Cancer Biology Core Course 2026

Session 4: TME & Metastasis

September 23rd 2026

Memorial Sloan Kettering Cancer Center

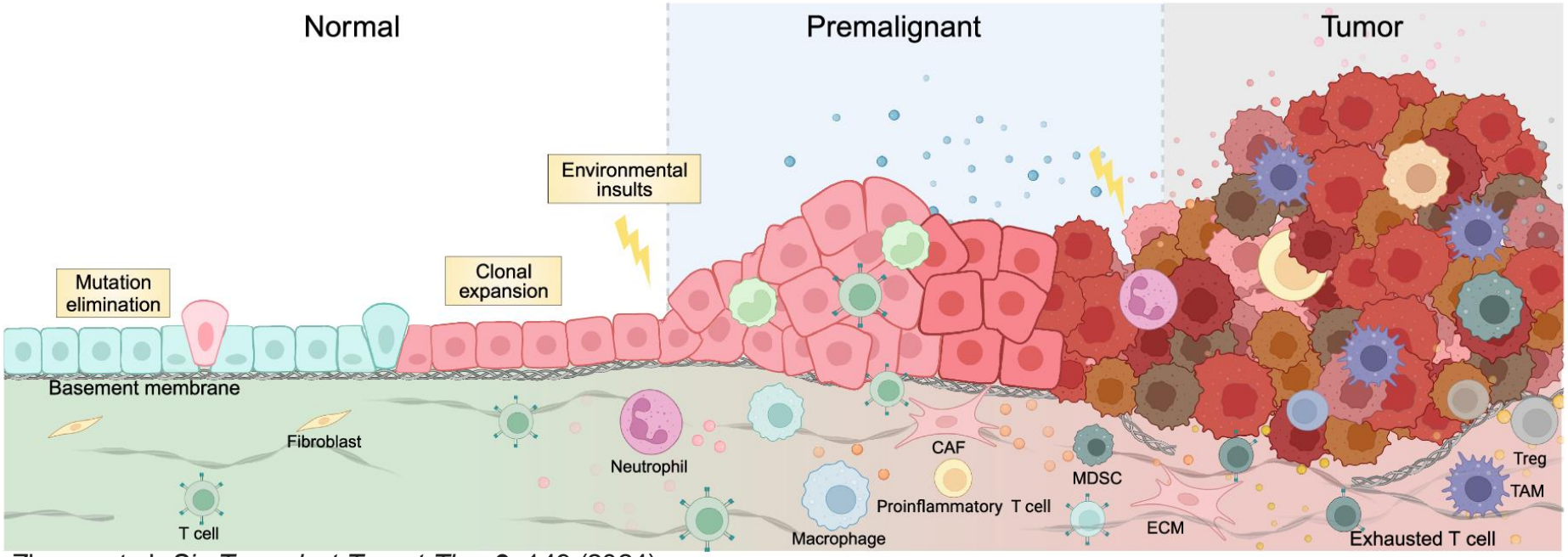
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Joan Massagué Lab
Cancer Biology & Genetics Program
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From initiation to evolution to dissemination

1st class: How does a normal cell become cancerous?

2nd class: **Once a tumor has formed, how does it change over time?**

This class: **What determines the fate of a tumor cell?**



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

Cancer is not static.

Session 4 – 9/23/26 | TME & Metastasis

Question: What determines the fate of a tumor cell?

Required recorded lectures:

- Tumor Microenvironment by Mara Sherman
- Metastasis by Joan Massagué

Topics covered in class:

- Metastatic cascade; Seed & soil;
- Metastasis initiating cells; Metastatic niche;
- Immune surveillance;
- Dormancy & Reawakening;
- Late recurrence; Organotropism.

Paper to discuss: Chia et al., Nature (2025) - Respiratory viral infections awaken metastatic breast cancer cells in lungs

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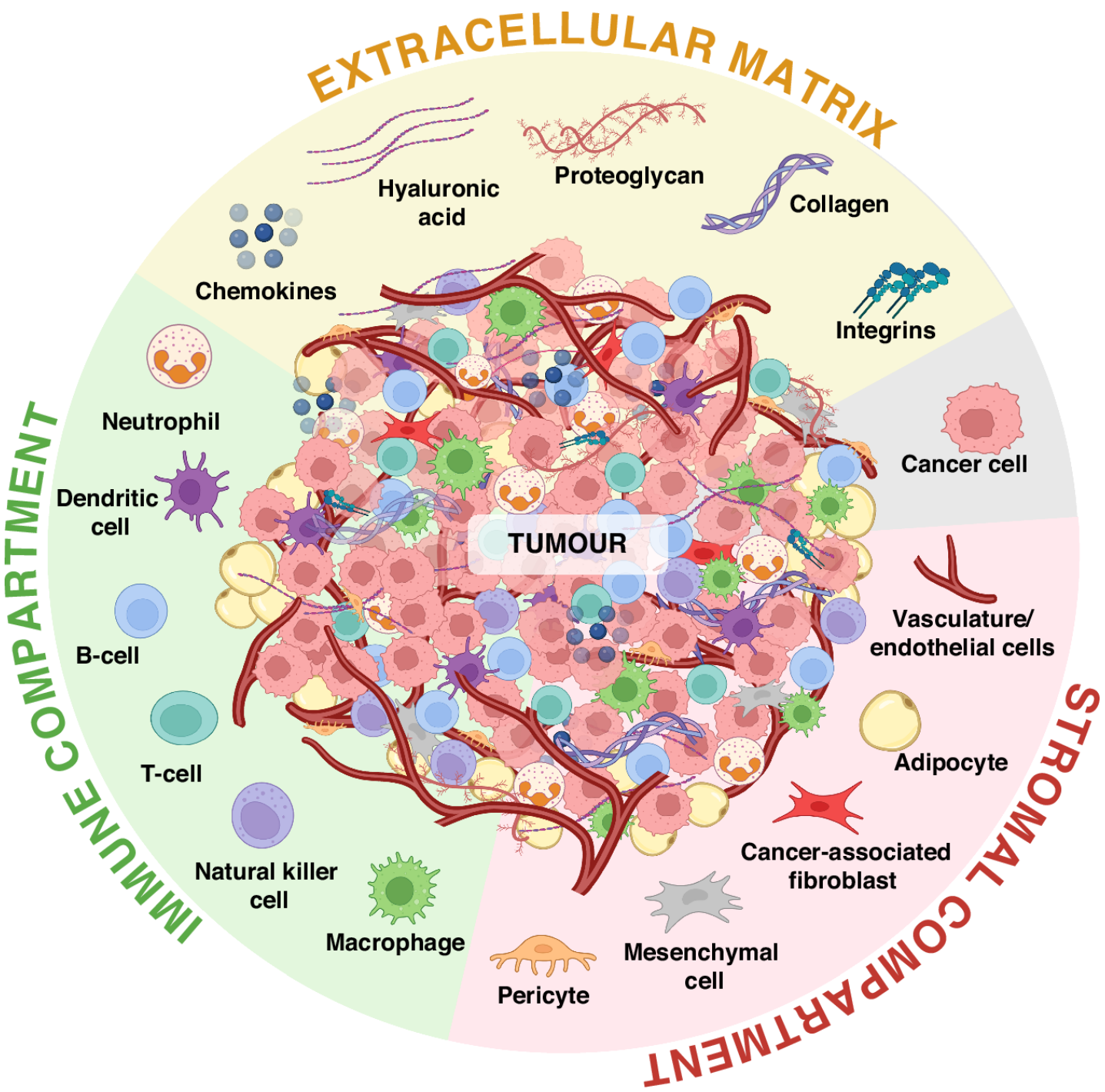
Tumor microenvironment



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Tumors are ecosystems

Tumor behavior emerges from interactions between cancer cells and their environment.



Extracellular matrix

- Collagens, fibronectin, laminins, proteoglycans, hyaluronic acid;
- Provides **structure**, but is also biologically active;
- Controls adhesion, migration and signaling through receptors - **integrins**;
- Can be **remodeled** to facilitate invasion.

Stromal/vascular compartment

- **Cancer-associated fibroblasts**: ECM production/remodeling, growth factors, cytokines;
- **Endothelial cells/vasculature**: oxygen + nutrients, route for dissemination
- Pericytes: vascular structure/function;
- Adipocytes and other mesenchymal cells can provide metabolic and paracrine signals .

Immune compartment

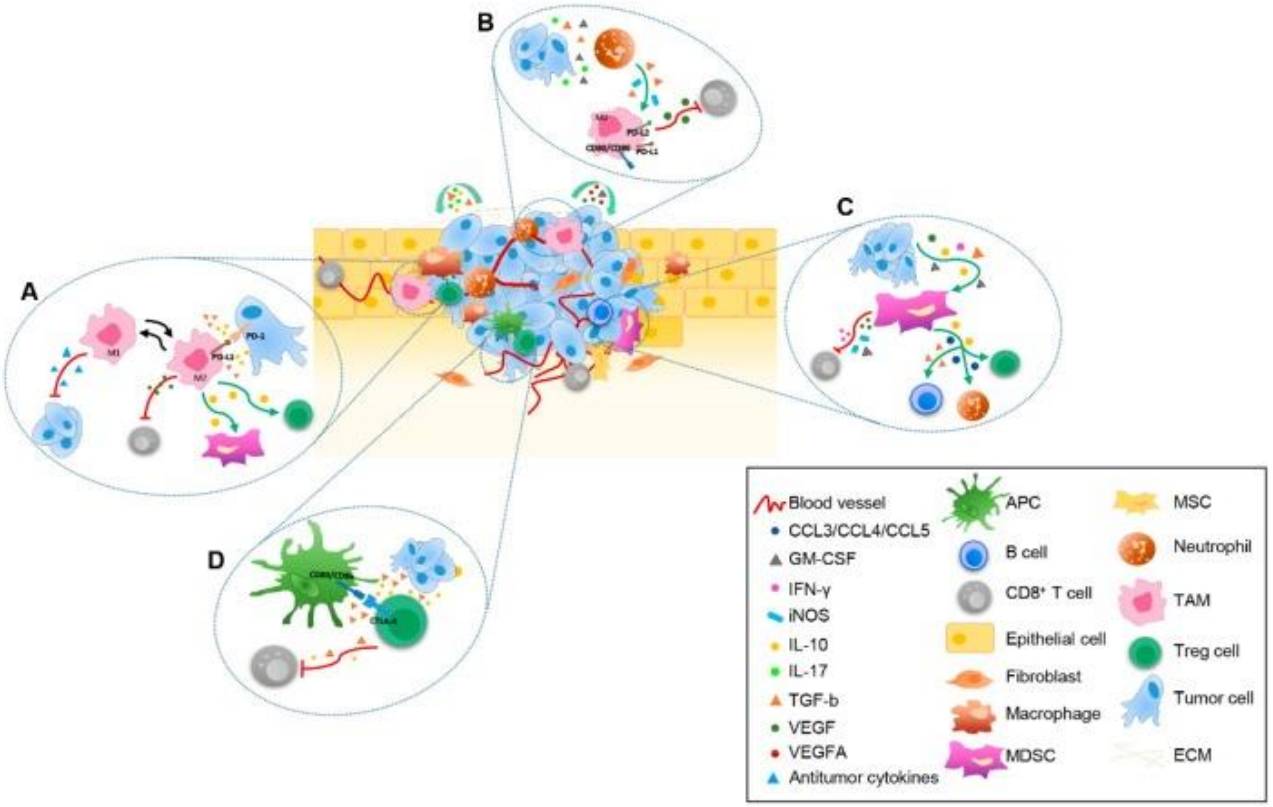
- **T cells / NK cells**: can recognize and eliminate cancer cells;
- **Macrophages / neutrophils**: can be tumor-restraining or tumor-promoting depending on their state/context;
- **Dendritic cells**: antigen presentation and initiation of adaptive immunity;
- **B cells**: antibody production and broader immune regulation.

Physical & chemical compartment – *"Abnormal"*

- Oxygen availability / **hypoxia**;
- Nutrient availability;
- pH / acidosis;
- Metabolites;
- Mechanical forces / pressure.

Communication

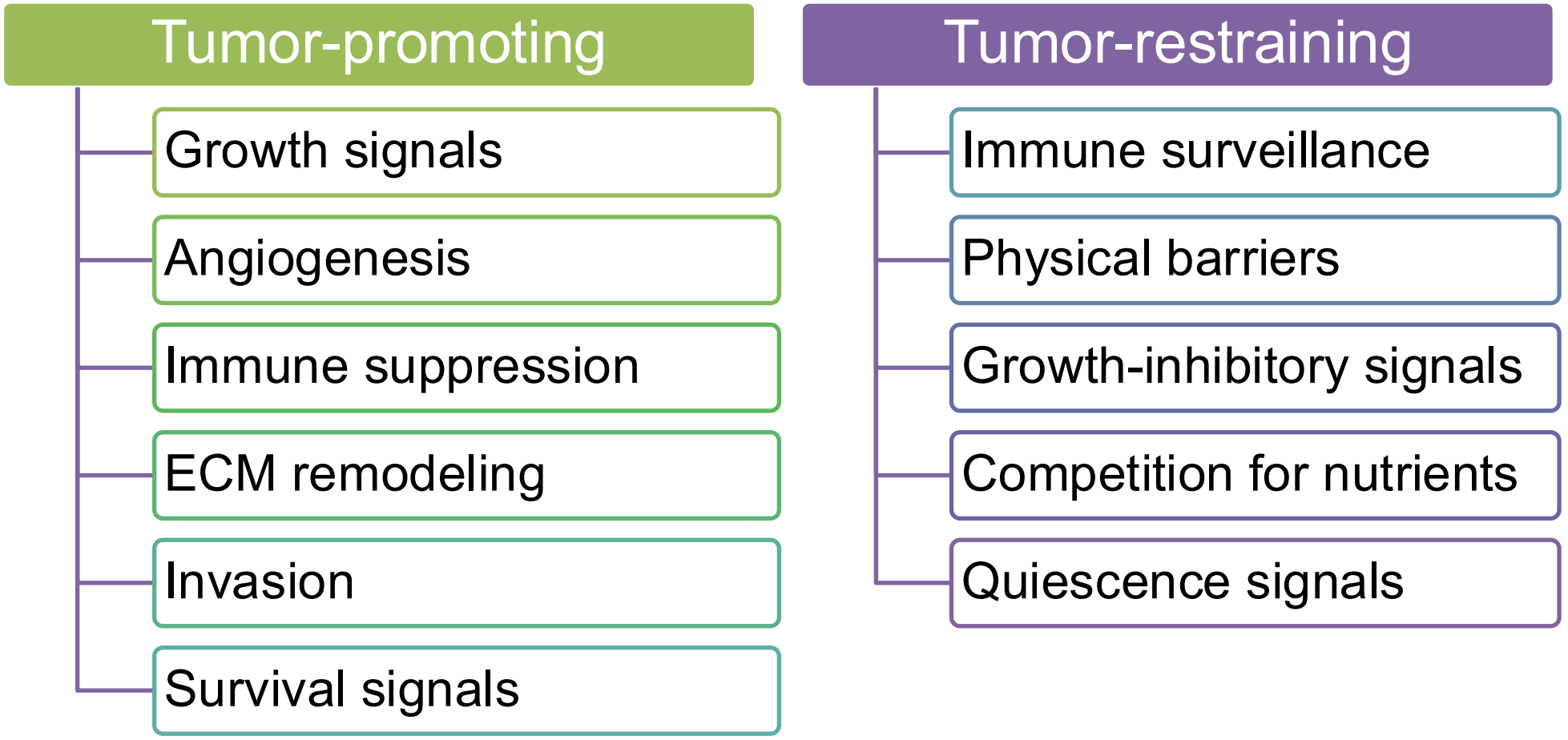
Cancer cells ⇄ immune cells ⇄ fibroblasts ⇄ vasculature ⇄ ECM



Mechanisms:

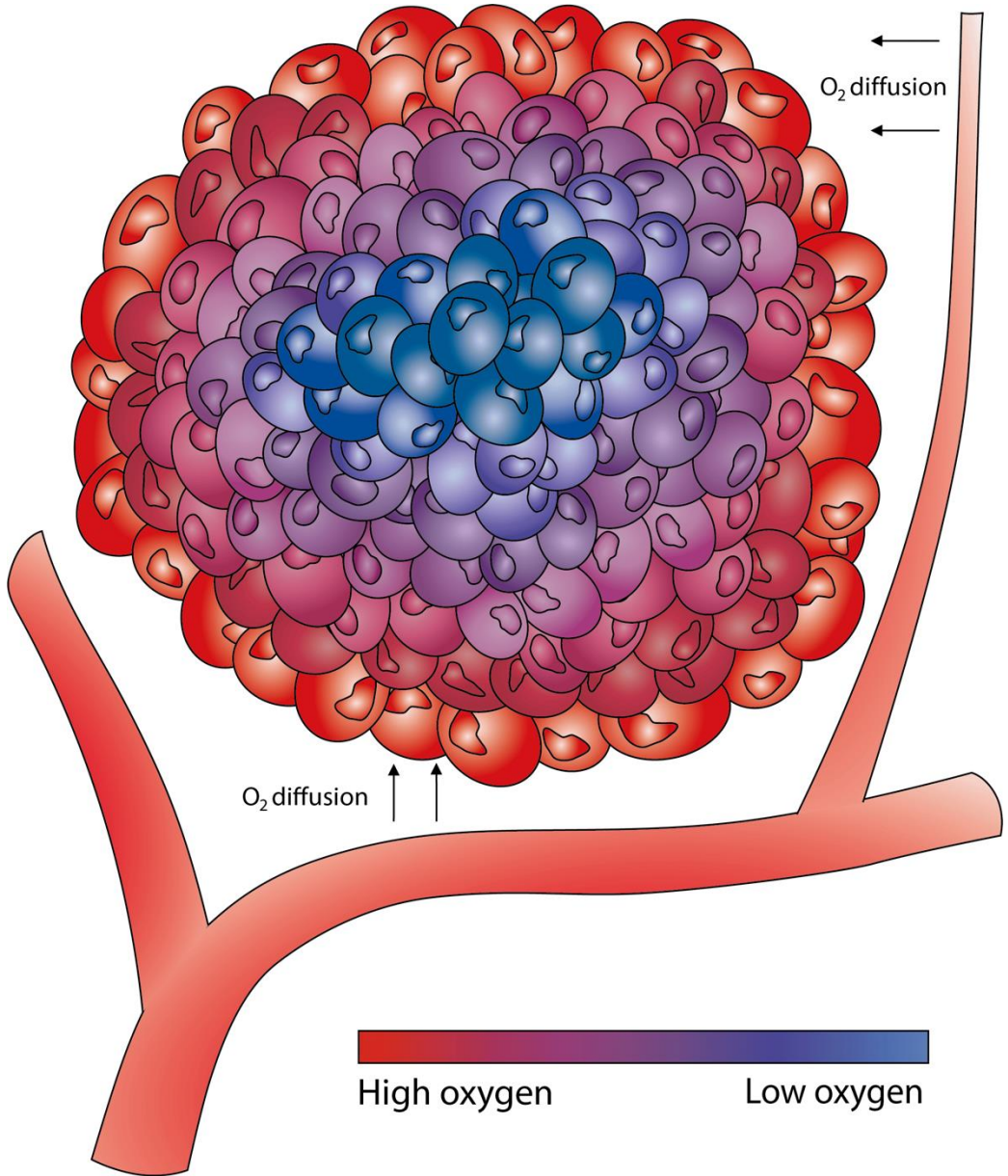
- ✓ Cytokines
- ✓ Chemokines
- ✓ growth factors
- ✓ cell-cell interactions
- ✓ integrin/ECM signaling

Roles of TME



The microenvironment is a selective pressure.

An example: hypoxia



Regulators

What controls the hypoxic response?



- Epigenetic regulation (e.g., KDMs, HDACs)
- Genetic regulation (e.g., HIF1A, VHL)
- Post-transcriptional regulation (e.g., mTOR, miRNAs)

Downstream Mediators

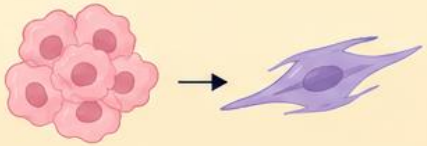
Key genes and pathways induced by hypoxia



- VEGF (angiogenesis)
- GLUT1 (glucose metabolism)
- CA9, CA12 (pH regulation)
- MCT4 (lactate export)
- ZEB1, Snail, TWIST (EMT/invasion)
- ABC transporters, CSC markers

Cellular Effects

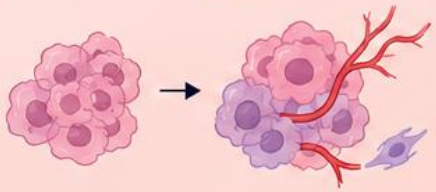
How does hypoxia change cancer cells?



- Altered proliferation and survival
- Secretion of angiogenic factors and extracellular vesicles
- Metabolic adaptation (↑ glycolysis, ↓ oxidative phosphorylation)
- Stemness and self-renewal
- EMT, increased motility and invasiveness
- Immune evasion (e.g., PD-L1 upregulation)

Pathological Outcomes

Impact on tumor progression



- Tumor growth and angiogenesis
- Invasion and metastasis
- Therapy resistance
- Maintenance of dormant or quiescent cell states
- Immunosuppression

The environment can change cancer-cell phenotype without changing its DNA.

Q: A tumor region becomes severely hypoxic. What is most likely to happen?

A

All cancer cells in the region die

B

Some cells alter their transcriptional state and adapt

C

Cells must acquire new mutations before they can respond

D

Hypoxia affects stromal cells but not cancer cells

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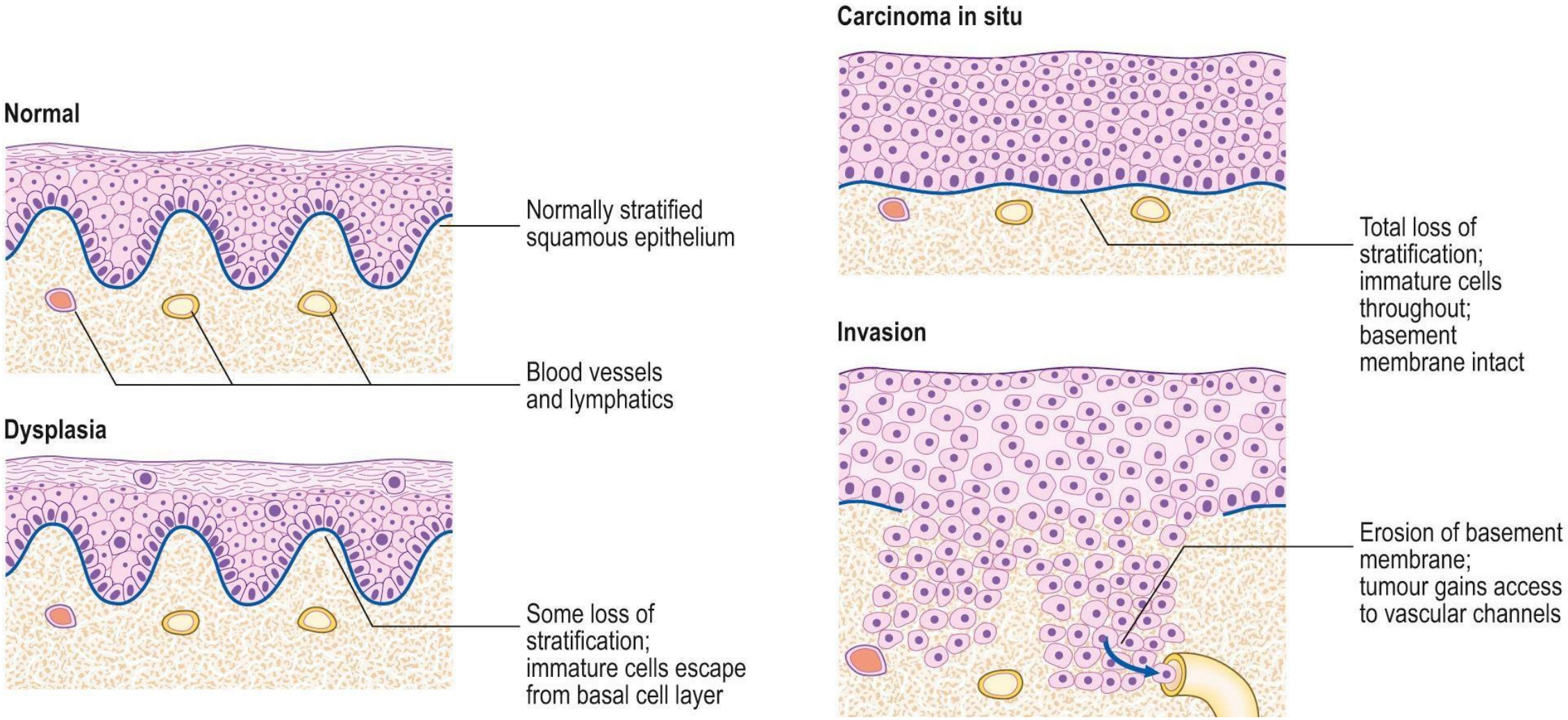
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Invasion

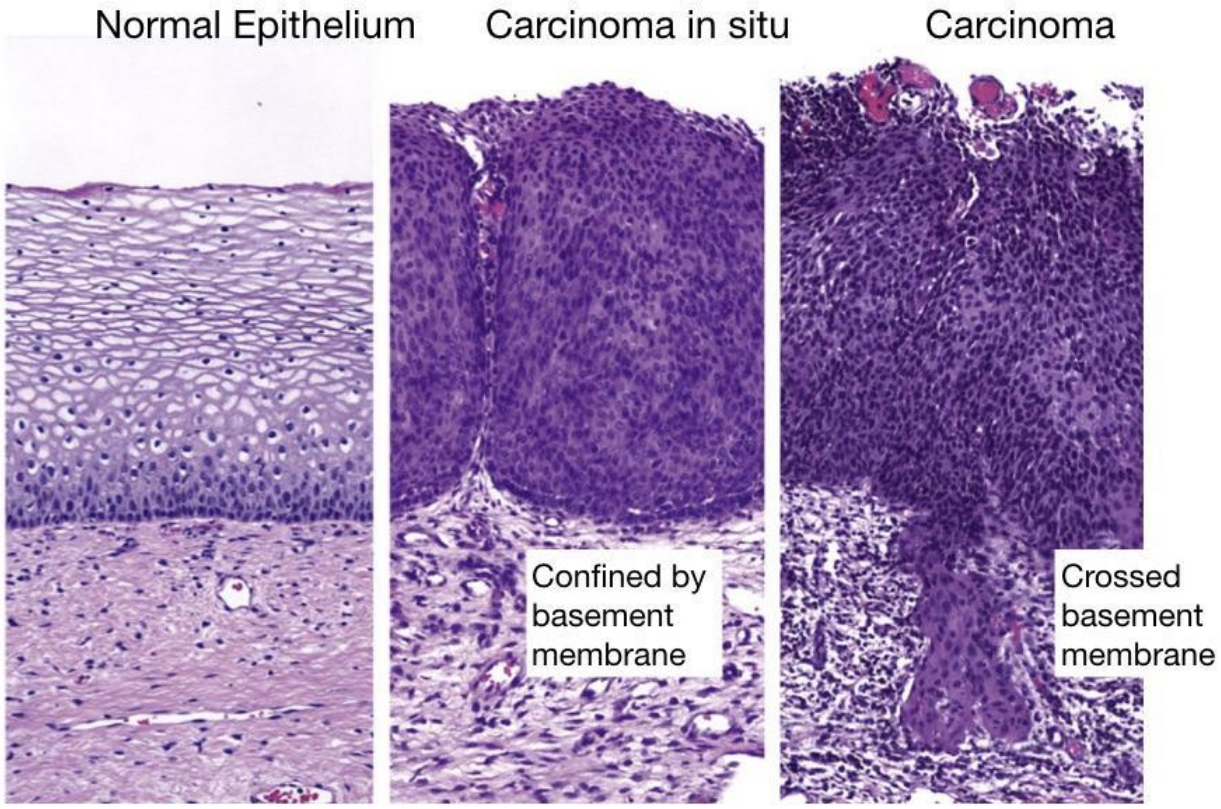


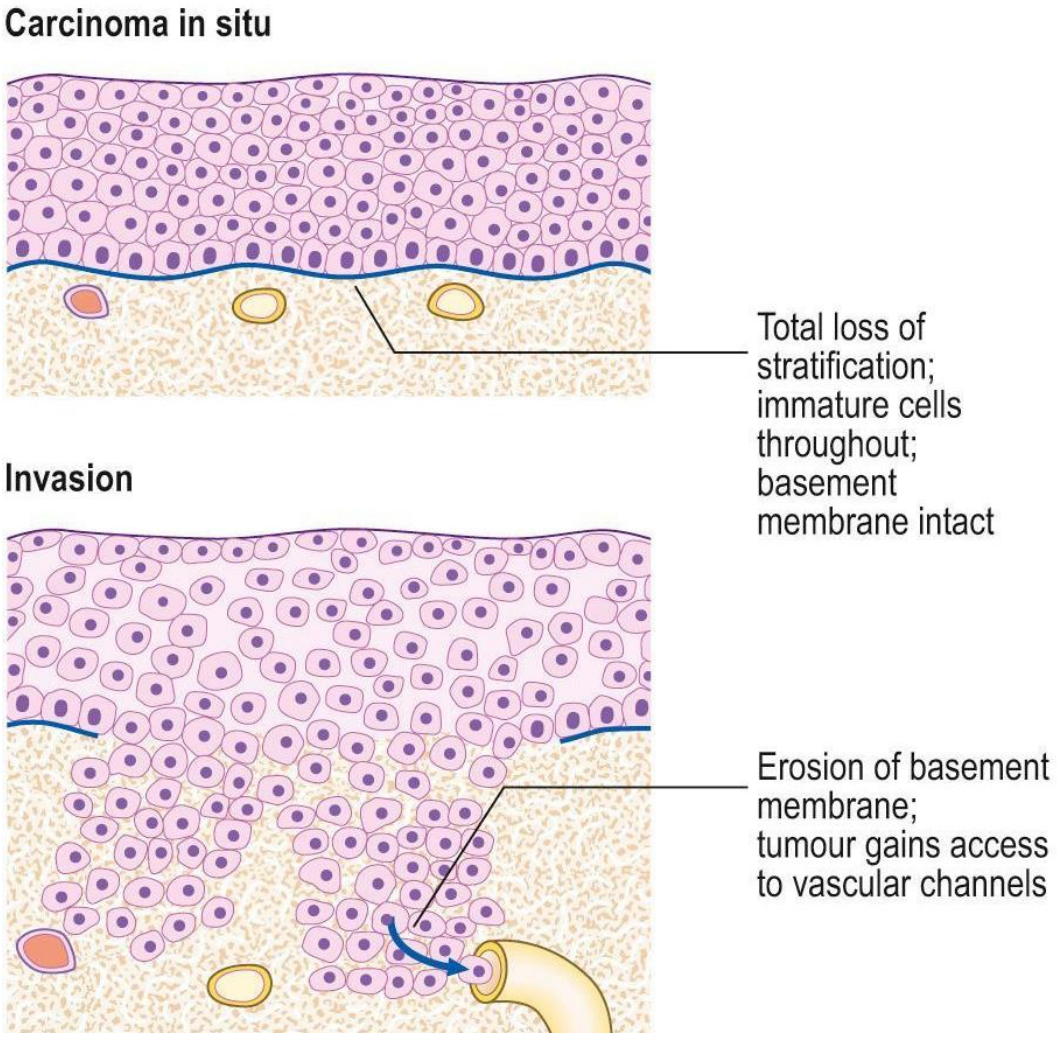
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Tumors don't stay contained

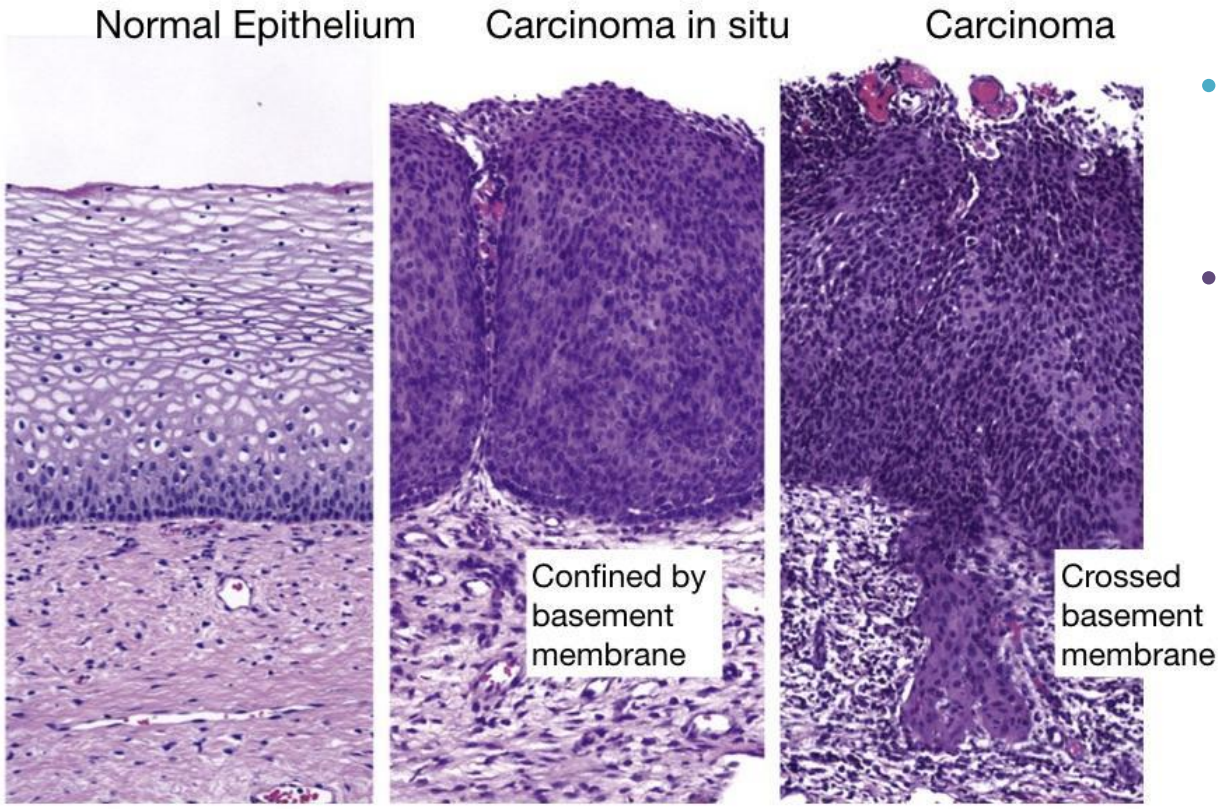


Tumors don't stay contained





Tumors don't stay contained



- **Growth/expansion:** tumor gets larger but remains confined.
- **Invasion:** cancer cells cross normal tissue boundaries, particularly the basement membrane, and enter surrounding stroma.

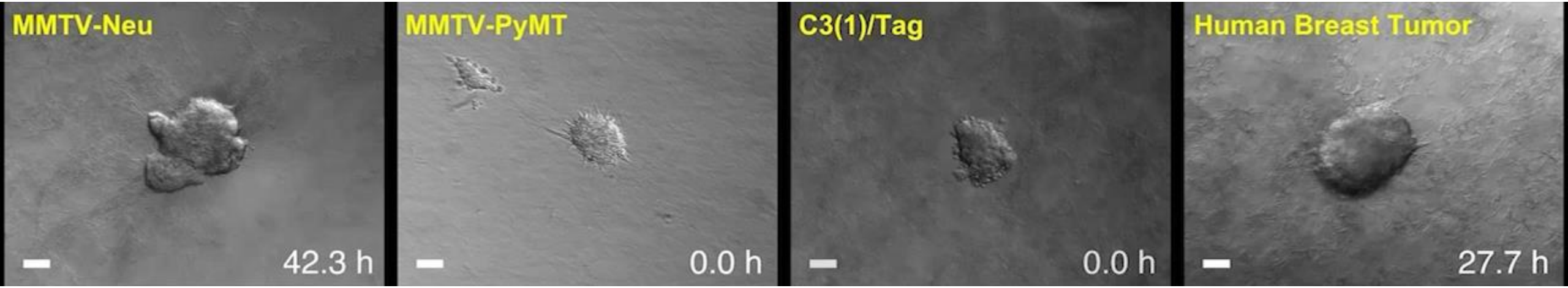
What enables invasion?

1. **Cancer-cell changes:** EMT/ altered adhesion / motility / plasticity

2. **ECM remodeling:** basement membrane and interstitial matrix barriers altered

3. **Stromal interactions:** fibroblasts, macrophages, etc.

4. **Proteases:** matrix degradation/remodeling



https://www.sciencedirect.com/science/article/pii/S0092867413014803

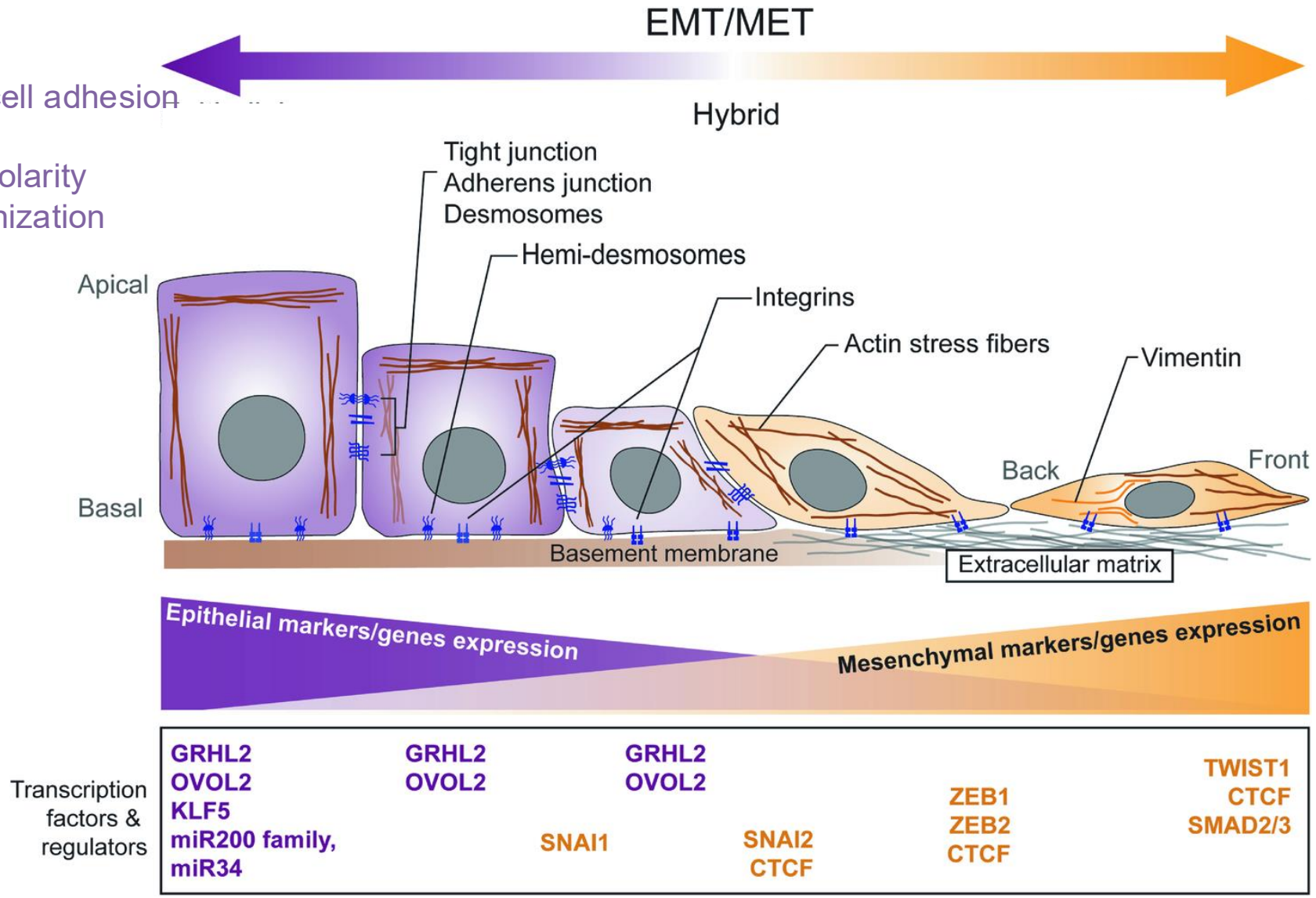
EMT: Epithelial to Mesenchymal Transition

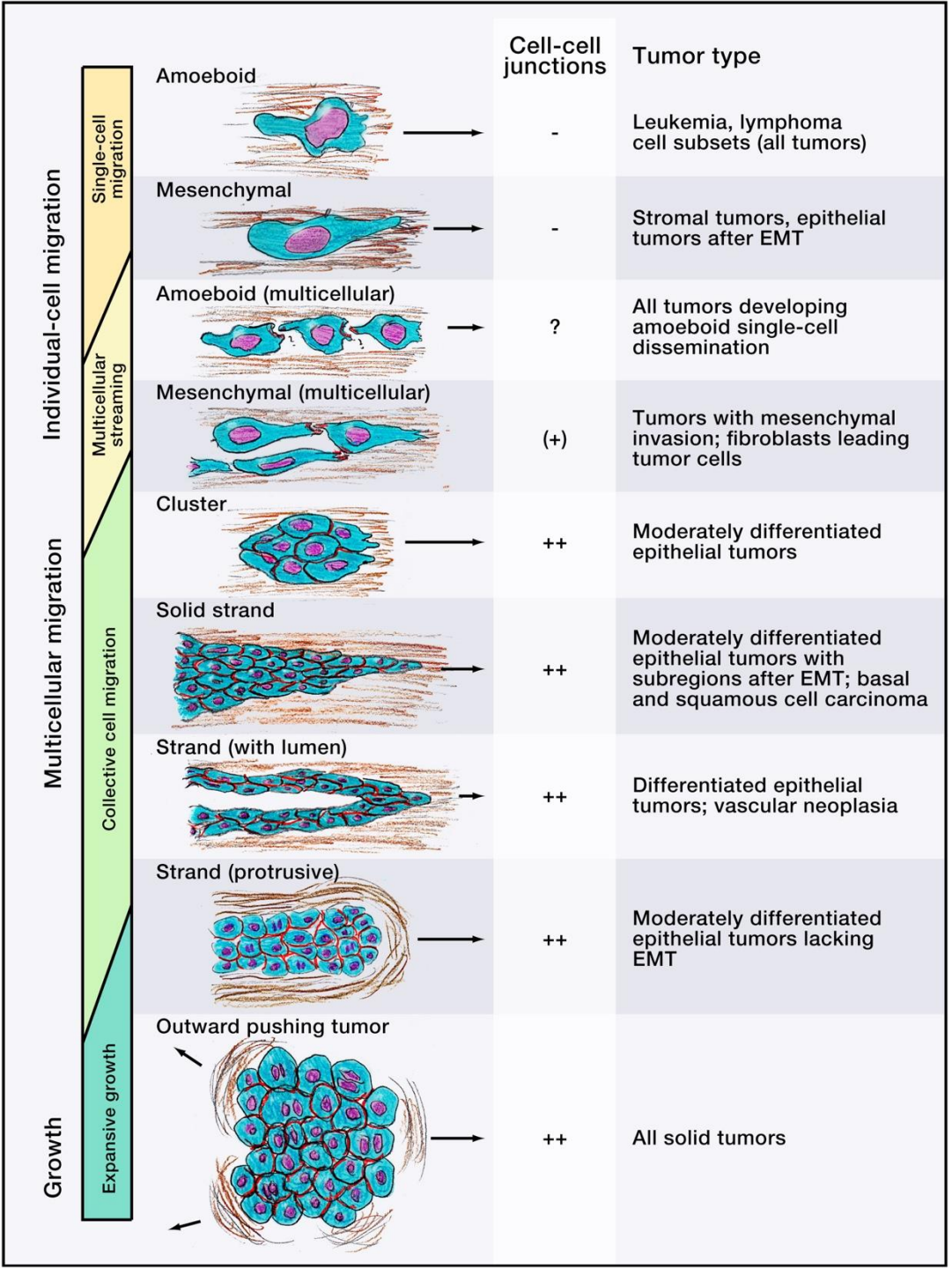
Epithelial

- ✓ Strong cell-cell adhesion
- ✓ E-cadherin
- ✓ Organized polarity
- ✓ Tissue organization

Mesenchymal

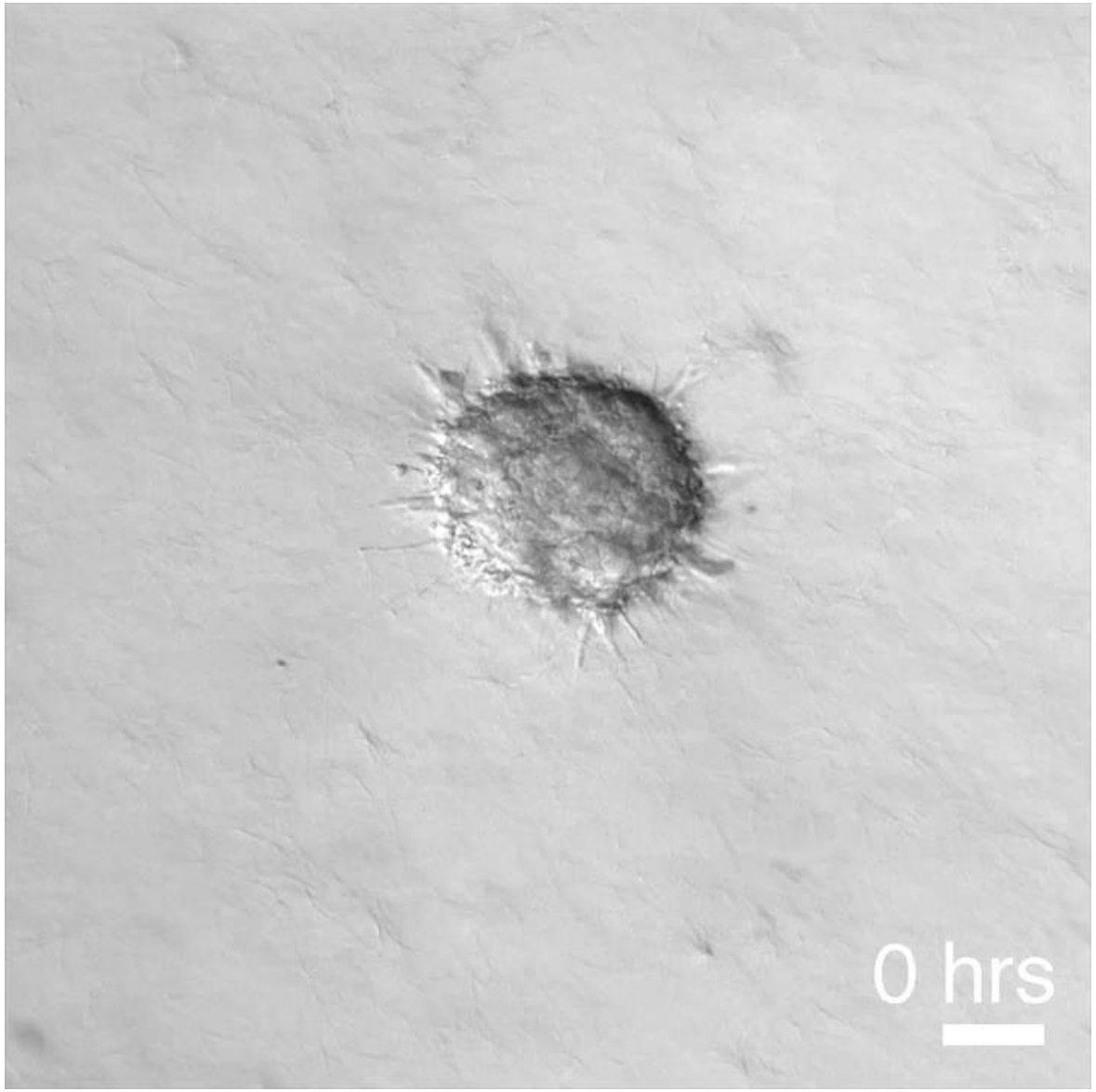
- ✓ Increased motility
- ✓ Vimentin
- ✓ Invasive behavior
- ✓ Stress resistance





A complete EMT is not required for metastasis!

Modes of invasion



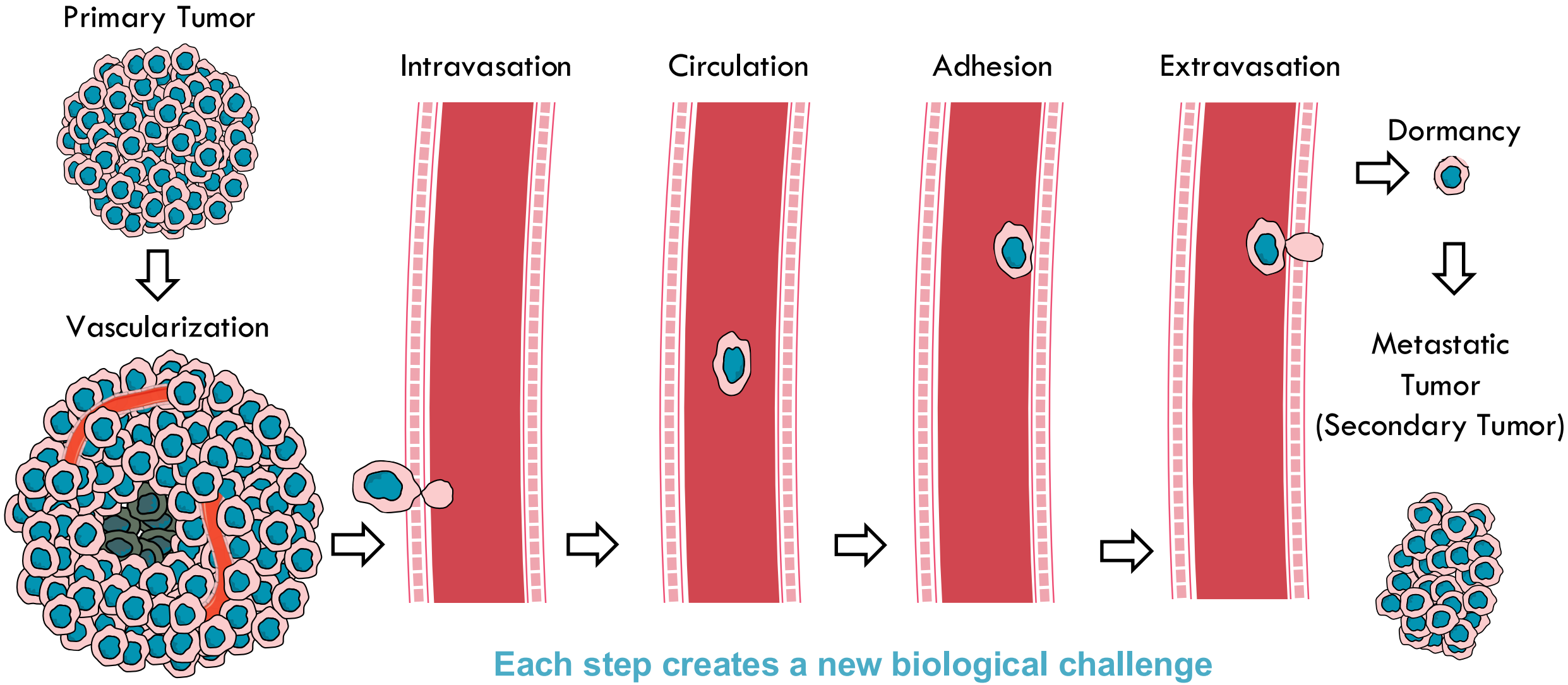
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Metastasis



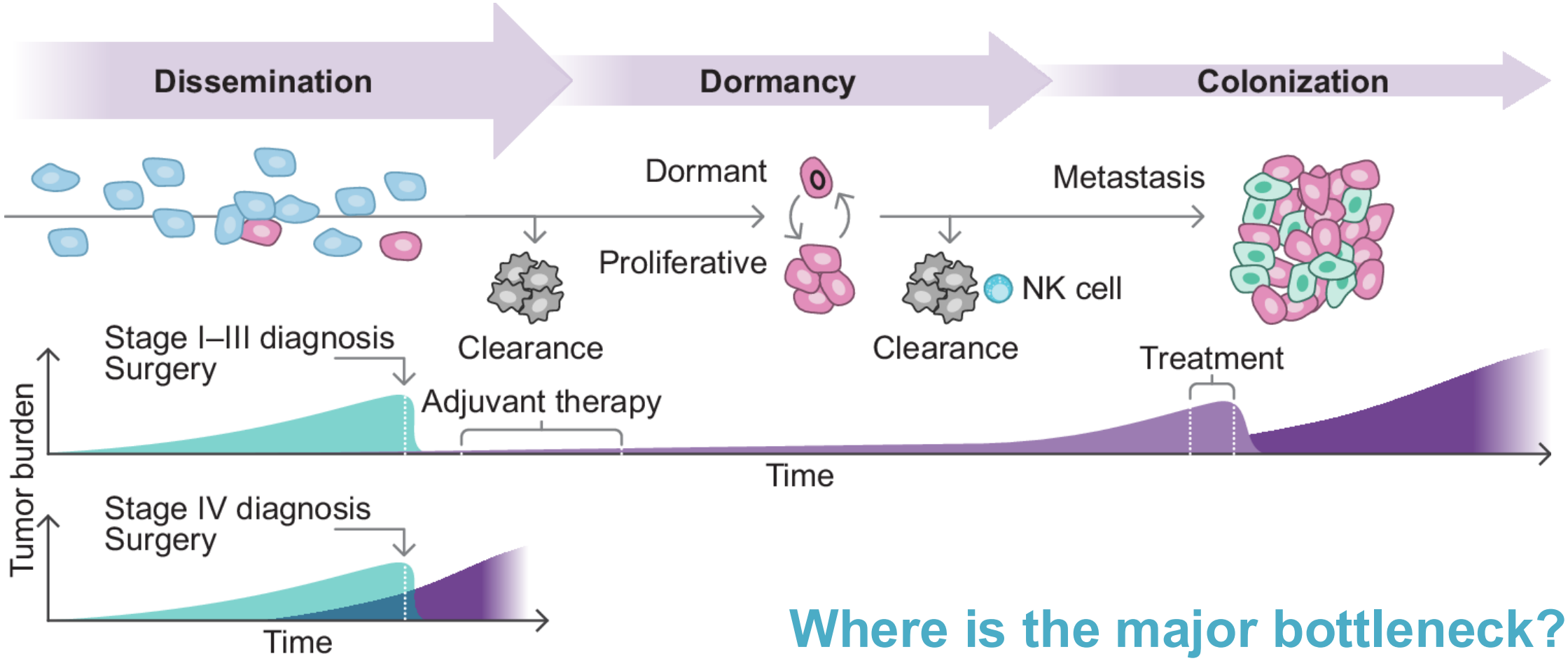
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Metastatic Cascade



Each step creates a new biological challenge

Metastasis is inefficient



Where is the major bottleneck?

Niu, G., Hagerling, C. Clinical metastatic cancer from initiation to colonization: emerging challenges and breakthroughs. *Oncogene* **45**, 4006–4018 (2026).

Q: A cancer cell is detected in the lung of a patient with breast cancer. What can we conclude?

A

The patient has a growing lung metastasis

B

The cell must have acquired additional driver mutations

C

The cell will eventually form a metastasis

D

The cell has successfully disseminated, but its future fate is uncertain

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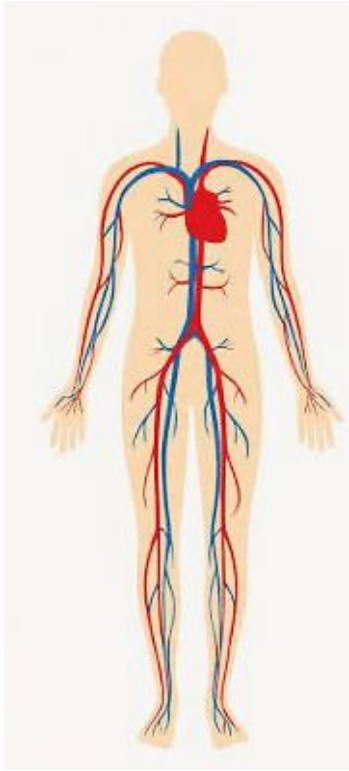
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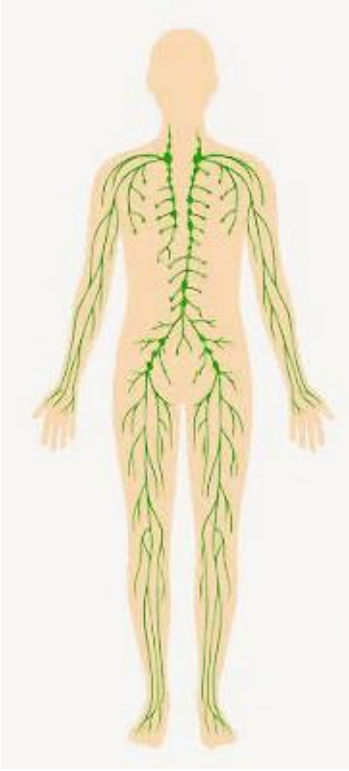
How do cancer cells spread?

Hematogenous spread



- Cancer cells **intravasate** into blood vessels
- Travel as single **CTCs** or multicellular clusters
- Arrest in distant capillary beds
- Extravasate into distant tissue
- Particularly important for distant organ metastasis

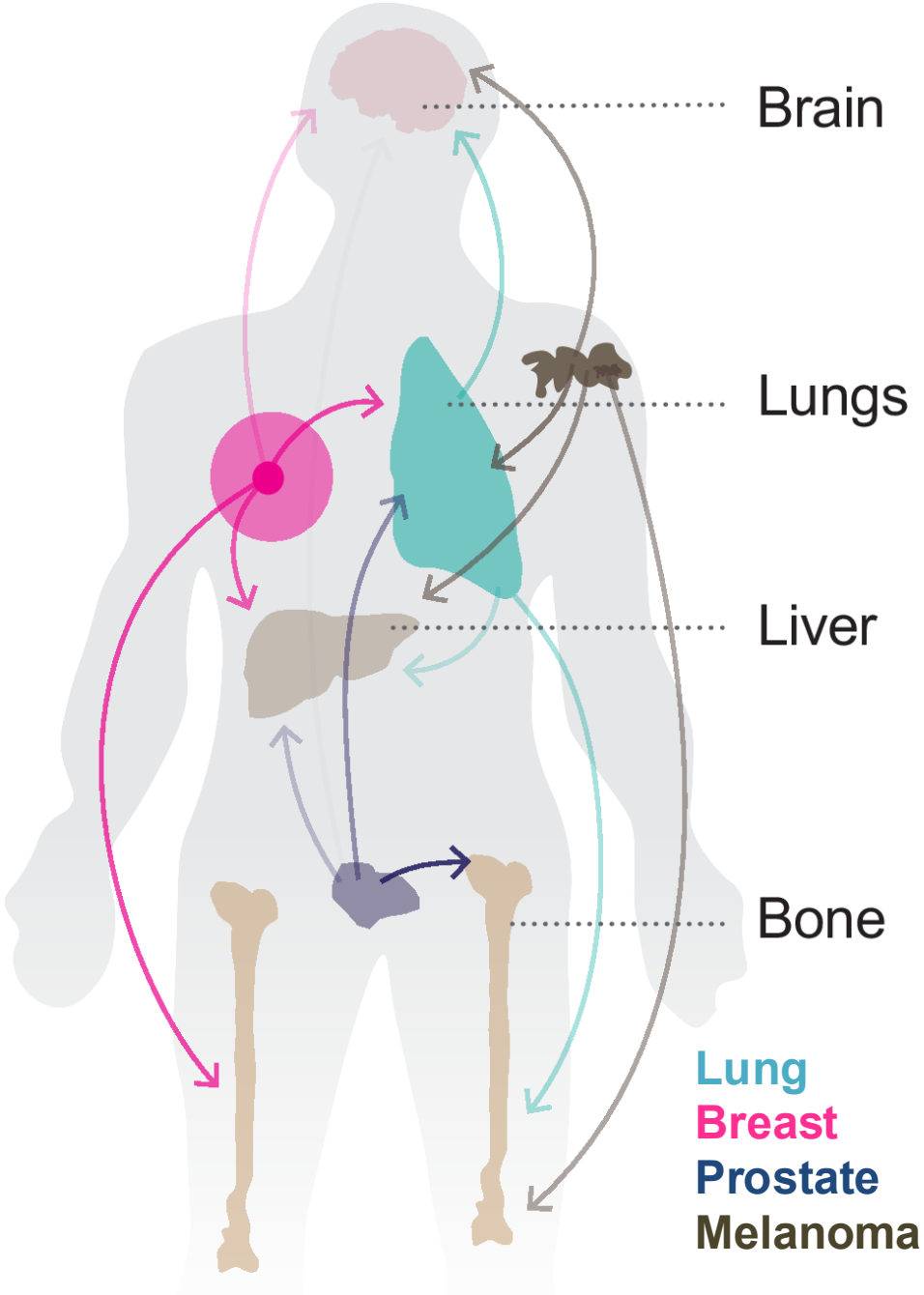
Lymphatic spread



- Tumor cells enter lymphatic vessels
- Can colonize regional/draining lymph nodes
- Lymph ultimately drains back into the venous circulation
- Lymphatic dissemination can also provide access to distant organs

The routes aren't mutually exclusive

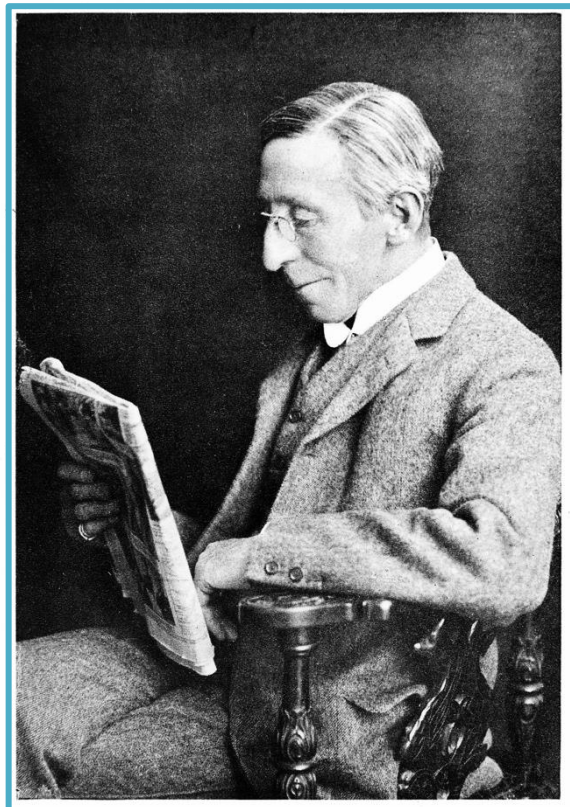
Why do cancers metastasize to particular organs?



If cancer cells circulate throughout the body, why isn't metastasis random?

Niu, G., Hagerling, C. Clinical metastatic cancer from initiation to colonization: emerging challenges and breakthroughs. *Oncogene* **45**, 4006–4018 (2026).

Seed and Soil - Paget, 1889



STEPHEN PAGET, M.A., F.R.C.S.
(*Founder of the Research Defence Society*).

He observed that metastases were **non-randomly distributed among organs** and that this distribution could not be explained simply by relative blood supply.

735 breast cancer autopsies

- **Liver: 241**
- **Spleen: 17**

He published "The Distribution of Secondary Growths in Cancer of the Breast" in *The Lancet* in 1889.

"Seed and soil" concept: disseminated cancer cells are the seed, while particular organ environments provide congenial soil for their growth.

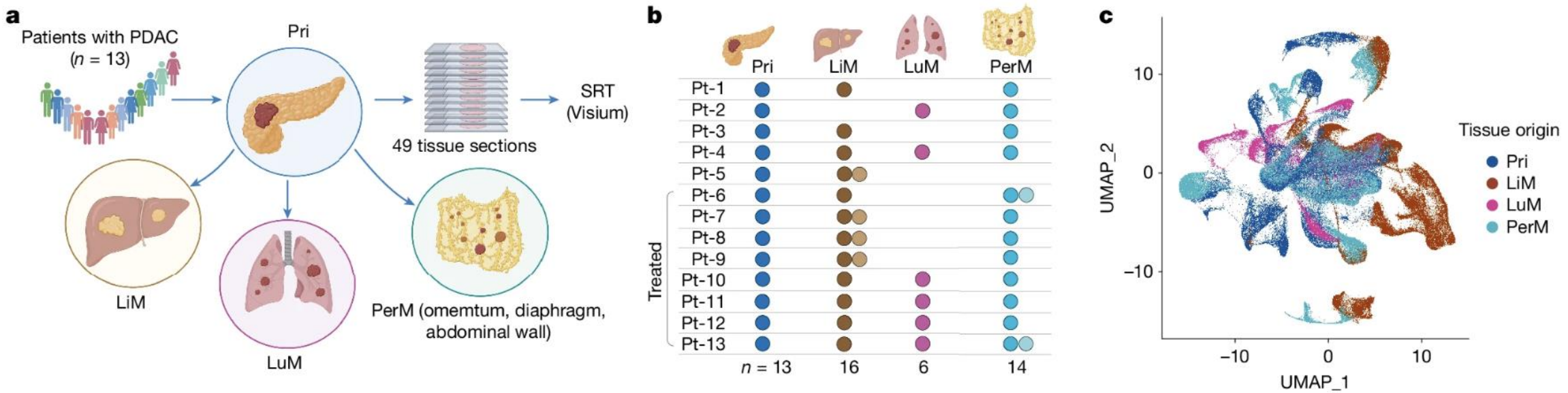
Metastatic growth requires compatibility between the disseminated cancer cell and the distant tissue.

Organ specificity

1. Organotropism: the preferential spread and growth of cancer cells in particular distant organs.

Anatomy & circulation → determines where cells are delivered and may initially arrest
Biological compatibility → determines whether they can survive and grow there

2. Organ-specific mimicry: Metastatic cells can adapt to the host organ by co-opting tissue-specific programs.



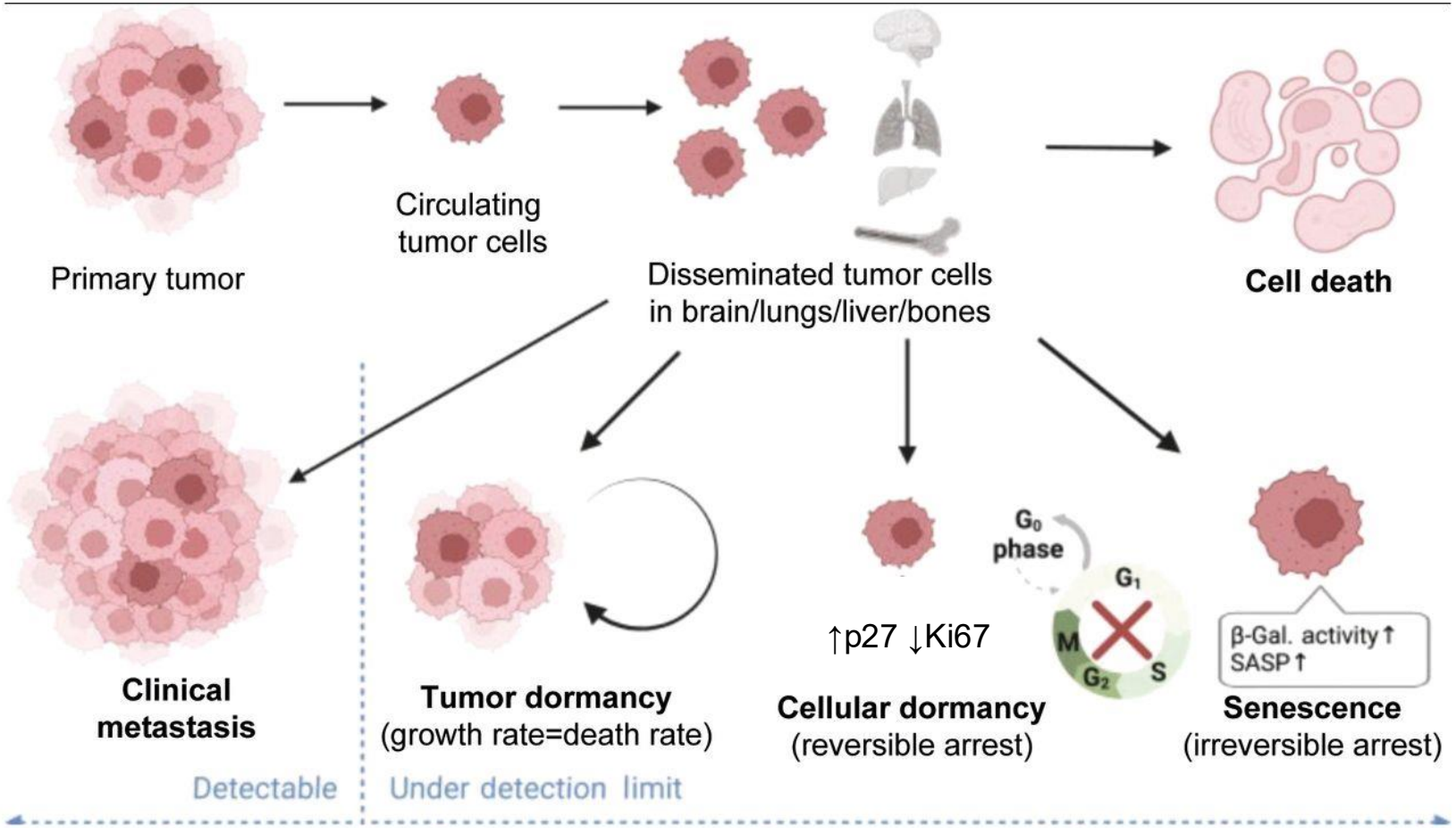
Pei, G., Min, J., Rajapakshe, K.I. *et al.* Spatial mapping of transcriptomic plasticity in metastatic pancreatic cancer. *Nature* **642**, 212–221 (2025). https://doi.org/10.1038/s41586-025-08927-x

The distant organ is a new microenvironment

A new microenvironment:

- ECM
- resident cells
- immune surveillance
- growth factors
- nutrients
- tissue architecture

From 2nd class:
Fitness is context-dependent!



Kefah Mokbel. Anticancer Research August 2024, 44 (8) 3317-3319;

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Dormancy

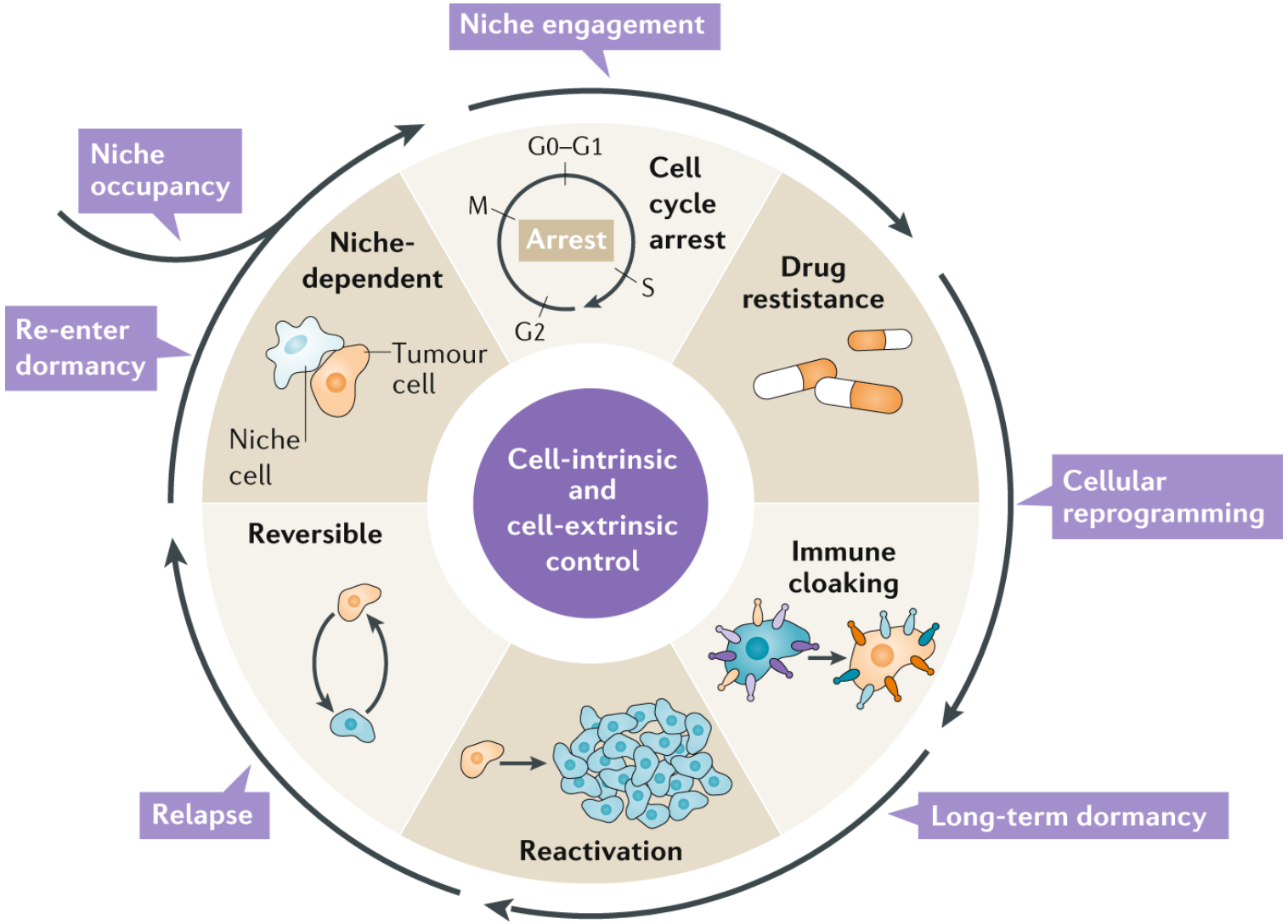




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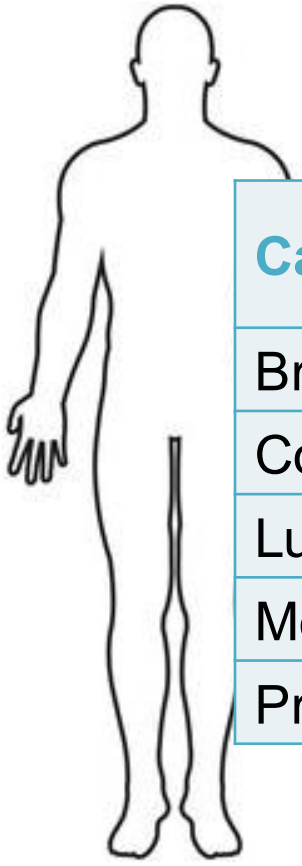
Dormancy

Phan, T.G., Croucher, P.I. The dormant cancer cell life cycle. *Nat Rev Cancer* **20**, 398–411 (2020). https://doi.org/10.1038/s41568-020-0263-0



Dormant ≠ dead. Dormant ≠ permanently arrested (senescent).

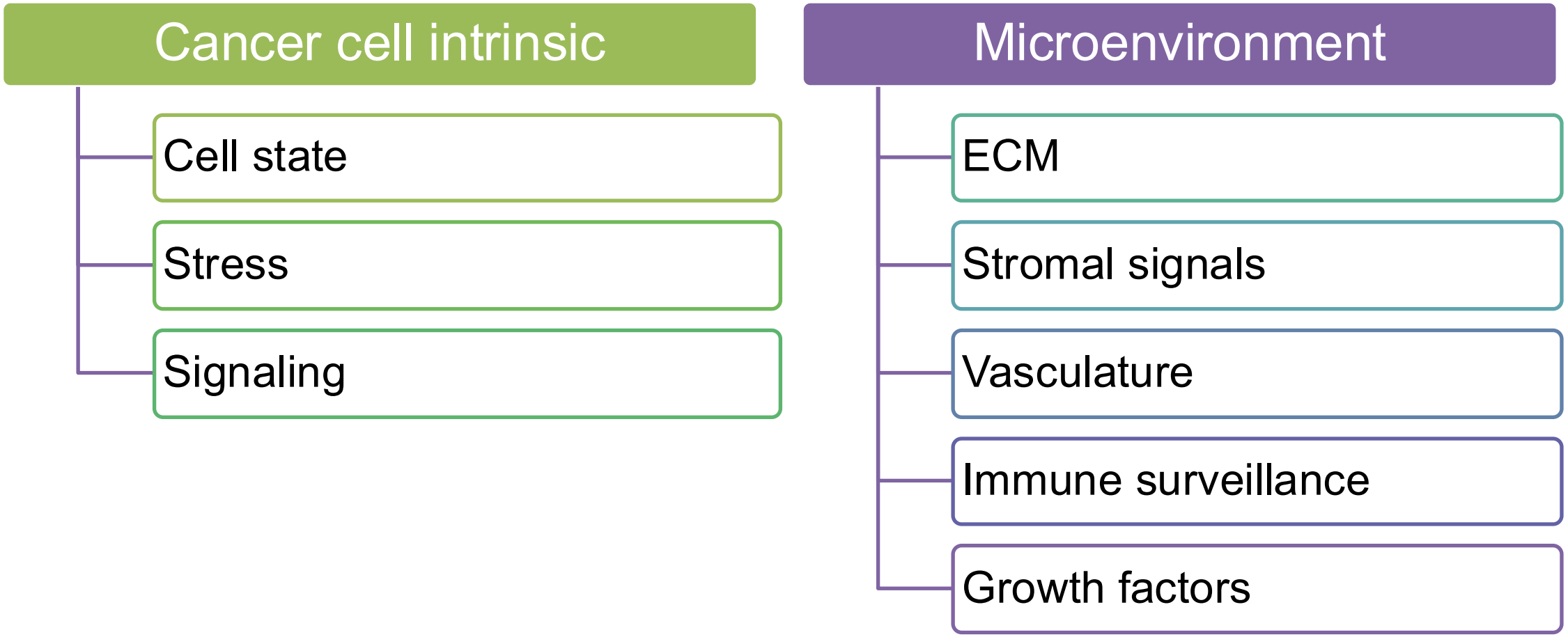
From dormancy to cancer relapse



Cancer	Approx. 5-year recurrence risk*	Typical timing	Late recurrence
Breast	~6–11%	Mostly first 5 yr	20+ yr
Colorectal	~13–25%	Mostly first 2–3 yr	>5 yr uncommon
Lung	~45–65%	Mostly first 2–5 yr	>10 yr rare
Melanoma	~10–40%	Mostly first few years	10–20+ yr
Prostate	~15–40%	Variable, often prolonged	15–20+ yr

Awakening: when a dormant cancer cell enters proliferation to cause relapse.

What determines dormancy vs outgrowth?



Q: What could wake a dormant cancer cell?

A

A new mutation

B

Change in local microenvironment

C

Altered immune surveillance

D

All of the above

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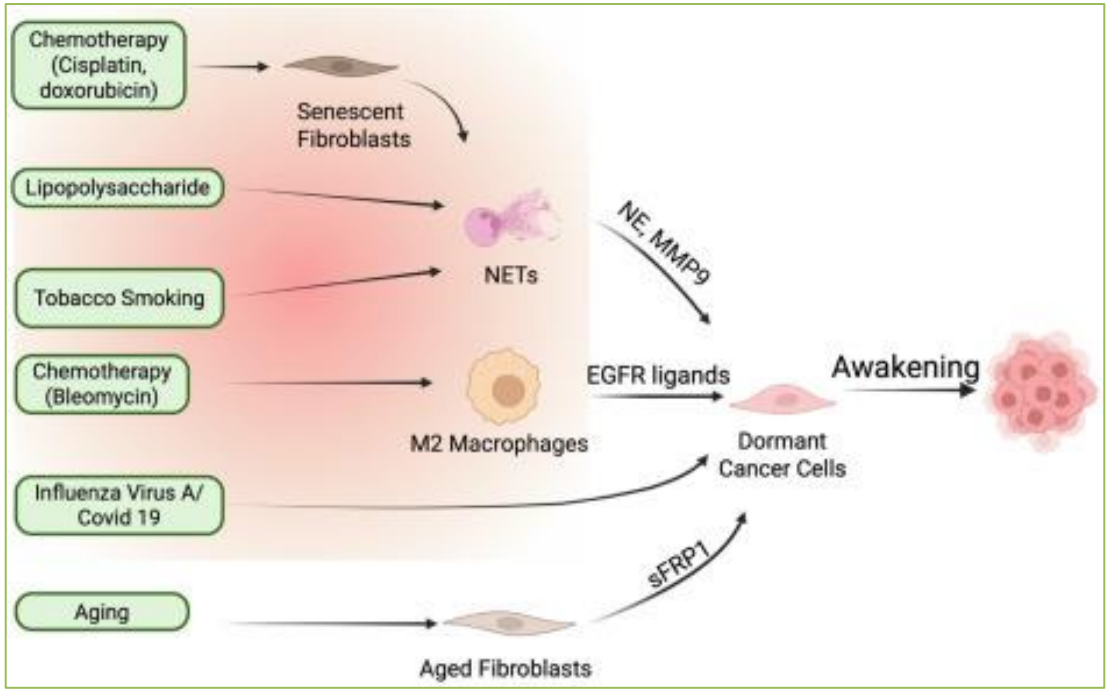
D

All of the above

The ‘soil’ is not static

Distant tissues change with:

- aging
- Injury
- Inflammation
- Infection
- Fibrosis
- Therapy
- altered immunity



Sarker P., Rao S.S., et al. *Biochimica et Biophysica Acta - Reviews on Cancer* • 2026, 189684

Summary

1. Tumors are ecosystems
Cancer cells both **shape and are shaped by** immune cells, stromal cells, vasculature, ECM, and the physicochemical environment.

2. Metastasis is a multistep and inefficient process
Invasion → dissemination → survival → extravasation → dormancy → colonization
Reaching another organ ≠ forming a metastasis.

3. Metastasis is not random
Organotropism reflects both anatomical routes and compatibility between the cancer cell (**seed**) and the distant microenvironment (**soil**).

4. Disseminated cancer cells can have different fates
Death ↔ Dormancy ↔ Outgrowth
The distant microenvironment helps determine which fate occurs.

5. The "soil" can change over time
Changes in inflammation, immunity, injury, aging, etc. may alter the fate of previously dormant cells.

Can a change in the distant microenvironment awaken dormant cancer cells?

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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

Respiratory viral infections awaken metastatic breast cancer cells in lungs

https://doi.org/10.1038/s41586-025-09332-0

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Open access

Check for updates

Shi B. Chia[1,24], Bryan J. Johnson[1,24], Junxiao Hu[2,3], Felipe Valença-Pereira[4], Marc Chadeau-Hyam[5,6,7], Fernando Guntoro[6,7,8], Hugh Montgomery[9], Meher P. Boorgula[3,10], Varsha Sreekanth[3,11], Andrew Goodspeed[3,10], Bennett Davenport[4], Marco De Dominici[1], Vadym Zaberezhnyy[1], Wolfgang E. Schleicher[1], Dexiang Gao[2,3], Andreia N. Cadar[12,13], Lucia Petriz-Otaño[14], Michael Papanicolaou[14], Afshin Beheshti[15,16,17], Stephen B. Baylin[15,18,19], Joseph W. Guarnieri[20,23], Douglas C. Wallace[20,21], James C. Costello[3,11], Jenna M. Bartley[12,13], Thomas E. Morrison[4], Roel Vermeulen[5,6,22,25], Julio A. Aguirre-Ghiso[14,25], Mercedes Rincon[3,4,25] & James DeGregori[1,2,3,4,25] ✉

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

Fig. 1 | Influenza A virus infection increases DCC in lungs.

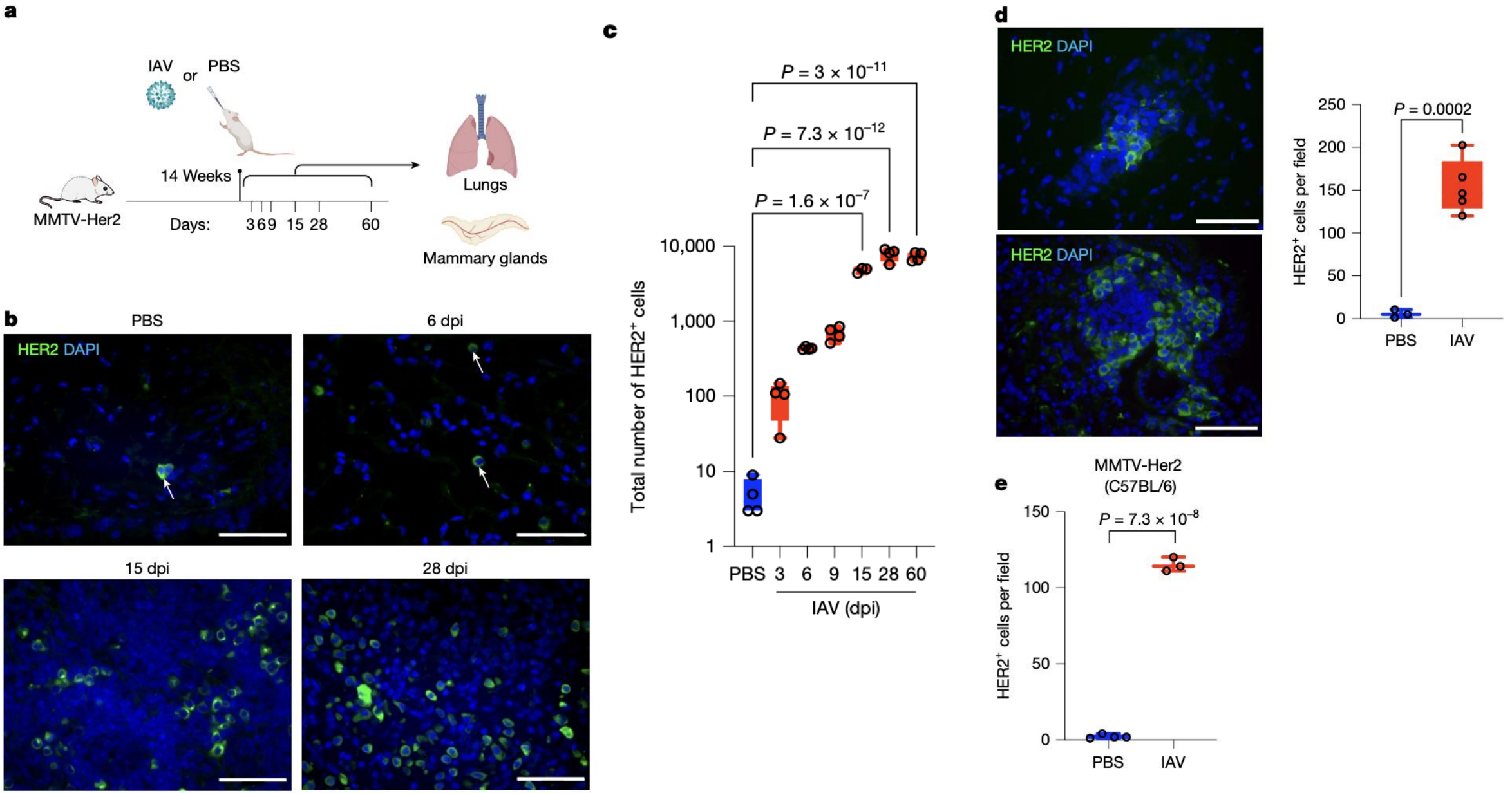
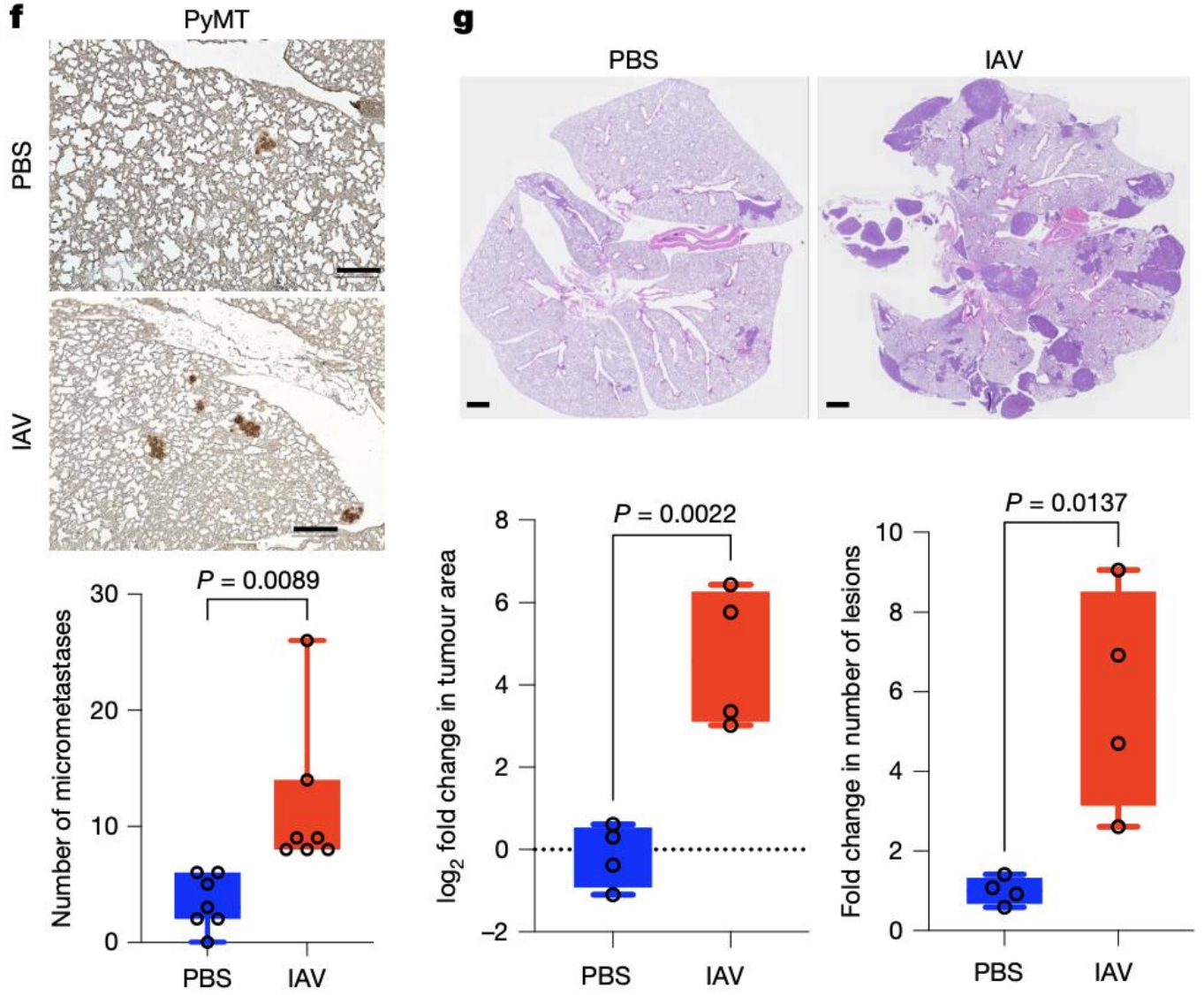
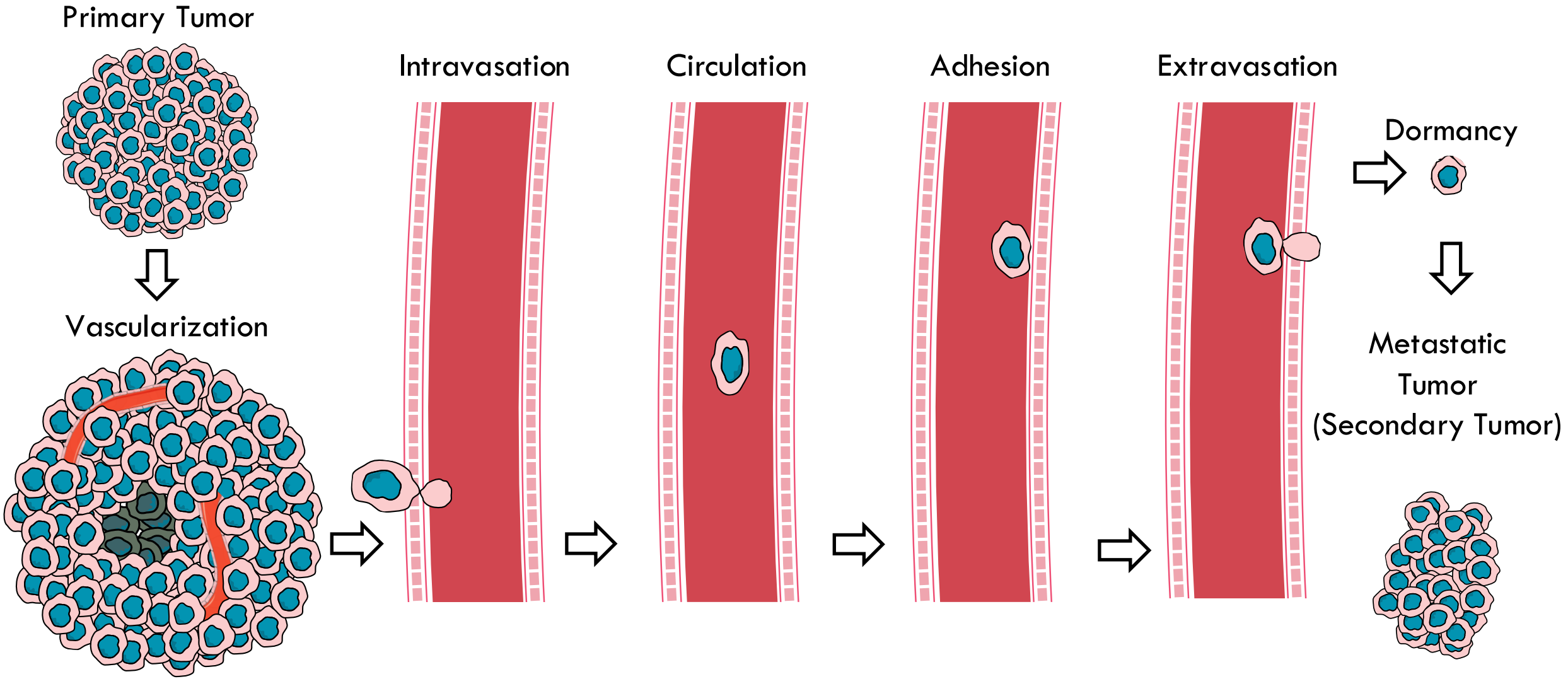


Fig. 1 | Influenza A virus infection increases DCC in lungs.



What can explain increased lung metastatic burden?



What hypotheses can justify this observation?

1.
2.
3.
4.

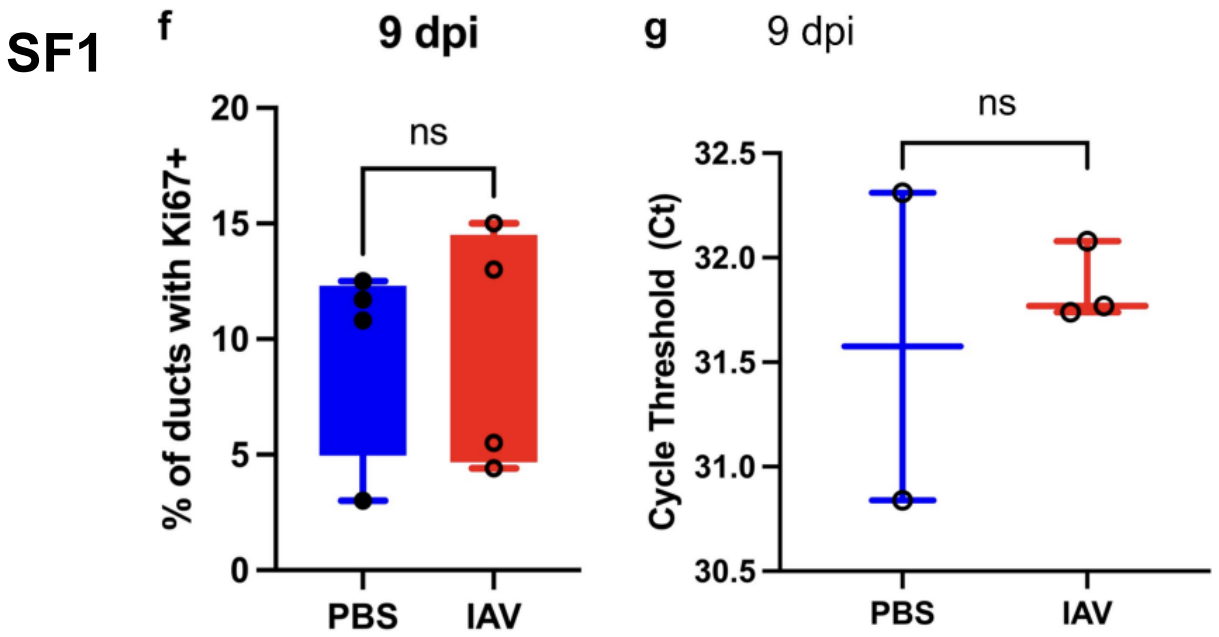


Fig. 2 | Influenza A virus infection promotes dormant DCC proliferation and phenotypic change.

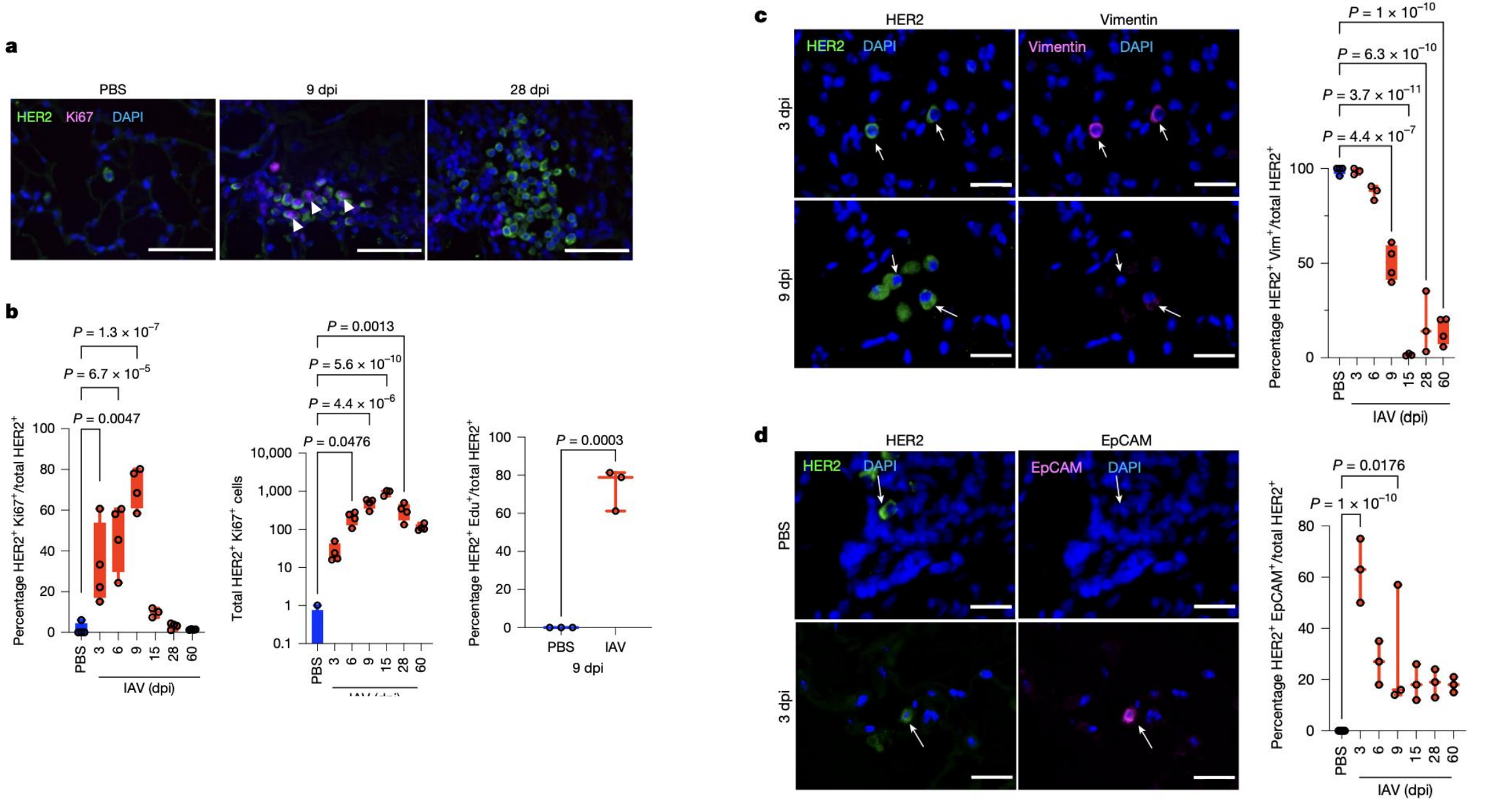


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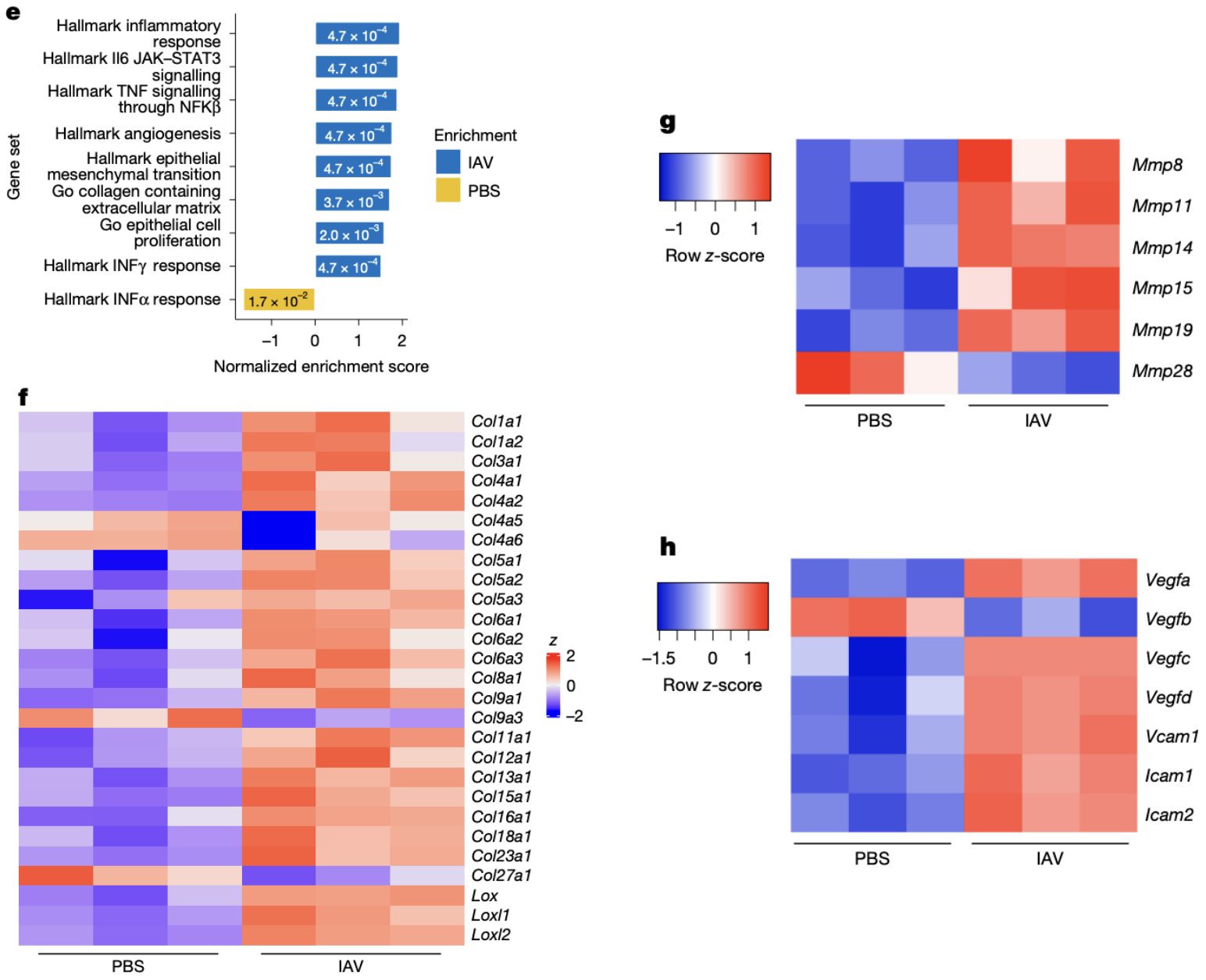


Fig. 3 | IL-6 contributes to the awakening of dormant DCCs and proliferation.

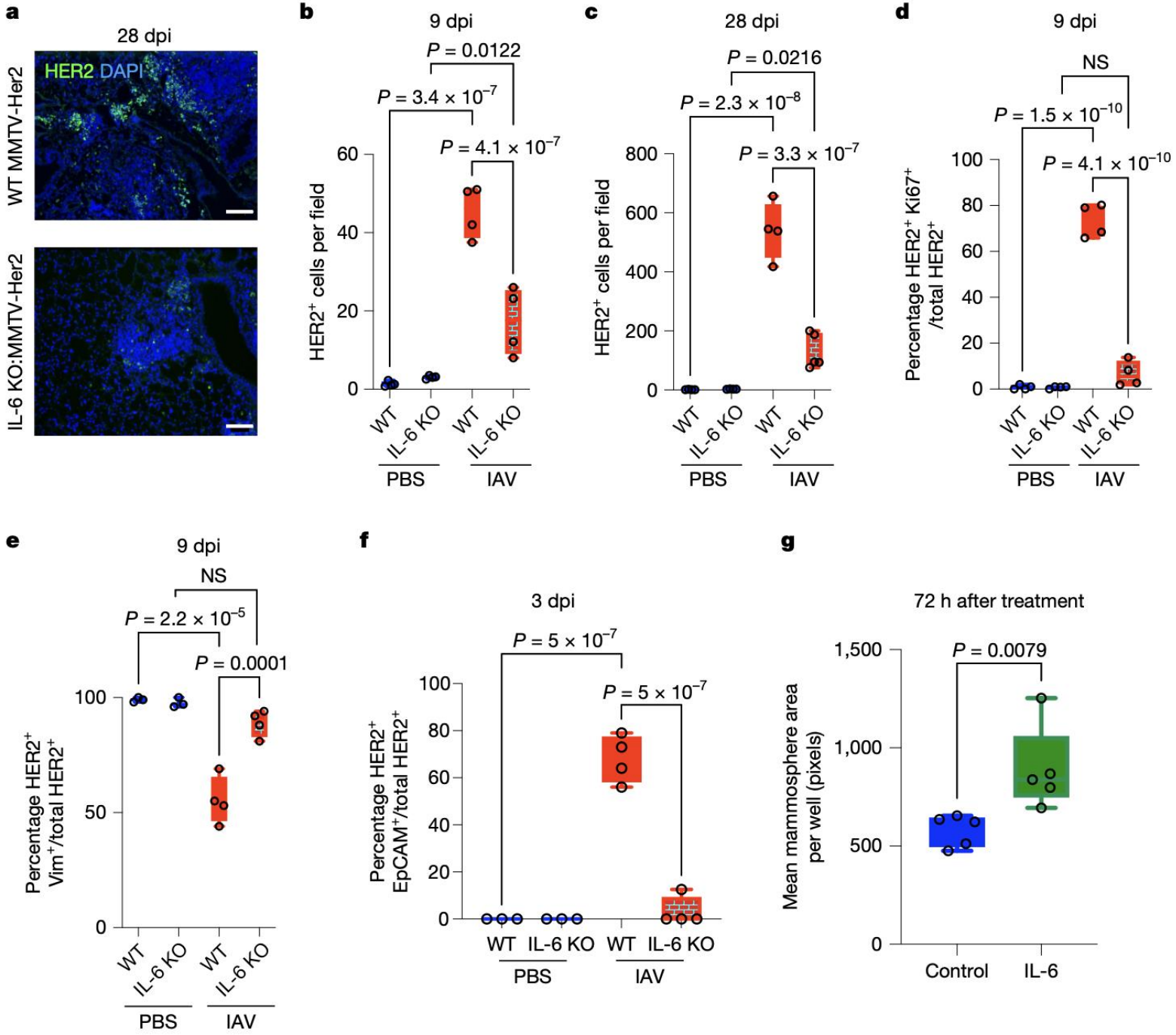


Fig. 4 | CD4+ cells are required to maintain expanded HER2+ DCCs after IAV infection.

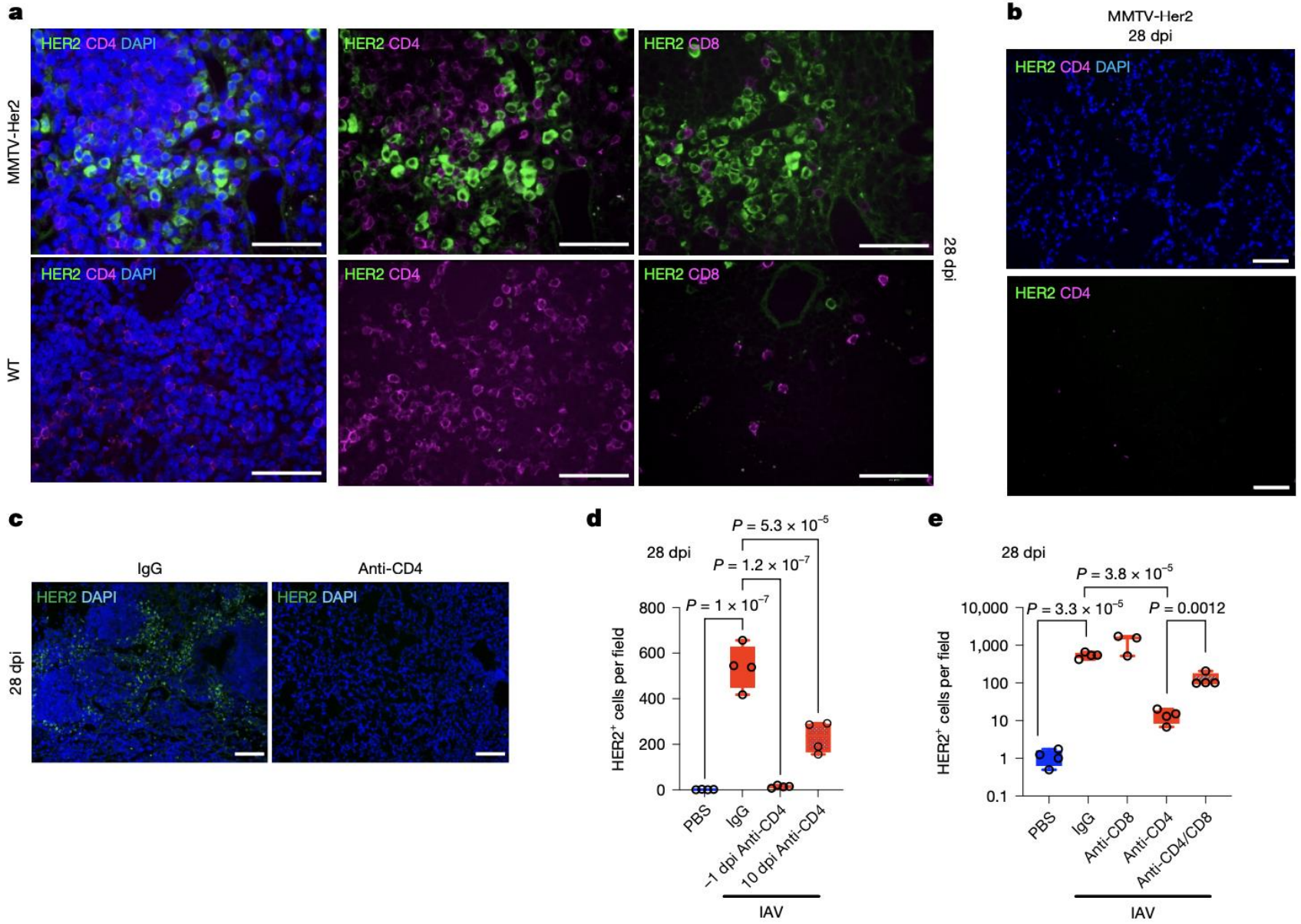
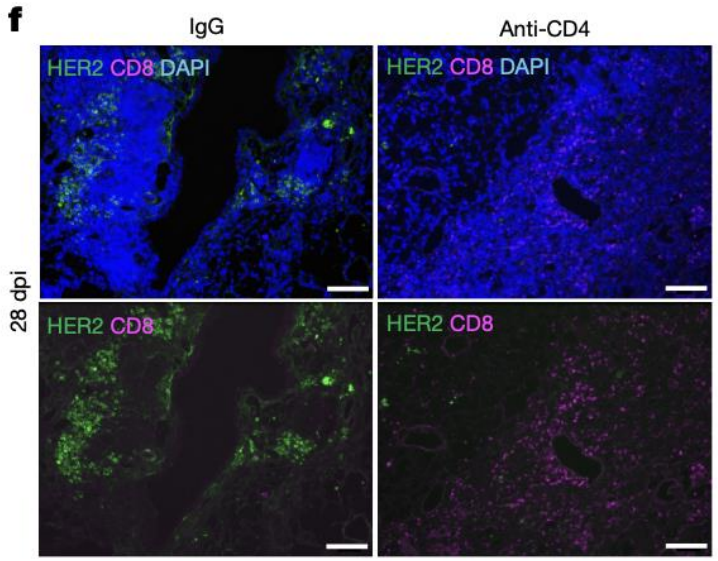
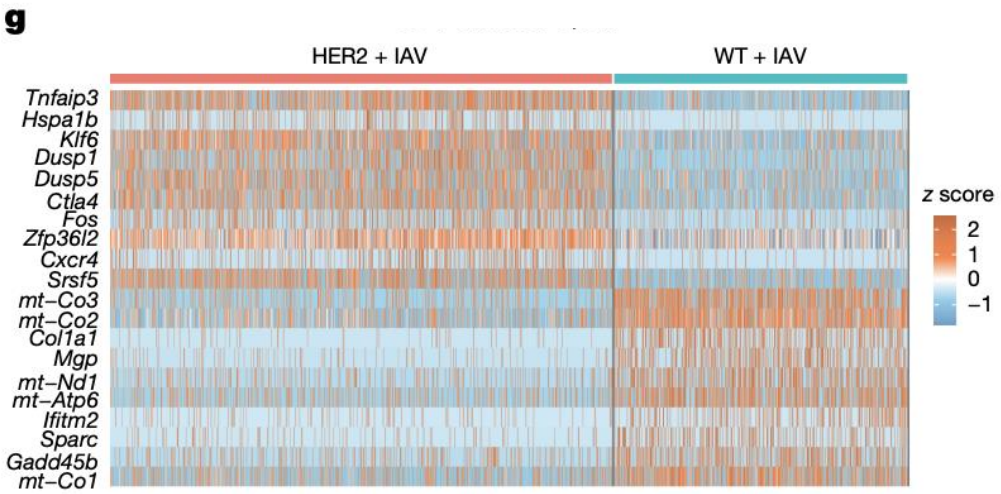
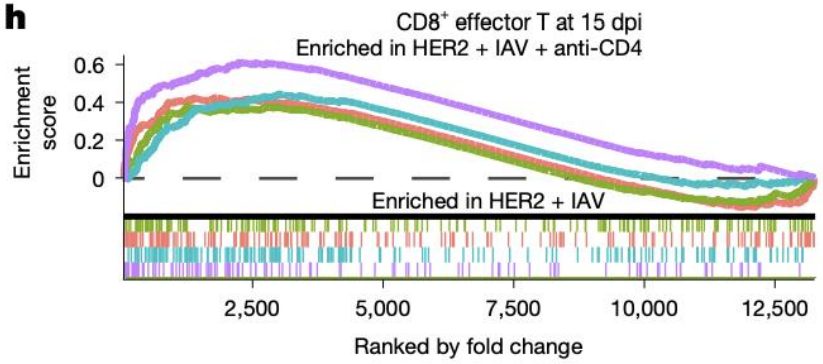


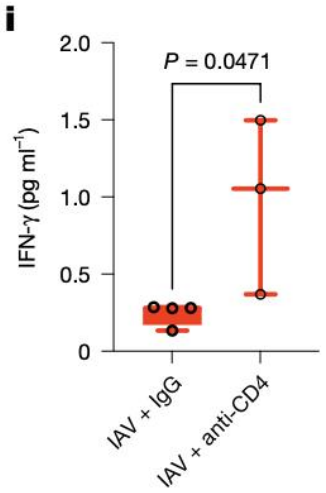
Fig. 4 | CD4+ cells are required to maintain expanded HER2+ DCCs after IAV infection.







	NES	FDR
Hallmark IL2–STAT5 signalling	1.55	0.0128
Hallmark MTORC1 signalling	1.38	0.0889
Hallmark MYC targets V1	1.61	0.0043
KEGG oxidative phosphorylation	2.08	2×10^{-6}



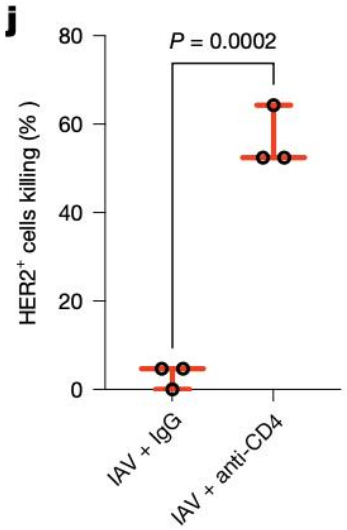


Fig. 5 | SARS-CoV-2 infection increases cancer progression, metastasis to lungs and mortality.

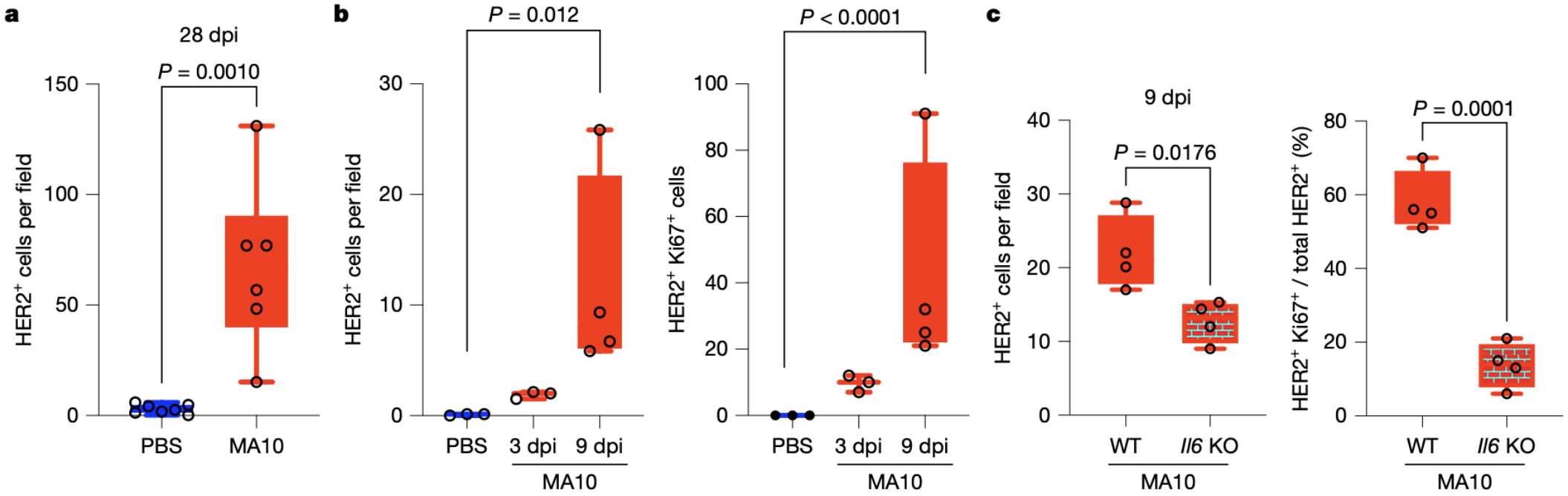
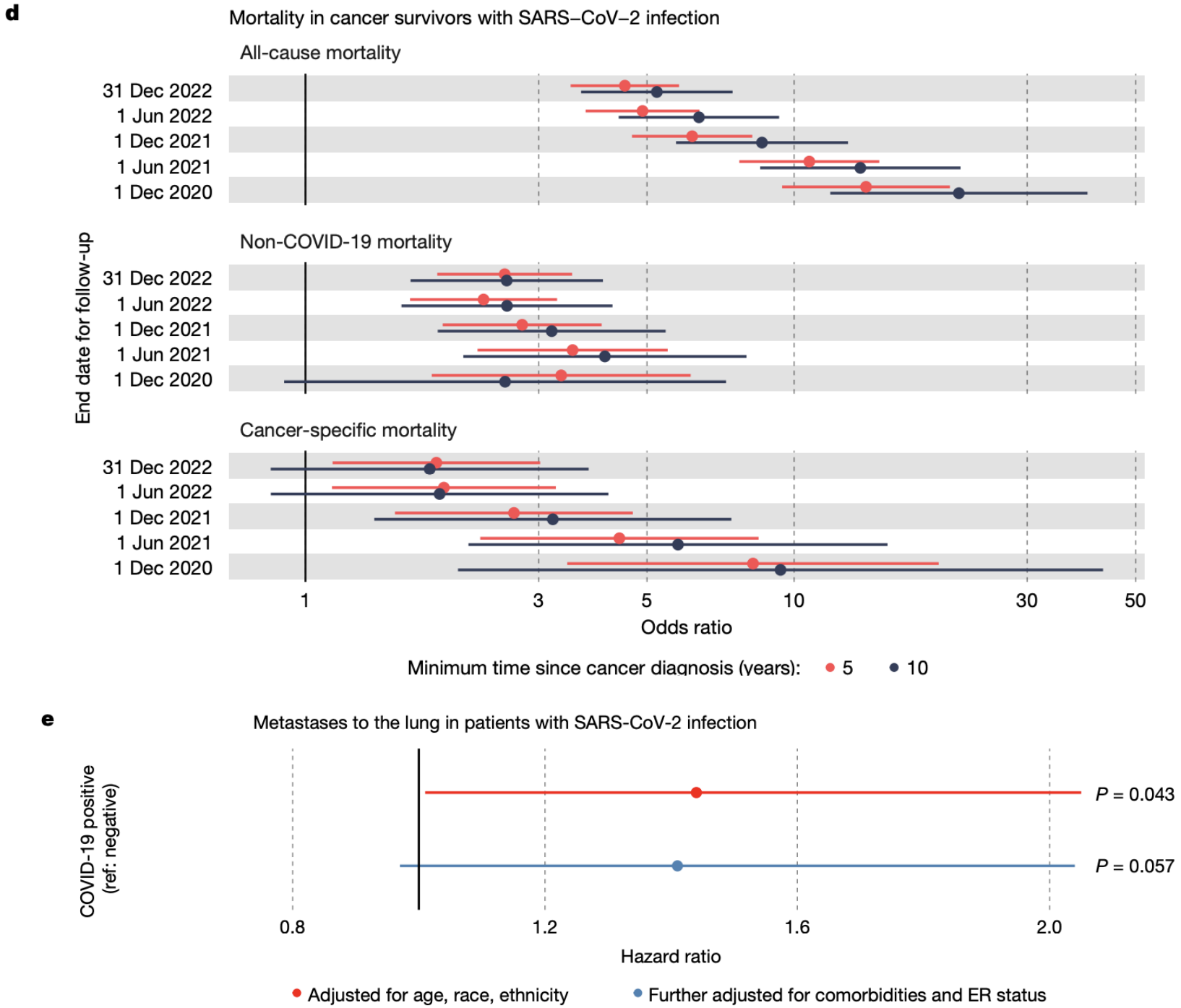


Fig. 5 | SARS-CoV-2 infection increases cancer progression, metastasis to lungs and mortality.



Any questions?

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