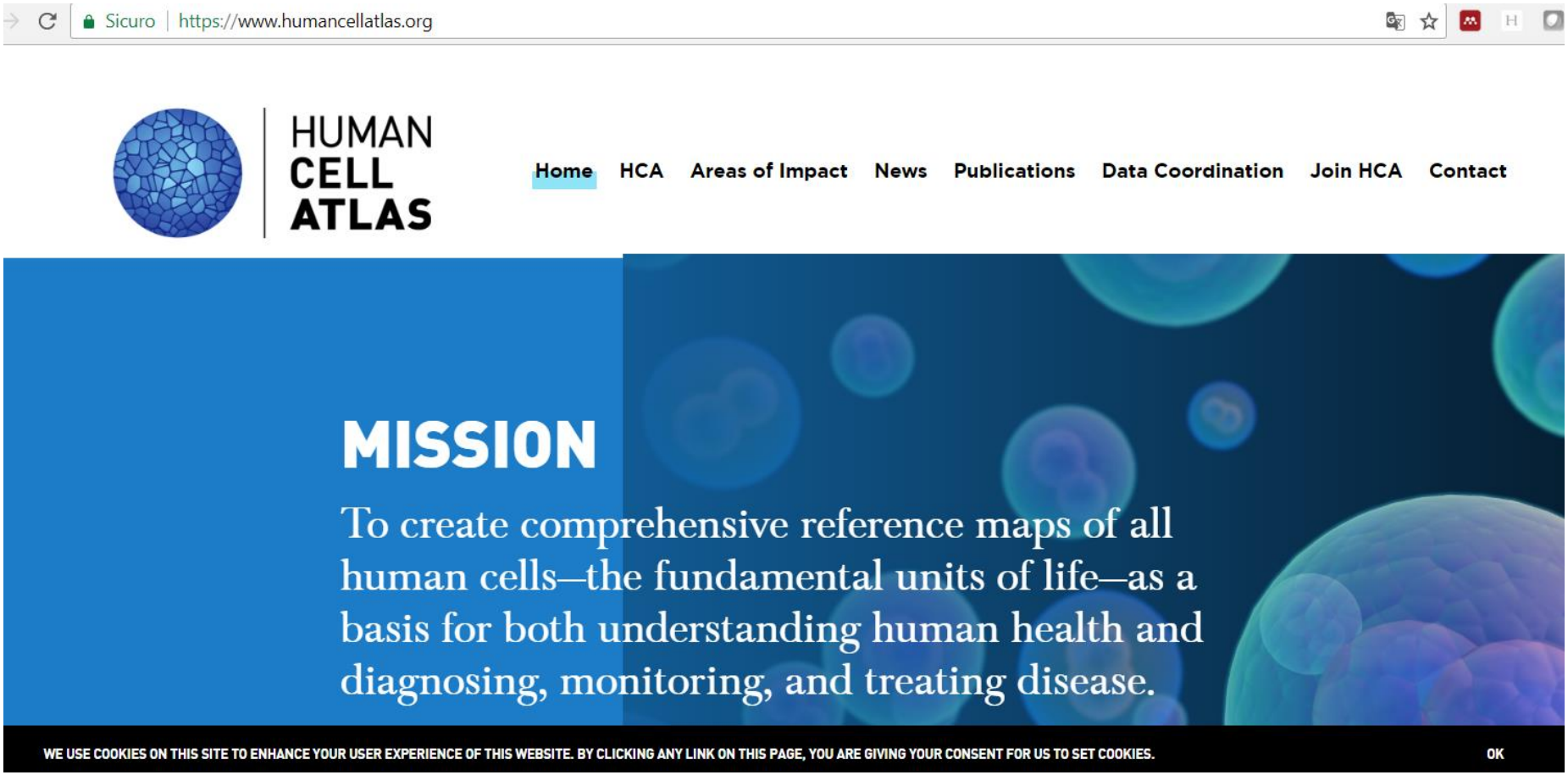
https://youtu.be/O5XAlOvZdMw

Aviv Regev video describes the goal, challenge and impact.



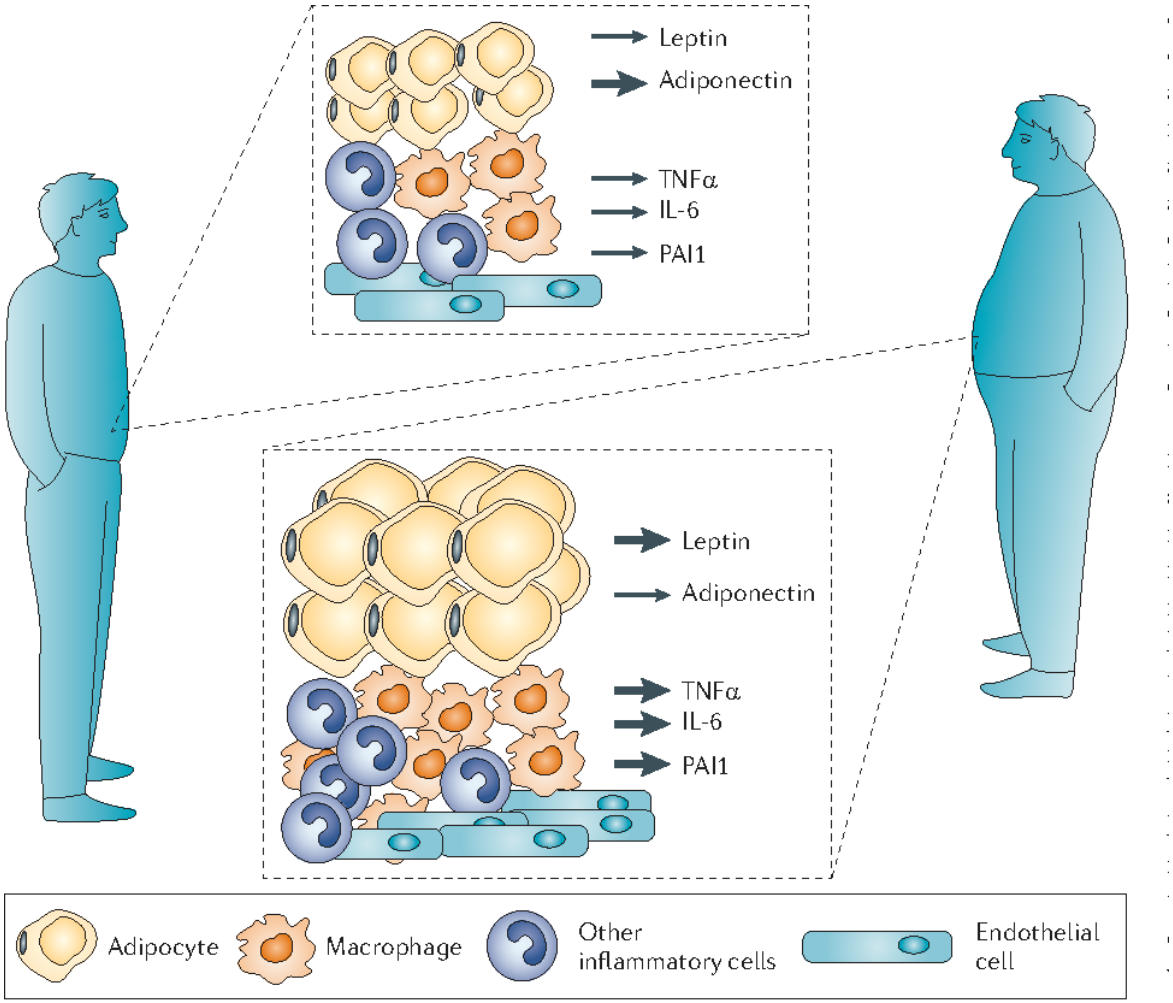
Three of the most fundamental questions in biology are:

how individual cells differentiate to form tissues

how tissues function in a coordinated and flexible fashion

which gene regulatory mechanisms support these processes.

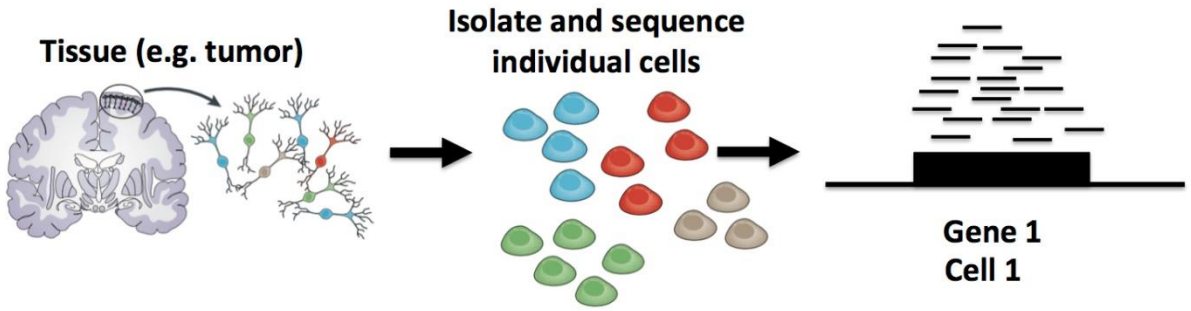
The answers to these questions open the way to understand molecular basis of disease and to identify potential drug targets.



Single-cell genomics

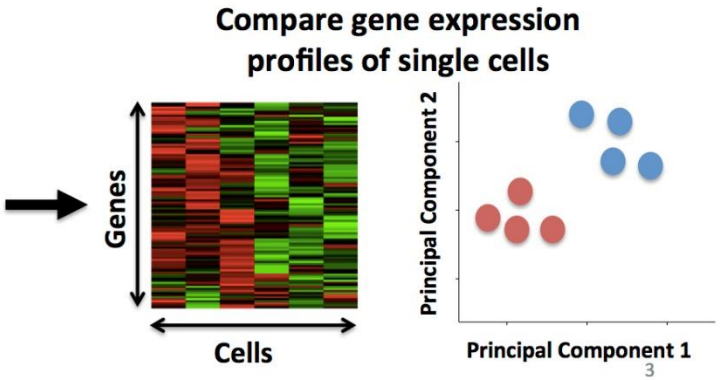
is opening up new ways to tackle these questions
by combining the **comprehensive nature of genomics** with the microscopic resolution that is required to describe complex multicellular systems.

Single-cell RNA-Seq (scRNA-Seq)

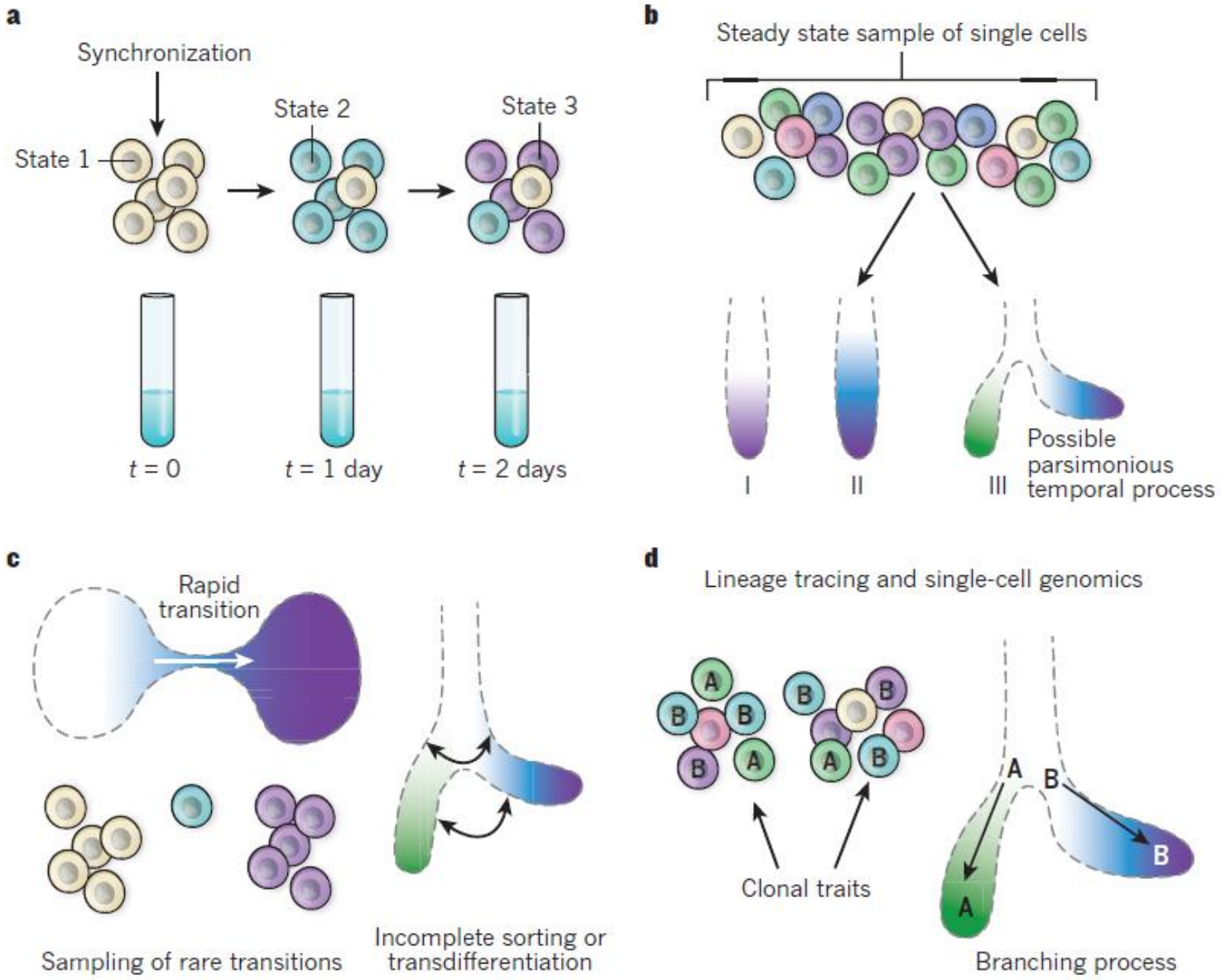


Read Counts

	Cell 1	Cell 2	...
Gene 1	18	0	
Gene 2	1010	506	
Gene 3	0	49	
Gene 4	22	0	
...			



TEMPORAL AXIS



Biological processes are dynamic at several timescale

minutes to hours (fast responses to environmental stimuli)
hours to days (cell differentiation)
up to years (pathogenesis).

- Dynamic processes require a **synchronization** or the ability to isolate specific subpopulations of cells at distinct functional points in the process

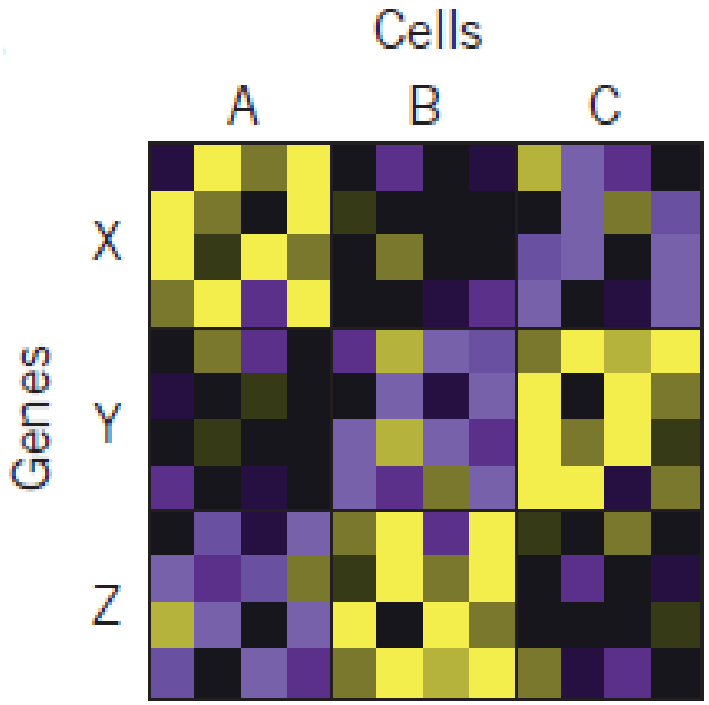
- Single-cell genomics partially alleviates these limitations.

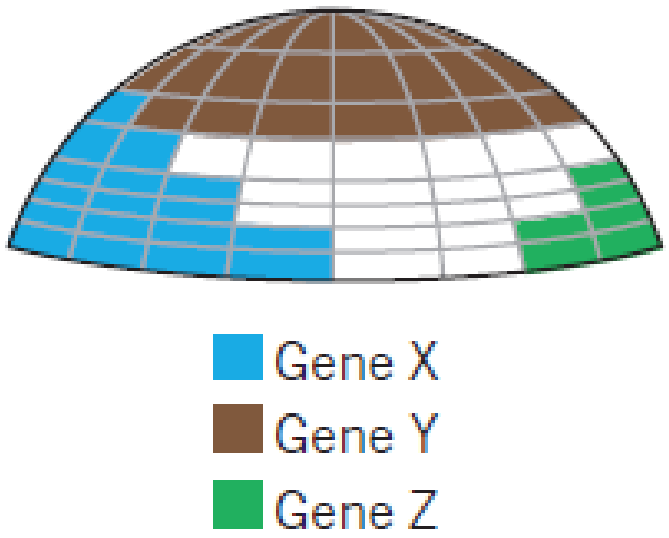
  Single-cell genomics therefore suggests, in principle, a universal, **computationally driven approach for inferring dynamics** in genome function and regulation.

  The principle is effective for inferring cellular dynamics that proceed directionally and irreversibly through a succession of focal points by means of coordinated **changes in gene expression**. In such cases, it should be possible **to infer the 'ordering' of cells** (that is, the point in the idealized temporal process that the cell is at) and the molecular states associated

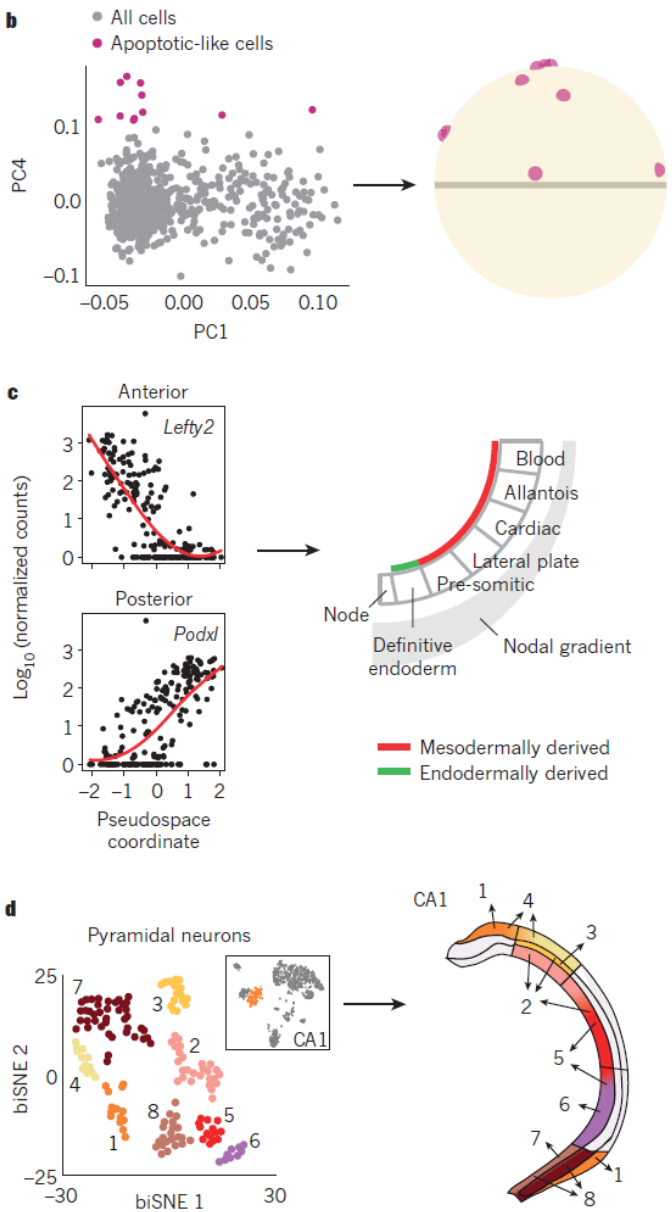
SPATIAL AXIS

Spatial mapping uses single-cell gene-expression profiles and a reference map of the spatial expression patterns of a small number of landmark genes as input. The expression profile of the landmark genes in a cell is used to determine its spatial position. (**Yellow indicates induced expression**, **purple shows repressed expression** and **black indicates no change in expression**.)





SPATIAL AXIS
Various examples of successful spatial mapping



b in the early fish embryo several cells with a distinct apoptotic-like profile (principal component (PC) analysis plot;

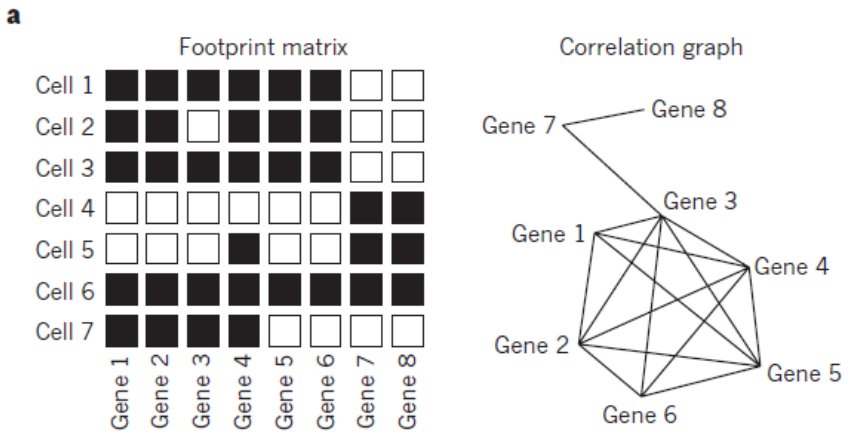
c in the early mesoderm, patterns of gene expression in single cells (left) can define an anterior–posterior inferred ‘pseudospace’ (right);

d in the hippocampus of the brain, pyramidal neuron cell clusters from the region CA1 first grouped by proximity in a dimensionality reduced space (biSNE plot, left) can be mapped to positions along the lateral–medial and anterior–posterior axes. biSNE, biclustering on stochastic neighbor embedding.

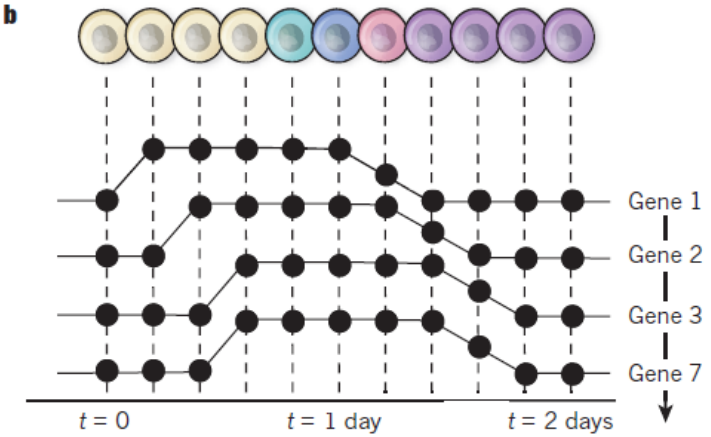
MECHANISM AXIS

The most basic approach takes a large number of single-cell profiles that capture various transcriptional states and generates candidate regulatory interactions by computing gene–gene correlations.

At higher resolution, single-cell analysis refines the definition of cell types and subtypes and enables the **sensitive identification of correlation (or its absence) in small cellular niches**, facilitating the progressive exclusion of more spurious gene–gene putative interactions. Such analyses have helped to predict the regulators that control cell types in immune cells, epithelial cells and neurons



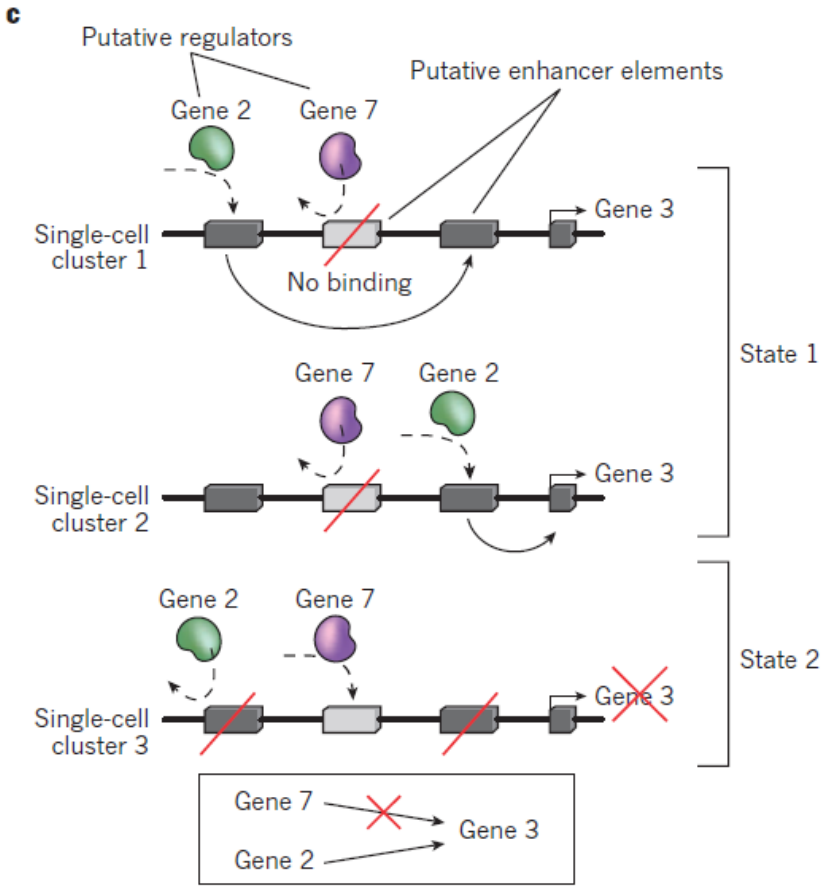
Definition of cell types



Description of cell differentiation

MECHANISM AXIS

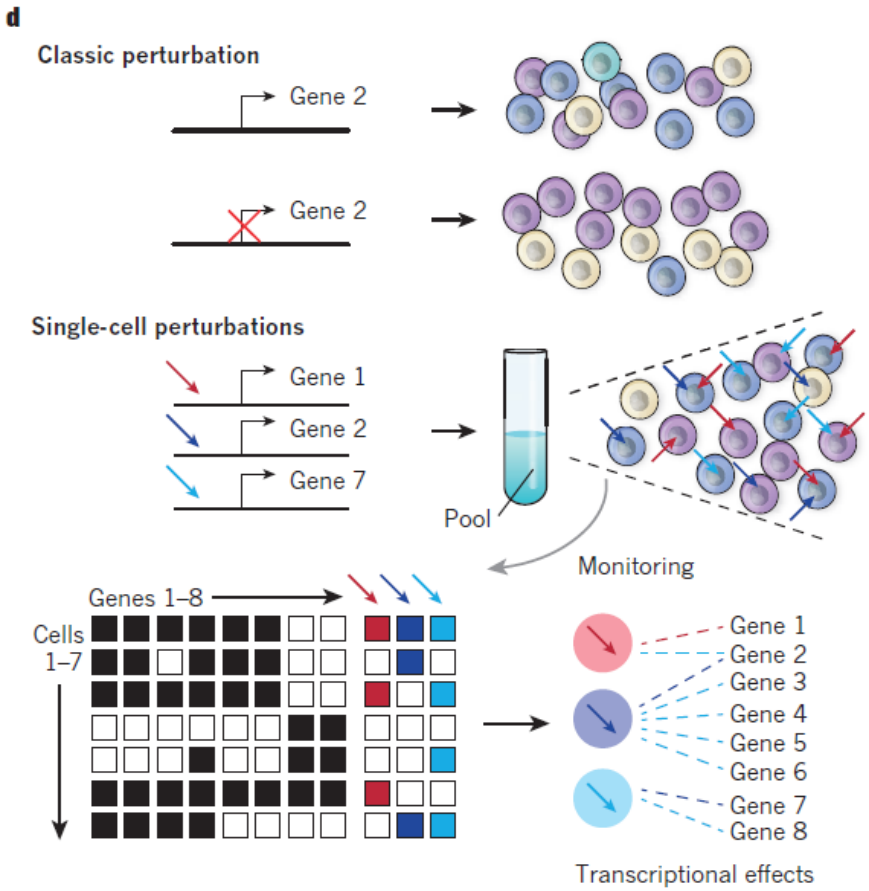
The refinement of regulatory models with **epigenetic information**. A regulatory region that surrounds gene 3 is depicted, including three putative enhancer elements that are targeted by two putative regulators, encoded by gene 2 (green) and gene 7 (purple). Pooled epigenomics data from single-cell clusters can be used to identify two states. In state 1, gene 3 is active and targeted by gene 2, and in state 2, gene 3 is inactive and targeted by gene 7. It can therefore be inferred that gene 2, but not gene 7, is activating gene 3.



MECHANISM AXIS

Combining single-cell genomics with experimental perturbations of the system of interest provides the most direct avenue for causal inference.

Modern high-throughput perturbation methods, especially those based on clustered regularly interspaced short palindromic repeat **(CRISPR) technology**, can be combined with single-cell genomics to perform causal analysis at an unprecedented scale and resolution.



ARTICLE

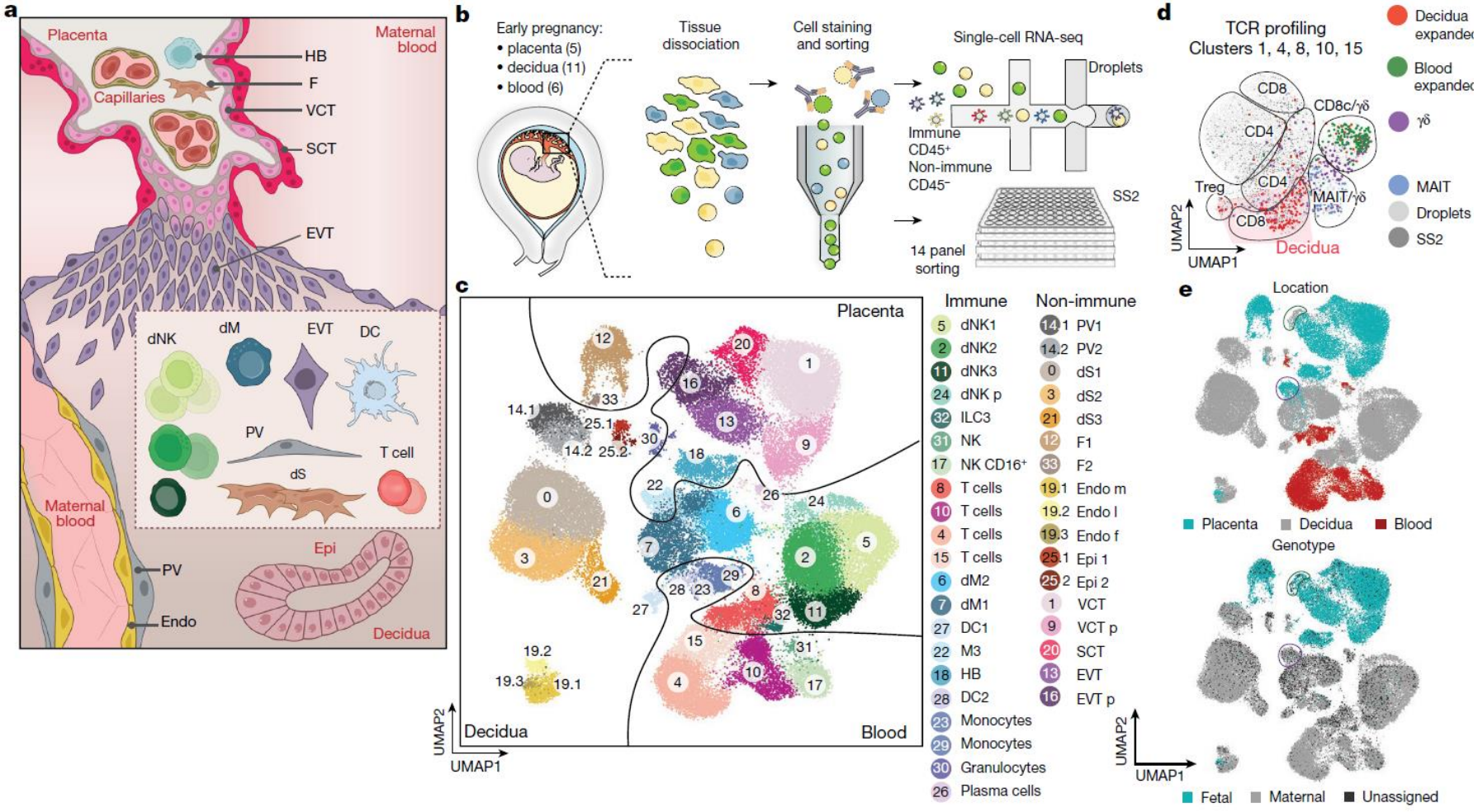
https://doi.org/10.1038/s41586-018-0698-6

Single-cell reconstruction of the early maternal–fetal interface in humans

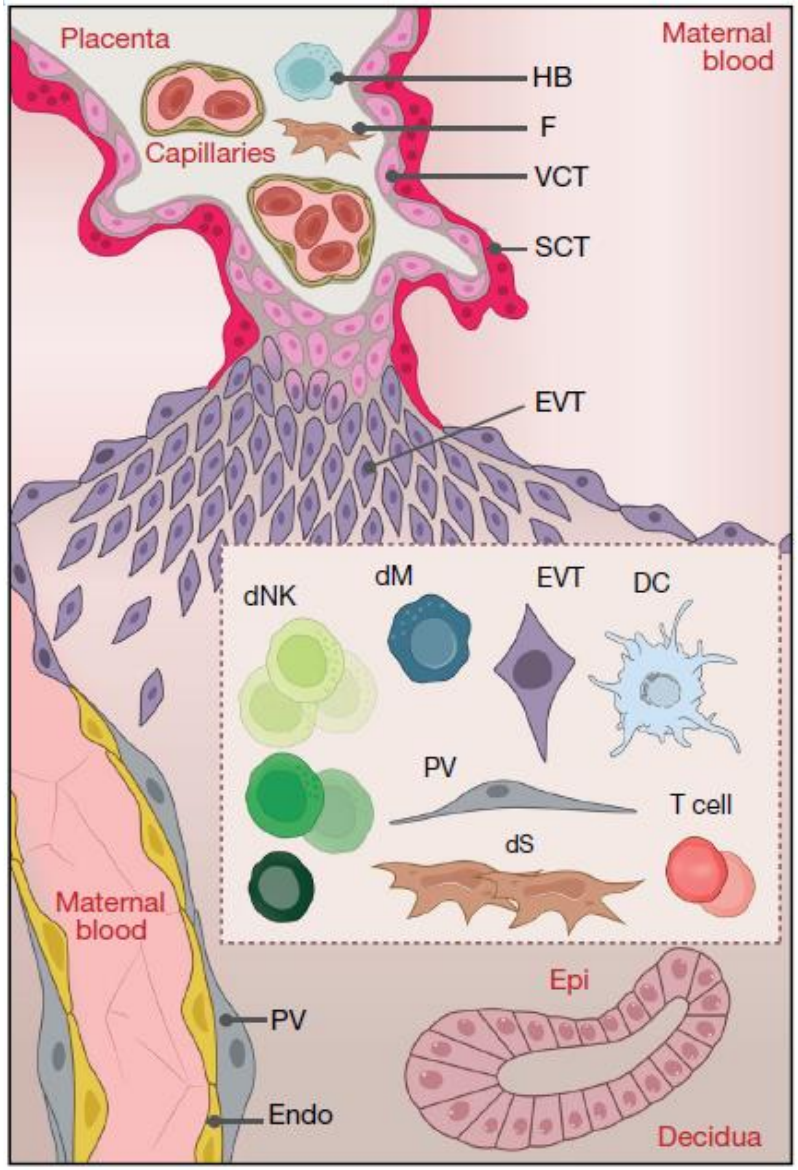
Roser Vento-Tormo[1,2,13], Mirjana Efremova[1,13], Rachel A. Botting[3], Margherita Y. Turco[2,4,5], Miquel Vento-Tormo[6], Kerstin B. Meyer[1], Jong-Eun Park[1], Emily Stephenson[3], Krzysztof Polański[1], Angela Goncalves[1,7], Lucy Gardner[2,4], Staffan Holmqvist[8], Johan Henriksson[1], Angela Zou[1], Andrew M. Sharkey[2,4], Ben Millar[3], Barbara Innes[3], Laura Wood[1], Anna Wilbrey-Clark[1], Rebecca P. Payne[3], Martin A. Ivarsson[4], Steve Lisgo[9], Andrew Filby[3], David H. Rowitch[8], Judith N. Bulmer[3], Gavin J. Wright[1], Michael J. T. Stubbington[1], Muzlifah Haniffa[1,3,10,14]*, Ashley Moffett[2,4,14]* & Sarah A. Teichmann[1,11,12,14]*

Nature **563**, 347–353 (2018)

Identification of cell types at the maternal–fetal interface.



Identification of cell types at the maternal–fetal interface.



villous cytotrophoblast (VCT) cells, which line placental structures called villi;

syncytiotrophoblast (SCT) cells that cover the villus surface;

extravillous trophoblast (EVT) cells, which line the maternal blood vessels and intermingle with maternal cells in the decidua.

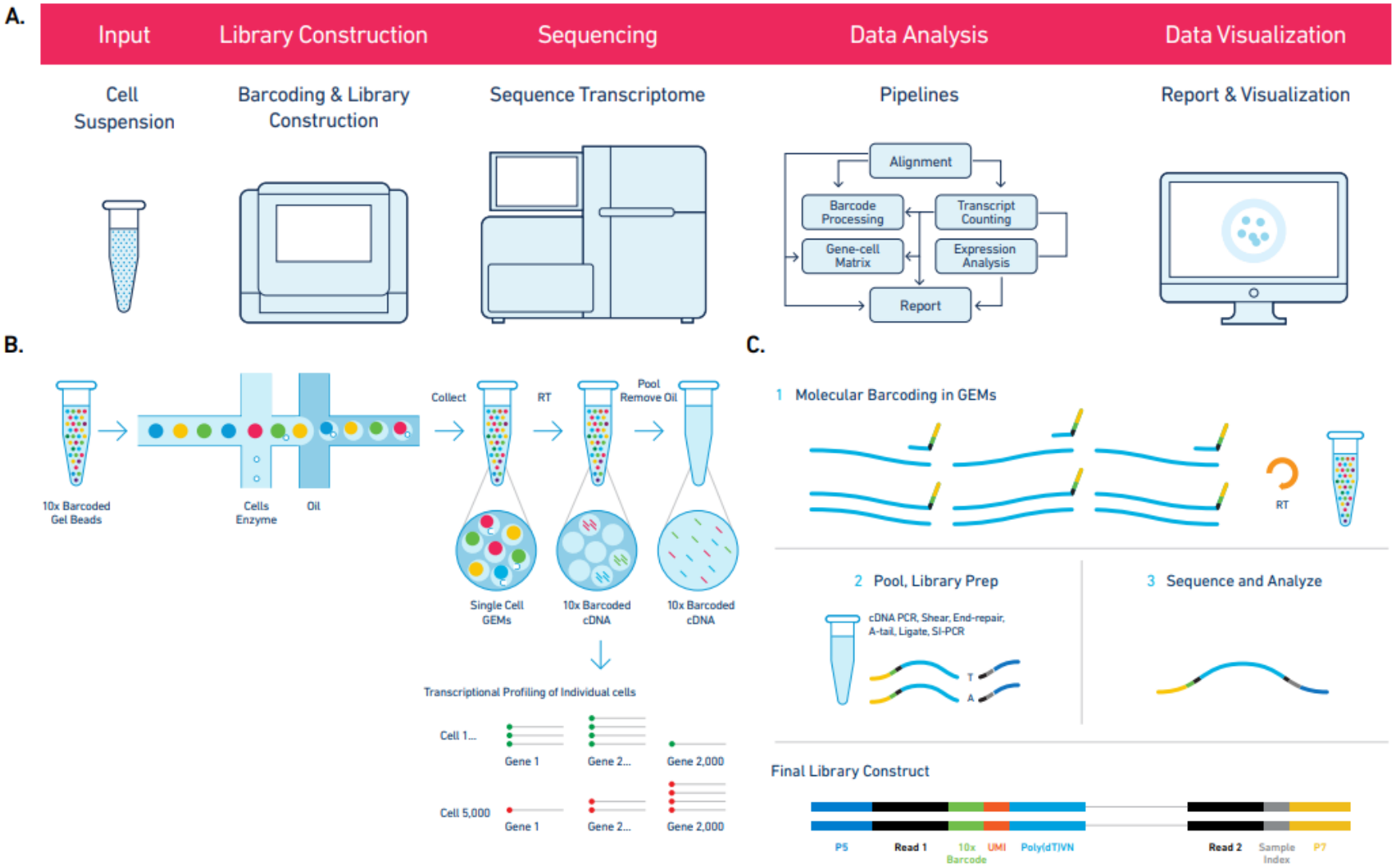
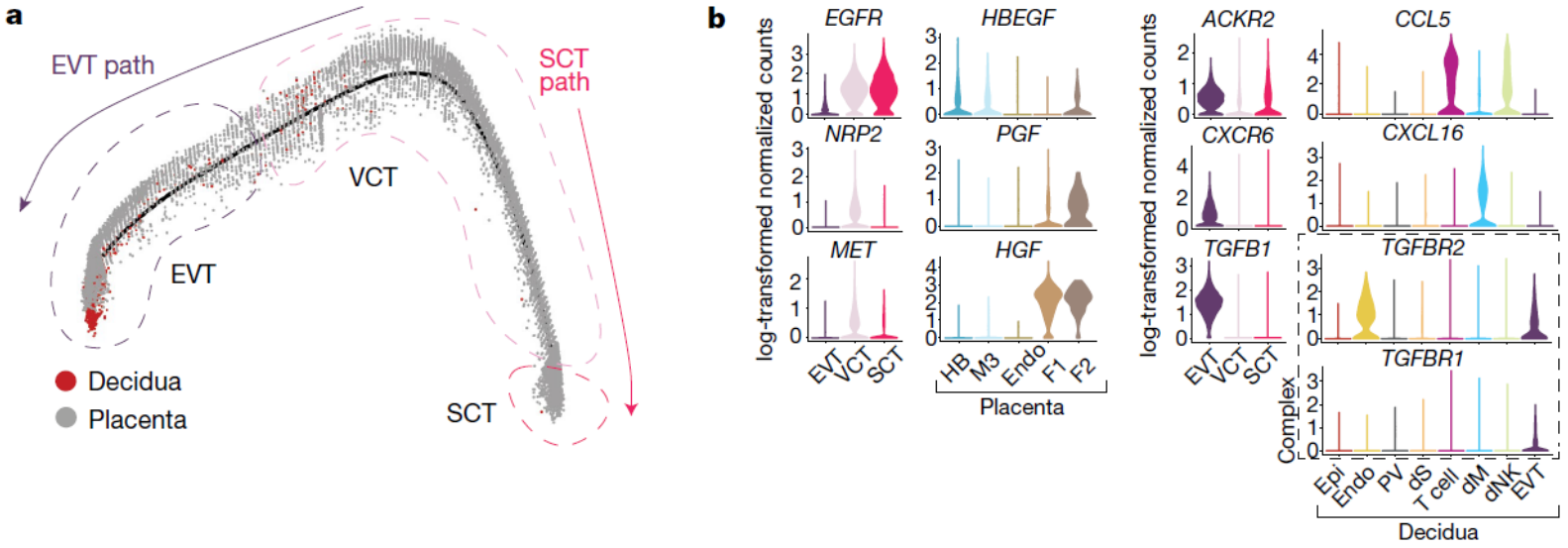


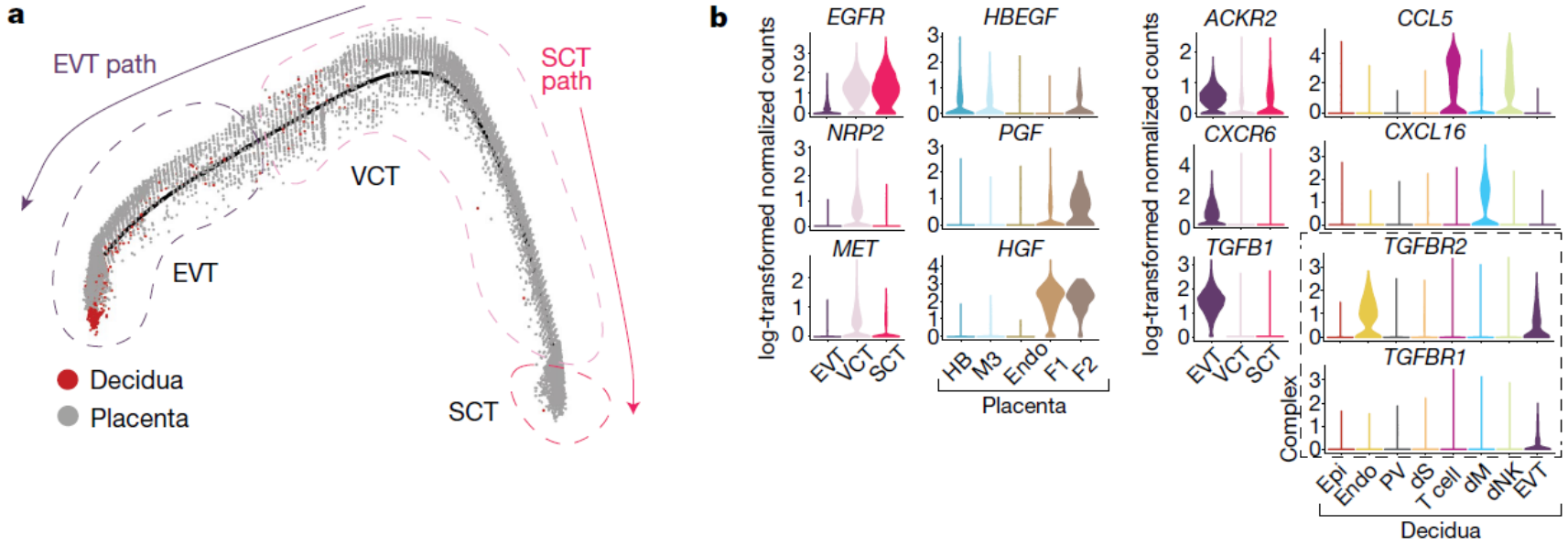
Figure 1. Chromium™ Single Cell 3' Solution. (a) Workflow schematic overview. (b) Formation of GEMs, RT takes place inside each GEM, which is then pooled for cDNA amplification and library construction in bulk. (c) v2 Single Cell Assay schematic overview.

What is the meaning of these results and how we can read this data

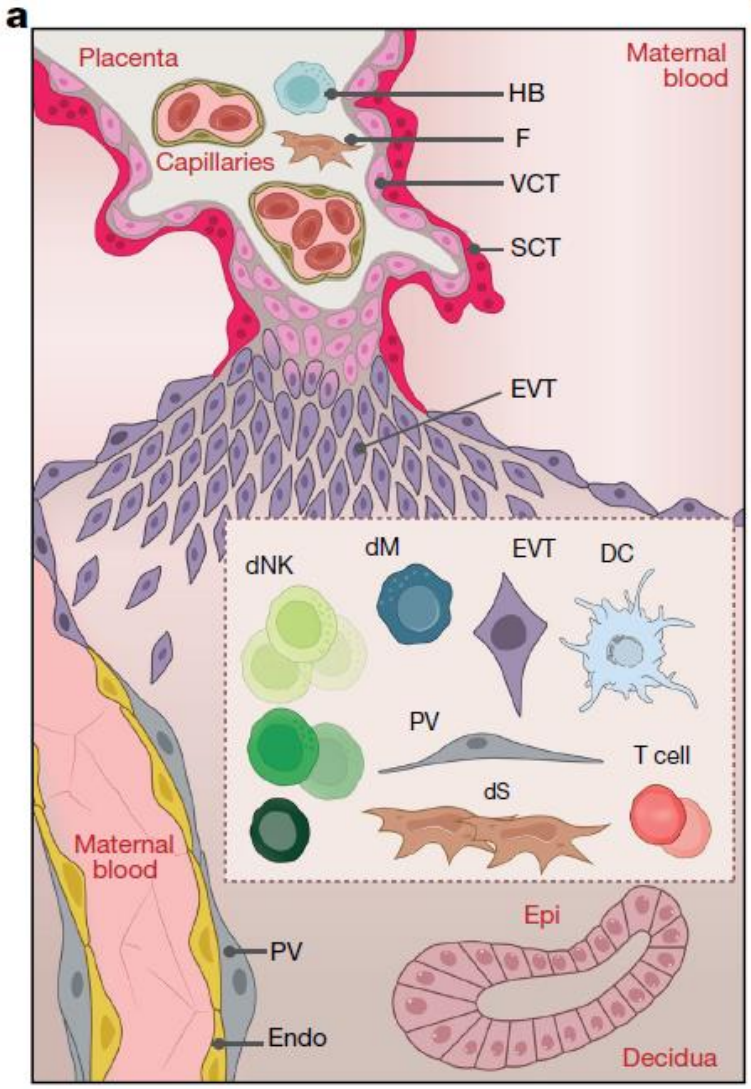
Identification of pathways that play role between cells of mother and fectus to create an «hybrid» tissue

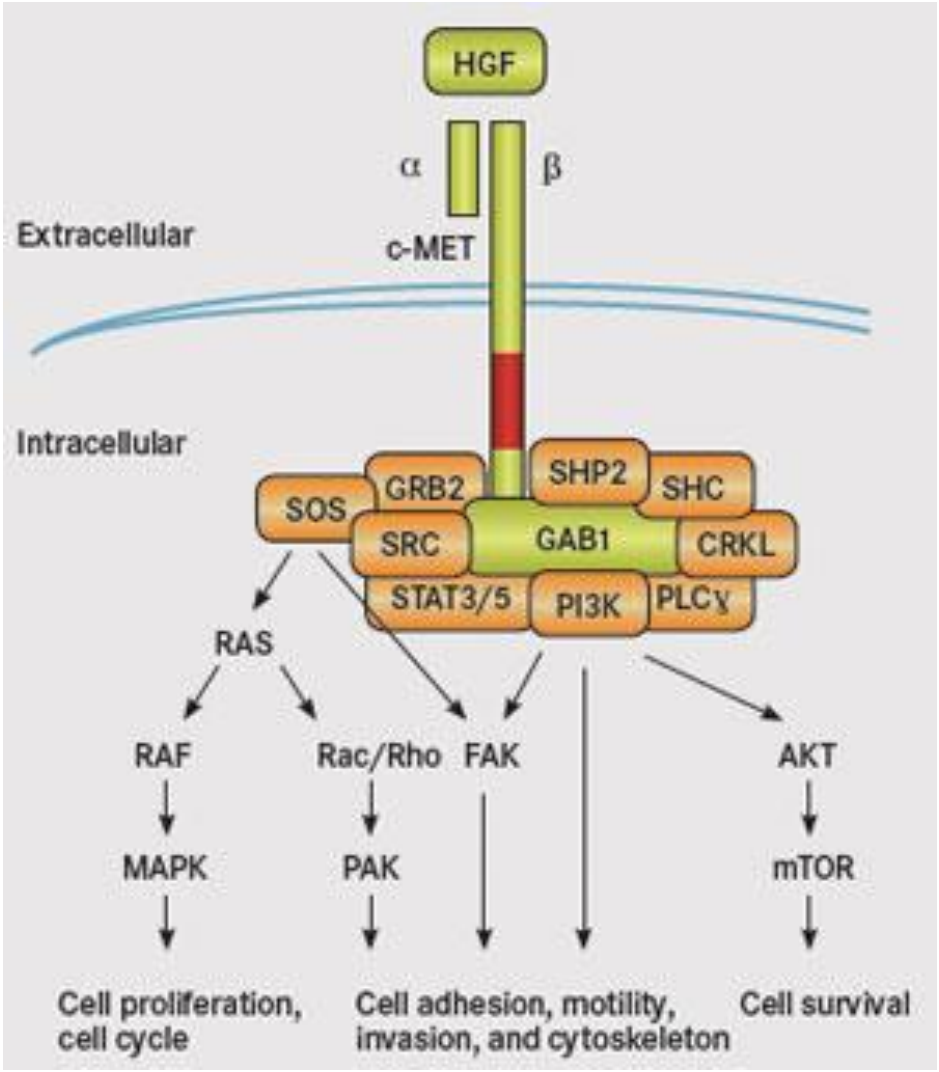


Ligand–receptor expression during EVT (extravillous trophoblast) differentiation.

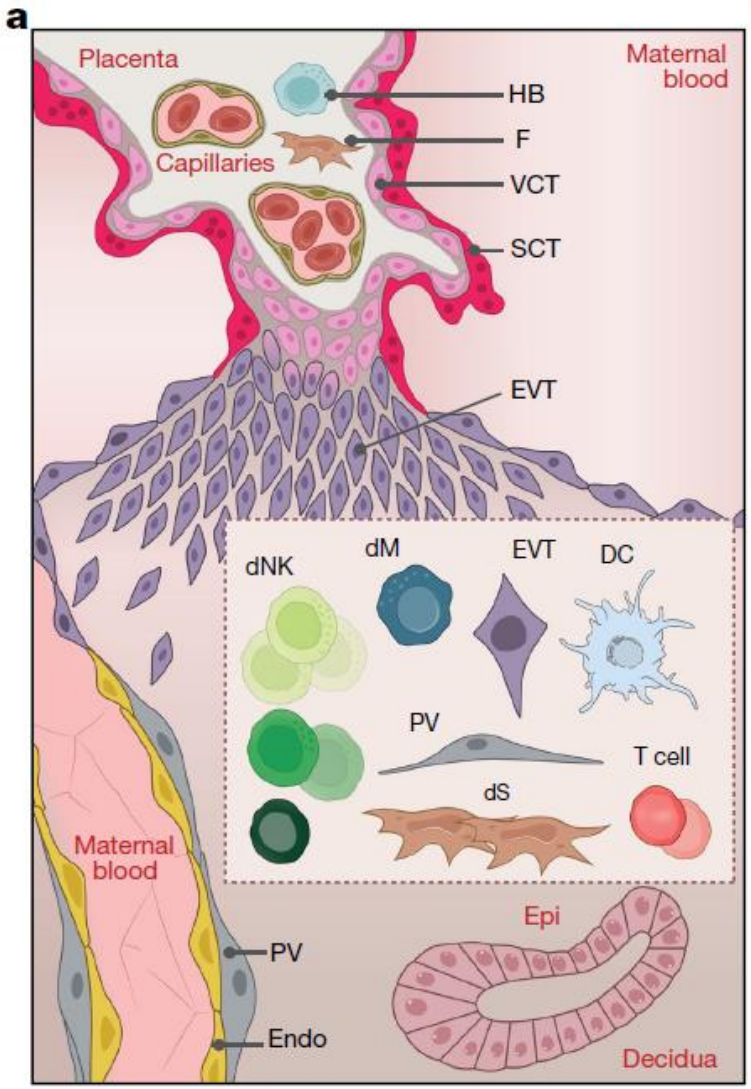


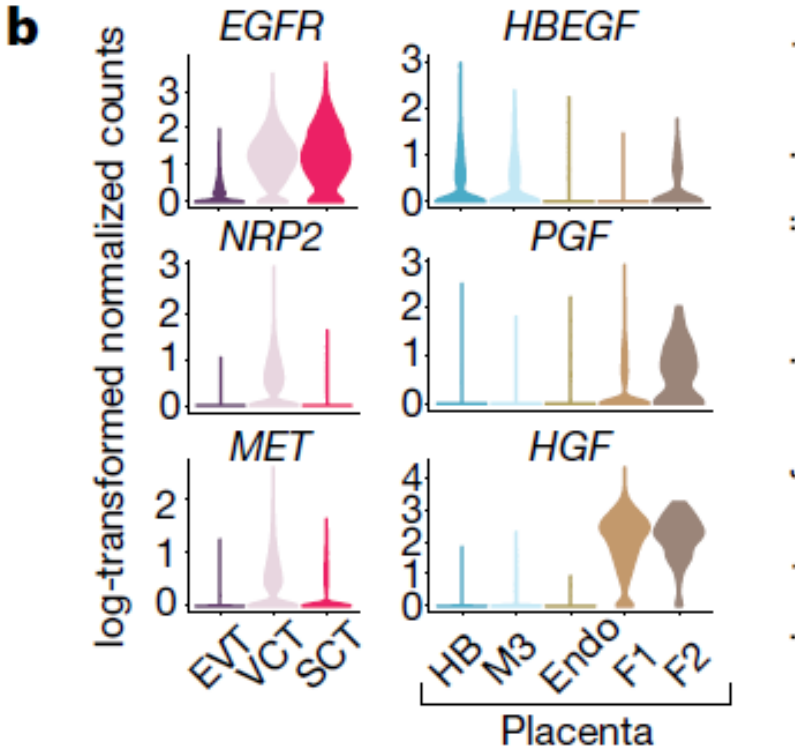
What is the role of HGF pathway in the maternal fetal interface?



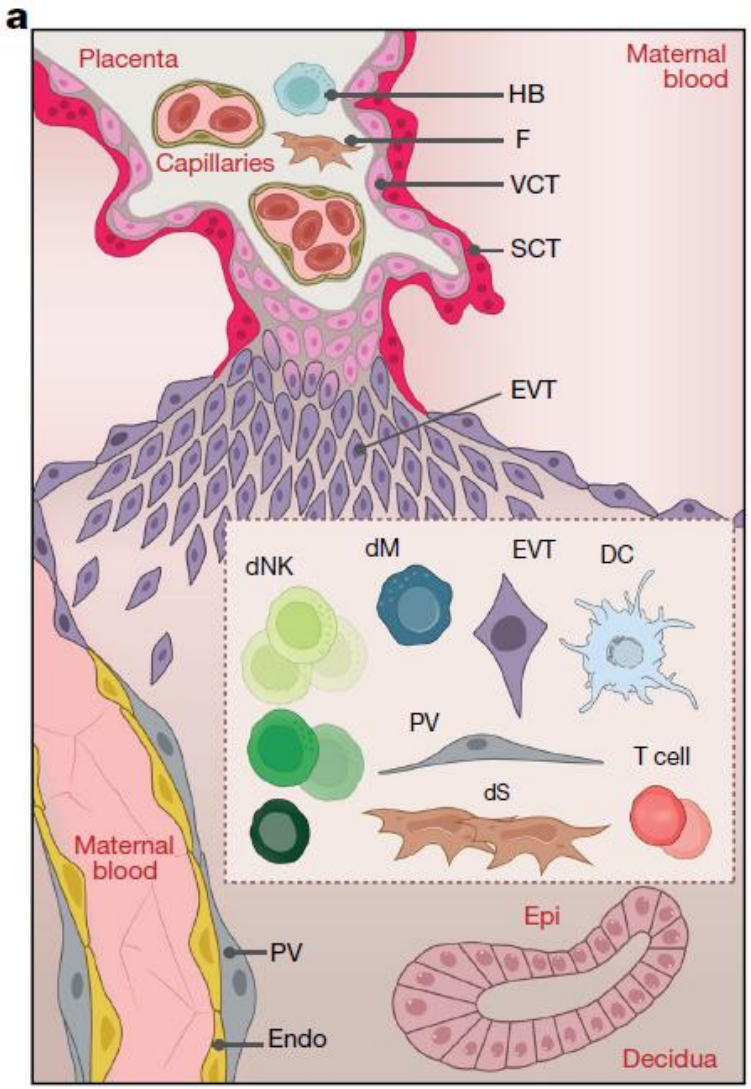


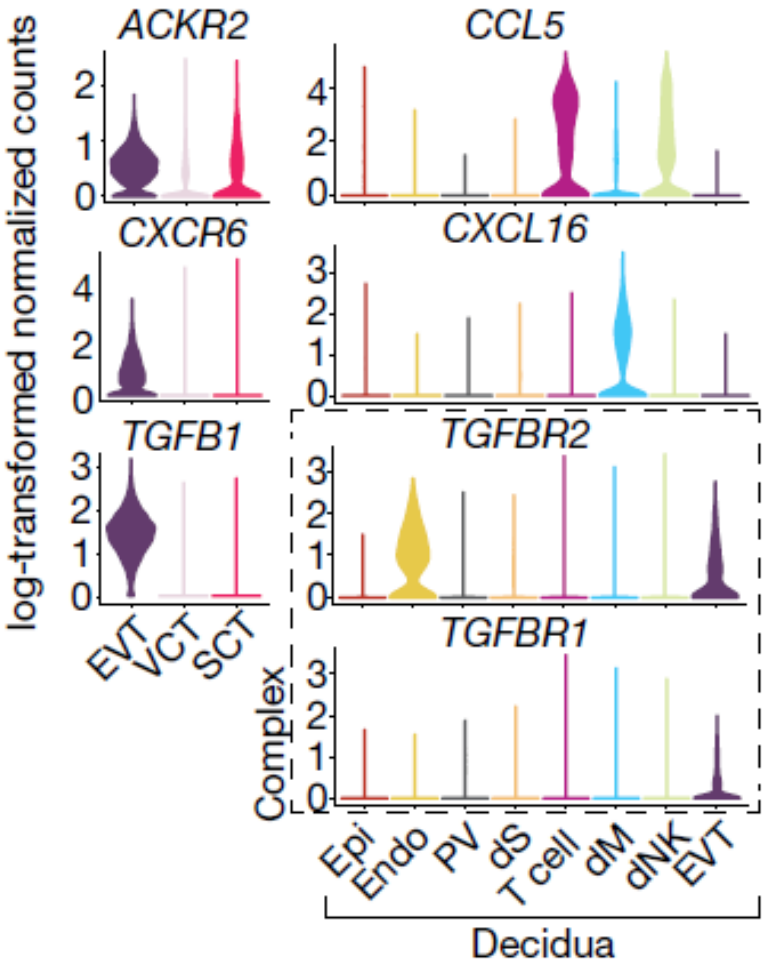
HGF is expressed in cell types, classified as Endo and F1-F2, while MET, HGF-receptor, is expressed in VCT



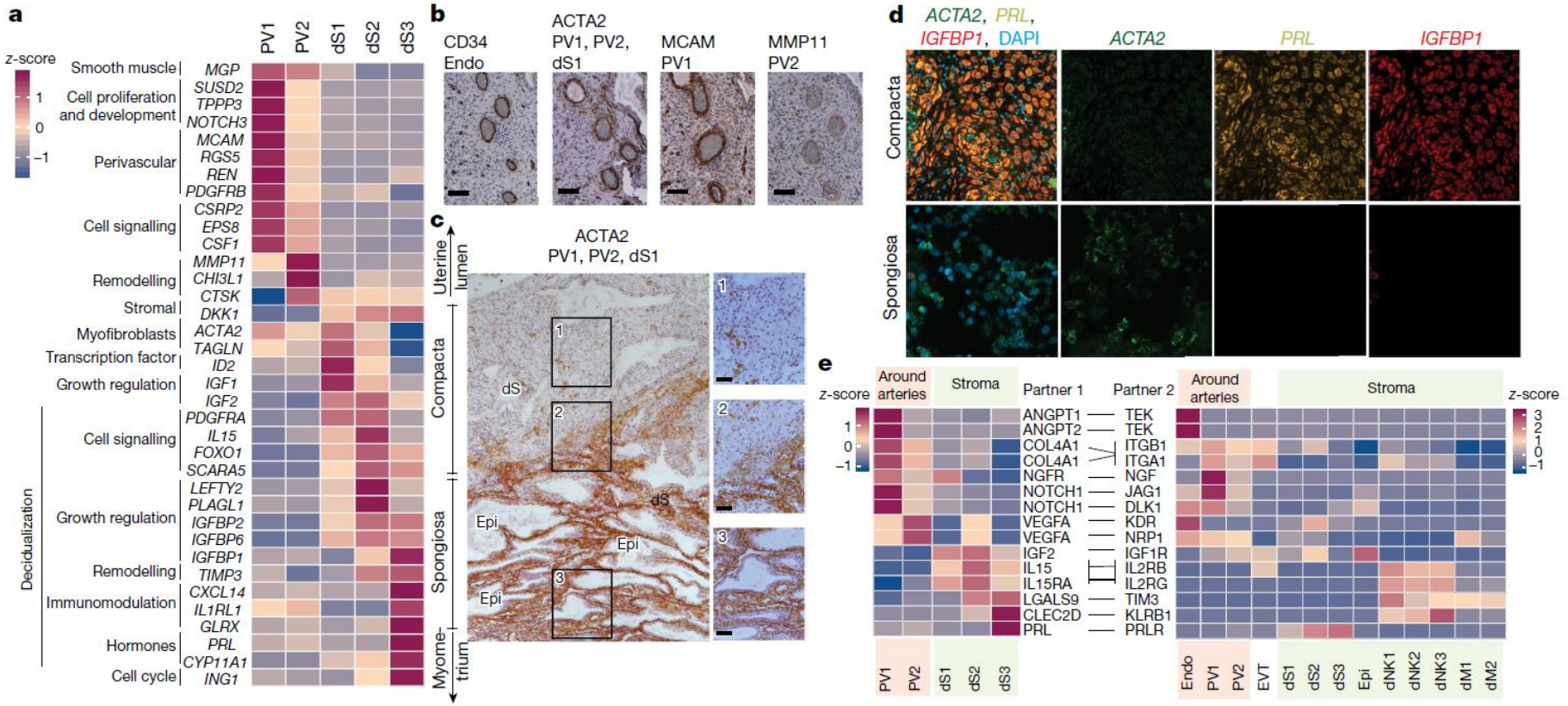


TGFB1 is expressed in EVT, while TGFBR2, TGFB1-receptor, is expressed in Endo and EVT





Stromal distribution in the two distinct decidual layers.



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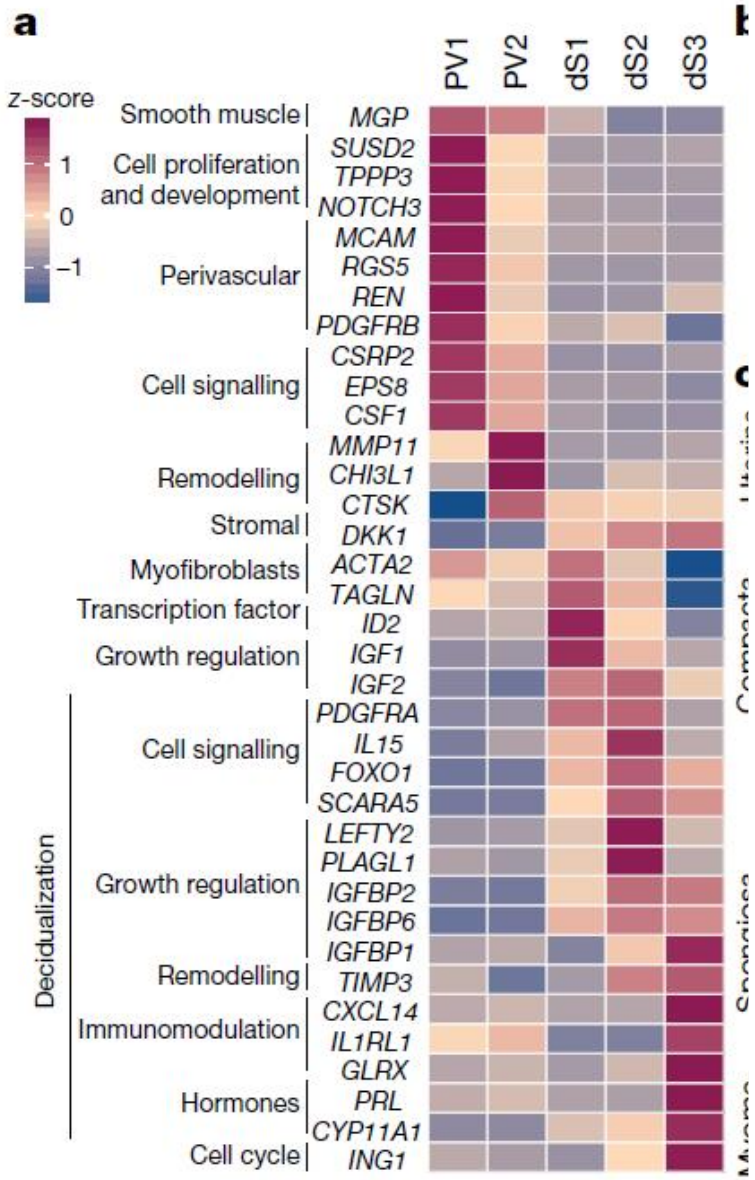
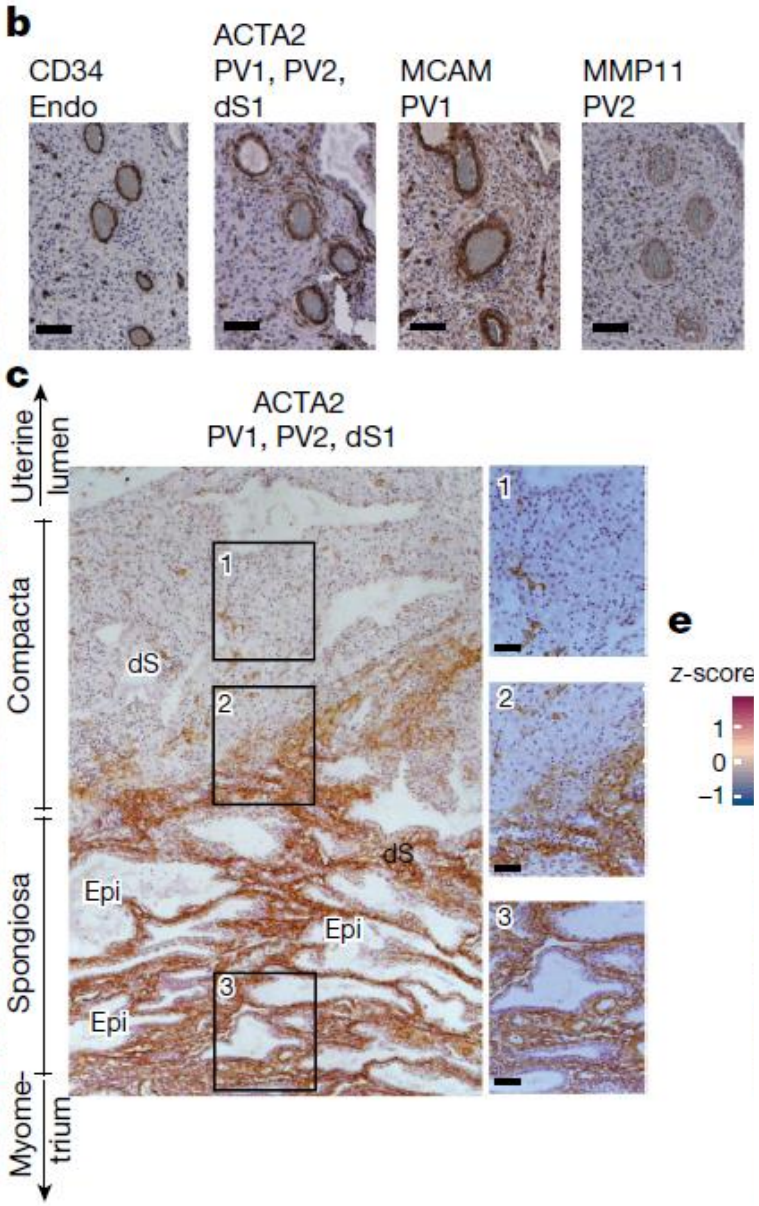
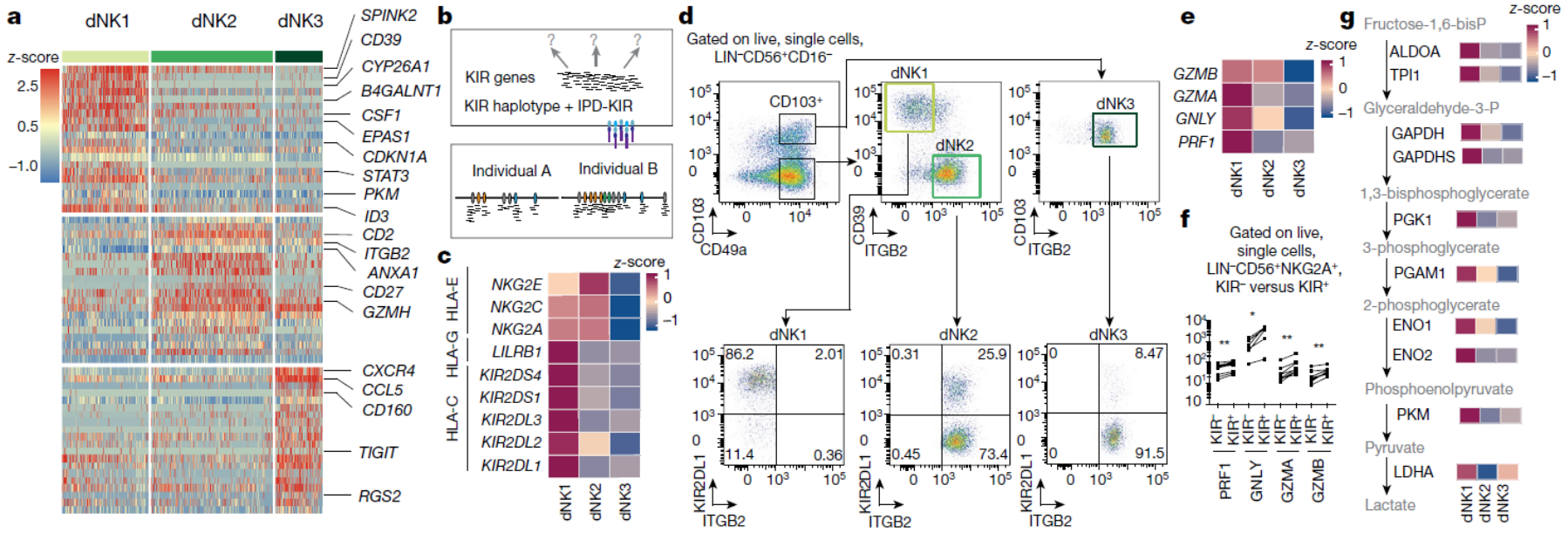


Decidual cell types localization



Three decidual NK cell states



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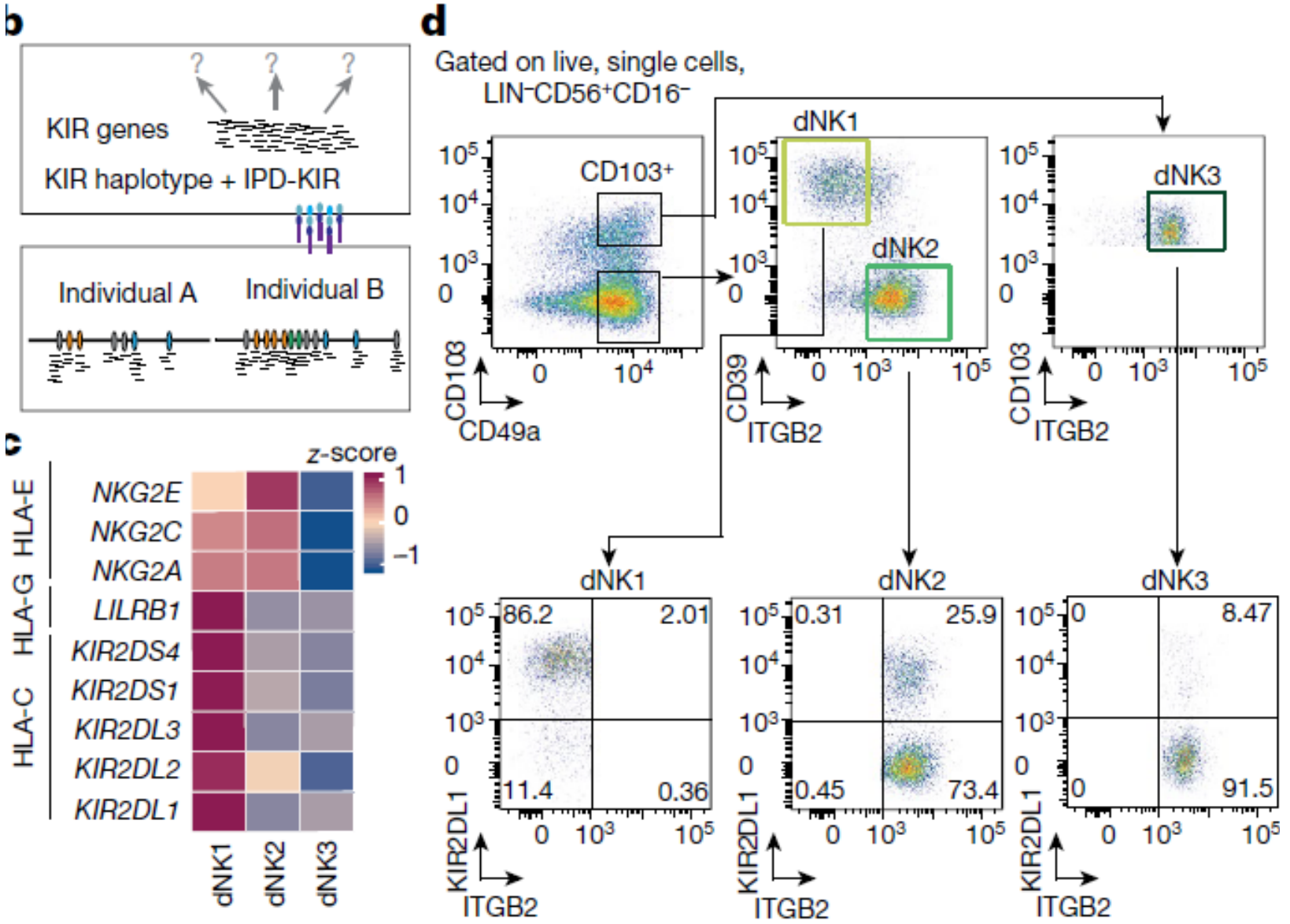
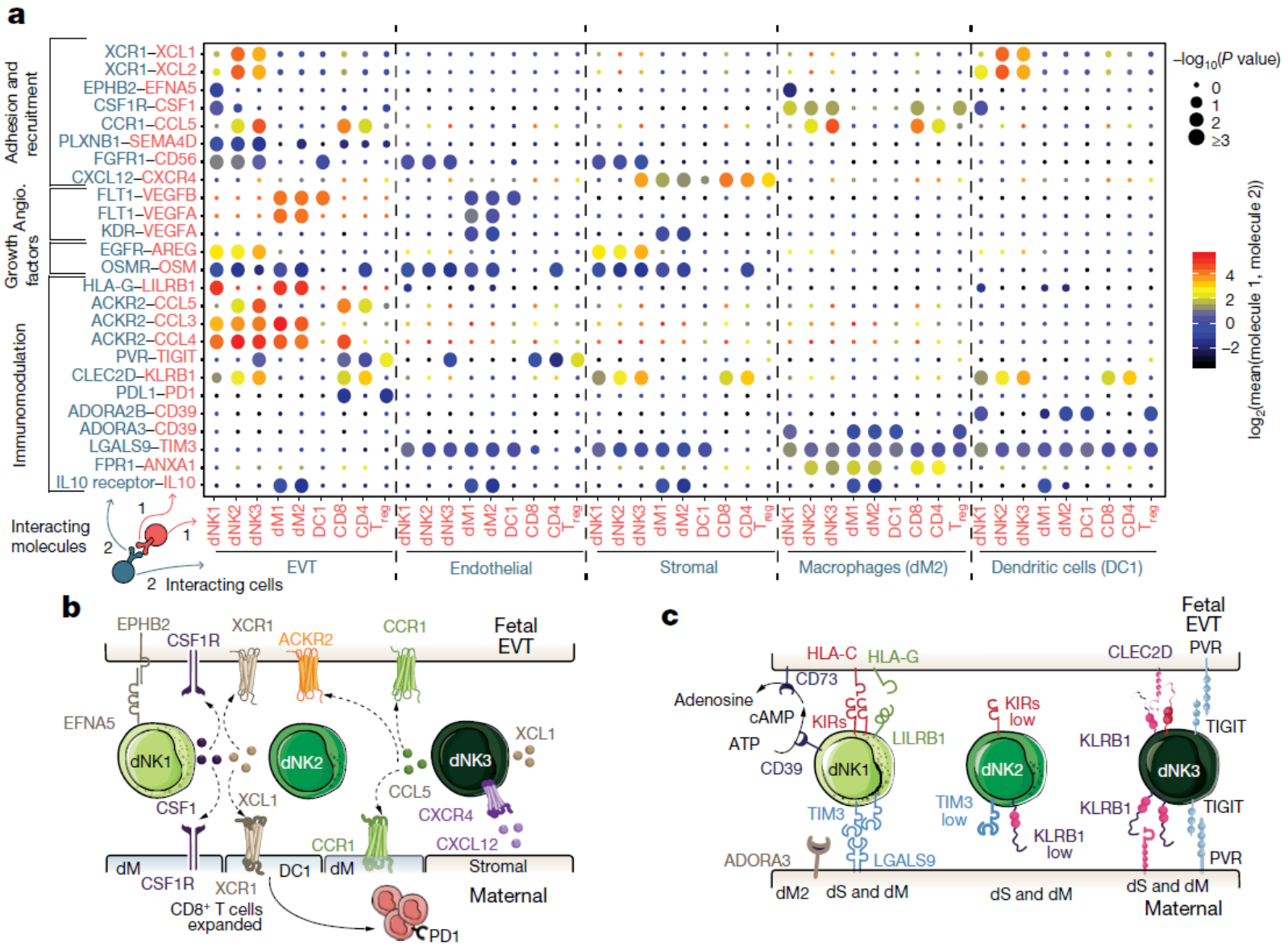
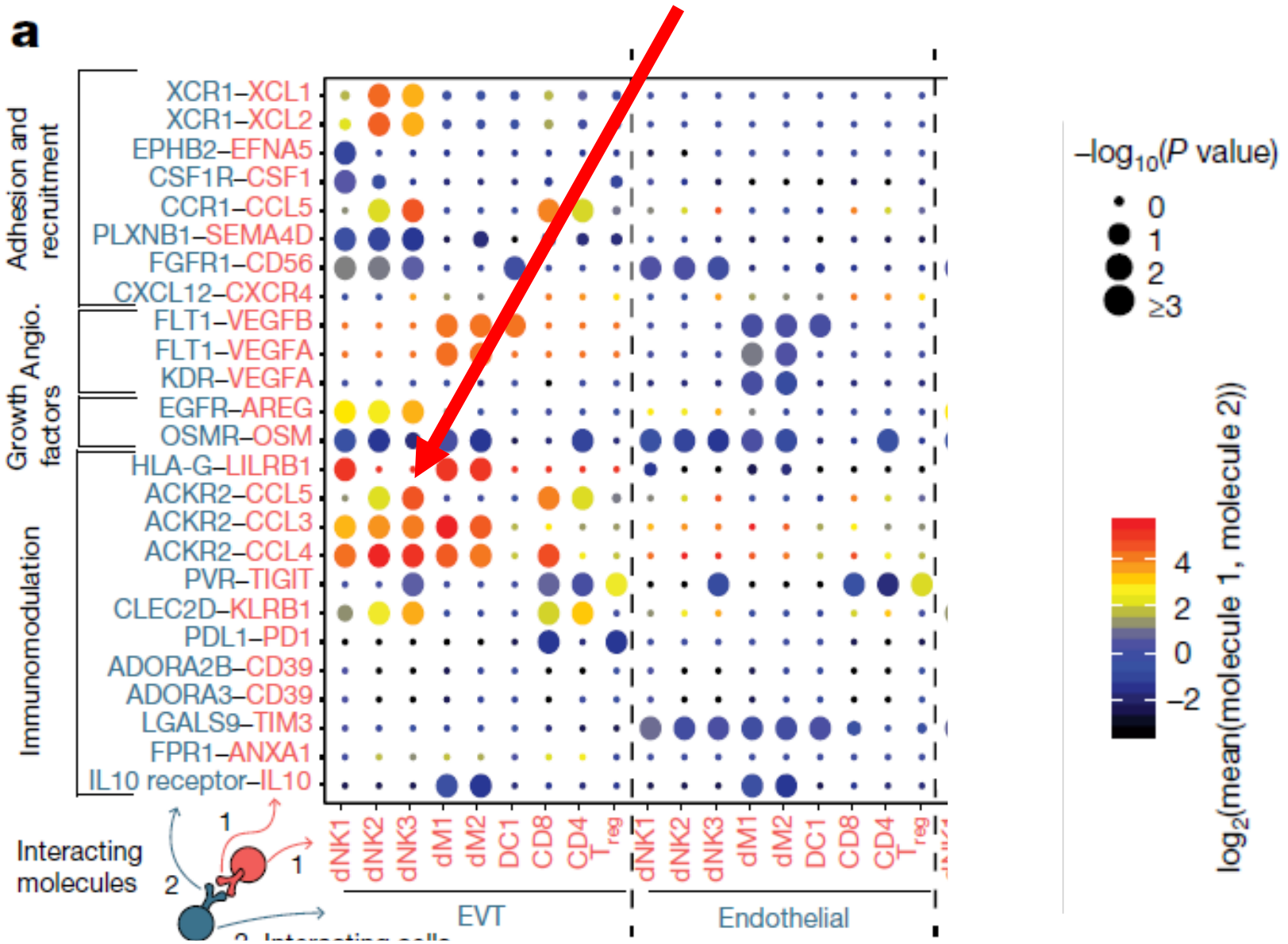


Multiple regulatory immune responses at the site of placentation. Interaction between Natural killer cells and placenta cell subsets



RECONTRUCTION OF CELL-CELL INTERACTION.
ES: ACKR2 RECEPTOR IS BOUND BY CCL5 LIGAND RELEASED FROM dNK3 cells



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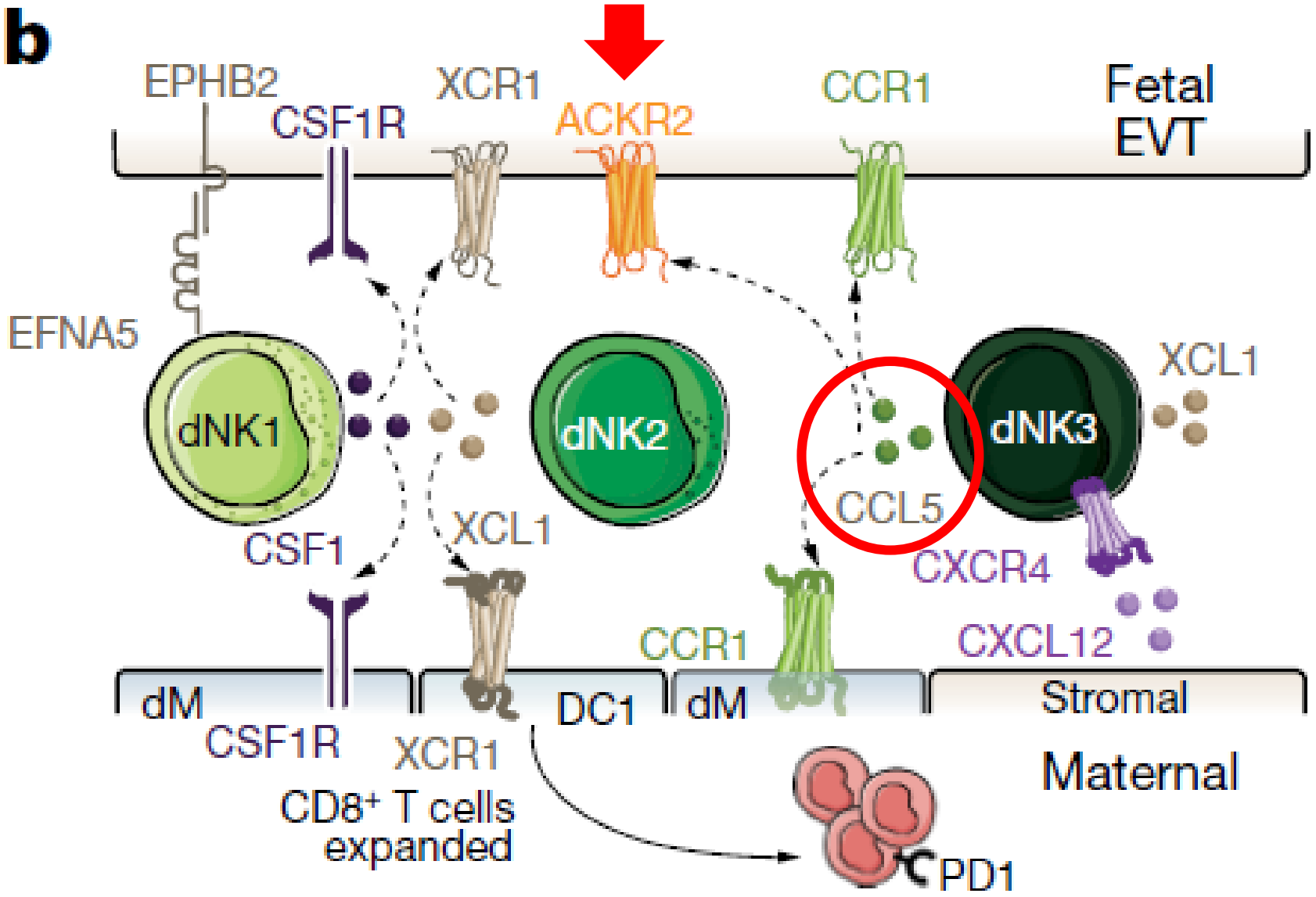
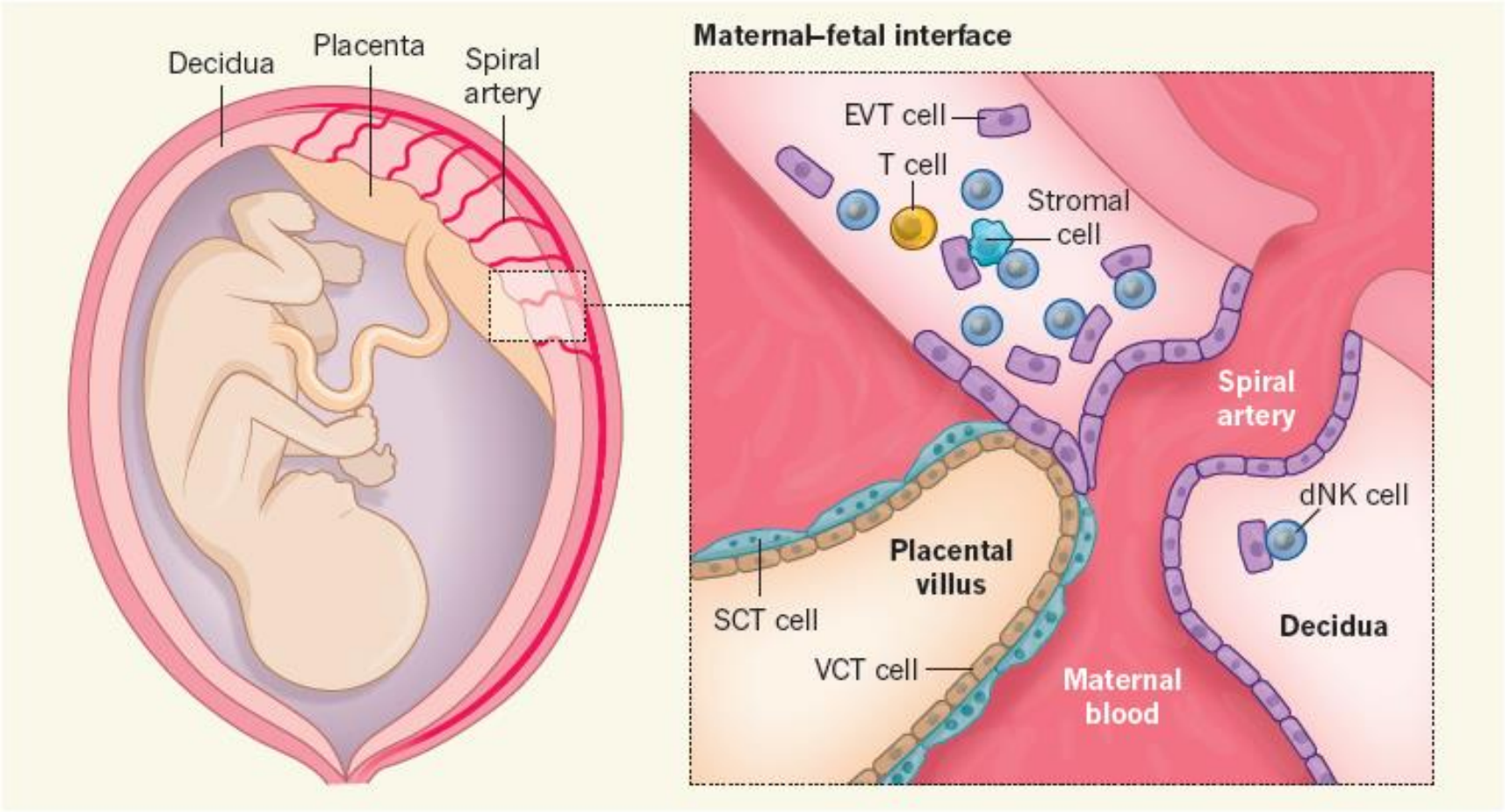


An atlas of cells at the maternal–fetal interface



During the first trimester of human pregnancy, **an interface forms between the maternal decidua (the lining of the pregnant uterus) and the fetal placenta**. Nutrients are delivered to the placenta down maternal spiral arteries.

RNA sequencing of thousands of single cells at this interface defines different cell types and predicts interactions between cells on the basis of the receptors and ligand molecules that they express.

villous cytotrophoblast (VCT) cells, which line placental structures called villi; syncytiotrophoblast (SCT) cells that cover the villus surface; and extravillous trophoblast (EVT) cells, which line the maternal blood vessels and intermingle with maternal cells in the decidua.

Several types of maternal immune cell, including T cells and three subsets of decidual natural killer (dNK) cell, and three types of stromal cell provide structural support for the decidua.

HUMAN CELL ATLAS IMPACT