Cancer Biology Core Course 2026

Session 2: Cancer Initiation

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Memorial Sloan Kettering Cancer Center

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Session 2 – 9/2/26 | Cancer Initiation

Required recorded lectures:

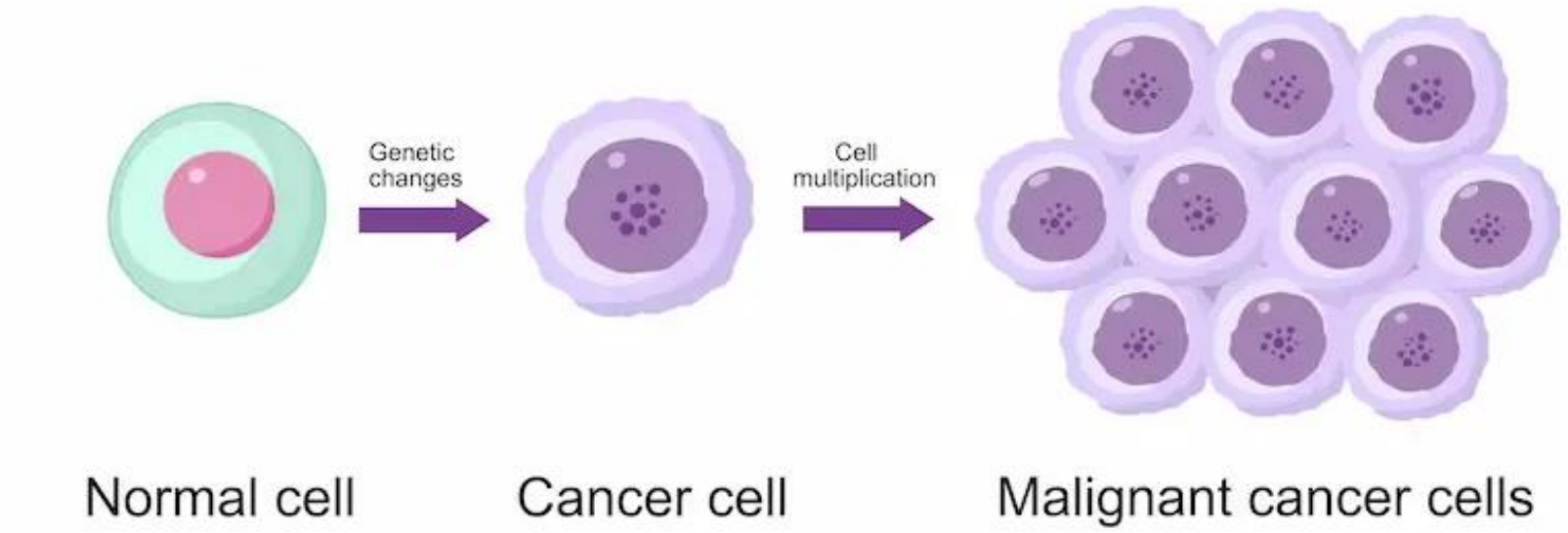
- Intro to Cancer Biology by Michael Overholtzer
- Oncogenes by Asmin Tulpule
- Tumor Suppressor Genes by Scott Lowe

Topics covered in class:

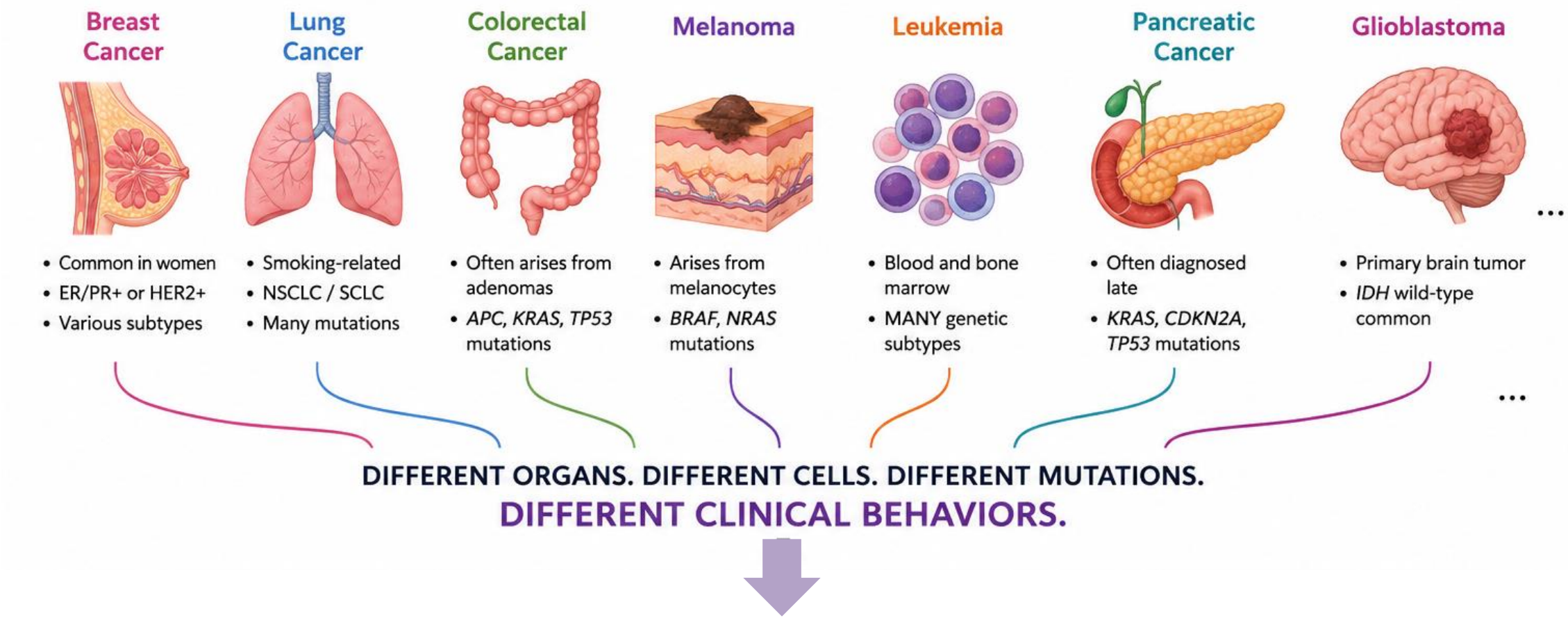
- Cancer as a disease;
- Cancer Hallmarks;
- Oncogenes vs Tumor suppressor genes;
- Initiation vs progression;
- Diagnosis and therapies.

Paper to discuss: Chan et al., Nature (2024) - *Titration of RAS alters senescent state and influences tumour initiation*

What makes a cell cancerous?

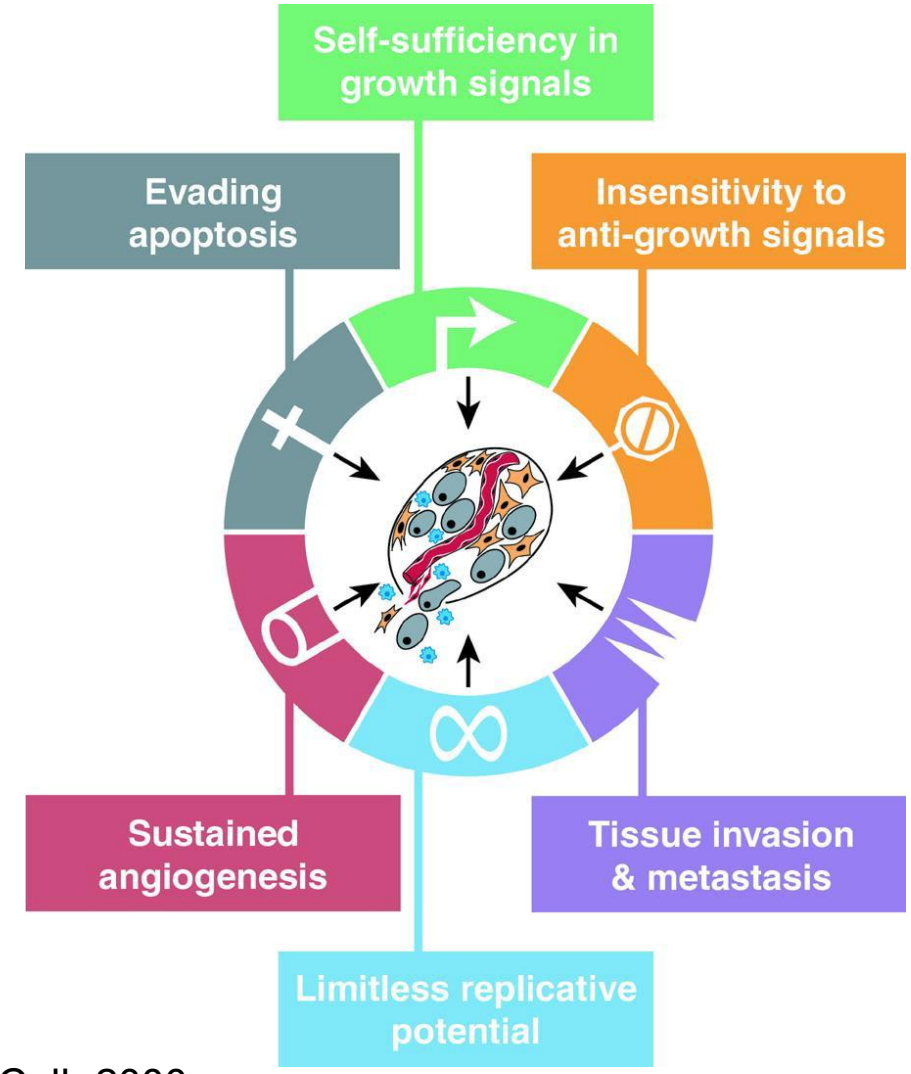


Cancer is not one disease



But cancers share common biological principles.

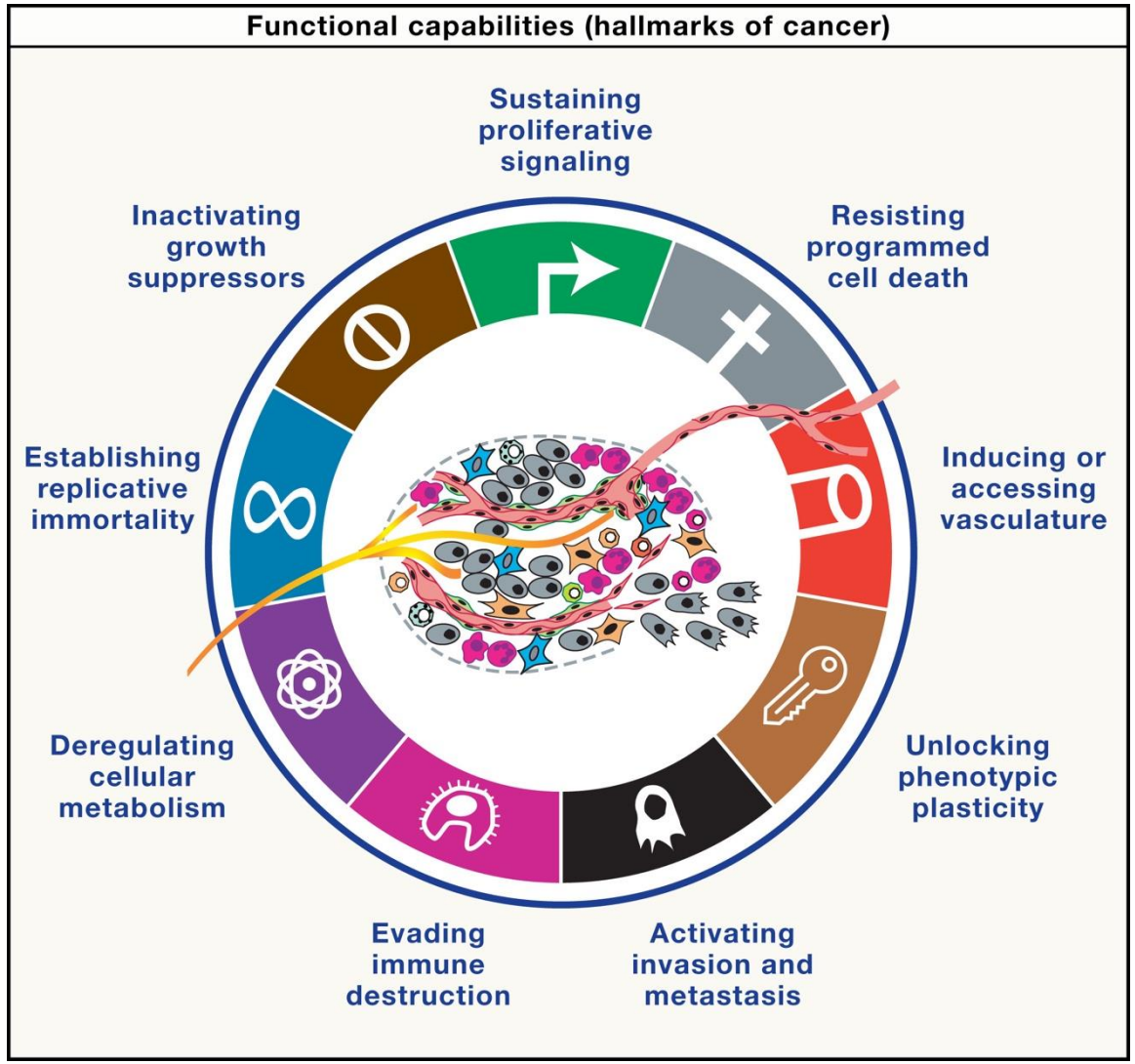
Cancer Hallmarks



Cell, 2000

Year	Paper	Main change
2000	Hanahan & Weinberg, The Hallmarks of Cancer, Cell	Proposed the original **6 hallmarks**
2011	Hanahan & Weinberg, Hallmarks of Cancer: The Next Generation, Cell	Added **2 emerging hallmarks + 2 enabling characteristics** and emphasized the TME
2022	Hanahan, Hallmarks of Cancer: New Dimensions, Cancer Discovery	Proposed **4 additional dimensions**, especially plasticity, epigenetics, microbiome and senescence
2026	Hanahan, Hallmarks of Cancer - Then and Now, and Beyond, Cell	Consolidated the framework into **9 true hallmarks + 5 enabling characteristics + TME cells + systemic factors**

Cancer Hallmarks



Cell, 2026

Dimension 2 - Hallmark-enabling characteristics

- Loss of genomic integrity / mutation / chromosomal instability
- Nonmutational epigenetic reprogramming
- Tumor-promoting inflammation
- Polymorphic microbiomes
- Innervation

Dimension 3 - Hallmark-conveying TME cells

The tumor is explicitly framed as a **cellular ecosystem**.

- vascular endothelial cells/pericytes
- CAFs
- immune cells
- other stromal populations
- neuronal elements
- senescent cells of multiple origins

Dimension 4 - Cancer as a systemic disease

Beyond cancer cell → tumor microenvironment, we now consider interactions between the tumor and the **whole organism**.

But how does a normal cell get there?

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The first hit

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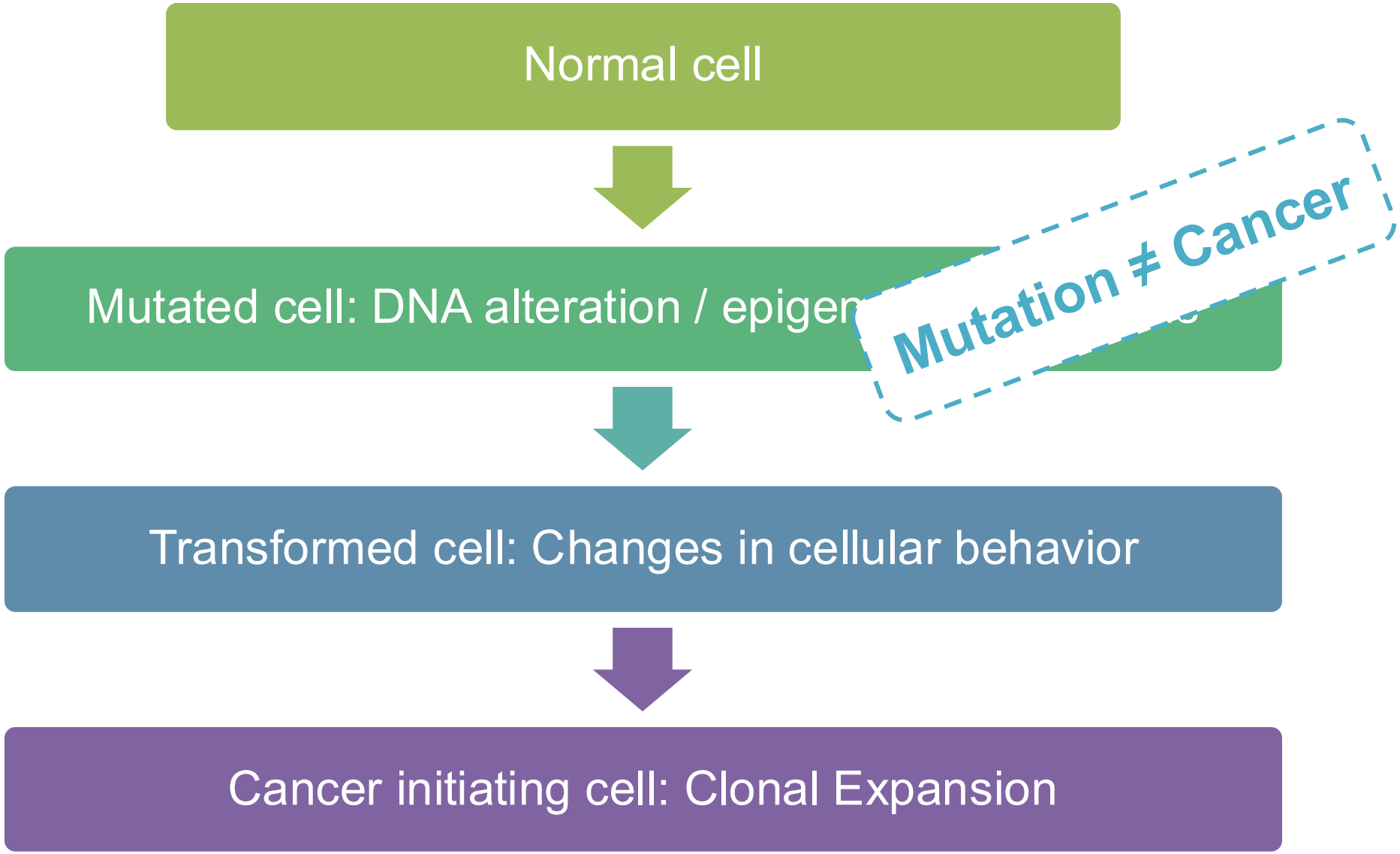
Cancer is a genetic disease



What causes the first alterations?

Cancer-causing alterations can arise from multiple sources.

Endogenous

- DNA replication errors
- Reactive oxygen species
- Spontaneous DNA damage
- Aging-associated processes

Exogenous

- Tobacco smoke
- UV radiation
- Ionizing radiation
- Occupational/environmental carcinogens
- Oncogenic infections

How did we learn that environmental exposures cause cancer?

Carcinogens > DNA DAMAGE / MUTATIONS > Driver Mutations

1775 | Percivall Pott
Chimney sweeps → scrotal cancer
→ First clear association between an occupational exposure and cancer

1915 | Yamagiwa & Ichikawa
Coal tar applied to rabbit skin → tumors
→ Experimental induction of cancer by a chemical carcinogen

1940s–50s | Tobacco & lung cancer
Epidemiologic connection becomes clear

Later | Molecular mechanism:
Carcinogens damage DNA → characteristic mutations → selection of altered clones

Q: Which statement about carcinogens is most accurate?

A

Carcinogens can promote cancer through both mutagenic and non-mutagenic mechanisms

B

Exposure to a carcinogen inevitably causes cancer

C

All carcinogens directly mutate DNA

D

Carcinogens only matter during the earliest step of tumorigenesis

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Mutations are everywhere

- Normal tissues accumulate mutations throughout life
- Aging normal tissues contain clones carrying mutations in classical cancer genes.

  Examples: **TP53 • NOTCH1 • KRAS • PIK3CA**

  Yet: **Most of these cells never form tumors.**

What converts a mutated cell into a cancer-initiating cell?

1. The mutation must actually alter fitness.
2. The cell must overcome intrinsic tumor-suppressive barriers.
3. The cell must acquire a compatible cell state.
4. The cell must achieve sustained self-renewal.
5. The cell must survive its local environment.
6. Clonal selection then reinforces the phenotype.

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Oncogenes

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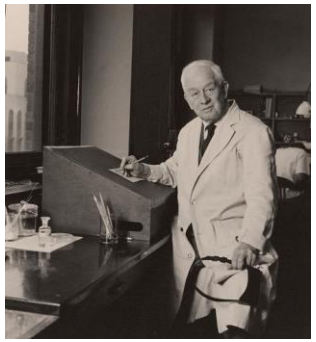
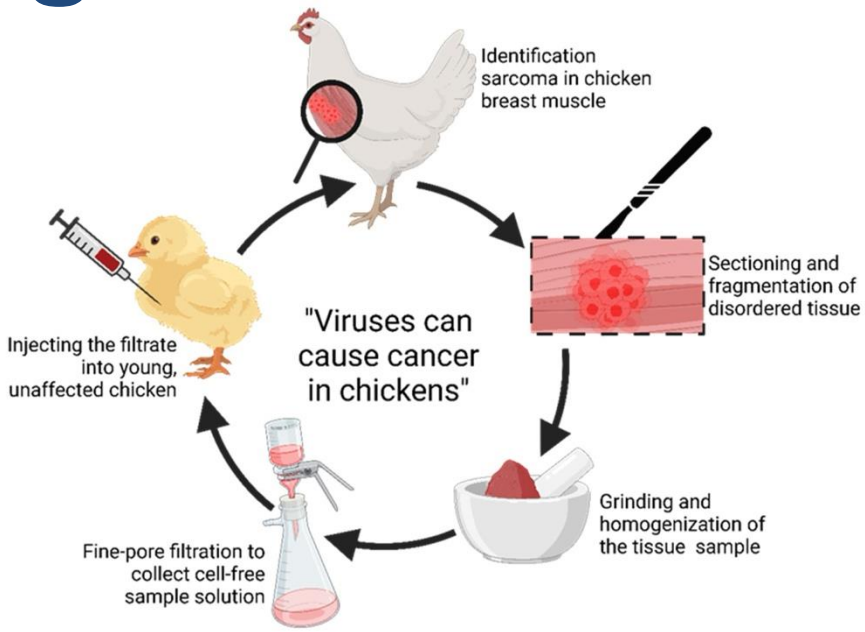
Can cancer be caused by a gene?



1911 | Peyton Rous
Chicken sarcoma → cell-free extract → new sarcoma

Rous sarcoma virus → v-Src (RNA retrovirus)



1970 | reverse transcriptase:
RNA tumor viruses can copy their information into DNA.

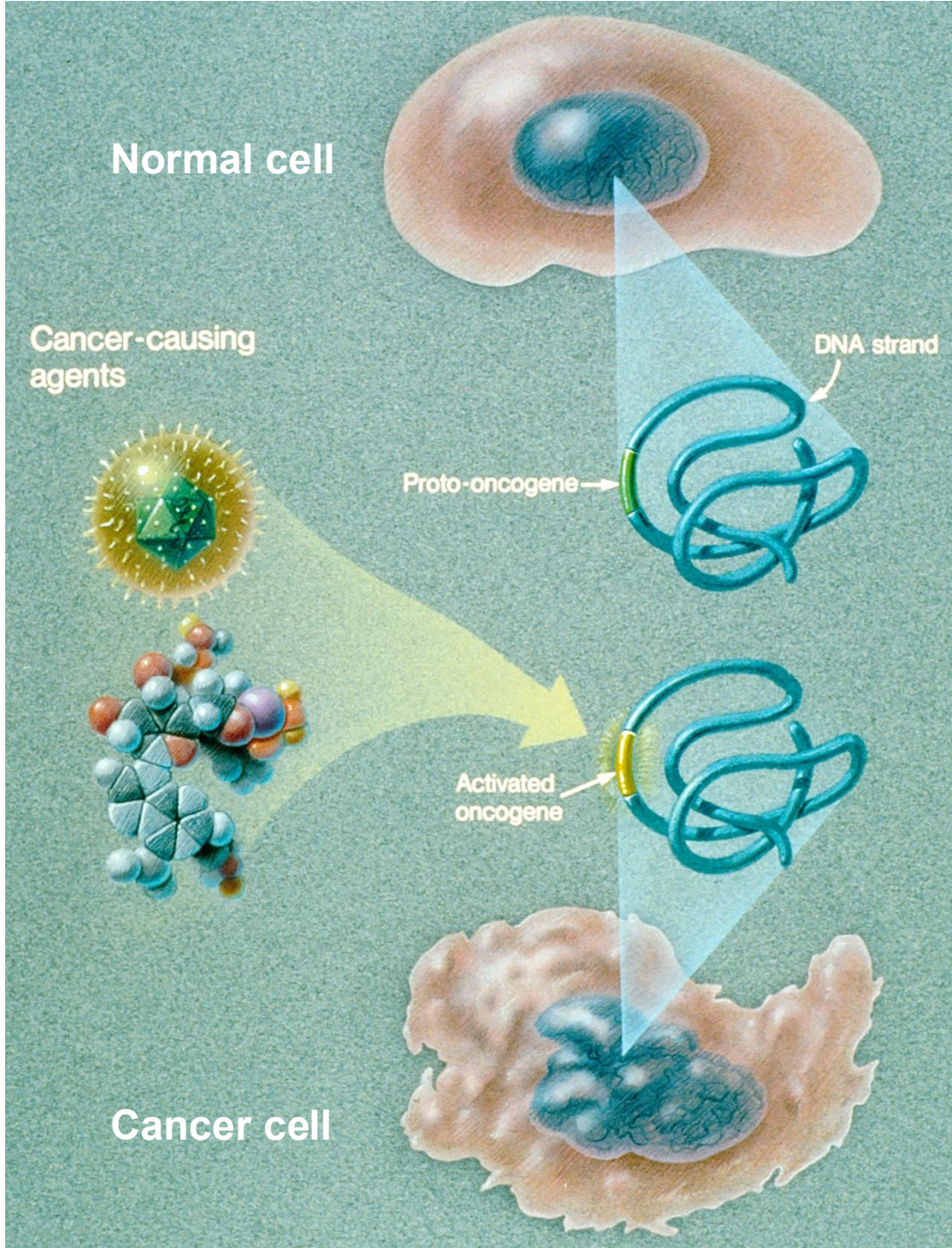
1976 | Bishop & Varmus:
The viral oncogene src originated from a normal cellular gene.

Modern cancer genetics:
Normal growth-regulatory genes can become oncogenes through mutation, amplification, translocation, etc.

The surprise: oncogenes came from us

When dysregulated:
Proto-oncogene → ONCOGENE

Cancer can hijack normal growth-control machinery.



Human cancers contain oncogenes

RAS: one of the first human oncogenes

Normal:

Growth factor → **RAS-GTP** → RAF → MEK → ERK → proliferation

Cancer:

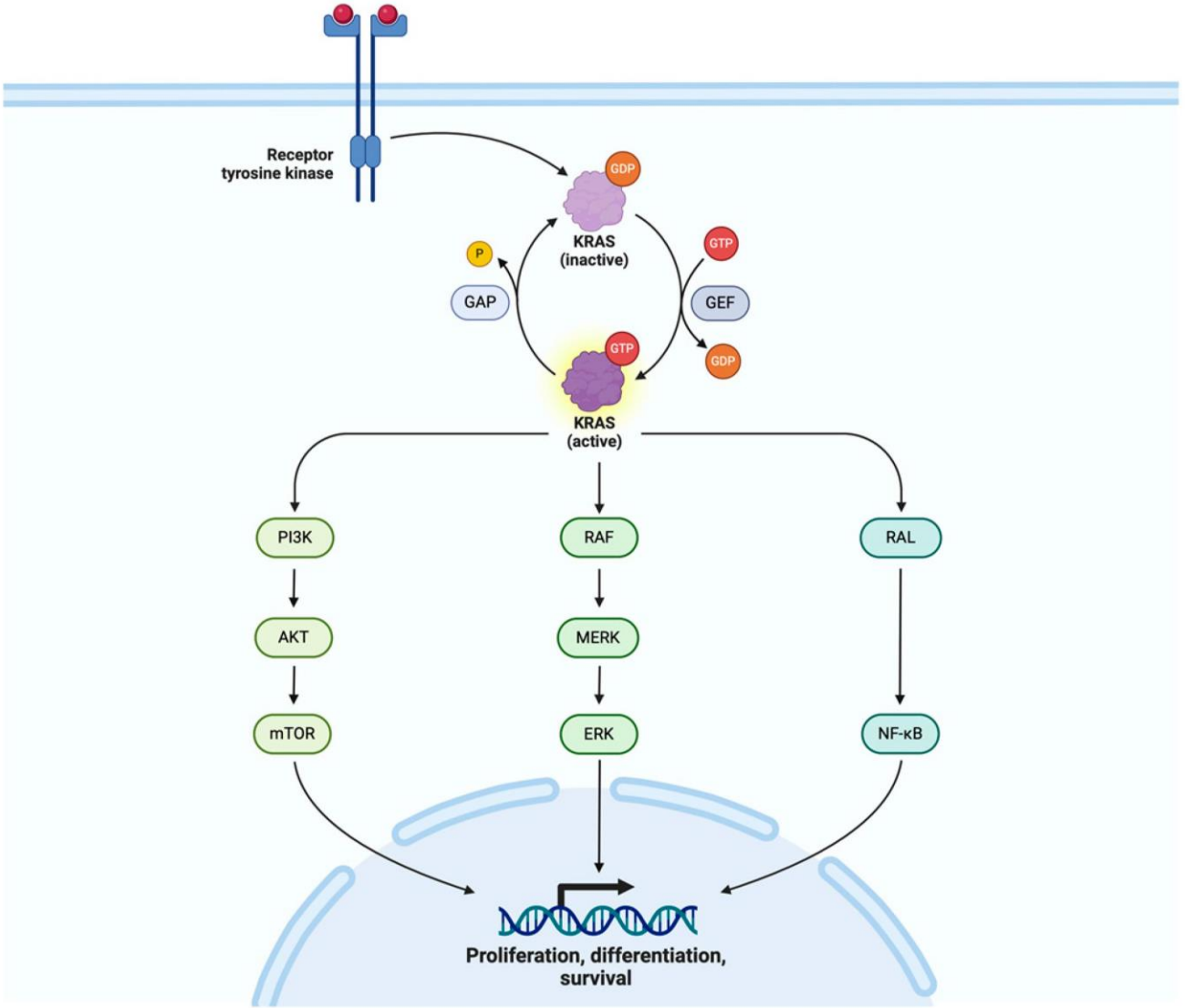
Mutant RAS

↓

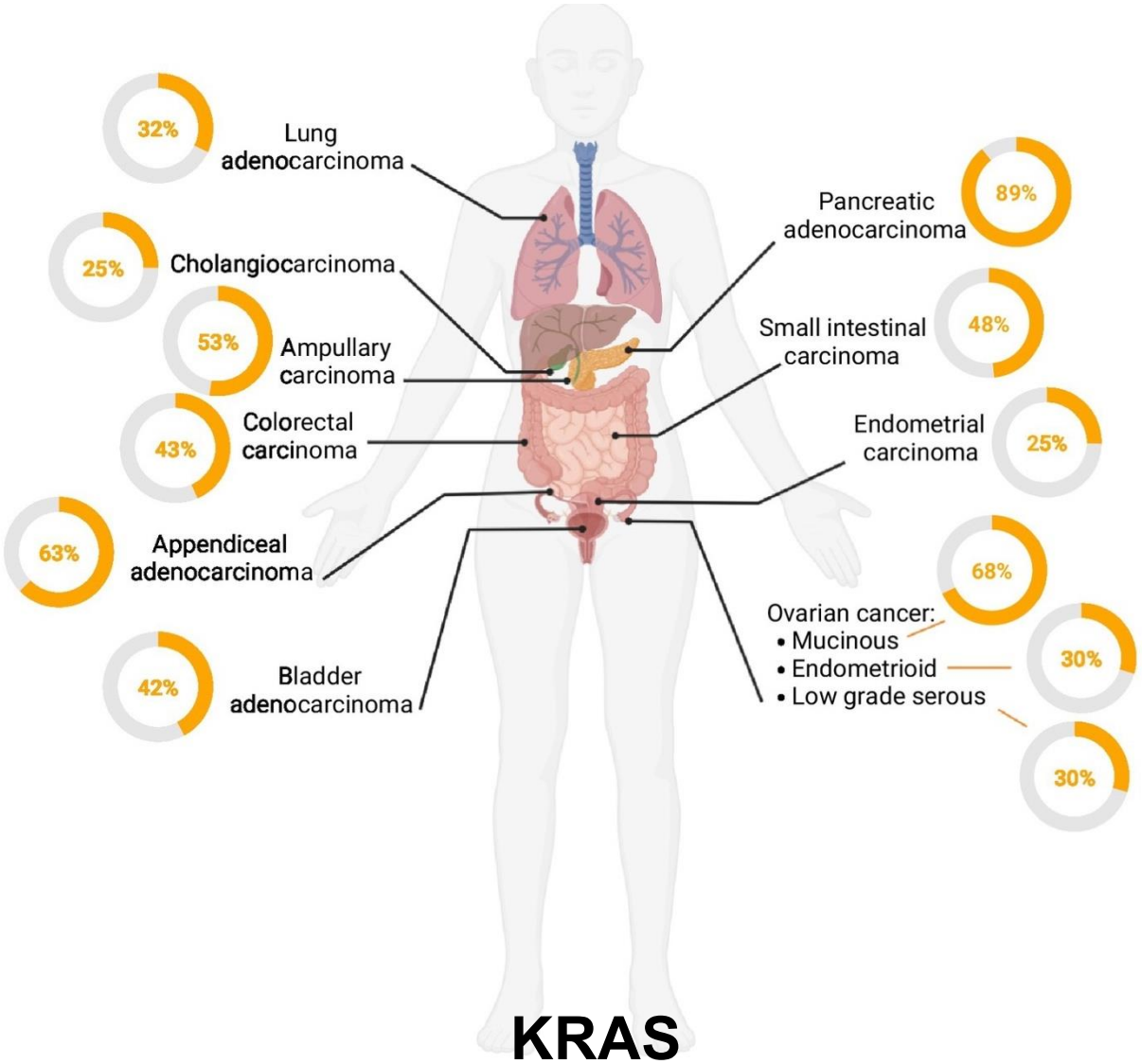
persistent signaling

↓

Proliferation



So, is that enough?



KRAS

Normal cell + oncogene = cancer?

Normal cell

↓

KRAS^{G12D}

↓

?

↓

Cancer

Is activation of an oncogene sufficient to transform a normal cell?

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Tumor supressor genes

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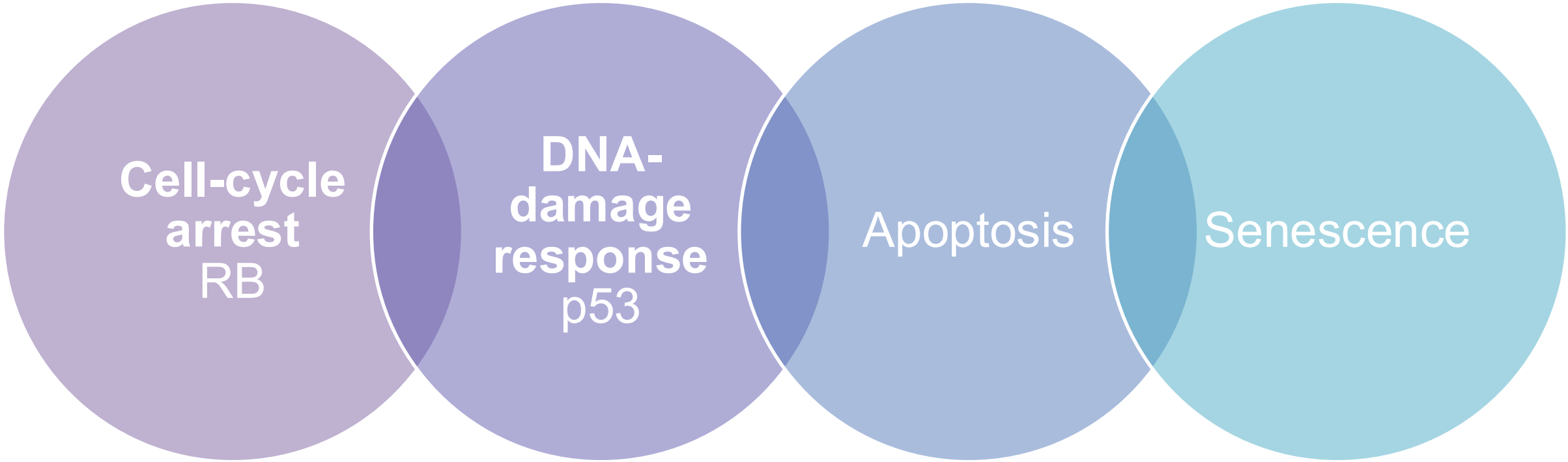
Cells resist transformation

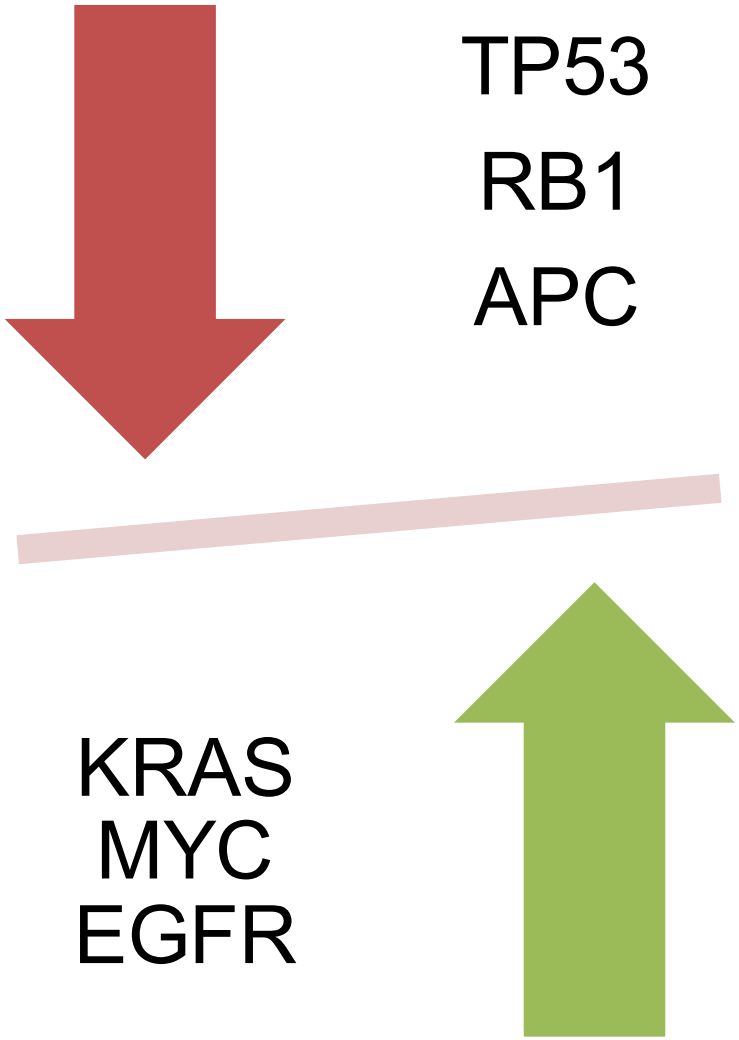


Oncogenic signaling can activate these barriers.

Tumor suppressors

Cancer requires releasing the brakes
Oncogene activation = accelerator
Tumor suppressor loss = brakes removed

Oncogenes promote growth.
Tumor suppressors constrain it.



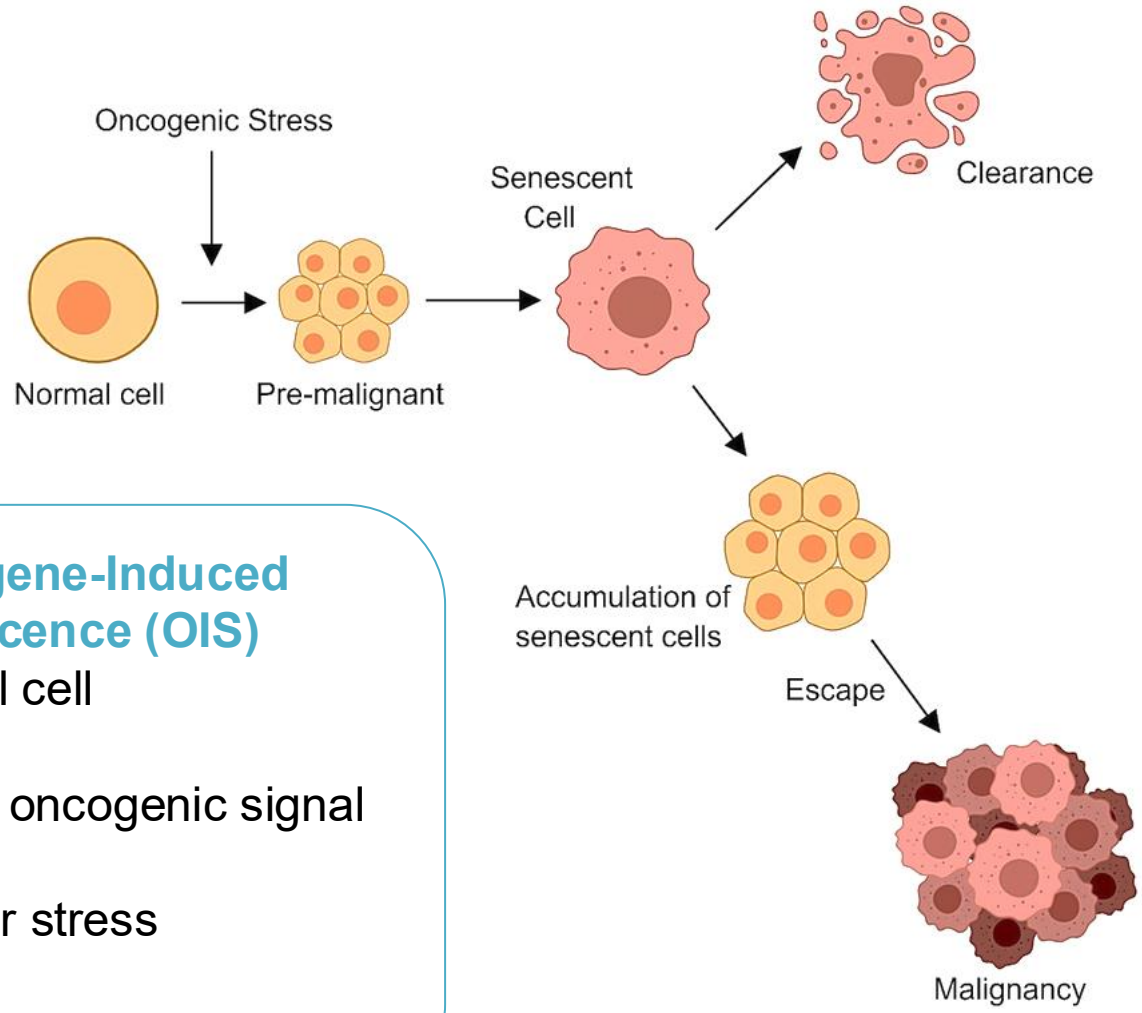
One important barrier: senescence

Cellular senescence

Stable cell-cycle arrest in response to cellular stress

Triggers include:

- DNA damage
- Telomere dysfunction
- Oxidative stress
- **Oncogene activation**



Oncogene-Induced Senescence (OIS)

Normal cell

↓

Strong oncogenic signal

↓

Cellular stress

↓

SENESCENCE

The oncogene paradox

More oncogenic signaling ≠ more cancer

Moderate RAS signaling:
Proliferation ↑

Strong RAS signaling:
Stress ↑ → Senescence

An oncogene can simultaneously promote AND suppress tumor formation.

Q: What happens when a normal cell acquires an activated oncogene?

A

It immediately becomes a cancer cell

B

It continuously proliferates and eventually forms a tumor

C

It may proliferate, arrest, or die depending on the strength of the oncogenic signal and cellular context

D

Nothing happens unless a tumor suppressor is already lost

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Cancer requires cooperation

Normal cell

↓

Oncogene activation

↓

Abnormal proliferation / stress

↓

Tumor suppressive barrier

↓

Normal cell

↓

Oncogene activation

+

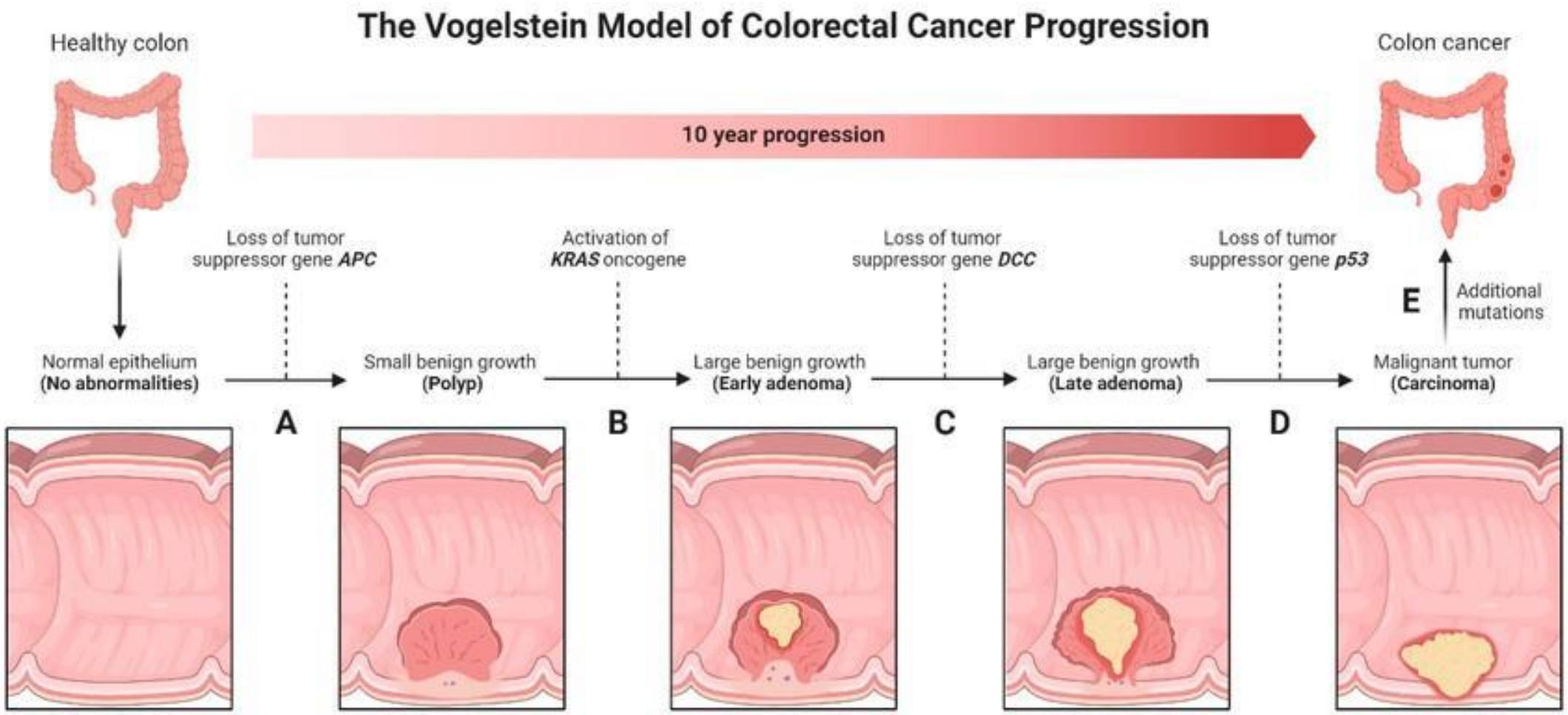
Tumor suppressor loss

↓

Clonal expansion

Cancer emerges through cooperating alterations.

Multistep tumorigenesis



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Beyond genetics

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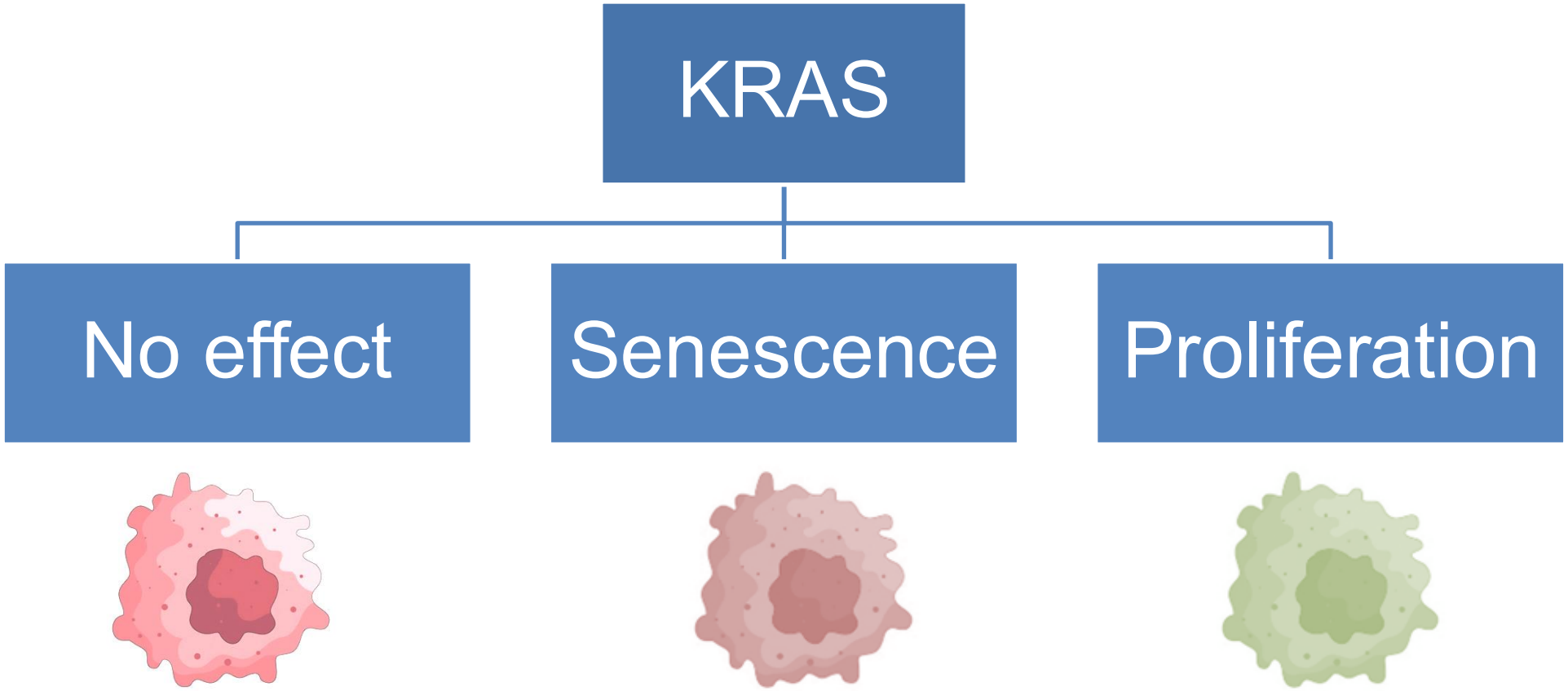
The cell of origin matters

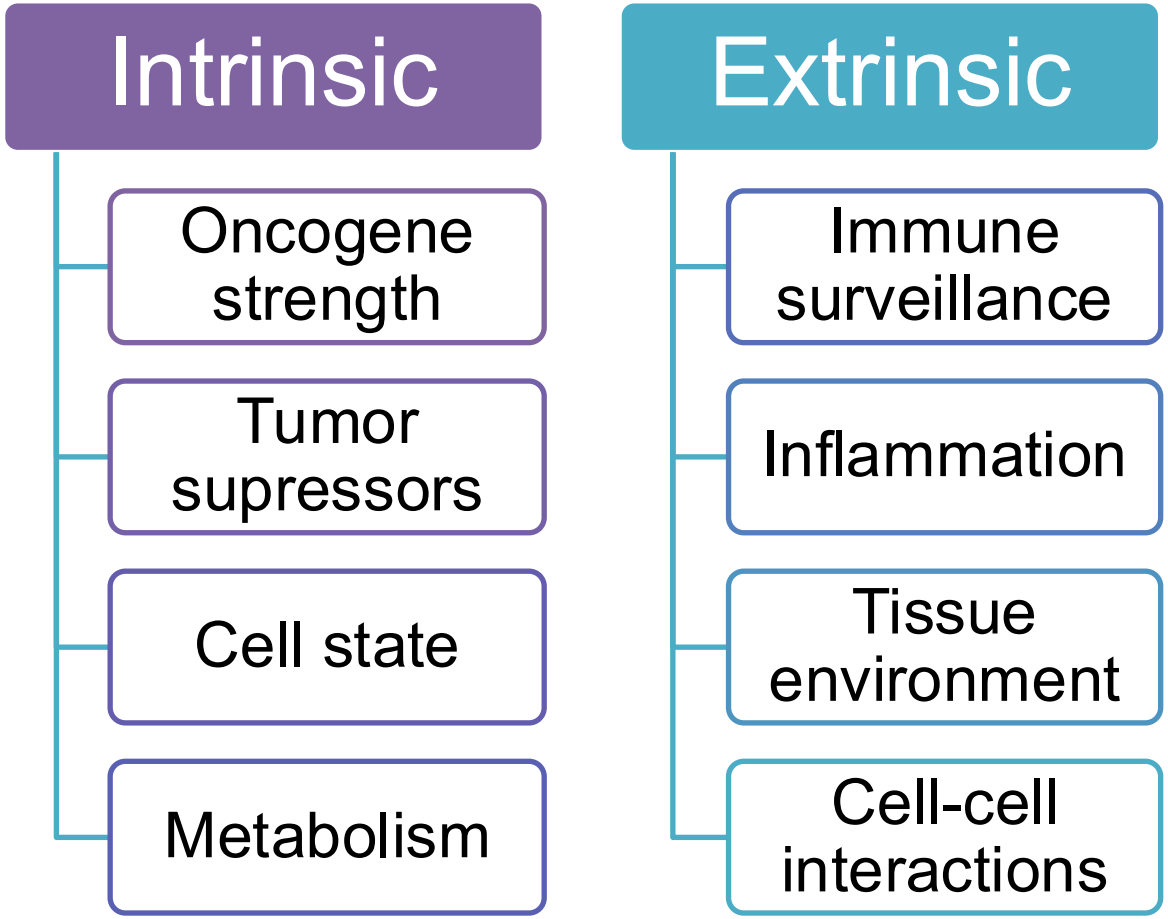
The same oncogene can have different consequences in different cells.



✔ Differentiation state ✔ Epigenetic state ✔ Existing mutations ✔ Signaling environment

Context matters

Tumor initiation is an ecosystem problem.
Whether an initiated cell survives depends on:

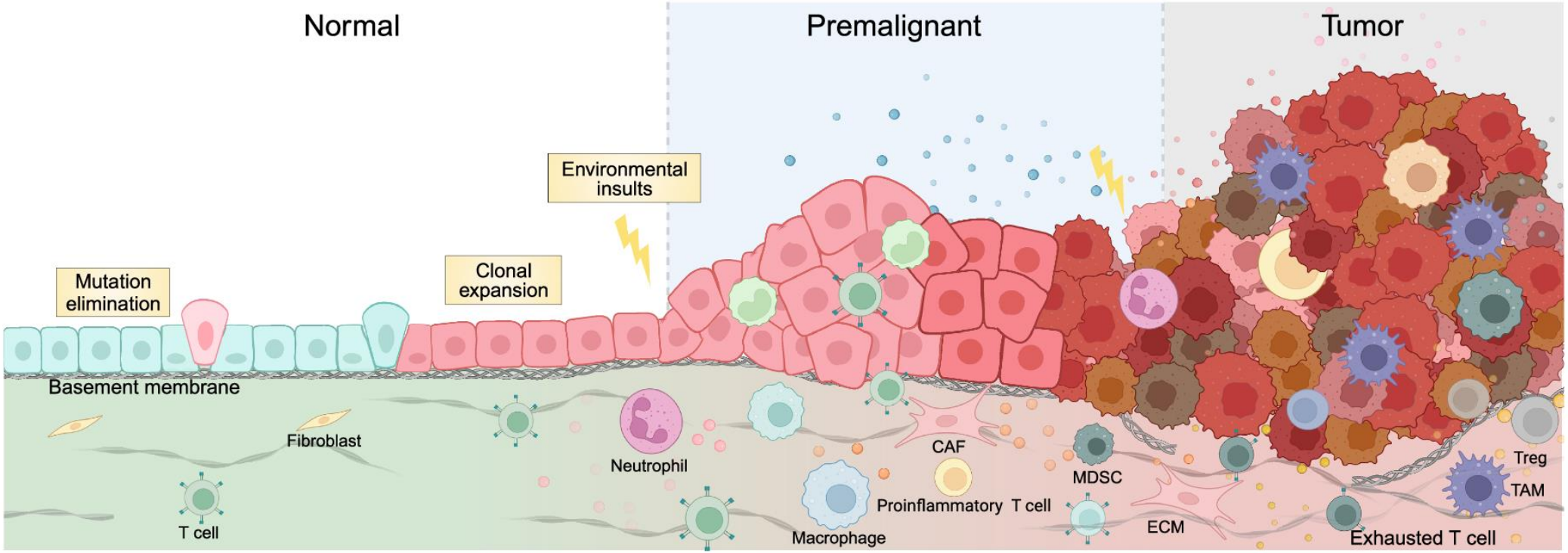


So, what initiates cancer?

ONCOGENIC ALTERATION > **Successful clonal expansion** > **Tumor initiation**

Signal strength
Tumor suppressive barriers
Cell of origin
Cell state
Additional alterations
Tissue / immune context

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



Q: Which event best defines successful cancer initiation?

A

A normal cell acquires a mutation

B

An oncogene becomes activated

C

An altered cell successfully escapes normal constraints and clonally expands

D

A tumor suppressor is lost

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If RAS is a potent oncogene, why doesn't every RAS-expressing cell initiate a tumor?

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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

Titration of RAS alters senescent state and influences tumour initiation

https://doi.org/10.1038/s41586-024-07797-z

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Adelyne S. L. Chan[1,13], Haoran Zhu[1,13], Masako Narita[1], Liam D. Cassidy[1], Andrew R. J. Young[1], Camino Bermejo-Rodriguez[2], Aleksandra T. Janowska[1], Hung-Chang Chen[1], Sarah Gough[1], Naoki Oshimori[3], Lars Zender[4,5,6,7], Sarah J. Aitken[1,8,9], Matthew Hoare[1,10,11] & Masashi Narita[1,12] ✉

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

Fig. 1. Single-cell transcriptomics reveals OIS spectrum driven by oncogenic dosage in vivo

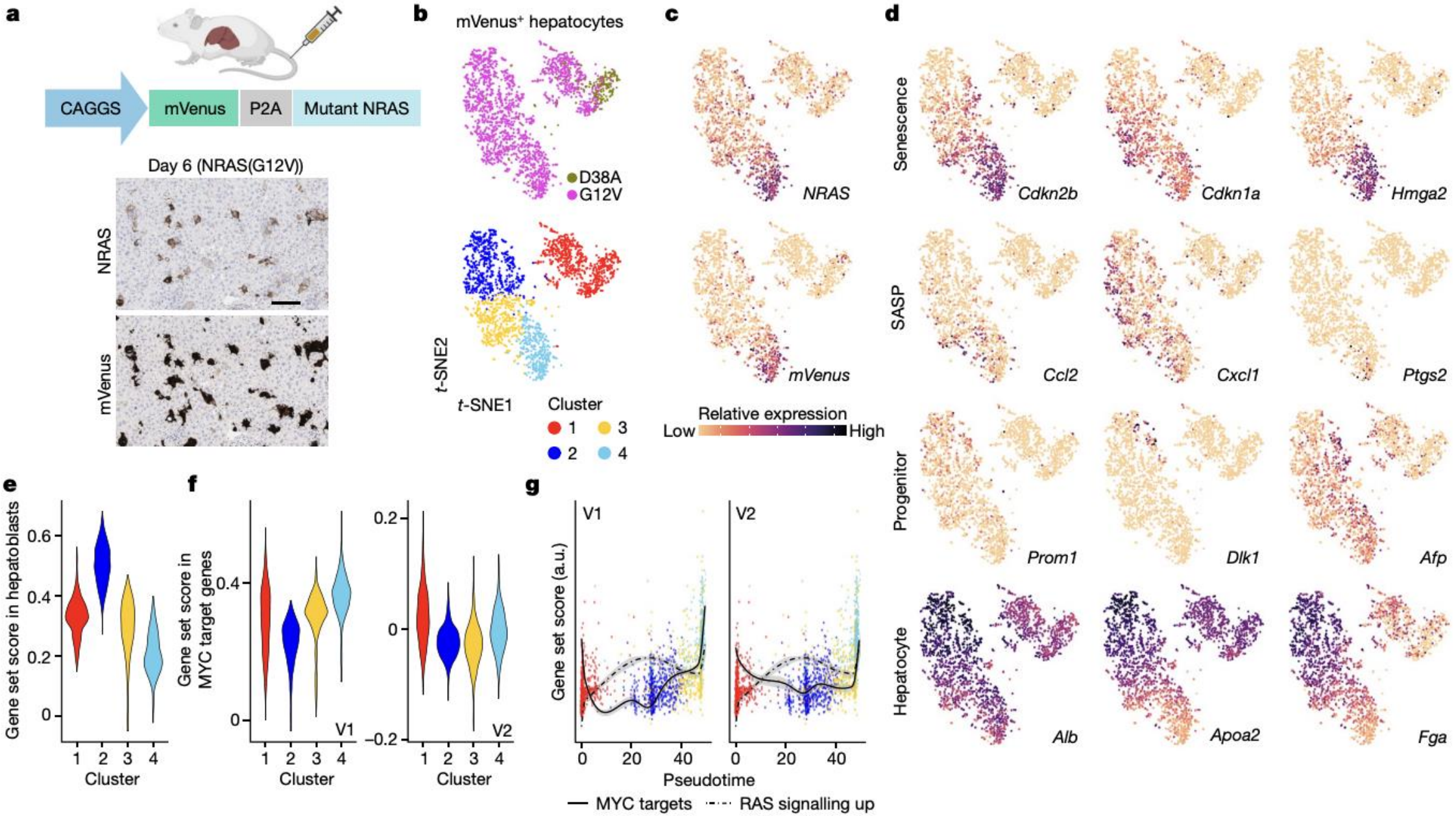


Fig. 2. Oncogenic RAS induces OIS-like slow-cycling phenotype in RPE1 cells

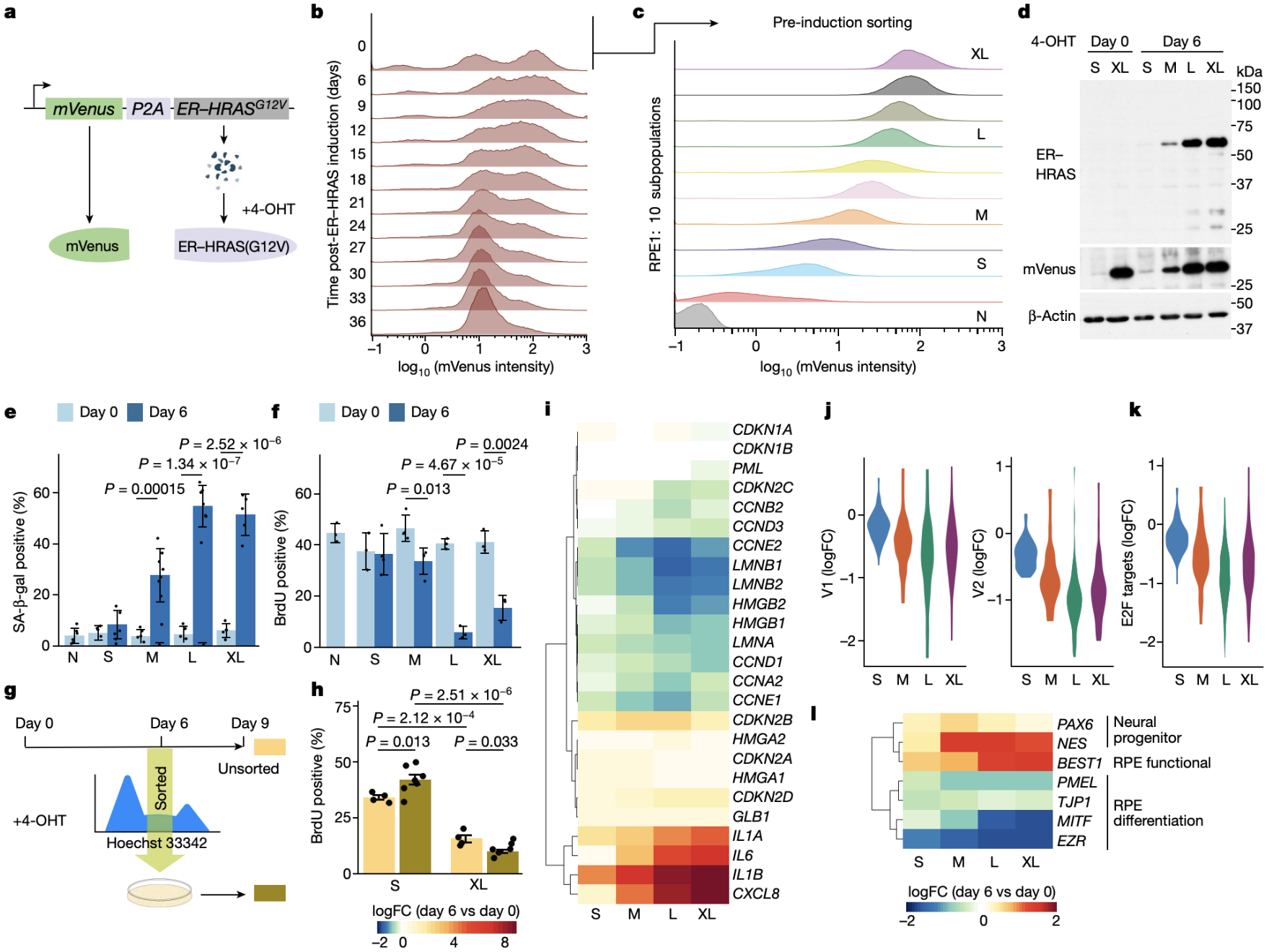


Fig. 3. Sub-OIS dosage of RAS is sufficient for tumorigenesis

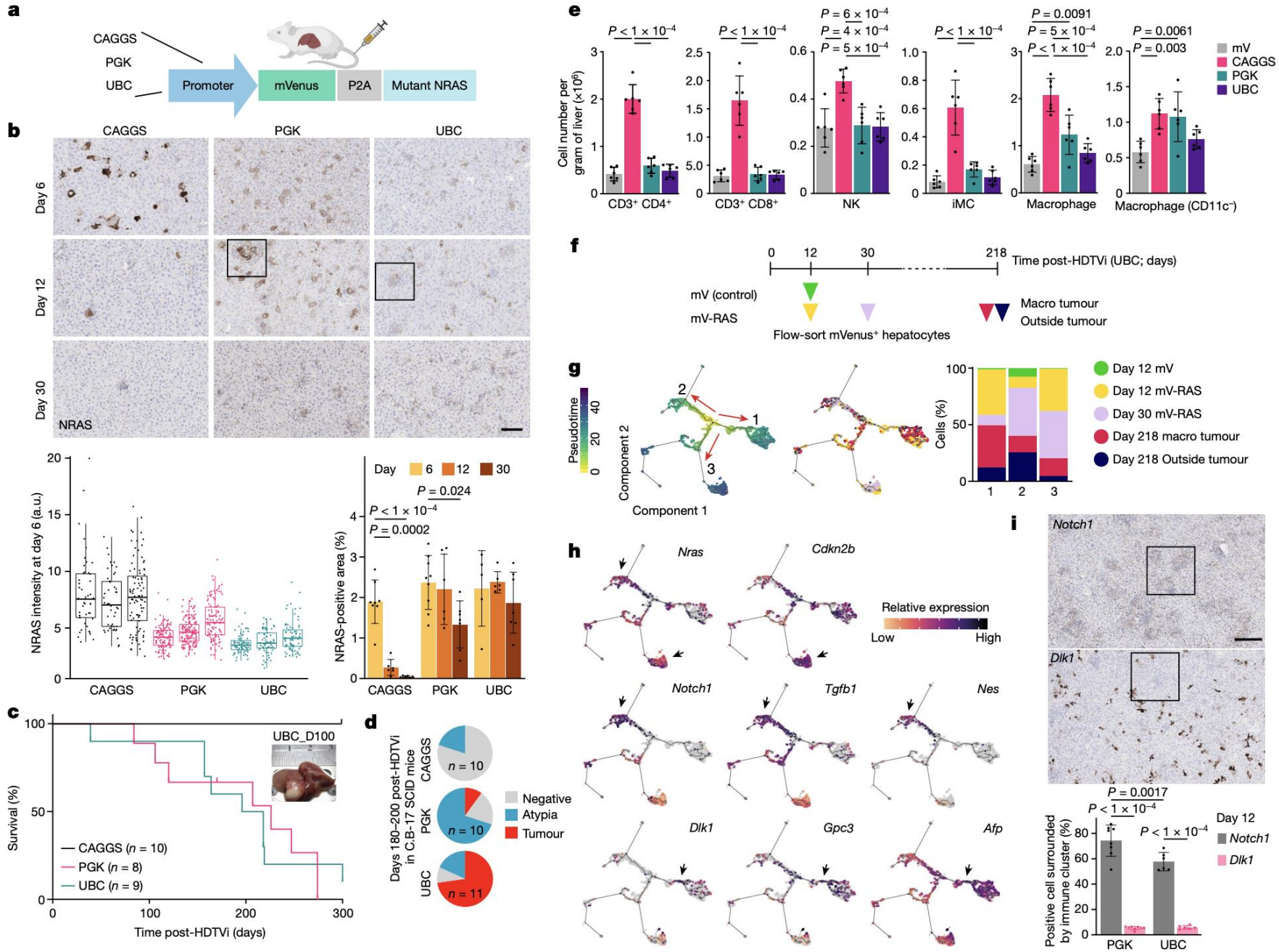
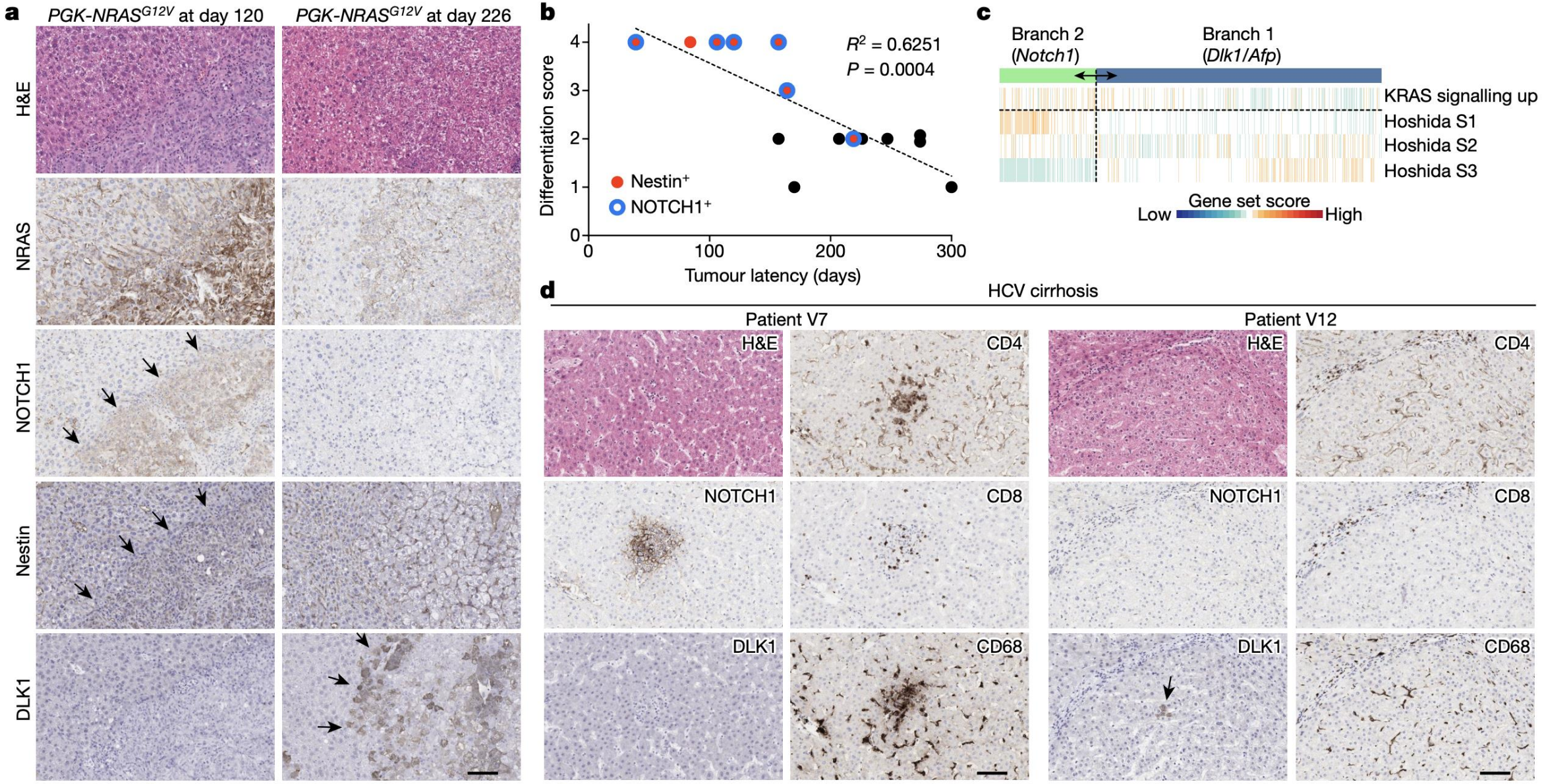


Fig. 4. Dichotomous Dlk1/Afp- and Notch1/Tg fb1/Nes-driven tumour initiating events in mice and human HCC



Any questions?

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