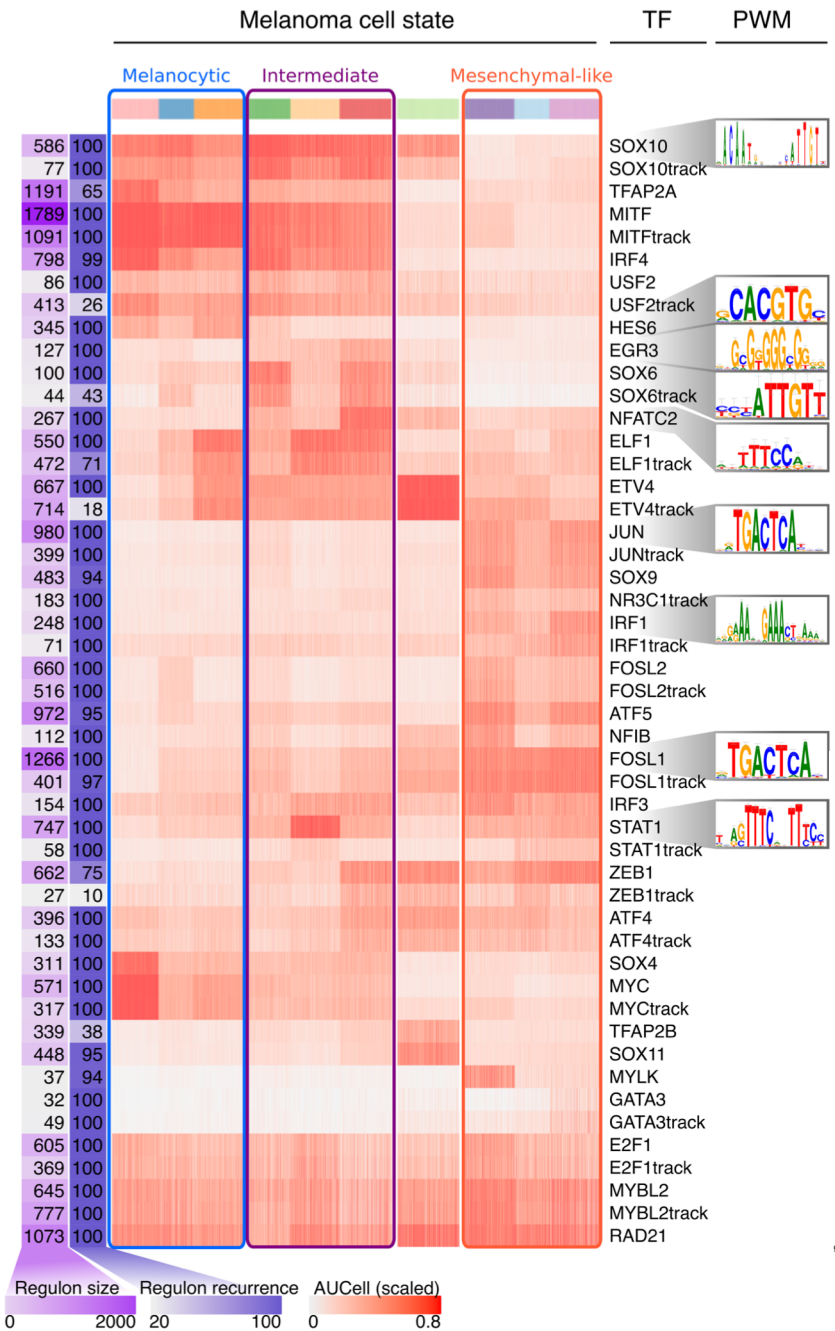


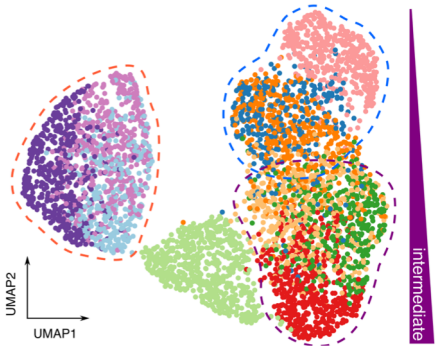
Cell migratory potential
according to scRNA-seq (Wu et al.)



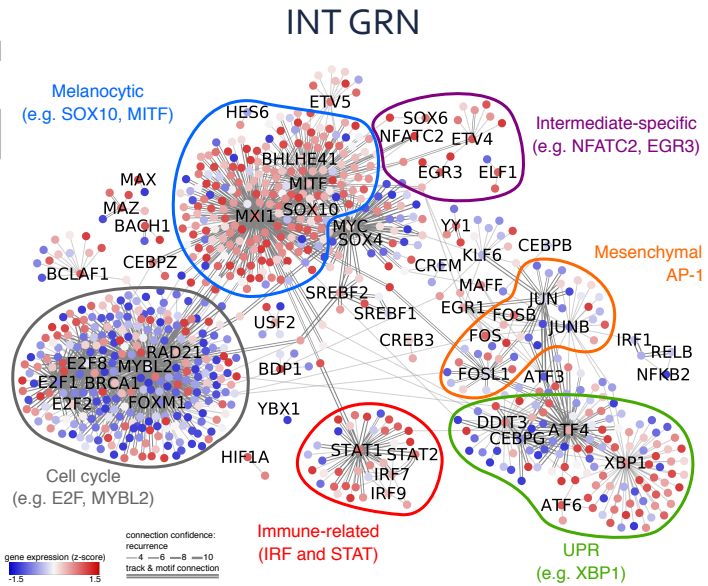
Intermediate (INT) cell state also displays INT migratory potential

C) Network inference reveals candidate regulators of INT state

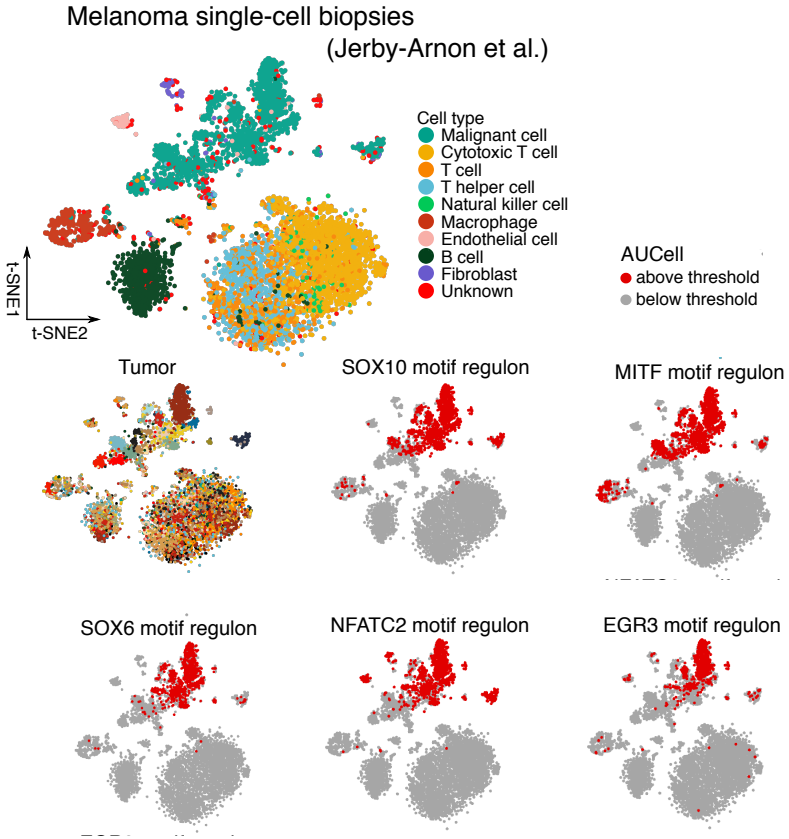




Unsupervised discovery of the three candidate cell states



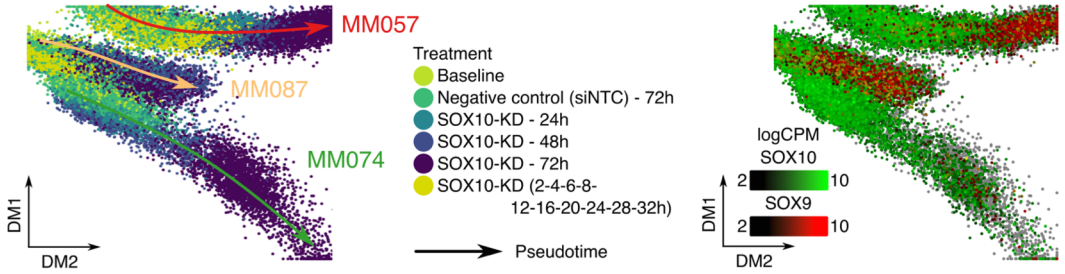
D) Validation of cell states in a larger cohort of cultures and biopsies

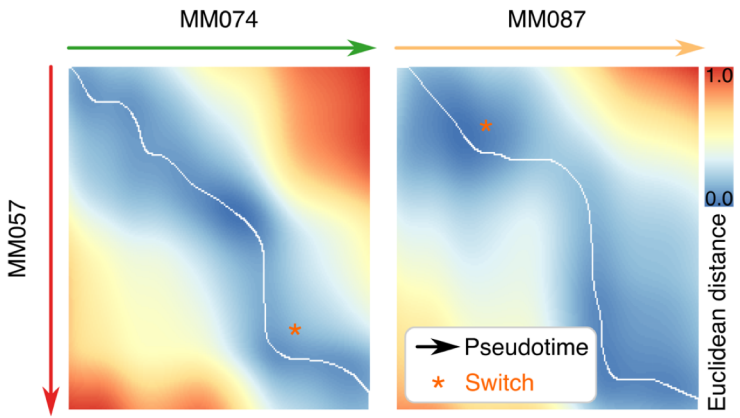


INT state also exists in human melanoma biopsies:

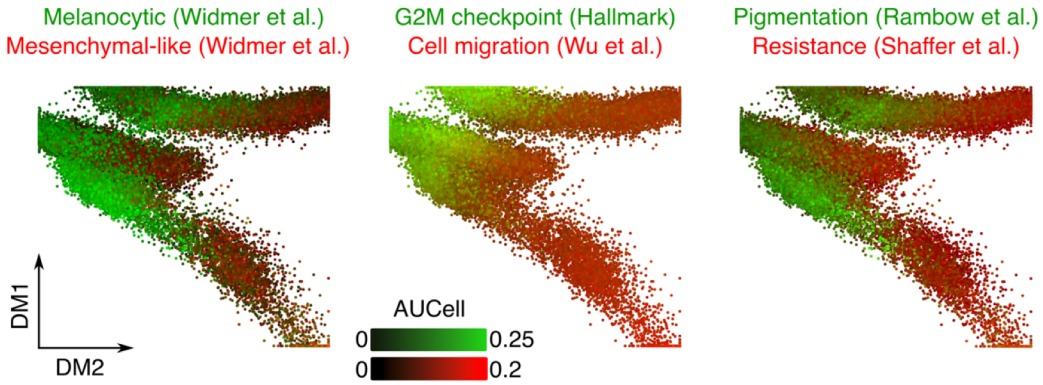
- scRNA-seq of 2,018 cells from 32 melanomas (Jerby-Arnon et al.)
- RNA-seq of 375 melanomas in The Cancer Genome Atlas (TCGA)
- ATAC-seq data of TCGA tumors (Corces et al.)

E) SOX10 perturbation leads to common state transitions

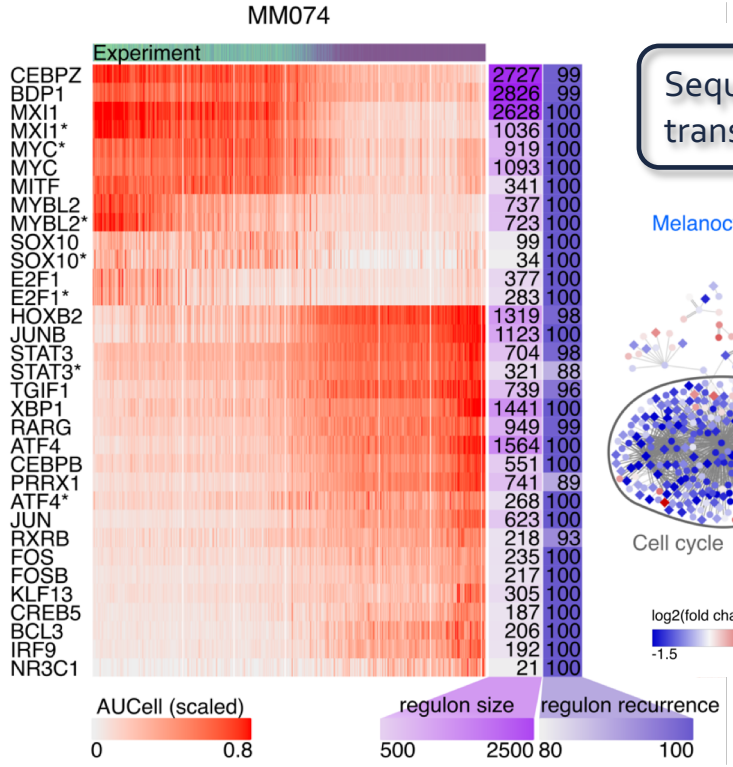




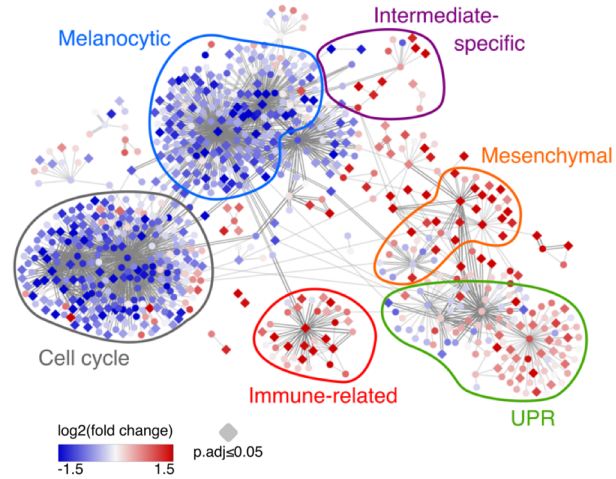
SOX10-KD reprograms INT cells to MES cells.
This switch is highly reproducible across cultures and displays varying dynamics



F) Network inference reveals the recurrent dynamic gene regulatory changes during phenotype switching



Sequential arrangement of transcriptional programs



Recapitulated in underlying epigenome