THE HALLMARKS OF CANCER

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Learning Objectives

- Define “driver” and “passenger” mutations in cancer.
- Estimate the number of “driver” and “passenger” mutations in a tumor.
- Identify processes commonly altered in cancer by genetic alterations.
- Exemplify how genetic alterations in cancer may influence tumor radiation response.

Radiobiology

- The response to radiation is different in normal tissues and cancer:
  - at the cellular level
  - at the tissue level

- These differences are due to the underlying biological properties of different tissues and cancers

Tumor Radiobiology

Fact: We deliver a known physical dose with a high degree of accuracy to similar tumors

Observation: The radiocurability of tumors varies widely

Aim: Understand the biological factors that influence the sensitivity of tumors and normal tissues to radiation

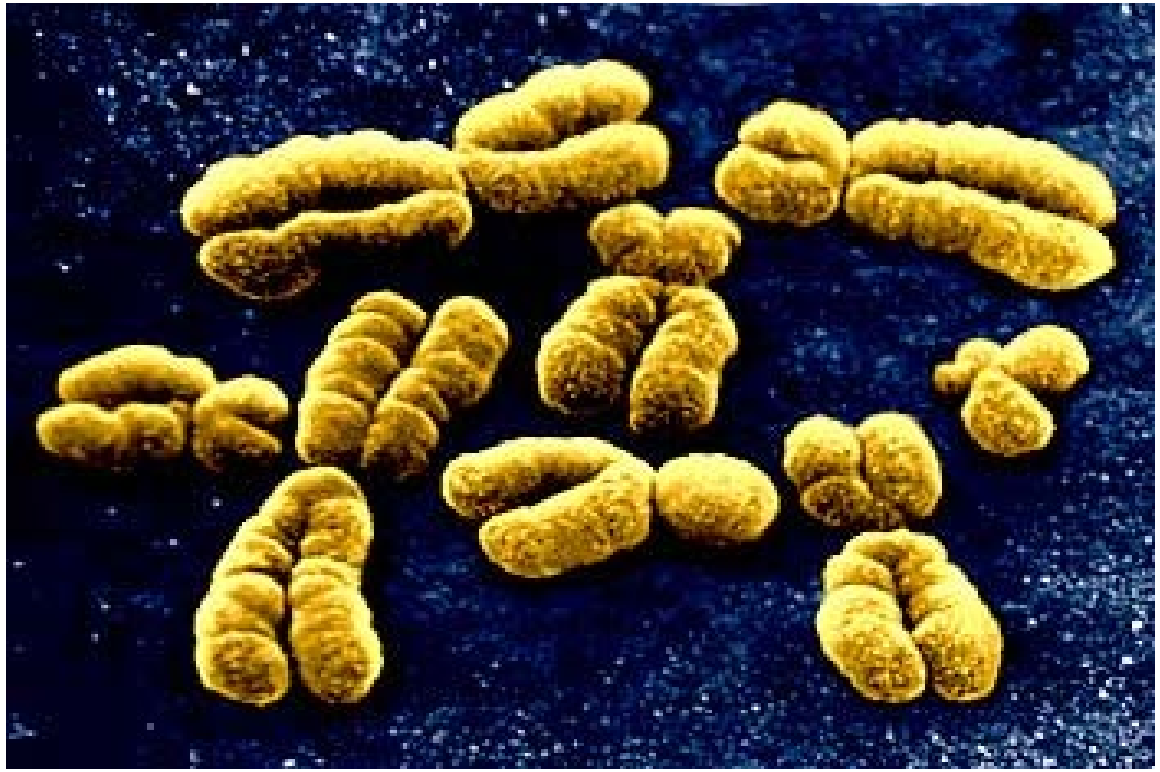
What is Cancer?

Cancer – Important Concepts

- Cancer cells are derived from normal cells in the body
- Cancer cells have acquired a series of changes which distinguishes them from normal cells.
  - These changes are the basis for much of the difference in the ways tumors respond to radiation compared to normal tissues
- There are multiple ways of creating cancer
  - This can explain why even tumors of the same type can differ dramatically in how they response to radiation

Cancer is a genetic disease

- Disease involving changes in the genome
  - point mutations
  - gene amplification
  - deletions, silencing
- 2 classes of cancer genes:
  - Oncogenes (gain of function)
  - Tumor suppressors (loss of function)
- “Driving” genetic alteration:
  - Confers growth advantage
  - Causative of cancer
- “Passenger” genetic alteration:
  - No growth advantage
  - No causative role in cancer



Article

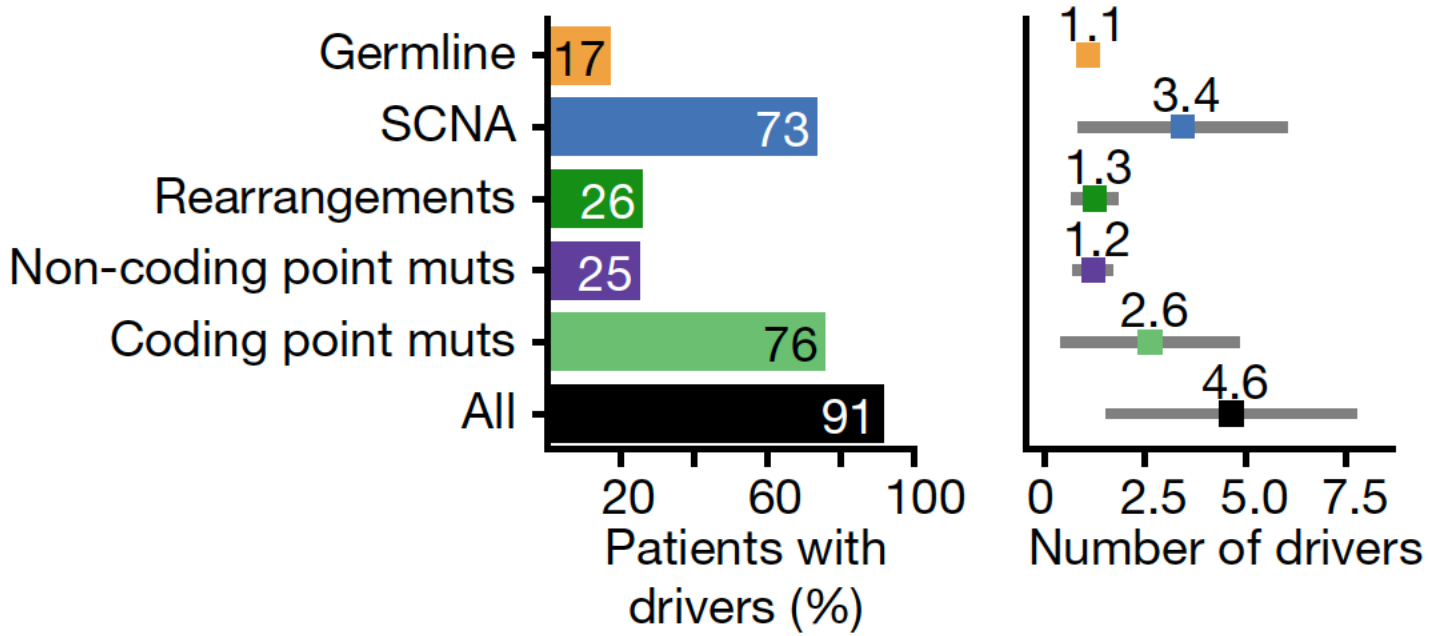
Pan-cancer analysis of whole genomes

82 | Nature | Vol 578 | 6 February 2020

https://doi.org/10.1038/s41586-020-1969-6

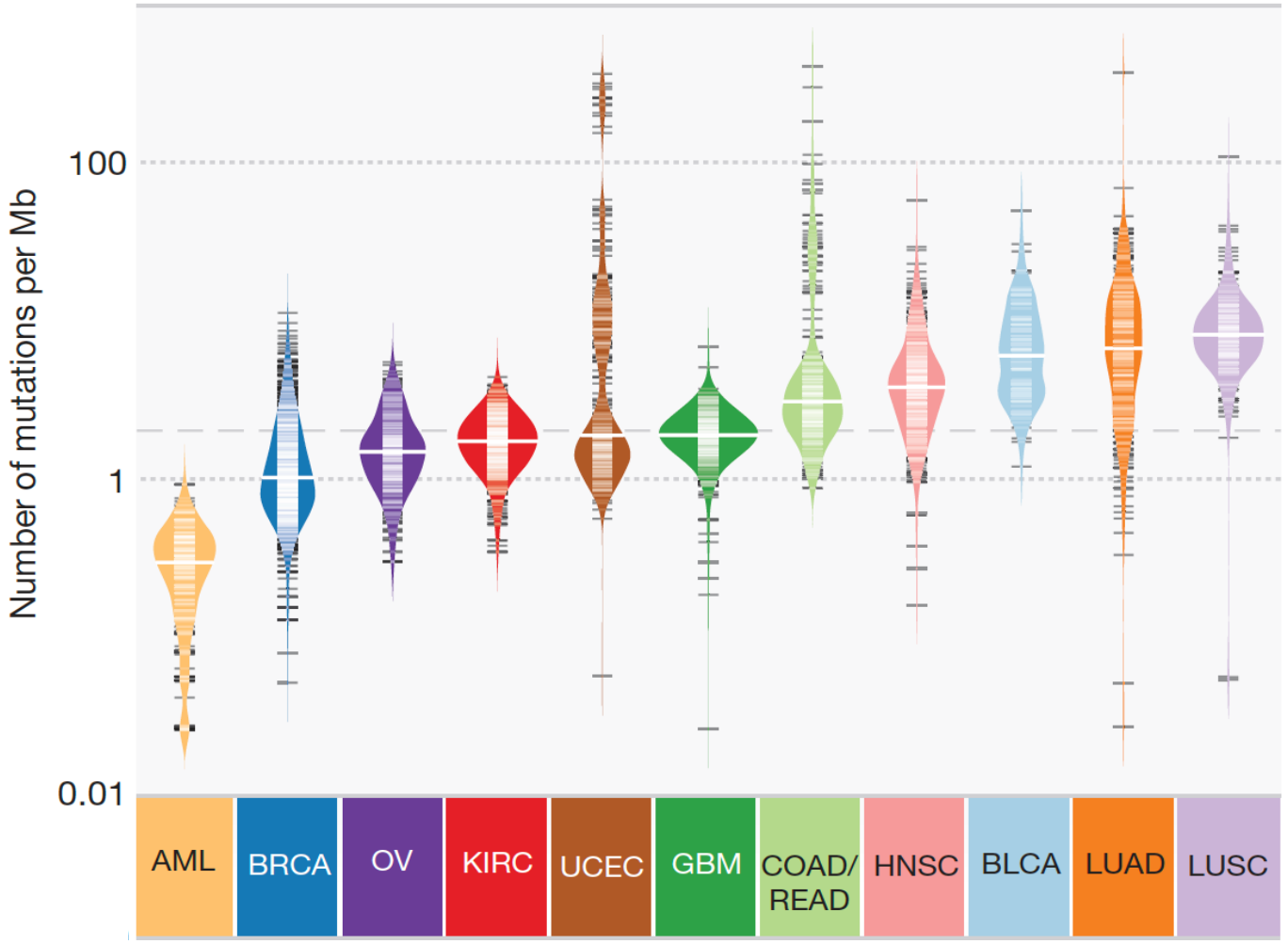
The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium

- ~2,500 cancer genomes
  - 43,778,859 somatic SNVs
  - 410,123 somatic MNVs
  - 2,418,247 somatic indels
  - 288,416 somatic SVs
  - 19,166 somatic retrotransposition
  - 8,185 mt DNA mutations
- ~20K alterations per cancer



ICGC=International Cancer Genome Consortium; TCGA=The Cancer Genome Atlas
SNV=Single Nucleotide Variant; MNV=Multiple Nucleotide Variant; SV=Structural Variant; mt=mitochondria; SCNA=Somatic Copy Number Alterations; muts=mutations

Cancer Genome Analysis - TCGA



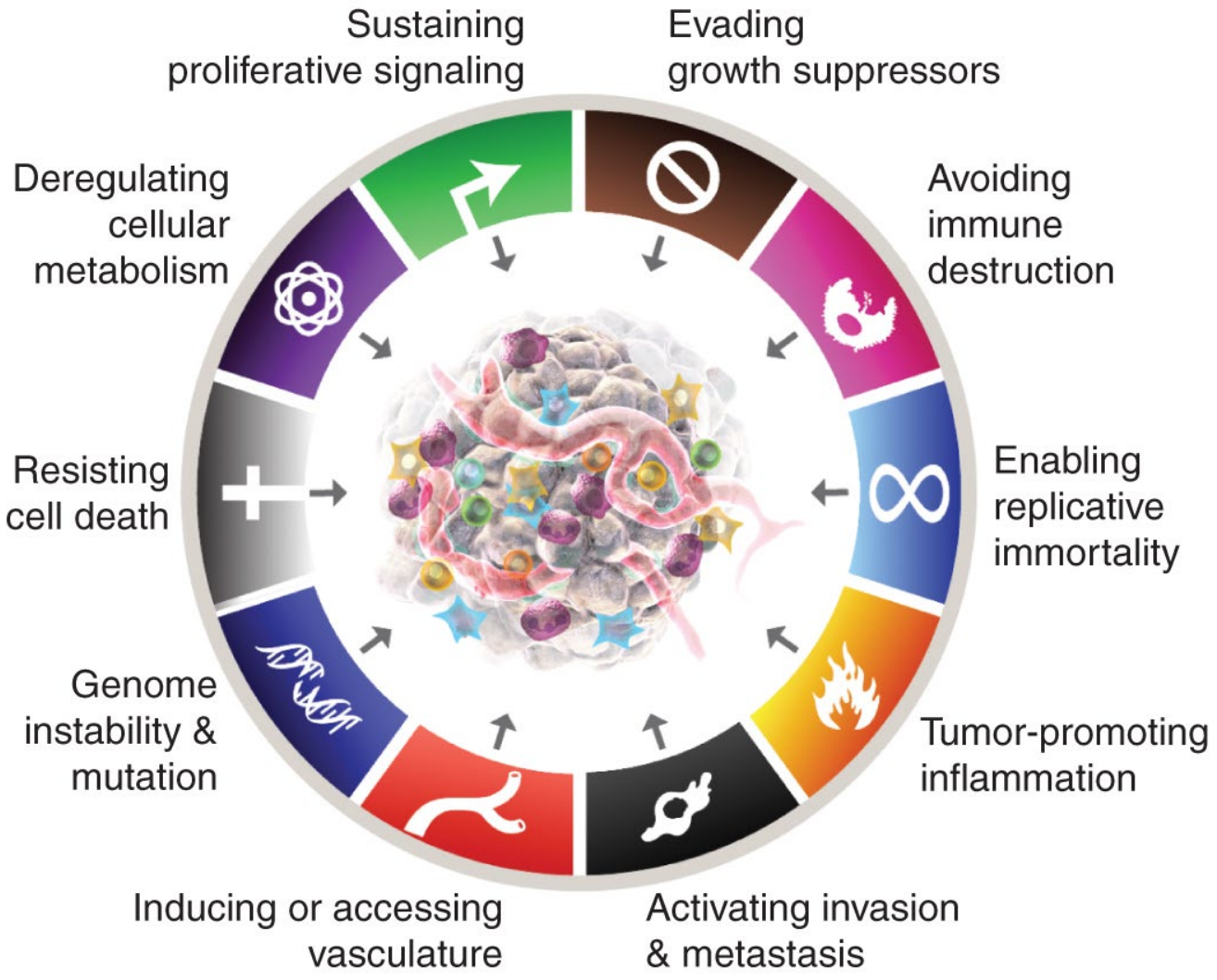
C Kandoth *et al. Nature* **502**, 333-339 (2013) doi:10.1038/nature12634

AML=Acute Myeloid Leukemia; BRCA=Breast Carcinoma; OV=Ovarian; KIRC=Kidney Renal Clear Cell Carcinoma; UCEC=Uterine Corpus Endometrial Carcinoma; GBM=Glioblastoma; COAD/READ=Colon/Rectal Adenocarcinoma; HNSC=Head and Neck Squamous Cell Carcinoma; BLCA=Bladder Carcinoma; LUAD=Lung Adenocarcinoma; LUSC=Lung Squamous Cell Carcinoma

Summary I

- Cancers have on average ~5 driver genetic alterations
- There are >300 cancer driver genes
  - Oncogenes
  - Tumor suppressors
- Enormous background of passenger alterations (~20K)
- Passenger mutations increase with age and mutagens

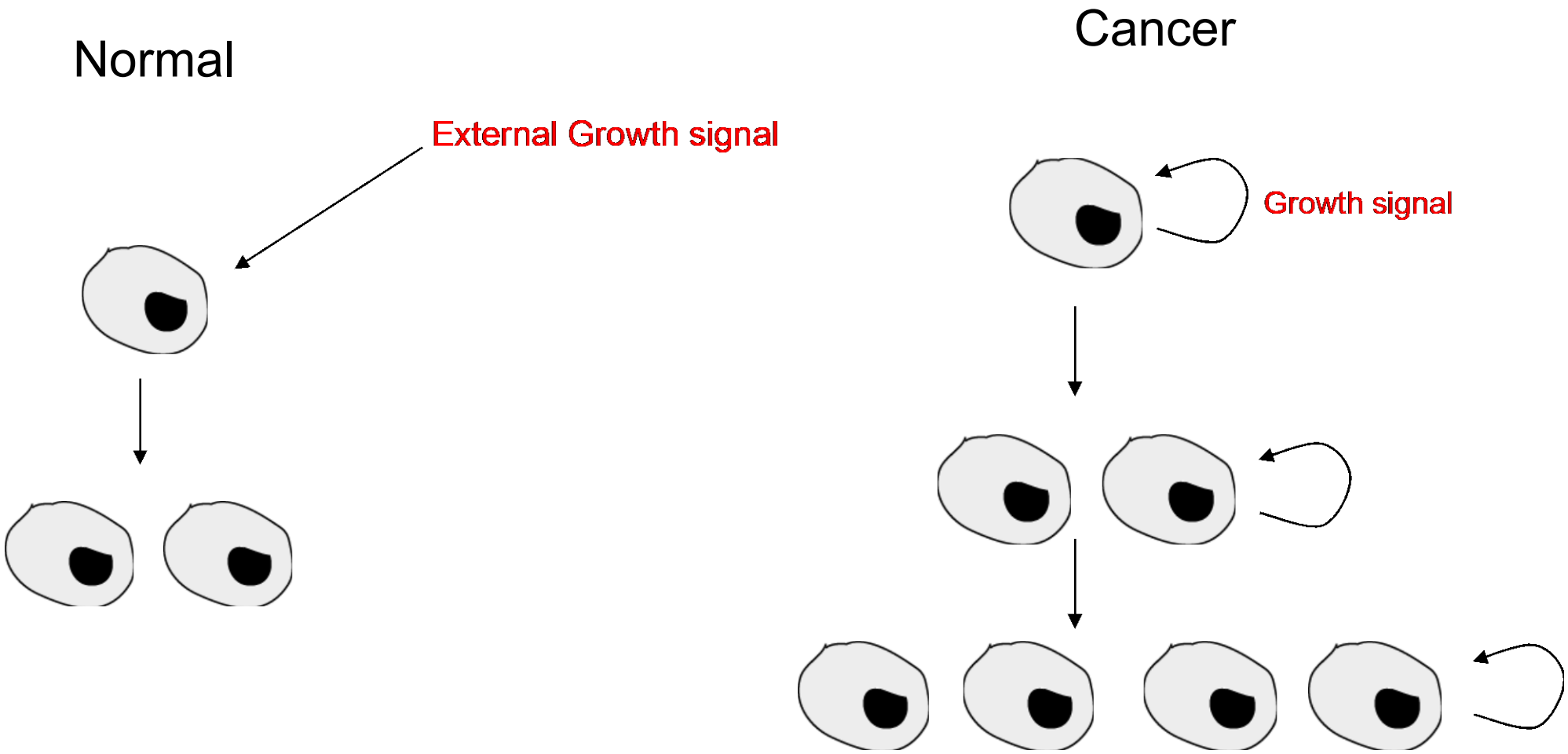
The Hallmarks of Cancer



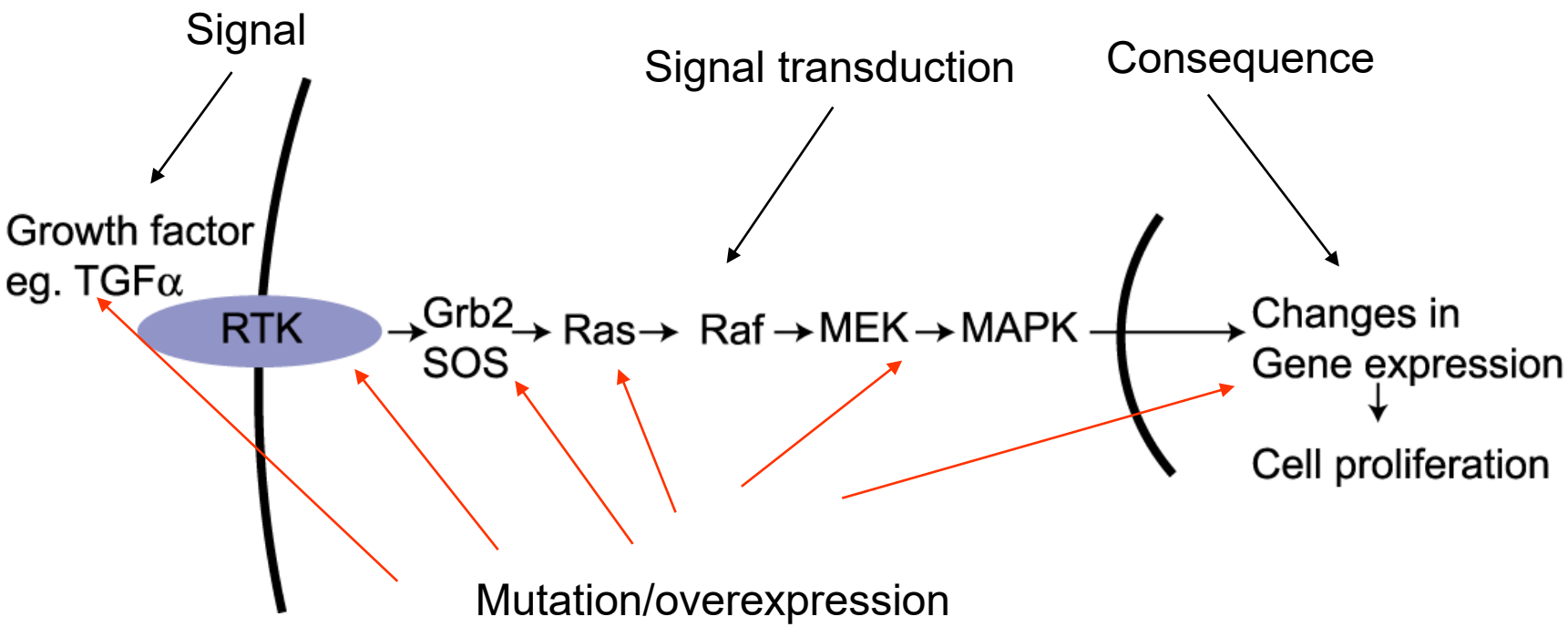
"The vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth"

Hanahan & Weinberg, Cell 2000
Hanahan & Weinberg, Cell 2011
Hanahan, Cancer Discovery 2022

1) Sustaining proliferative signaling



1) Sustaining proliferative signaling

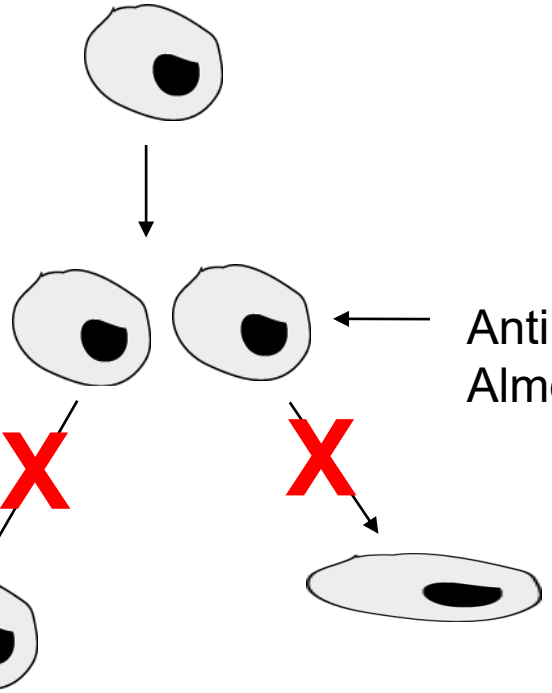


RTK: Receptor Tyrosine Kinase. TGF: Transforming Growth Factor. Grb2: Growth factor receptor bound. SOS: Son Of Sevenless. Reticular Activating System. Raf: Rapidly Accelerated Fibrosarcoma. MEK: Mitogen activated ERK kinase. MAPK: Mitogen Activated Protein Kinase

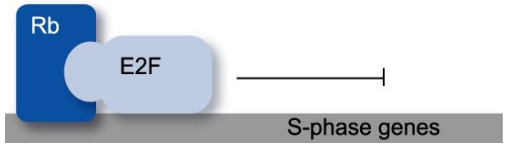
2) Evading growth suppressors

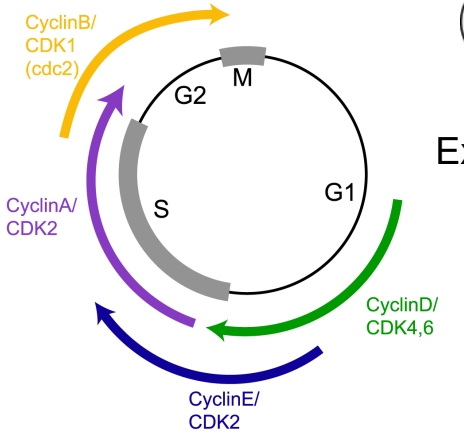
Normal cells

Cancer cells



Antiproliferative signal
Almost always through Rb



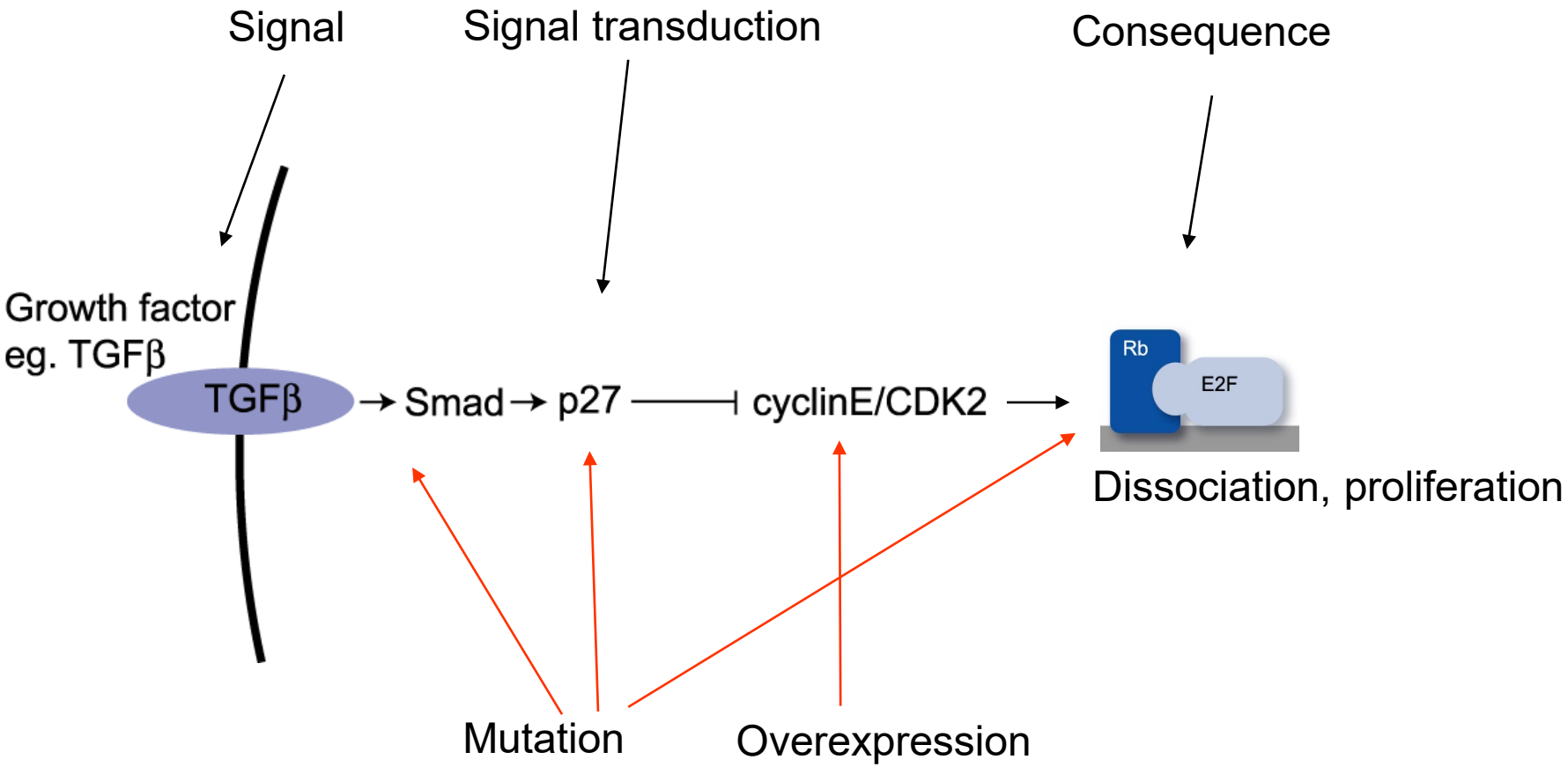


Exit the cell cycle - Go

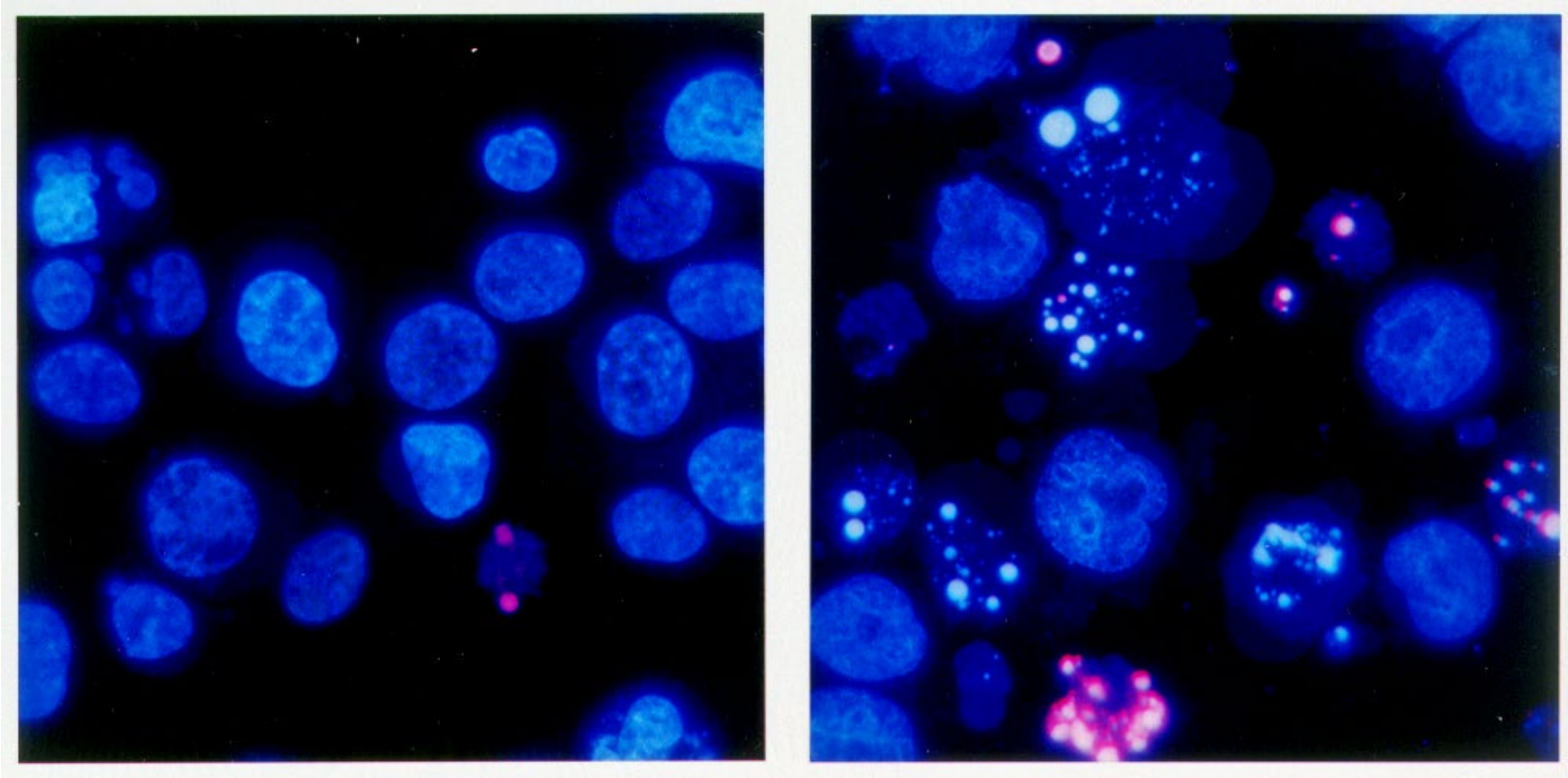
Differentiation,
senescence

Rb: Retinoblastoma. CDK: Cyclin dependent kinase.

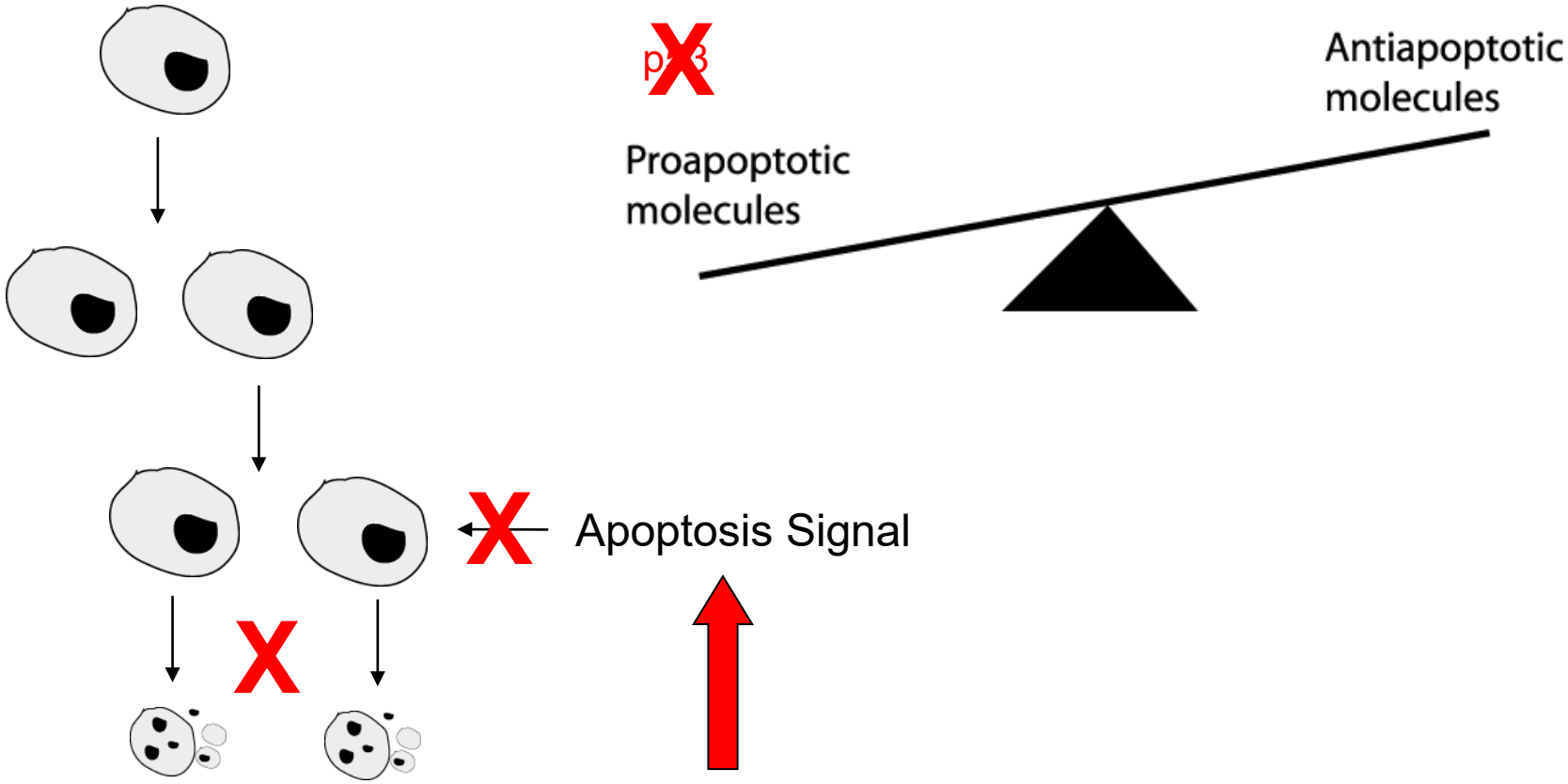
2) Evading growth suppressors



3) Resisting death

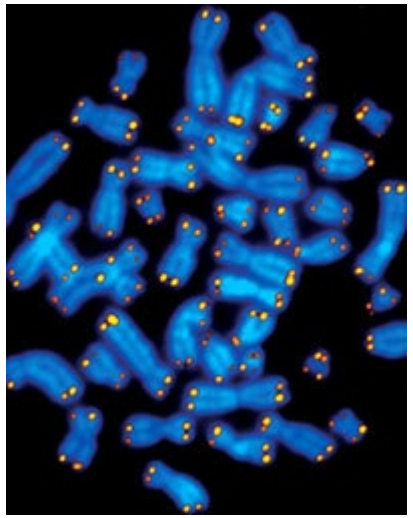


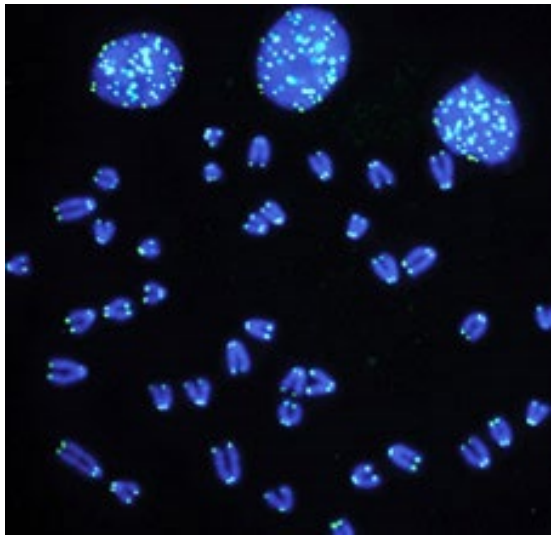
3) Resisting Apoptosis

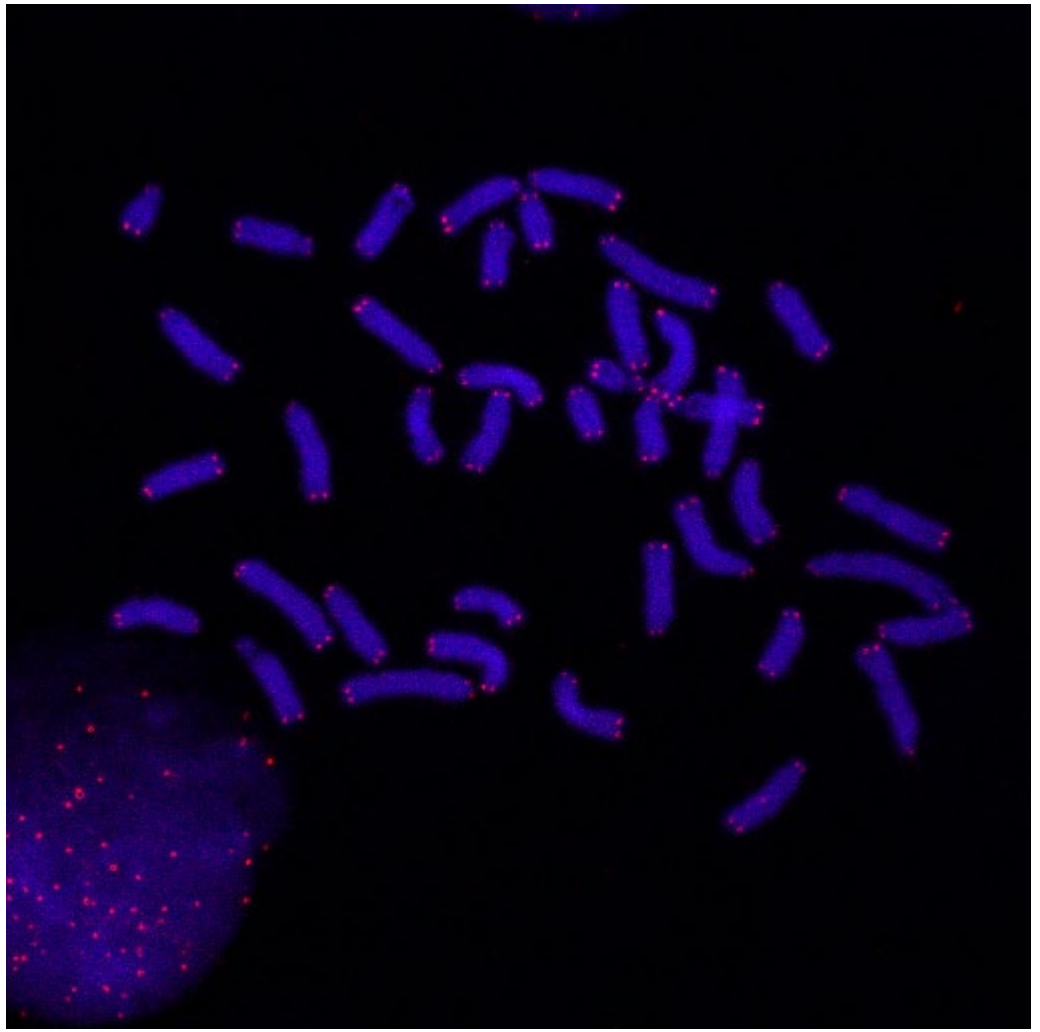


Tumor suppressor

4) Enabling Replicative Immortality







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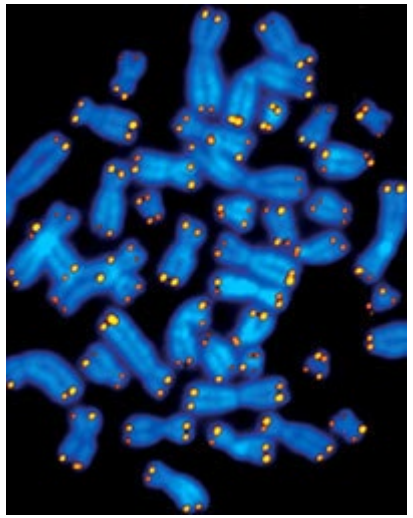
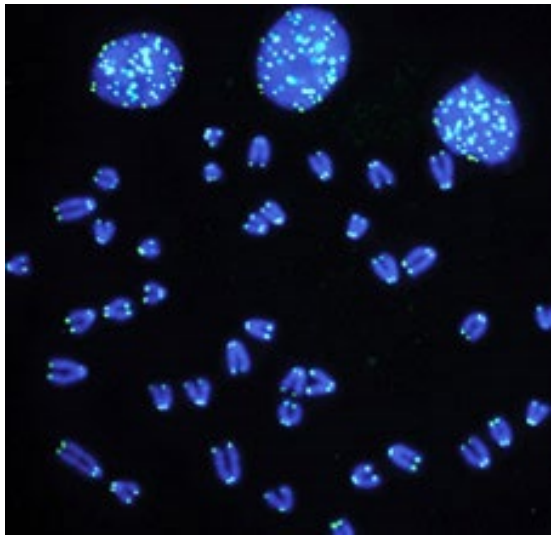
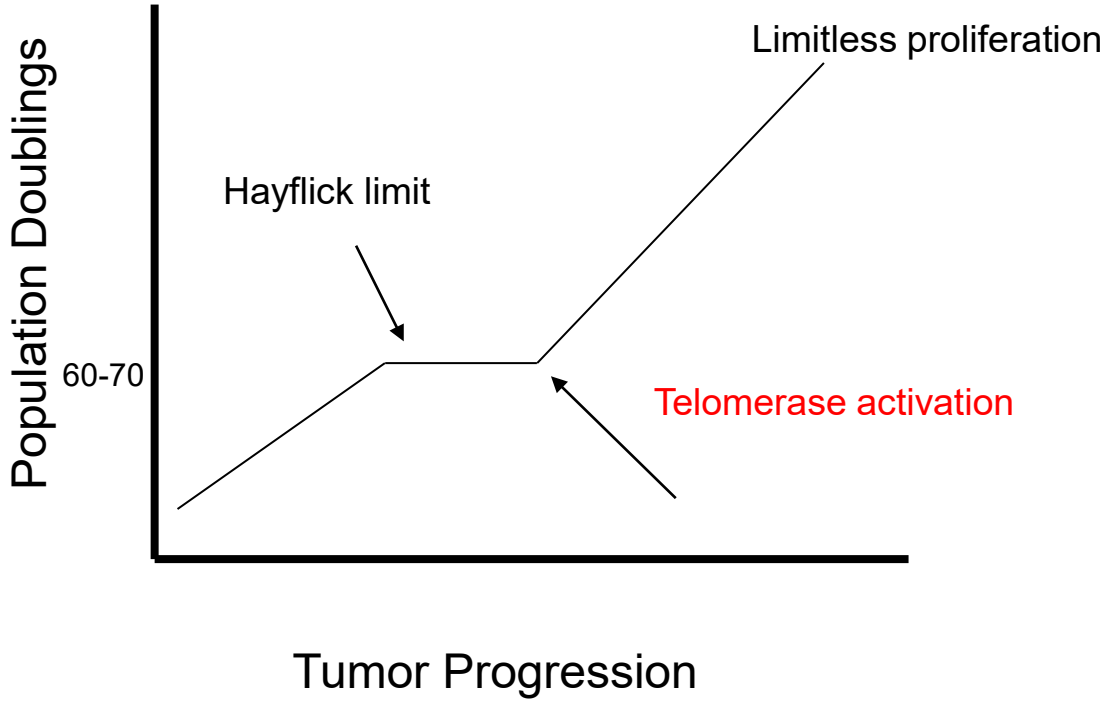
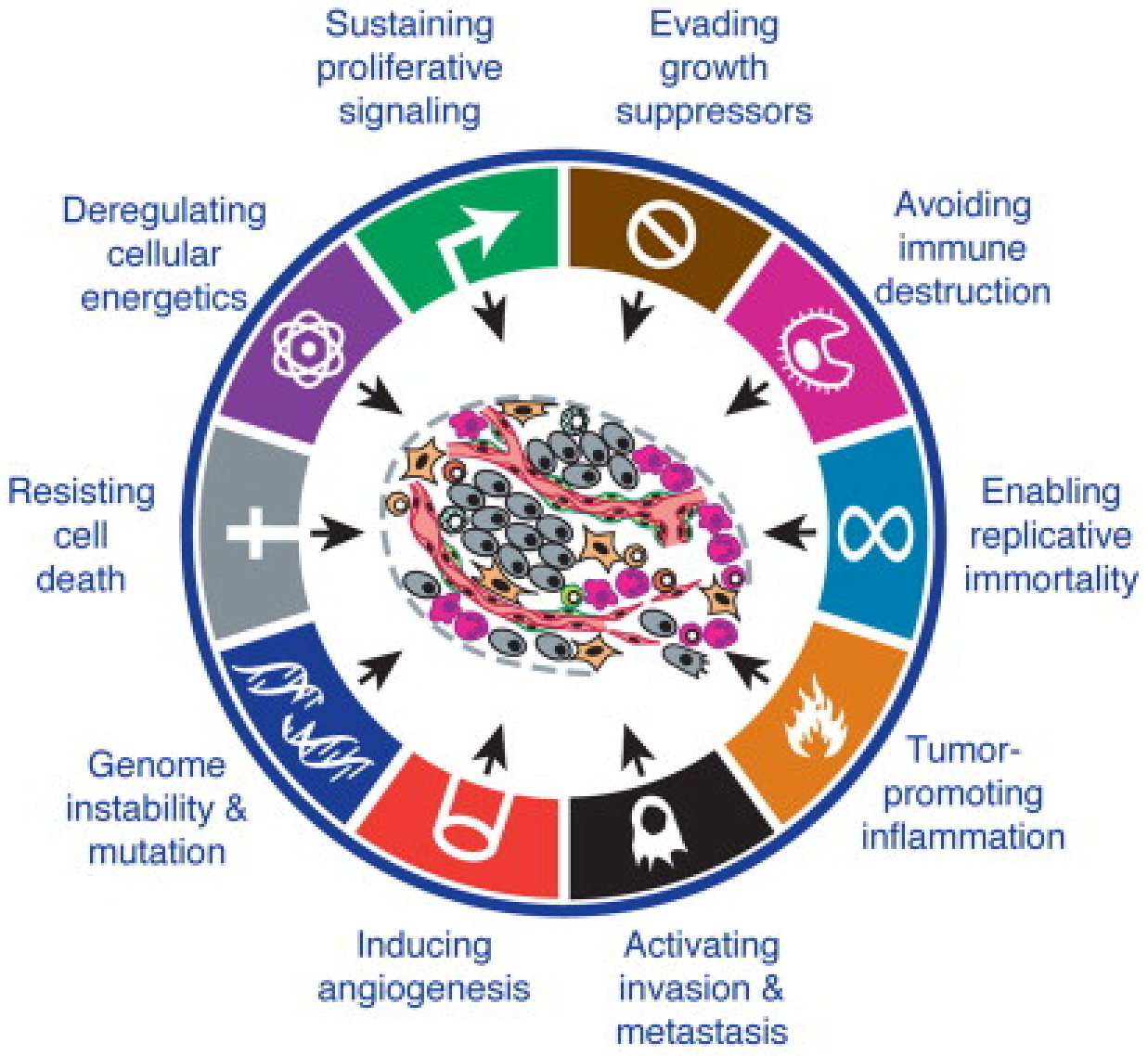




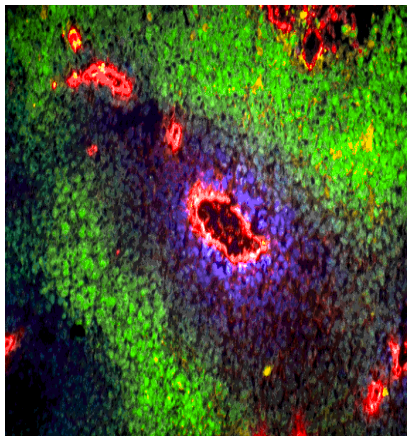


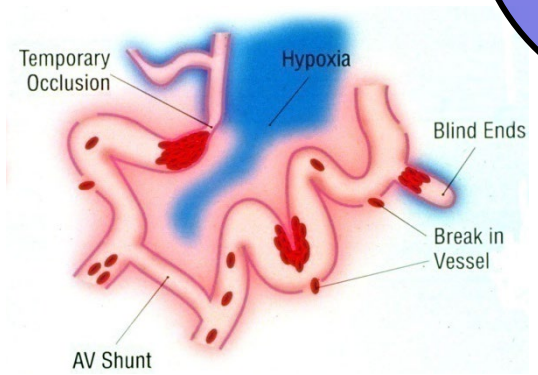
The Hallmarks of Cancer

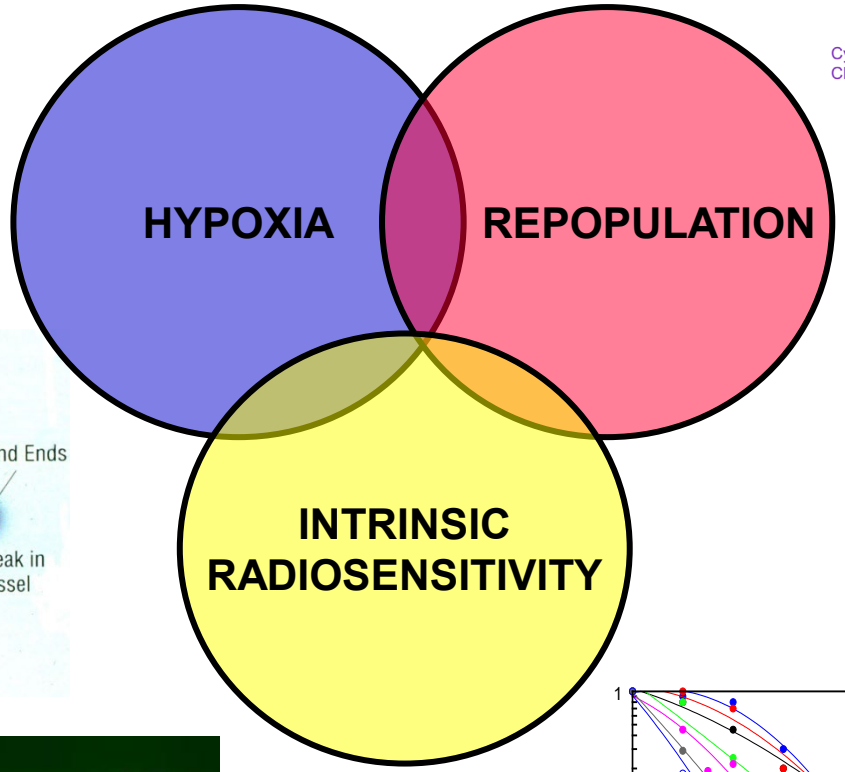


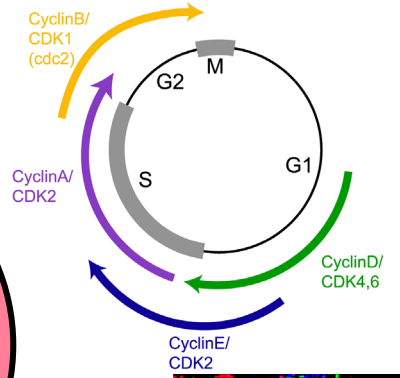
Hanahan & Weinberg, Cell 2011

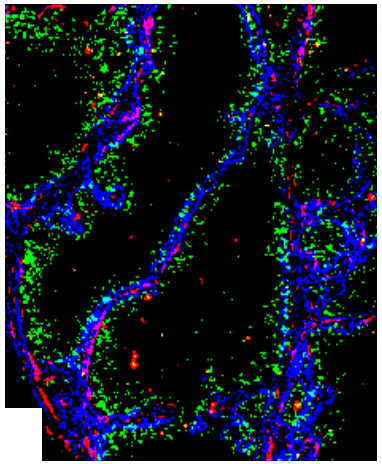
Biological contributors to outcome

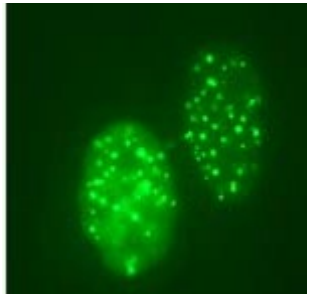


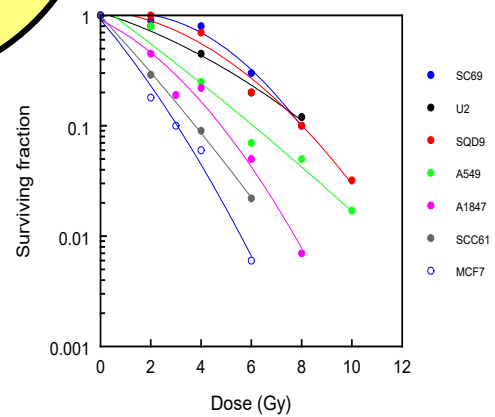


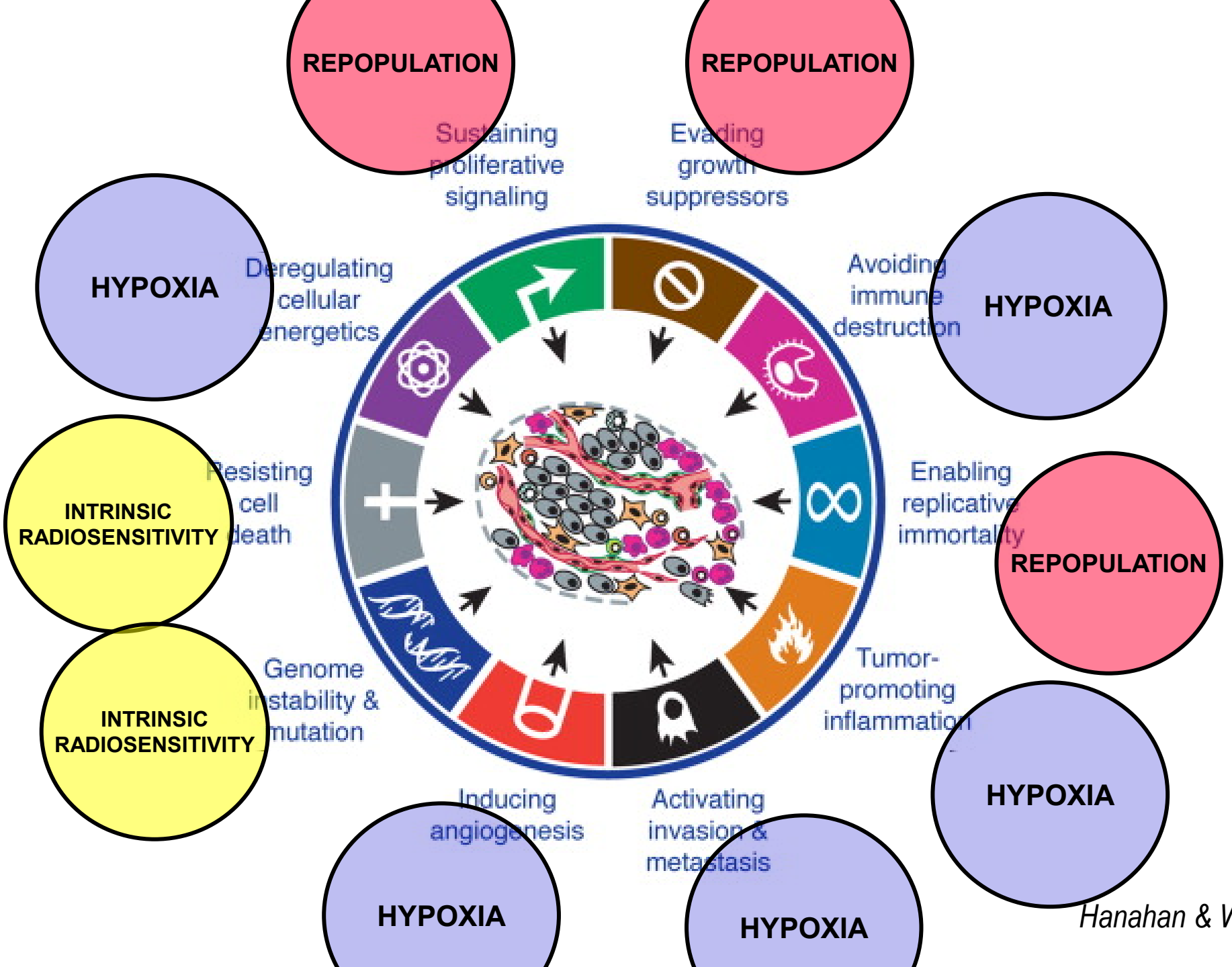












Hanahan & Weinberg, Cell 2011

Conclusions

- Cancer is caused by a series (~5) changes in the genome
  - Additional ~20K passenger genetic alterations
- The changes can be classified into 10 essential hallmarks
- The hallmarks of cancer can be arrived at by many genetic routes
  - Tumors are very heterogeneous at the genetic level
- These hallmarks (and accompanying genetic alterations) affect treatment and radiation sensitivity in complex ways.
  - Understanding the molecular basis of cancer is important to understand radiation response

Thank you!

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