Dynamic Transcriptional Networks in the Progression of Pluripotency Revealed by Integrative Statistical Learning

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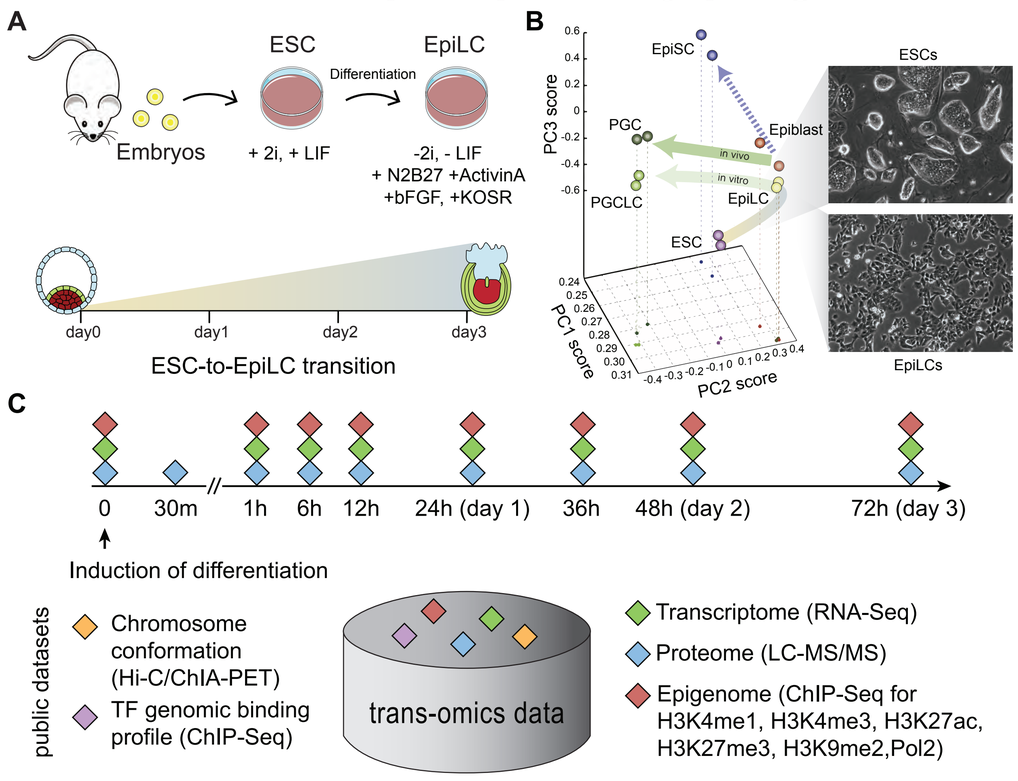
Highlights

- Precise identification of target genes of TFs in pluripotency progression
- Target genes of formative TFs are poised for induction in naive pluripotency
- Dense TF hierarchies for signal propagation in naive pluripotency
- Precise timing of transcriptional network rewiring in pluripotency progression

Introduction

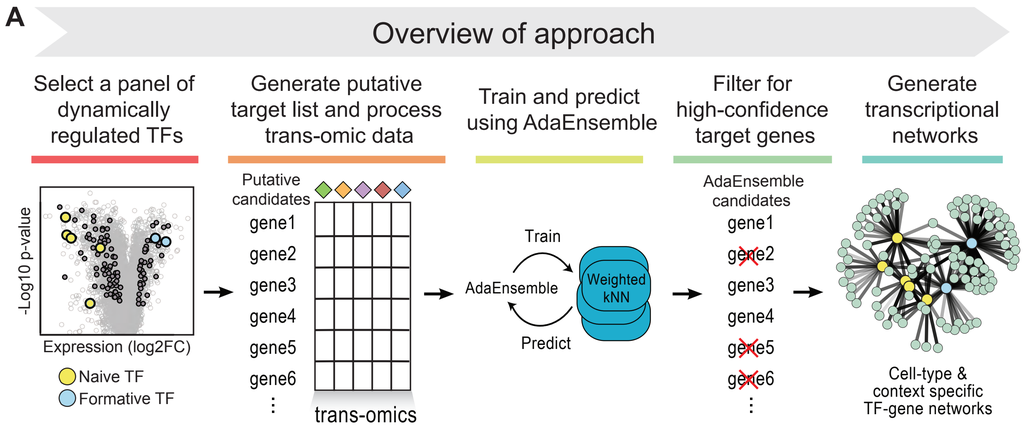
Embryonic stem cells (ESCs) have the remarkable capacity to self-renewal and to differentiate into any cell type in the body. Understanding the regulatory networks underpinning the transition of ESCs to cells committed to distinct lineages is critical for stem cell therapy. Using machine learning of trans-omics data, we delineate the transcriptomic networks that govern pluripotency transition of mouse ESCs to epiblast-like cells (EpiLCs), thereby profiling the progression from naive to formative pluripotency.

Trans-omics of pluripotency progression



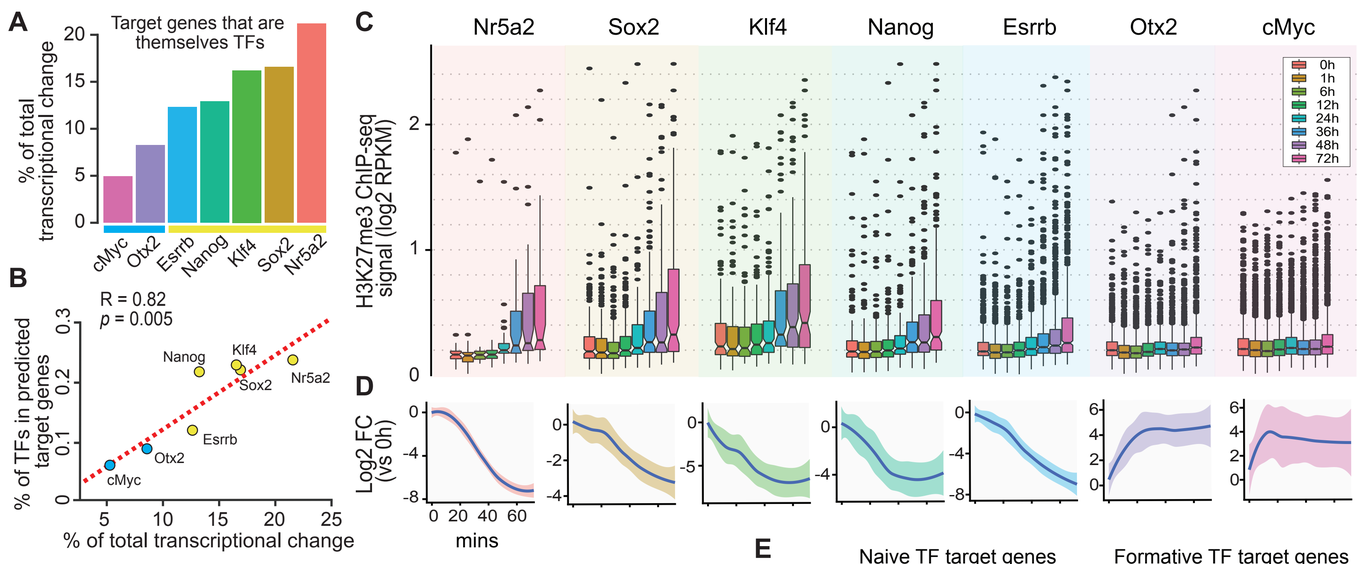
(A) The ESC to EpiLC progression. **(B)** PCA of the transcriptome of pluripotent cells (adapted from [1]). **(C)** Trans-omic datasets used in the study [2].

TF target identification in naive and formative networks via integrative learning



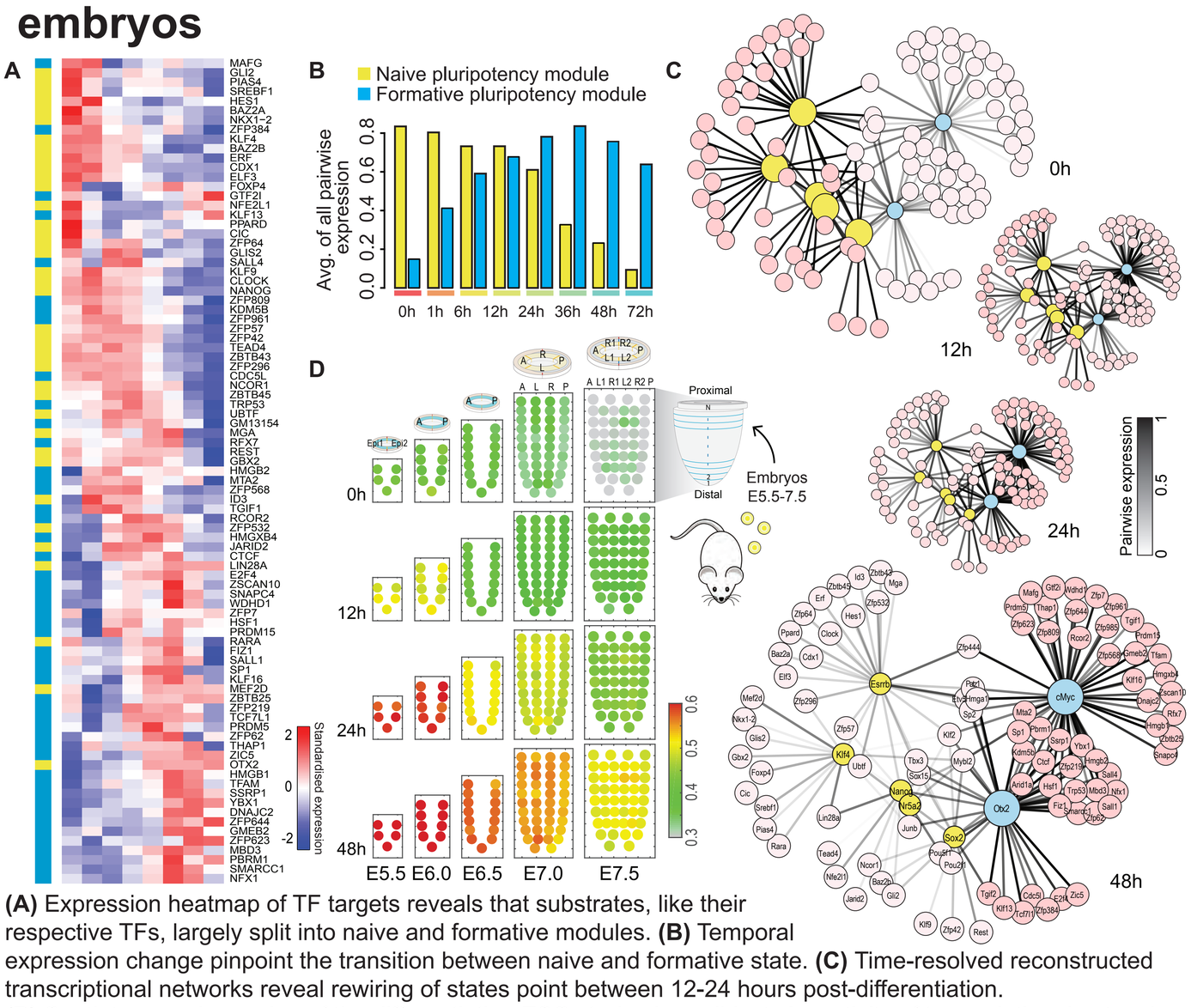
(A) Overview of integrative learning for TF target identification. **(B)** mRNA and protein profiles of AdaEnsemble-identified TF targets closely resemble those of their respective TFs. **(C)** Heatmap showing TF targets form two seperate transcriptional networks, naive and formative.

Dense transcription factor hierarchies and permissive epigenetic landscape distinguish pluripotency states



(A) Target genes that are themselves TFs contribute more to the overall expression change in naive networks (yellow strip). **(B)** Correlation between the percentage of target genes that are themselves TFs and their contribution to overall expression change (as in A) for each TF. **(C)** Temporal H3K27me3 change at the promoters of TF target genes of naive and formative networks during pluripotency progression. **(D)** Temporal mRNA expression of TF target genes. **(E)** Proposed model of the permissive chromatin associated with formative target genes in naive pluripotency.

Spatiotemporal mapping of transcriptional network rewiring during pluripotency progression in *in vivo* embryos



(A) Expression heatmap of TF targets reveals that substrates, like their respective TFs, largely split into naive and formative modules. **(B)** Temporal expression change pinpoint the transition between naive and formative state. **(C)** Time-resolved reconstructed transcriptional networks reveal rewiring of states point between 12-24 hours post-differentiation. **(D)** Spatiotemporal mapping of the differentiating ESCs to *in vivo* epiblasts by activity of transcriptional networks.

Summary: Molecular roadmap of pluripotency transition

Through a trans-omics approach, we identified target genes regulated by a panel of key TFs during pluripotency transition. We found naive transcriptional networks are governed by denser TF hierarchies. We also found permissive epigenomic signatures at formative TF target genes in the naive state, indicating that they are poised for expression prior to pluripotency transition. Finally, our reconstructed transcriptional networks enabled the precise spatiotemporal mapping of differentiating ESCs to mouse epiblasts.

Acknowledgements and References

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[1] Hayashi K et al. (2011) Cell, 146(4):519-32.
[2] Yang P et al. (2019) Cell Systems, 8:427-445.

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