Cancer Biology Core Course 2026

Session 3: Tumor Evolution

September 9th, 2026

Memorial Sloan Kettering Cancer Center

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Session 3 – 9/9/26 | Tumor evolution & plasticity

Required recorded lectures:

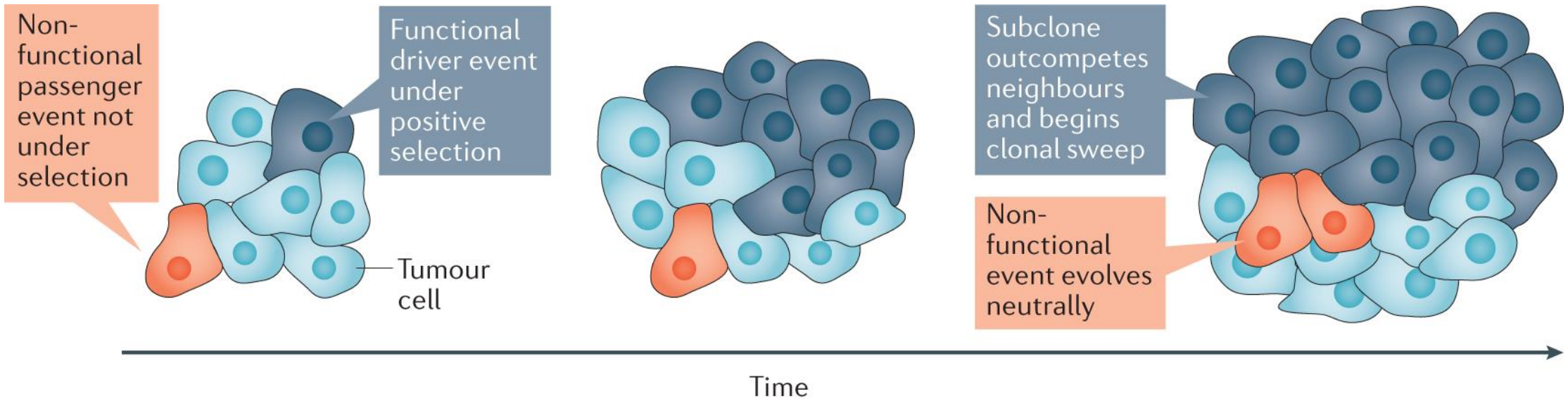
- Tumor Evolution by Tuomas Tammela
- Epigenetic Control of Oncogene Signaling by Ping Chi

Topics covered in class:

- Clonal evolution;
- Cancer heterogeneity;
- Genetic vs non-genetic mechanisms;
- Cell states & Plasticity;
- Selection; Therapies as selective pressure;

Paper to discuss: Chan et al., Nature (2026) - Critical role for a high-plasticity cell state in lung cancer.

Why aren’t cancer cells the same?



Black, J.R.M., McGranahan, N. Genetic and non-genetic clonal diversity in cancer evolution. *Nat Rev Cancer* **21**, 379–392 (2021).

Session 3: Tumor Evolution

Heterogeneity



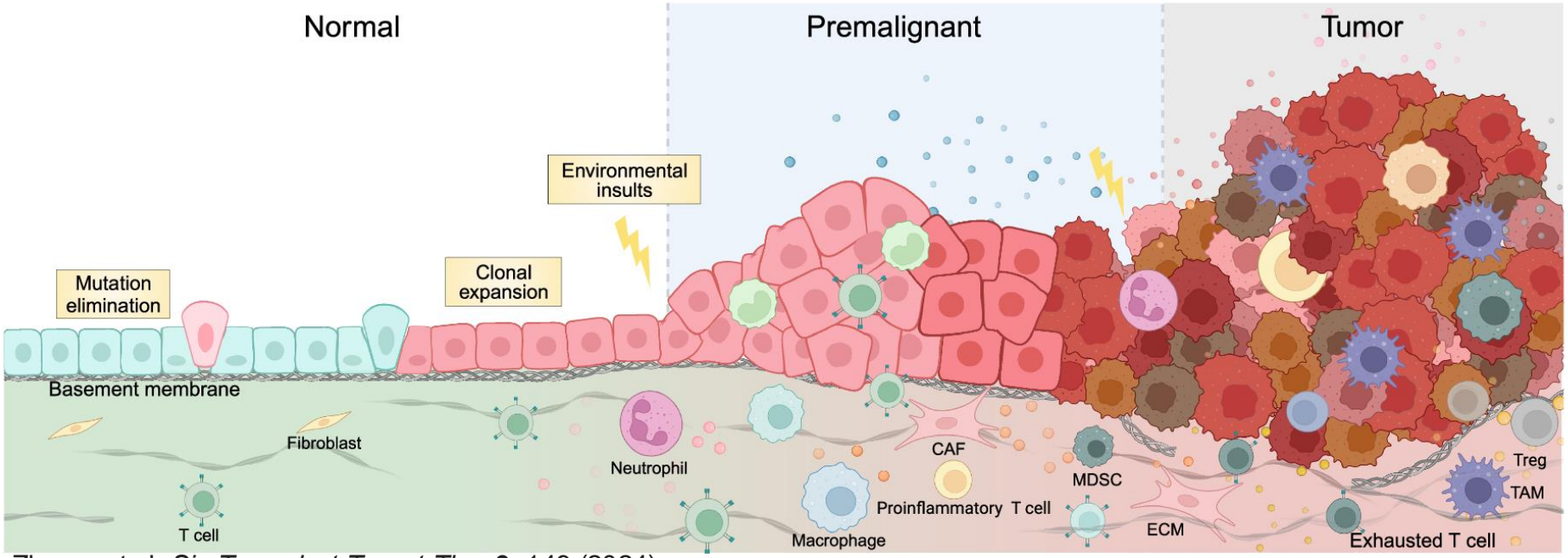


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From initiation to evolution

Last class: **How does a normal cell become cancerous?**

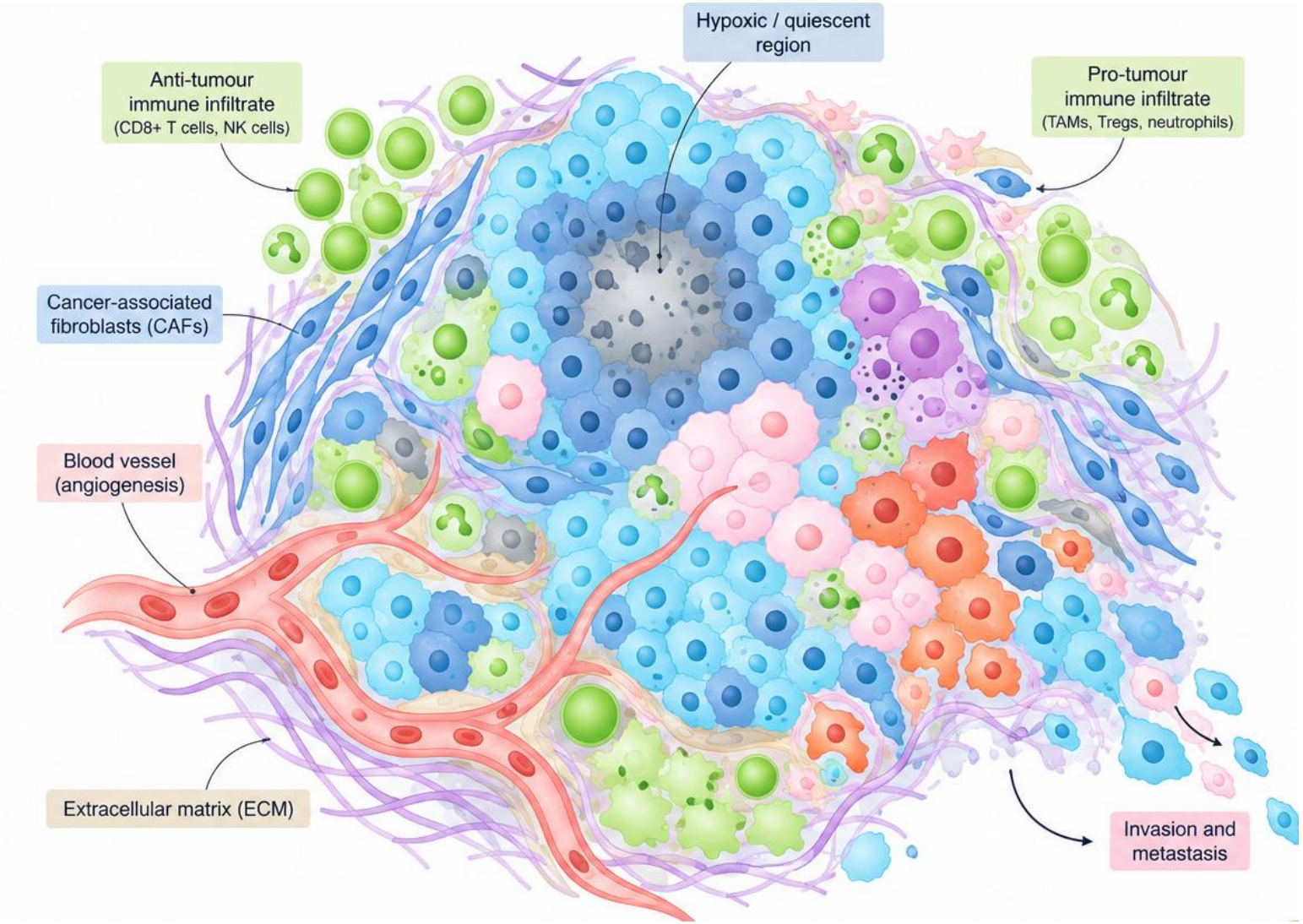
This class: **Once a tumor has formed, how does it change over time?**

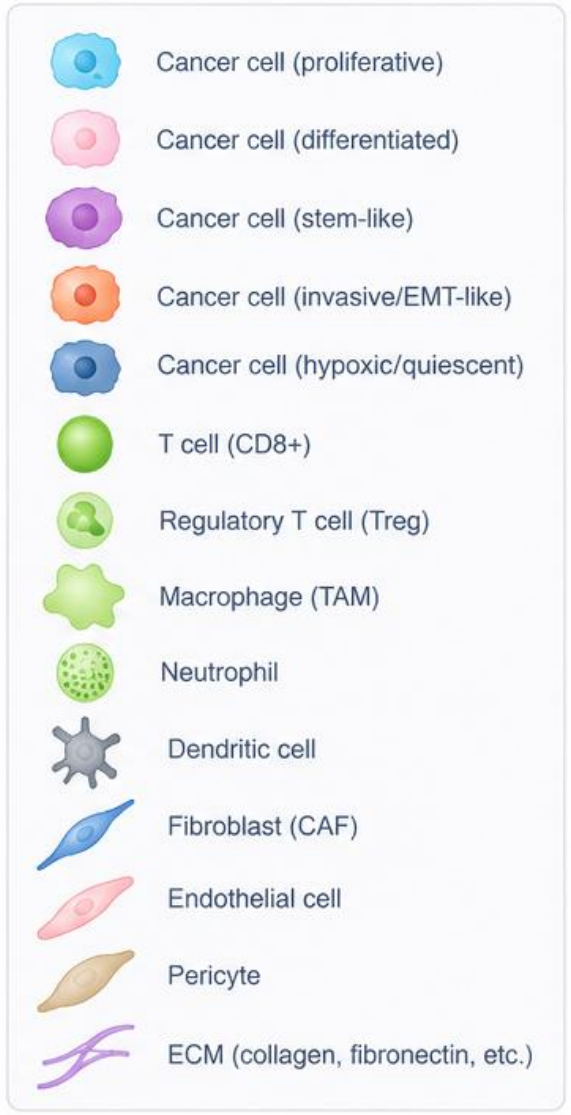


Zhang, et al. *Sig Transduct Target Ther* **9**, 149 (2024).

Cancer is not static.

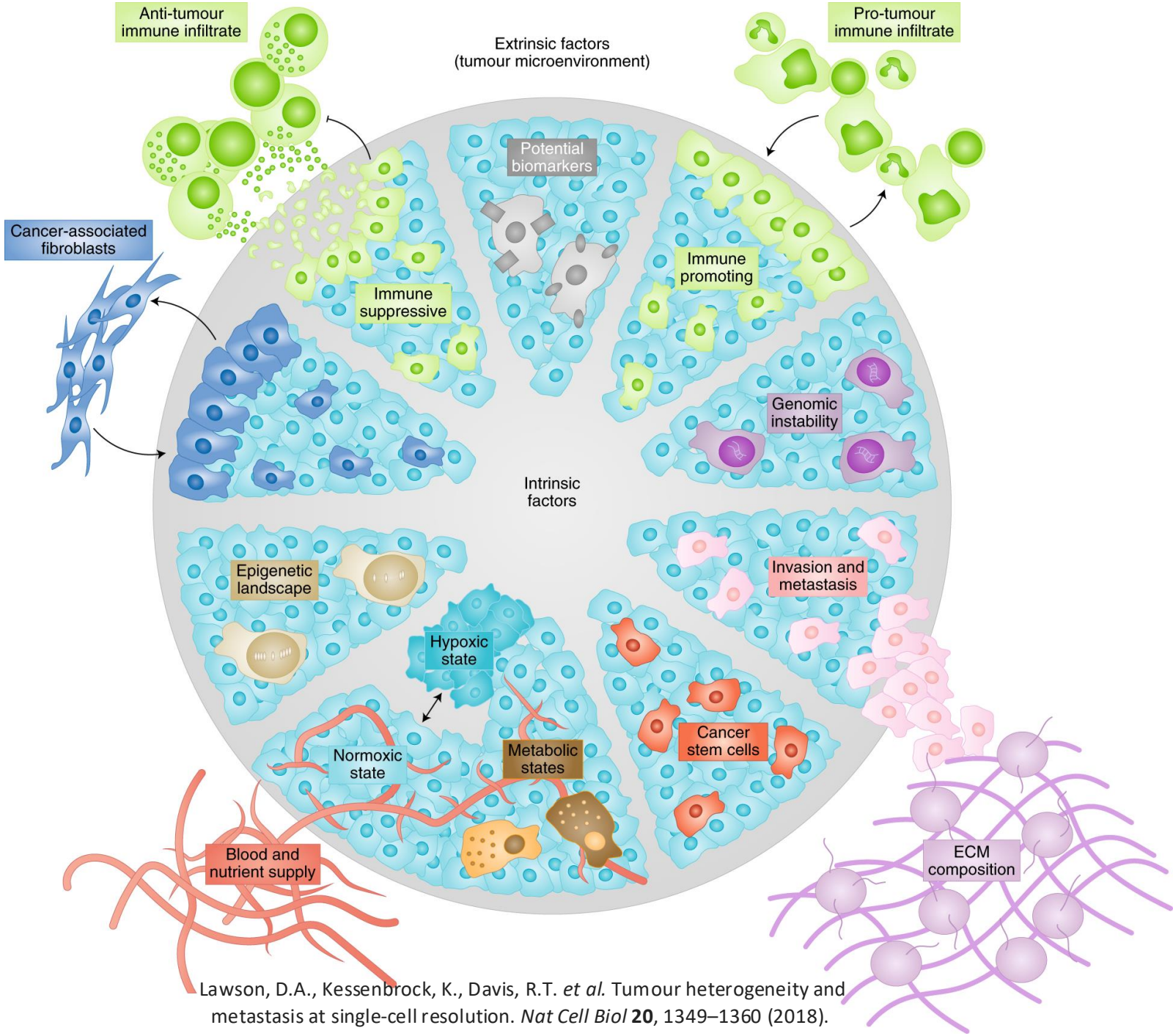
Tumors are heterogeneous





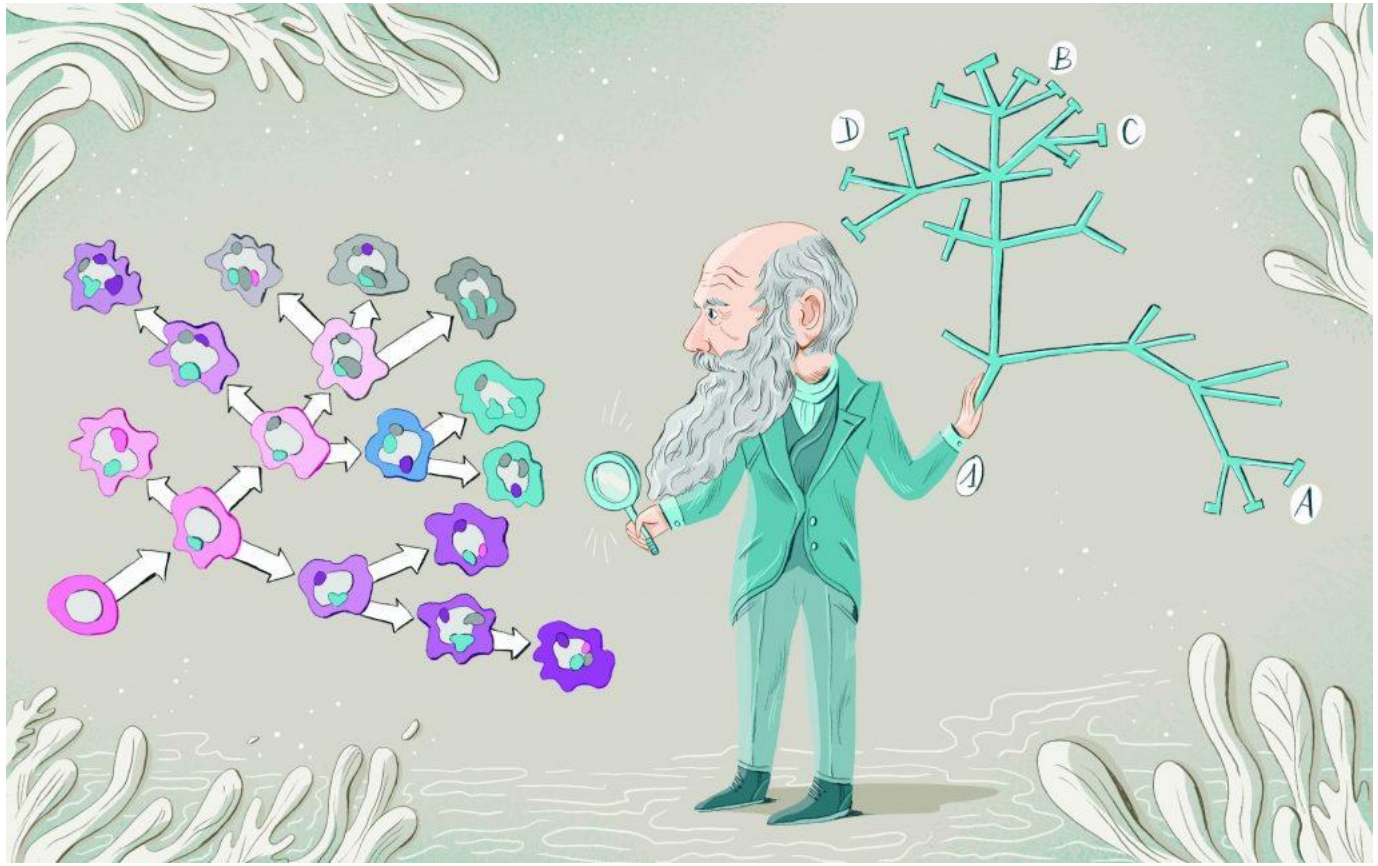
Where does this diversity come from?

Tumors are heterogeneous



Lawson, D.A., Kessenbrock, K., Davis, R.T. *et al.* Tumour heterogeneity and metastasis at single-cell resolution. *Nat Cell Biol* **20**, 1349–1360 (2018).

Cancer as an evolutionary process

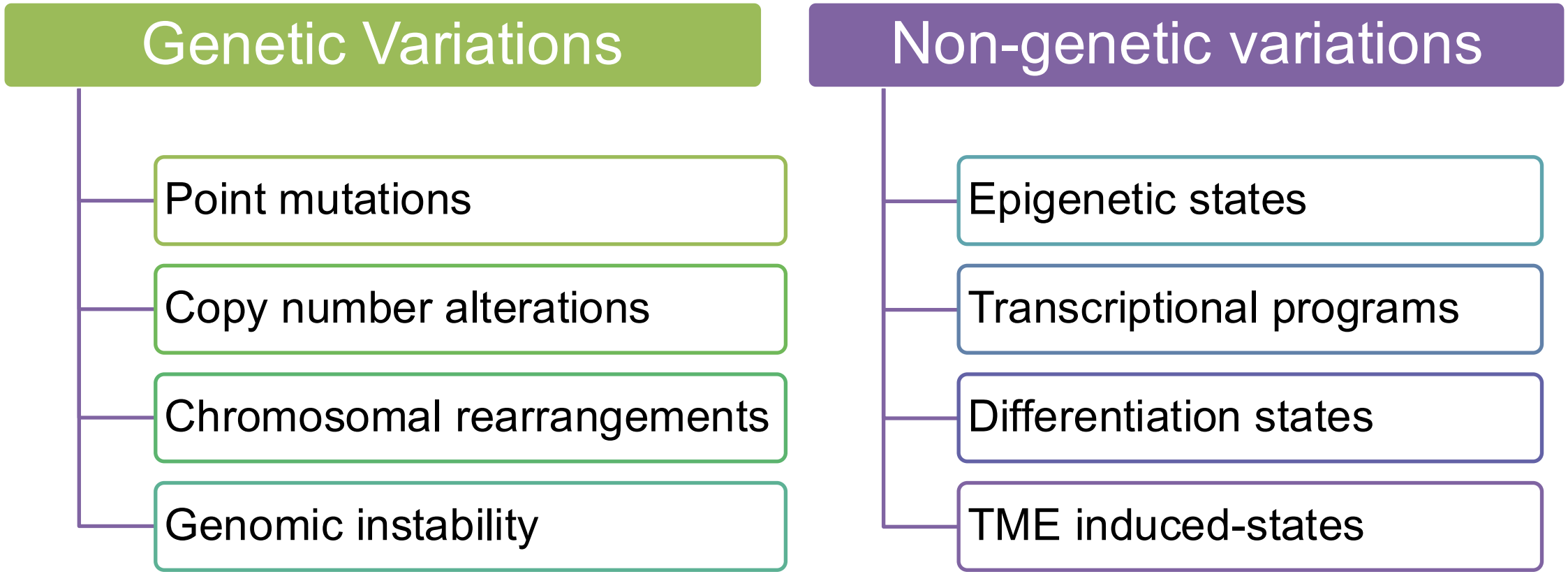


VARIATION → SELECTION → EXPANSION

- Cancer evolution follows natural selection;
- Variation exists among cancer cells: genetic & phenotypic;
- Some variants have higher fitness in a particular environment;
- Those cells preferentially survive and expand.

Tumor evolution is evolution occurring within the body.

Where does the variation come from?



Not every phenotypic difference requires a new mutation.

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Clonal evolution



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Clonal evolution models

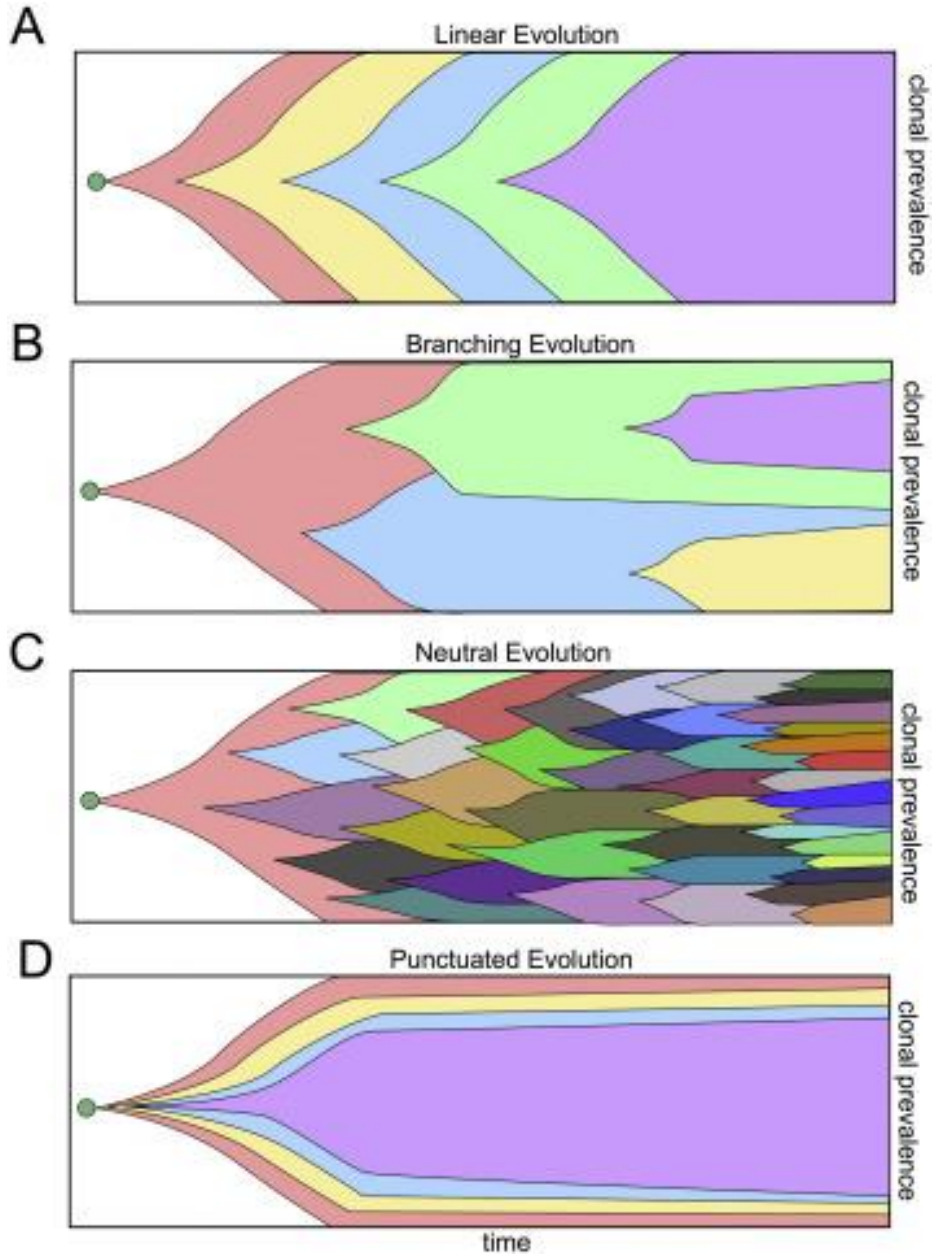
Tumors can evolve in different ways

Architecture
- Linear
- Branched

Tempo
- Gradual
- Punctuated

Selective dynamics
- Darwinian selection
- Neutral / Big Bang-like expansion

Outcome under similar pressures
- Convergent evolution



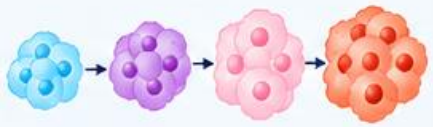
Tumors can evolve in different ways

Genetic evolution
(models based on DNA alterations)

1. Clonal / sequential evolution

Nowell, 1976
The clonal evolution of tumour cell populations

Stepwise accumulation of alterations in a single lineage, with successive clones replacing the previous one.



Evolutionary tree (linear)

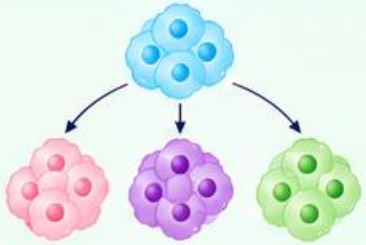


- Early model of tumour progression.
- Each new alteration provides a selective advantage.
- Less common in solid tumours, but can be seen in some settings (e.g. certain leukaemias).

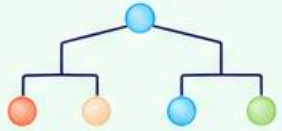
2. Branched evolution

Gerlinger et al., 2012
N Engl J Med
Intratumour heterogeneity and branched evolution revealed by multiregion sequencing.

Multiple subclones arise from a common ancestor and evolve in parallel, acquiring distinct alterations in different regions.



Evolutionary tree (branched)

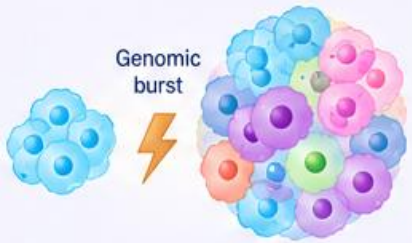


- Common in many solid tumours.
- Explains spatial heterogeneity within a tumour and between primary and metastatic sites.

3. Punctuated evolution

Gao et al., 2016
Nat Genet
Punctuated copy-number evolution and clonal stasis in triple-negative breast cancer.

Large numbers of alterations accumulate in short bursts, followed by periods of relative stability (clonal stasis).



Evolutionary tree (punctuated)

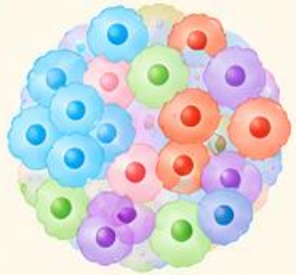


- Major genomic changes can occur over short time periods.
- Followed by long periods of relative stability.
- Observed in several solid tumours (e.g. breast cancer).

4. Neutral evolution / "Big Bang" model

Sottoriva et al., 2015
Nat Genet
A Big Bang model of human colorectal tumor growth.

Many subclones arise early during tumour growth and expand in parallel, with limited strong selection later (effective neutral evolution).



Evolutionary tree (early diversification)

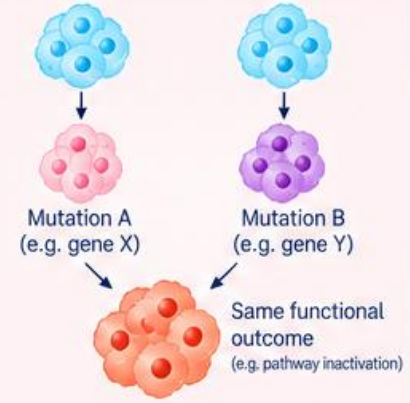


- Extensive intratumour heterogeneity is established early.
- Many subclones persist with similar fitness (no major selective sweeps).
- Supported by multiregion and single-cell sequencing.

5. Convergent evolution

Gerlinger et al., 2012
N Engl J Med
Recurrent evolution of inactivating mutations in SETD2 in renal cancer.

Independent subclones acquire different genetic alterations that lead to the same functional outcome under similar selective pressures.



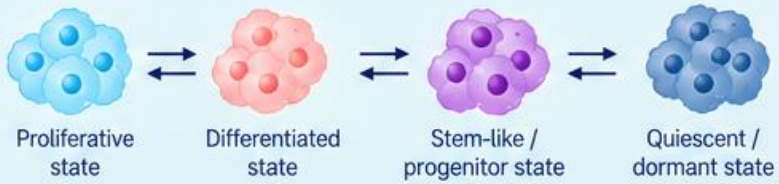
- Different genetic routes to the same phenotype.
- Highlights that evolution selects for functions, not specific mutations.
- Observed in multiple cancer types and in response to therapy.

Evolution is not purely genetic

Non-genetic evolution
(cell-state plasticity)

6. Cell-state plasticity (non-genetic evolution)
(multiple contributors, 2010s–present)
Emerging paradigm from developmental biology, epigenetics and cancer plasticity literature.

Cancer cells can switch between different phenotypic states without acquiring new genetic alterations. These states can be dynamic, reversible or semi-stable, and can be selected in specific environments.



Examples of state changes:
- EMT / MET
- Differentiation ↔ progenitor-like
- Proliferative ↔ quiescent
- Drug-sensitive ↔ tolerant
- Environment-induced states (e.g. hypoxia, inflammation)

Cellular Plasticity

- epigenetic
- transcriptional
- differentiation-state changes
- environmentally induced states
- potentially reversible

Q: A tumor begins from one transformed cell. Months later, several genetically distinct subclones are present. What best explains this?

A

All subclones were already present in the original cell

B

Each subclone arose from an independent cancer initiation event

C

Cancer cells acquire additional variation, followed by selection and clonal expansion

D

Each subclone arose from an independent cancer initiation event

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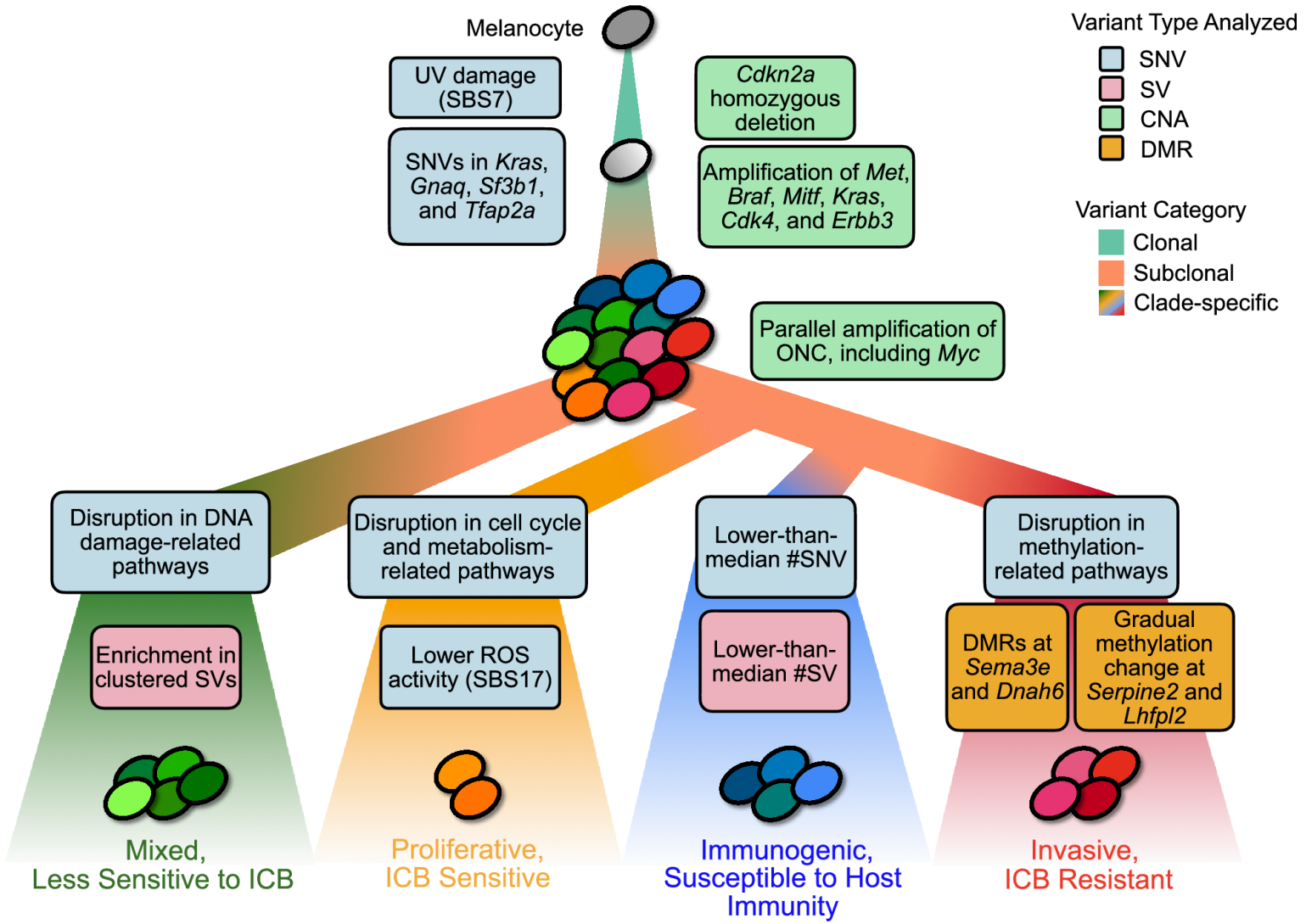
D

Each subclone arose from an independent cancer initiation event

Selection depends on context

Intrinsic Factors:
- ✓ Proliferation
- ✓ Survival
- ✓ DNA repair
- ✓ Metabolism
- ✓ Cell state

Extrinsic Factors:
- ✓ Oxygen
- ✓ Nutrients
- ✓ Immune signals
- ✓ **Therapy**



Liu, Y., Goretsky, A., Keskus, A.G. *et al.* Long-read sequencing of single cell-derived melanoma sublines reveals divergent and parallel genomic and epigenomic evolutionary trajectories. *Nat Commun* **17**, 8740 (2026).

Therapy is a selective pressure

Many populations coexist

↓

Treatment

↓

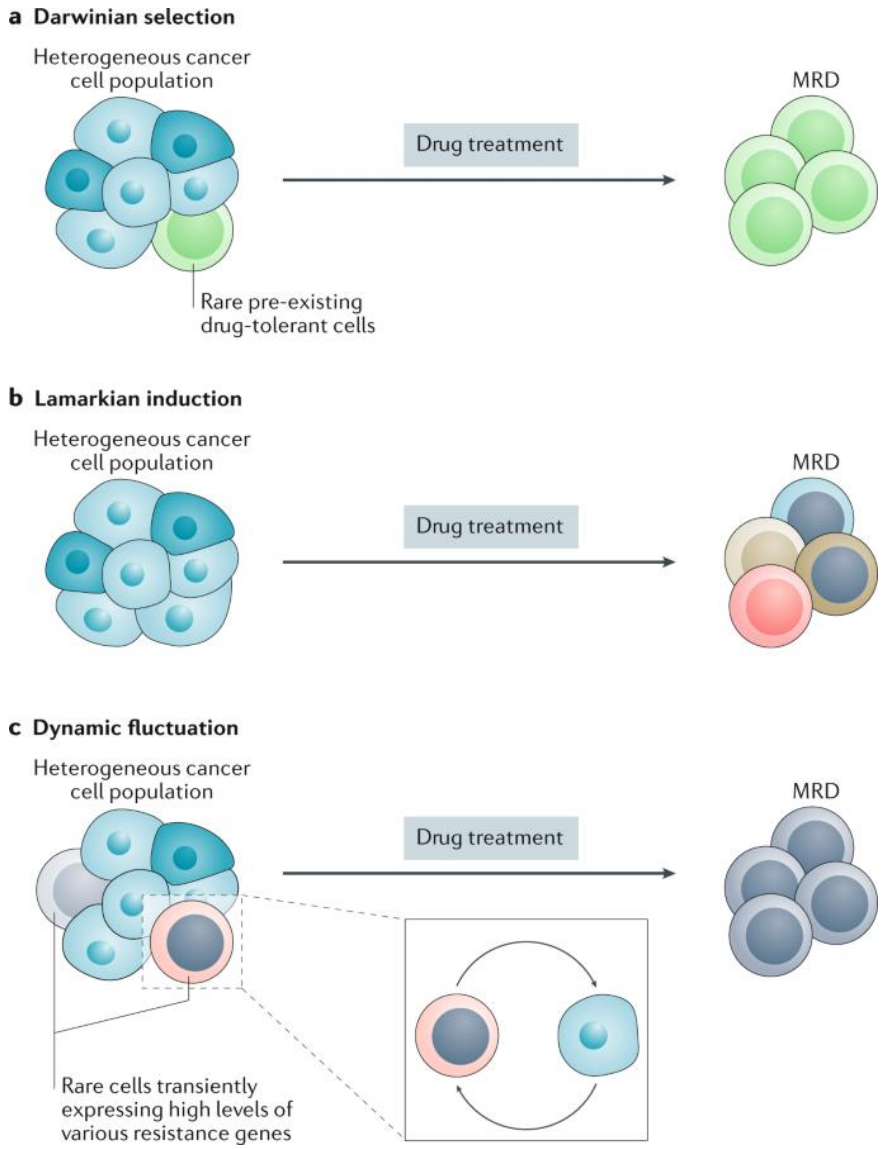
Sensitive cells ↓

↓

Pre-existing or adaptive resistant cells survive

↓

Population composition changes



Boumahdi, S., de Sauvage, F.J. The great escape: tumour cell plasticity in resistance to targeted therapy. *Nat Rev Drug Discov* **19**, 39–56 (2020).

Genotype is not the whole story

Cancer cells with the same genotype can behave differently.

Same mutations, but one cell may be:

- Proliferative
- Quiescent
- Differentiated
- Stem/progenitor-like
- Invasive
- Drug tolerant

How?

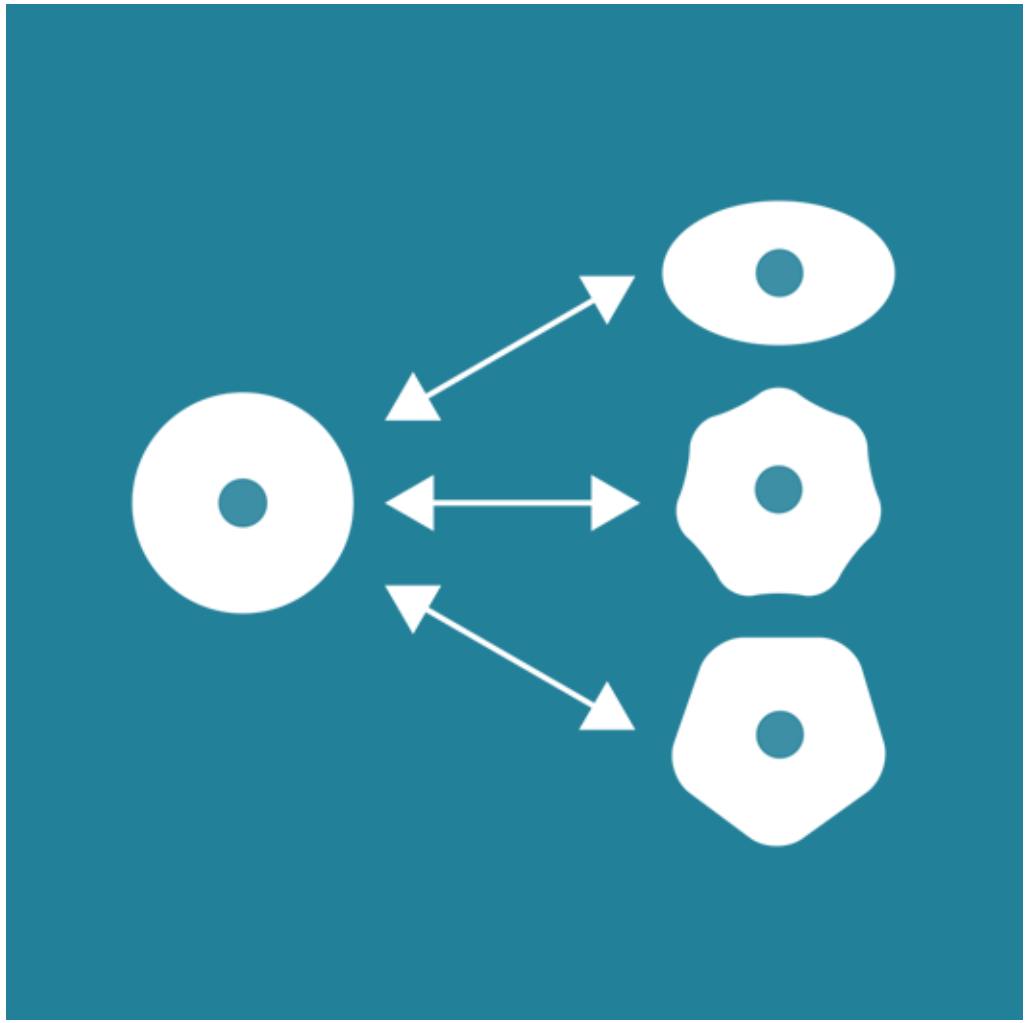
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Plasticity



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What is cellular plasticity?



Plasticity: Cellular plasticity is the ability of a cell to change its phenotypic state without necessarily acquiring a new genetic alteration.

Examples:

- Differentiated ⇄ progenitor-like
- Epithelial ⇄ mesenchymal-like
- Cycling ⇄ quiescent
- Drug-sensitive ⇄ tolerant

Q: Two cancer cells have the same driver mutations but behave very differently. Which explanation is most plausible?

A

This is impossible if their genomes are the same

B

One cell must contain an undetected oncogene

C

One of the cells must not actually be malignant

D

Differences in epigenetic or transcriptional state can generate different phenotypes

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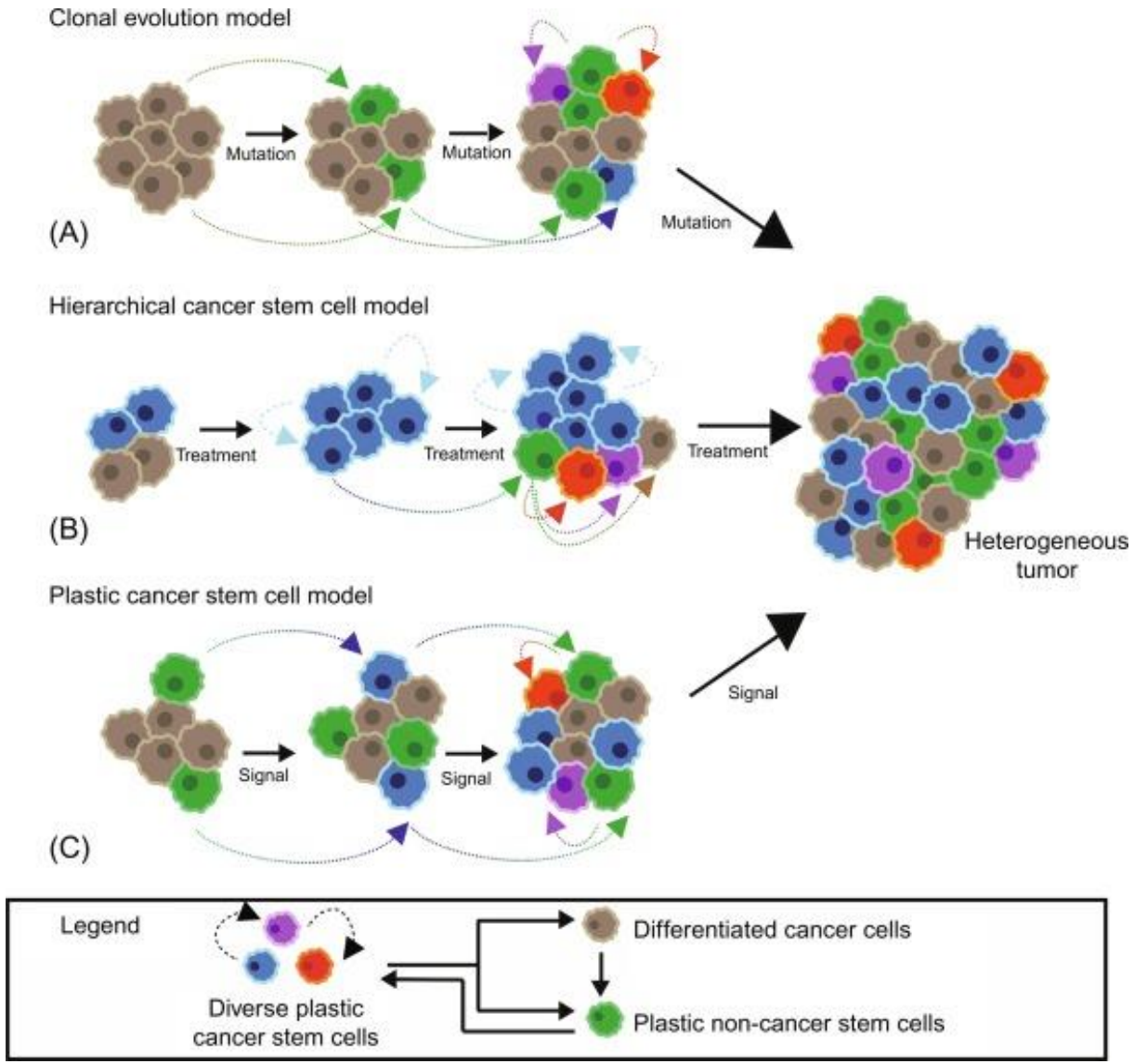
Differences in epigenetic or transcriptional state can generate different phenotypes

Genetic evolution vs plasticity

Genetic evolution	Cellular plasticity
DNA sequence changes	Cell-state changes
Often relatively stable	Can be reversible
Generates distinct clones	Can occur within one clone
Selected over time	Can rapidly respond to environment

Both can generate heterogeneity.

Plasticity can shape evolution



Example:

Environmental stress

↓

A subset of cells enters a tolerant/progenitor-like state

↓

Those cells survive

↓

Surviving cells expand

↓

Additional stable alterations may later accumulate

Key idea:

A transient cell state can influence which cells remain available for future evolution.

Evolution does not require a “super” cell in every way

A selected cell does not need to be:

- fastest growing
- most mutated
- most aggressive in every context

It only needs to have **higher fitness under the current conditions**.
A slow-cycling cell may lose in untreated growth but win during chemotherapy.

Fitness is context dependent.

Q: Which statement best describes tumor evolution?

A

Tumors become progressively more homogeneous over time

B

The most highly mutated clone will always dominate

C

Variation and selection can act on both genetic differences and non-genetic cell states

D

Cellular plasticity makes genetic evolution irrelevant

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D

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Summary: What creates tumor heterogeneity?

Genetic alterations
+
Epigenetic / transcriptional states
+
Cellular plasticity
+
Environmental selection
↓
Heterogeneous tumor populations
↓
Progression / metastasis / treatment response

Tumor evolution reflects both changes in genotype and changes in cell state.

Session 3: Tumor evolution

Journal Club



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Journal club – what are we trying to learn?

Think like a scientist, not just a reader
The goal is NOT to memorize what the authors concluded.

For every paper, ask:

WHY?
What is the scientific question? Why did they do this study?

HOW?
How did they design the experiments to answer that question?

WHAT?
What do the data actually show?

SO WHAT?
Do the data support the authors' conclusions? Why does it matter?

WHAT NEXT?
What is missing? What would you do next?

Article

Critical role for a high-plasticity cell state in lung cancer

https://doi.org/10.1038/s41586-025-09985-x

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Jason E. Chan[1,2,10], Chun-Hao Pan[1,10], Jonathan Rub[1,3], Gary Guzman[1], Klavdija Krause[1], Emma Brown[1], Zeda Zhang[1], Hannah Styers[1], Griffin Hartmann[1], Zhuxuan Li[4], Xueqian Zhuang[1], Scott W. Lowe[1,5], Doron Betel[6,7], Yan Yan[1,8,9]✉ & Tuomas Tammela[1]✉

WHY? HOW? WHAT? SO WHAT? WHAT NEXT?

Fig. 1. The Slc4a11MCD/+ reporter system marks the HPCS in vivo

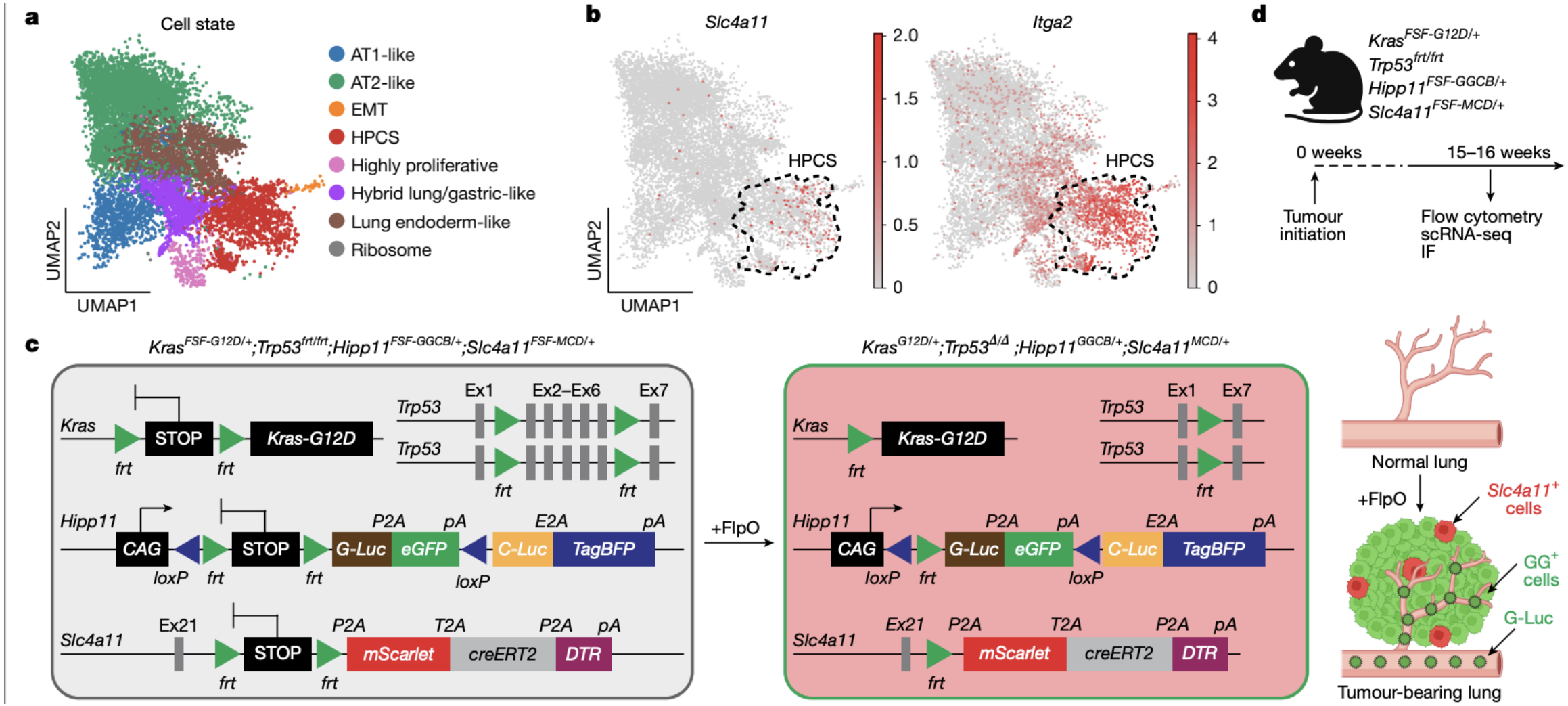


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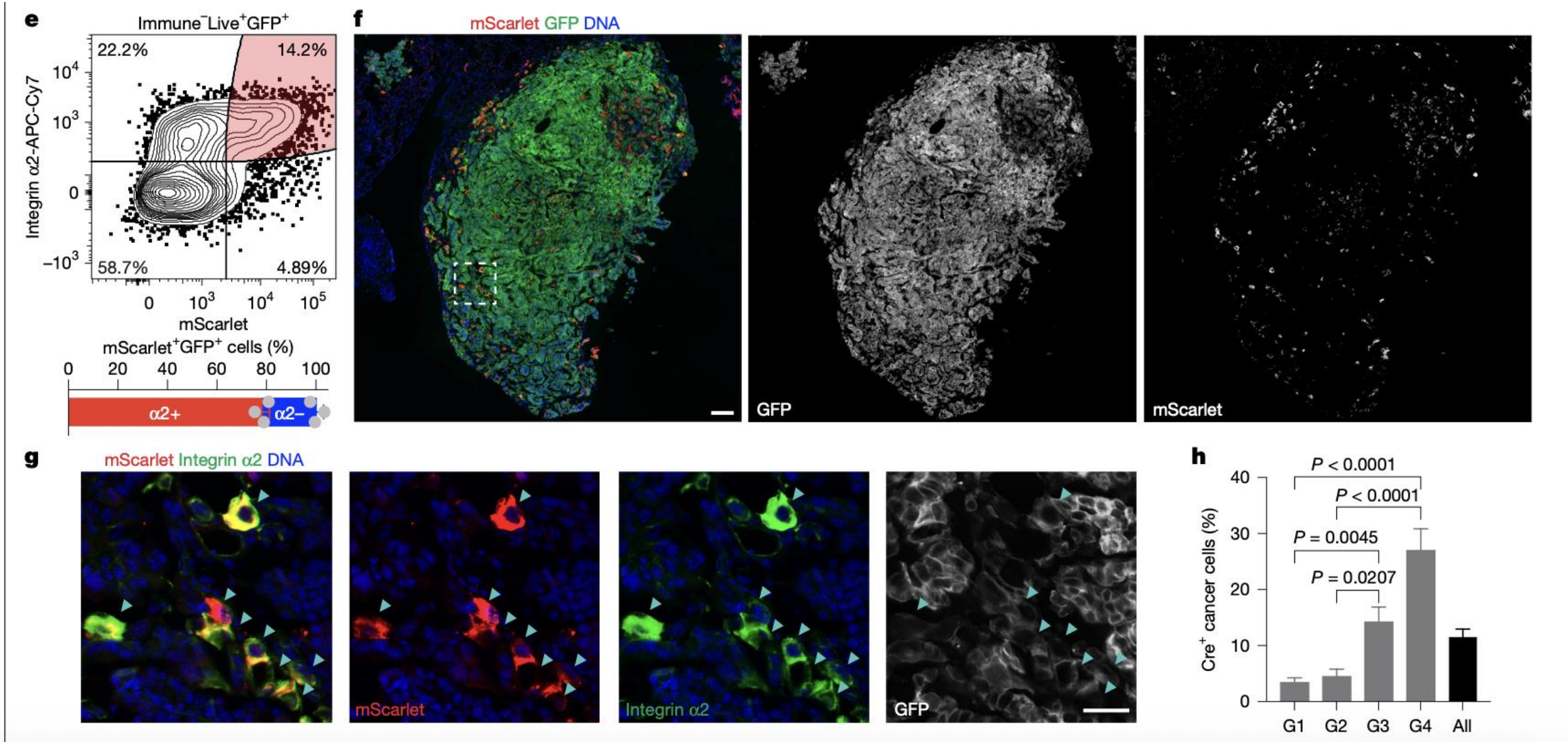


Fig. 2. The HPCS is a hub for cell state transitions in vivo

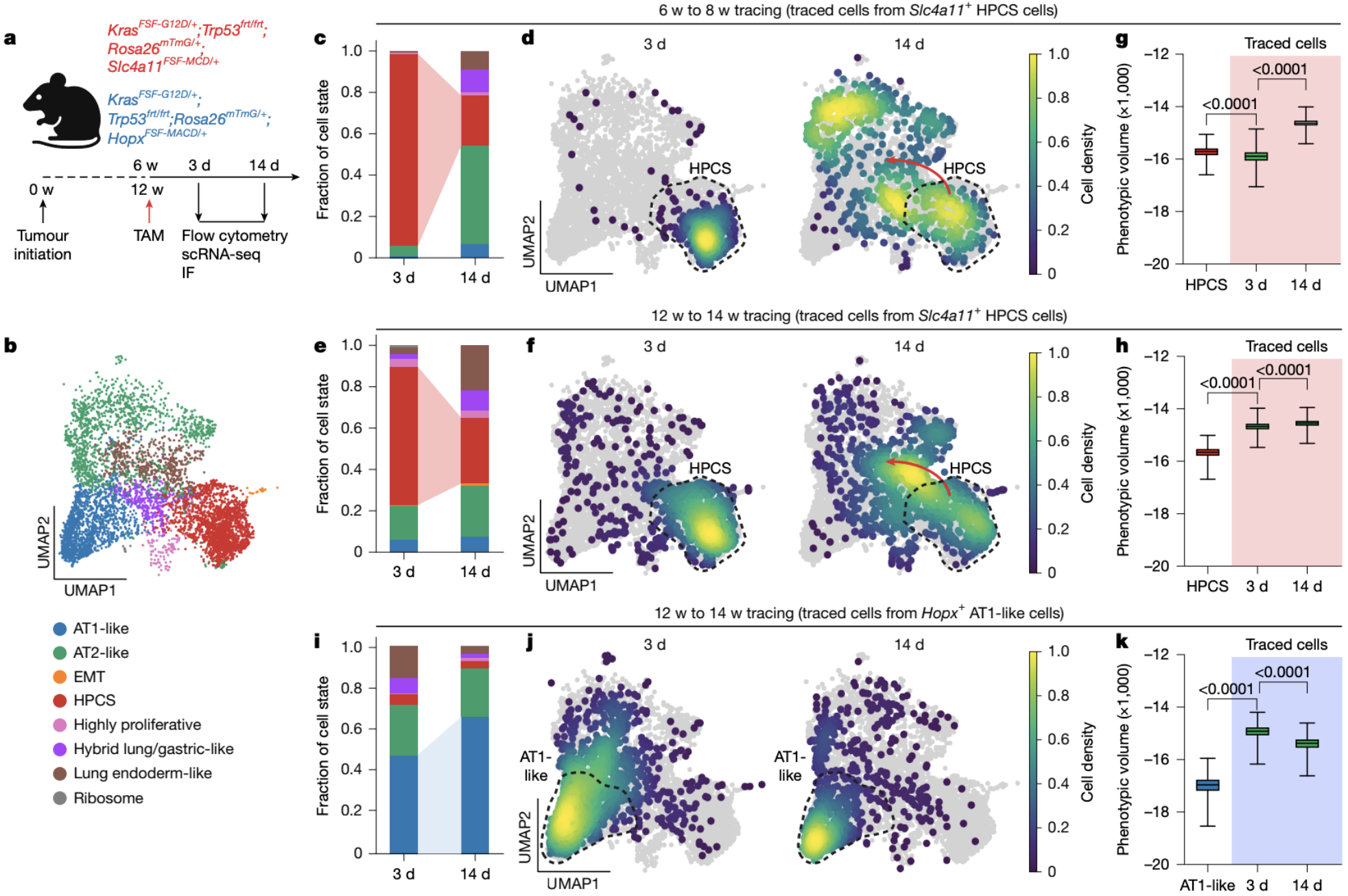


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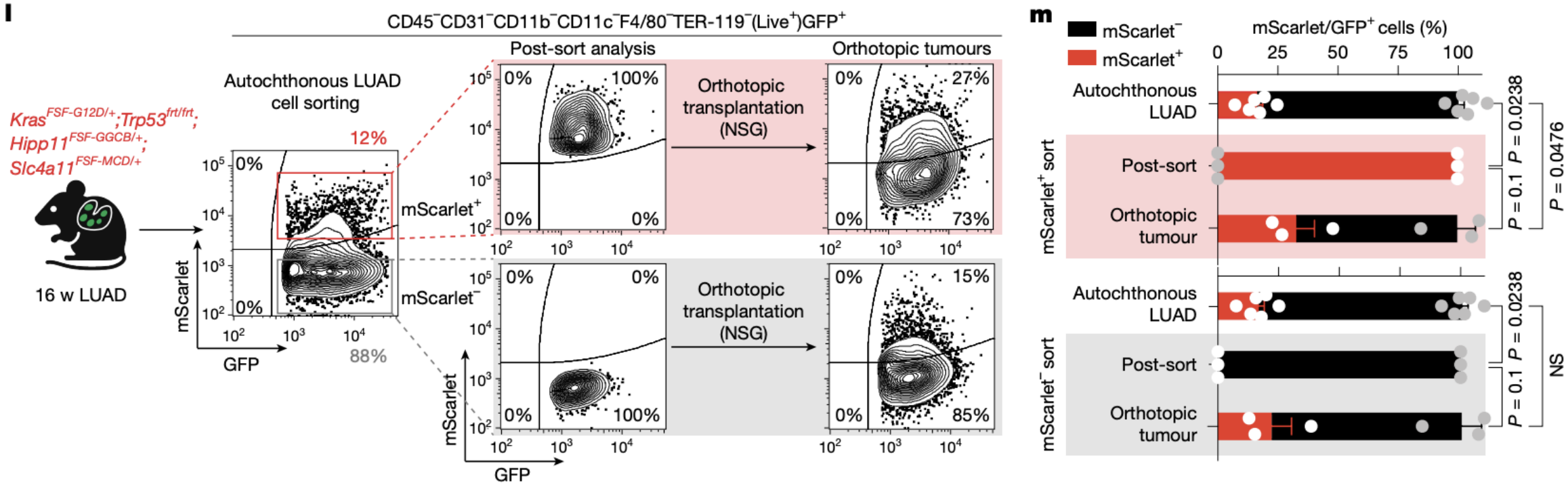


Fig. 3. The HPCS drives tumour growth

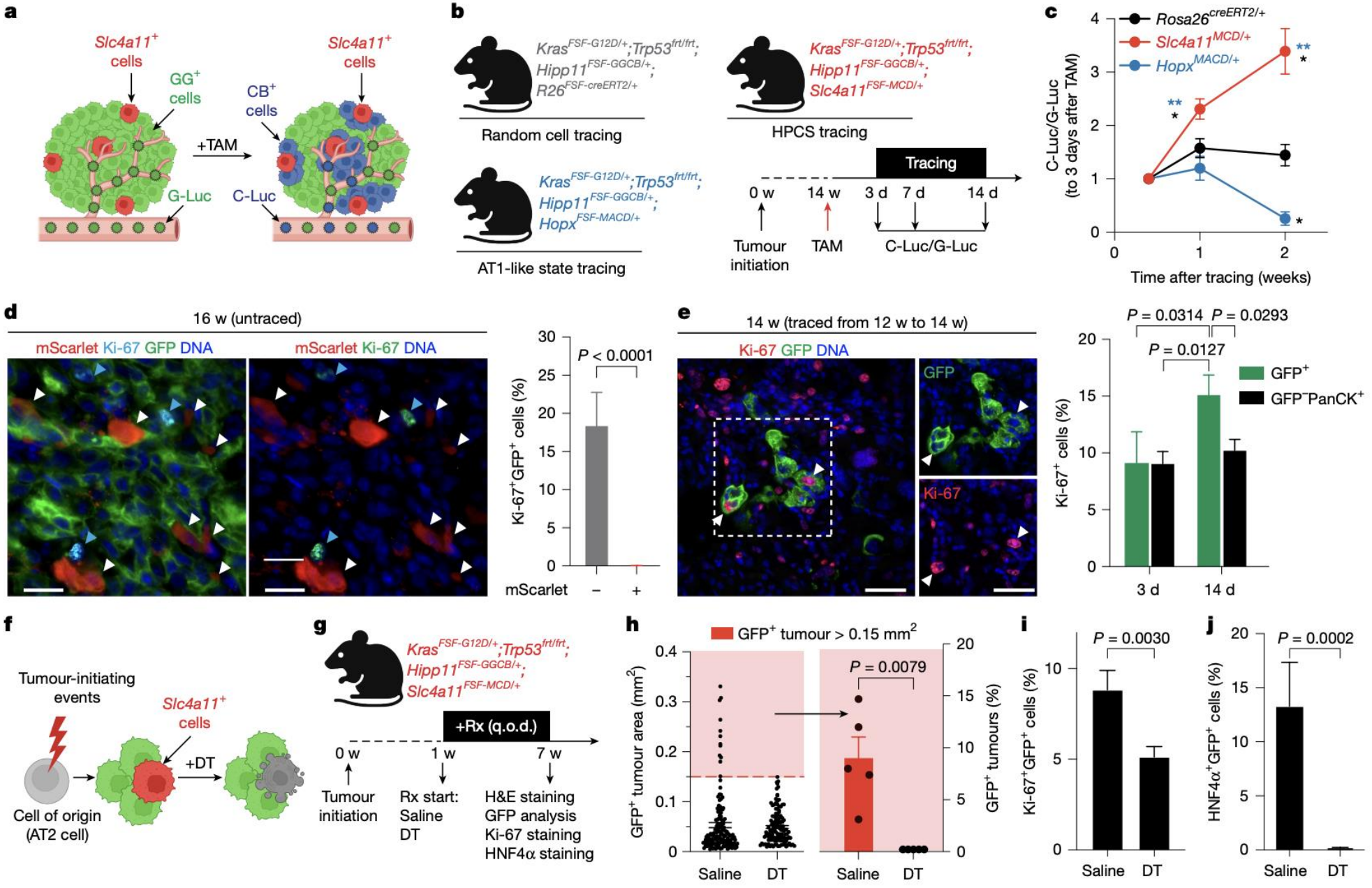


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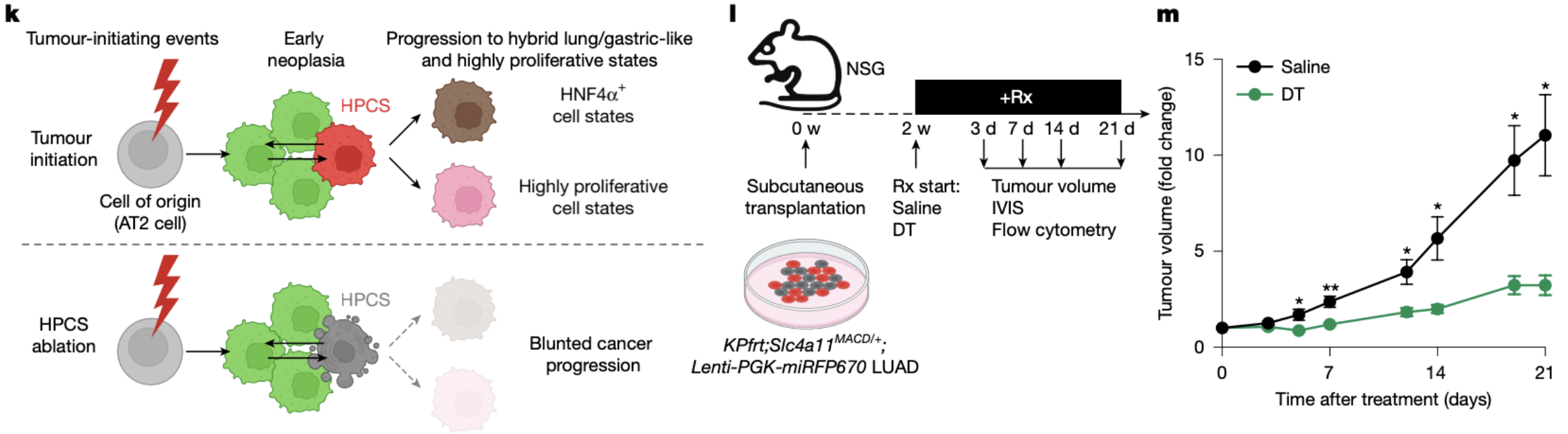


Fig. 4. Drug-resistant cell states originate from the HPCS

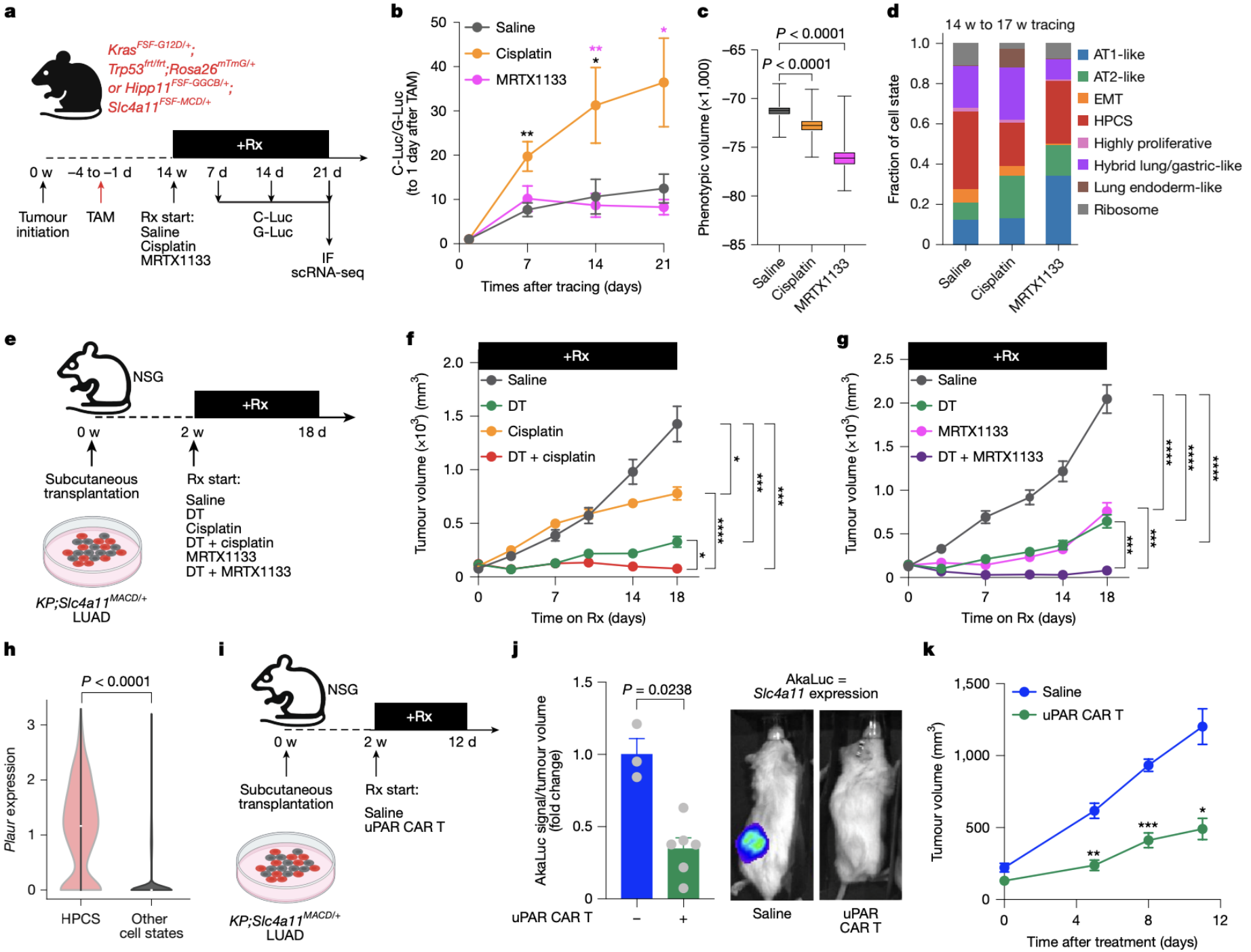
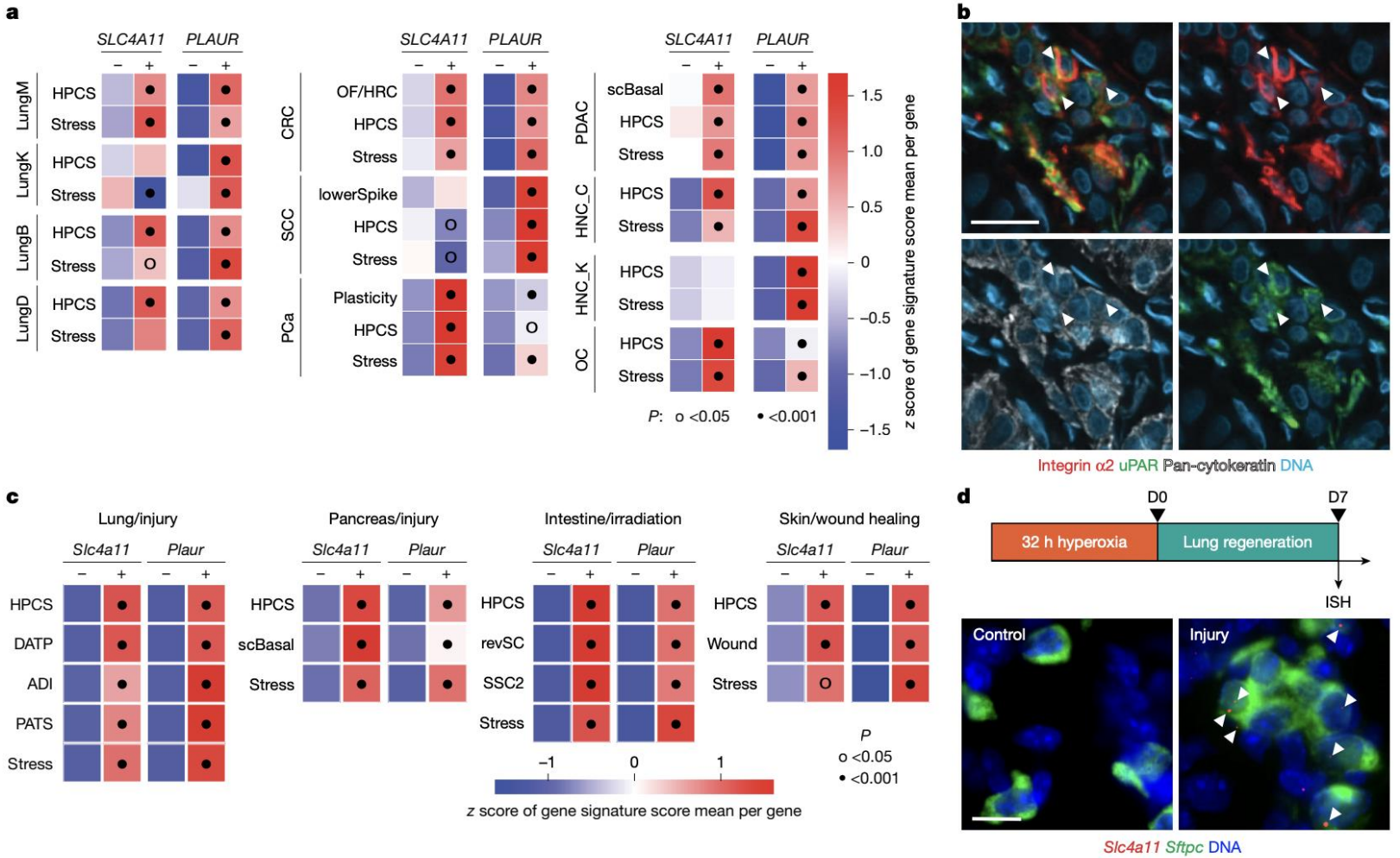


Fig. 5. An HPCS-like state marked by Slc4a11 and Plaur is ubiquitously present in multiple carcinomas and regenerating epithelia



Any questions?

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