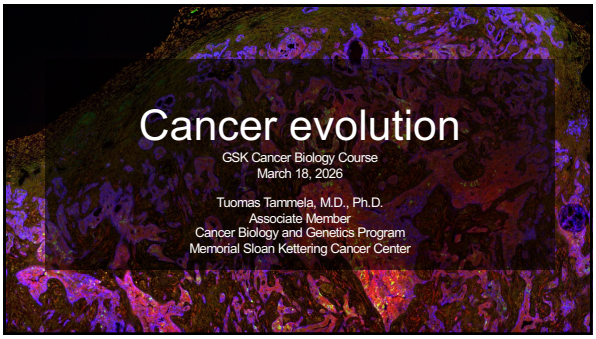
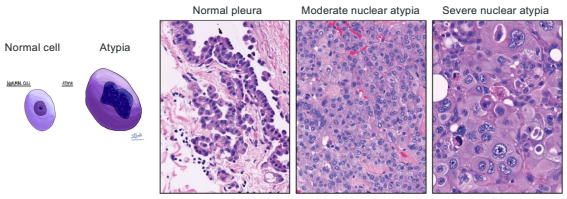


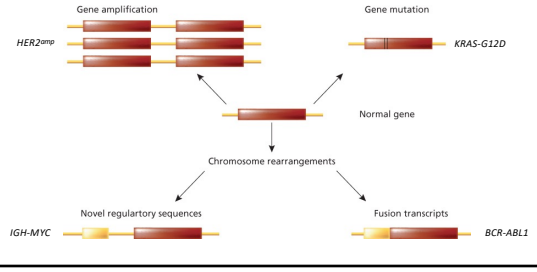
1

Cancer is a genetic disease



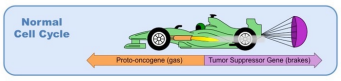
2

Oncogenes arise from cellular genes (proto-oncogenes) through amplification and/or mutations that alter the DNA sequence



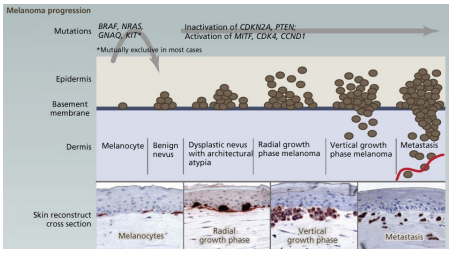
3

Proto-oncogenes and tumor suppressors



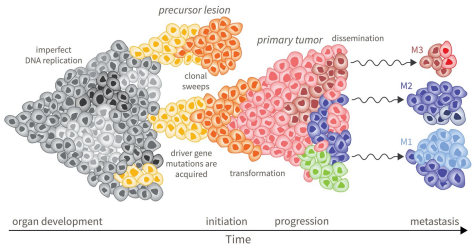
4

Stage of tumor evolution is a matter of life and death



5

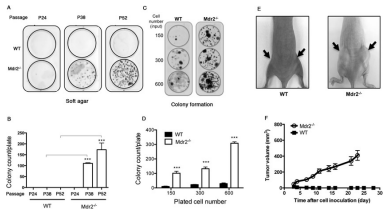
Cancer evolution



6

Properties of transformed cells

- Altered morphology
- Loss of contact inhibition
- Anchorage independence (evasion of anoikis)
- Immortalization
- Growth factor independence
- Increased glucose transport (glycolytic metabolism)
- High saturation density
- Tumorigenicity



Tebbi et al., Carcinogenesis, 2015

7

Nomenclature

- Neoplasia ("new growth", umbrella term for aberrant growths)
- Benign:
  - Hyperplasia (overgrowth of normal tissue, e.g. prostate hyperplasia)
  - Metaplasia (change in histological appearance, e.g. Barrett's esophagus)
  - Dysplasia (abnormal cells within tissue)
  - –oma (pre-malignant tumor, e.g. adenoma, lipoma)
- Malignant
  - Carcinoma (epithelial origin, e.g. adenocarcinoma)
  - Sarcoma (mesenchymal origin, e. g. liposarcoma)
  - Lymphoma (lymphocytic origin, e.g. T cell lymphoma)
- Blood disorders:
  - -emia (predominant feature of the blood, e.g. leukemia or anemia)
  - -penia (lack of something in the blood, e.g. neutropenia or thrombocytopenia)

8

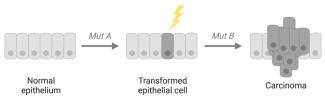
The Hallmarks of Cancer

Hallmarks of Cancer: New Dimensions
Hanahan, Cancer Discovery, 2022

9

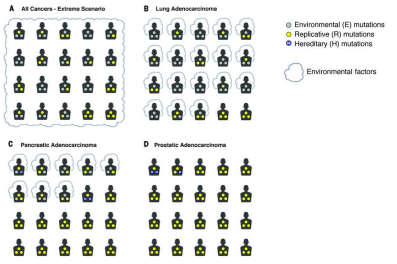
How do mutations in cancer arise?

- Stochastic errors in DNA replication
  - correlation with "replicative aging" and organismal age
- Exposure to carcinogens
  - UV light
  - Cigarette smoke
  - Radon
- Viruses and other pathogens
  - Hepatitis viruses
  - Human papilloma virus
  - *H. pylori*
- Familial cancer predisposition
  - Breast and ovarian cancer (*BRCA1*, *BRCA2*)
  - Peutz-Jegher's syndrome (*STK11*)
  - Li-Fraumeni syndrome (*TP53*)
  - Lynch syndrome (*MLHL*, *MSH2*, *MSH6*, *PMS2*)



10

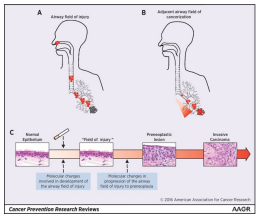
Different cancers have different etiologies



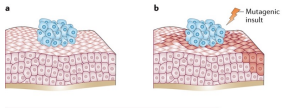
Tomasetti et al., Science, 2017

11

Field cancerization generates a large pool of mutant cells



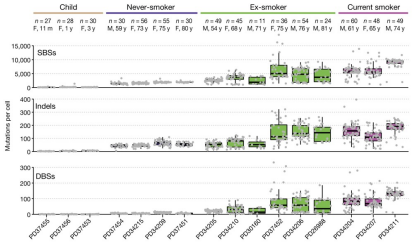
Kadara, et al., Cancer Prev Res, 2016



Kurtius et al., Nature Reviews Cancer, 2017

12

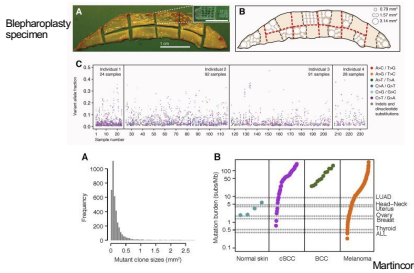
Field cancerization in the lung airway



Yoshida et al., Nature, 2020

13

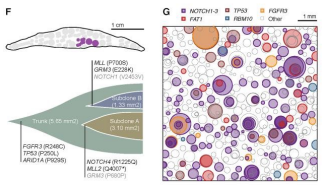
Cancer-causing mutations are very common, but cancer is rare – why?



Martincorena et al., Science, 2015

14

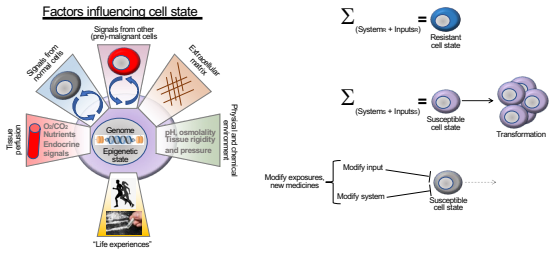
Cancer-causing mutations in tissues are common, but cancer is rare – why?



Martincorena et al., Science, 2015

15

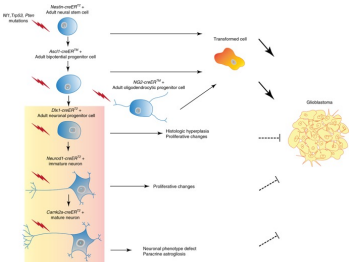
The cellular substrate of oncogenic mutations defines transformation potential



Tammela & Sage, *Annual Reviews Cancer*, 2019

16

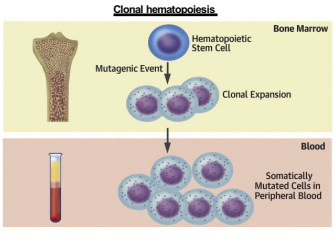
Stem and progenitor cells – but not differentiated cells – are susceptible to transformation



Alcantara Llaguno et al., Nature Neurosciene, 2019

17

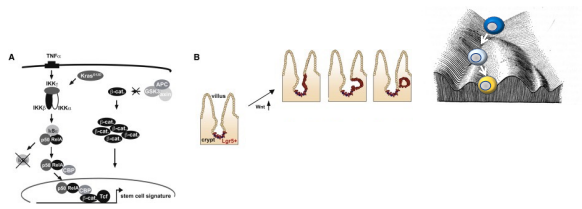
Mutations in stem cells lead to an expanded pool of cells with potential for transformation



Libby et al., Am J Cardiol, 2019

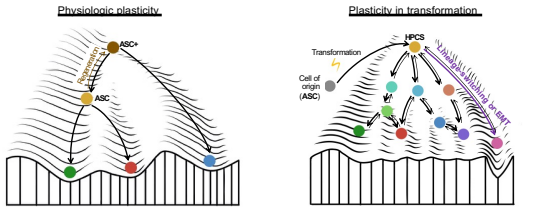
18

Changes in cell state may enable transformation



19

Transformation requires cooption of regenerative plasticity



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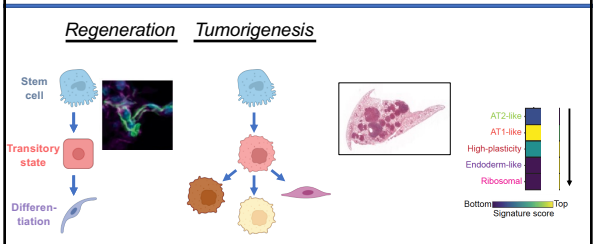
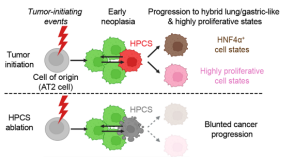
Transformation requires cooption of regenerative plasticity



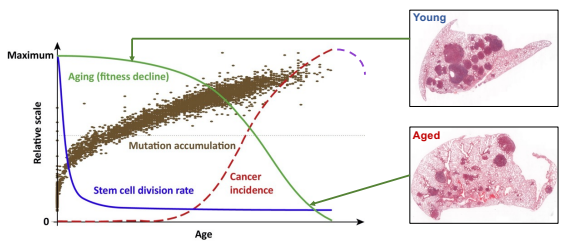
21

High-plasticity cell state cytoablation blunts cancer progression *in vivo*



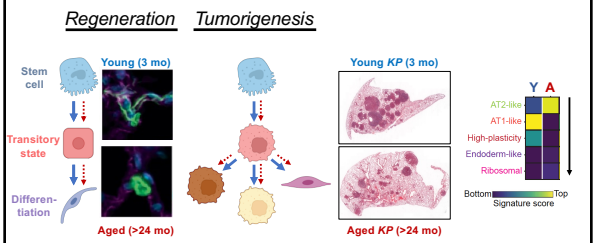
22

Non-linear correlation of number of mutations and cancer incidence



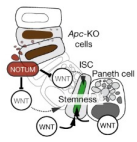
23

Aging profoundly alters cellular plasticity: implications for tumorigenesis

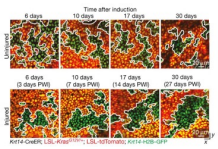


24

Early neoplasias must compete with normal cells for growth-supporting niche



Flanagan, Pentinmikko et al., *Nature*, 2021



Gallini et al., *Nature*, 2023

25

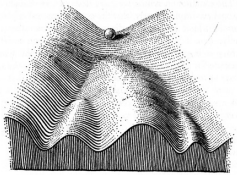
Cancer-causing mutations in tissues are common, but cancer is rare – possible explanations

- Sequence of mutations matters
  - Evolutionary dead ends
- Non-cell autonomous factors
  - Immune surveillance
  - Suppressive niche signals or lack of promoting niche
  - Systemic factors (metabolic, endocrine)
  - Failure to outcompete normal cells
  - Impaired angiogenesis
- Cellular context matters
  - Lack of oncogene expression
  - Differentiation state – tumors predominately originate from stem or progenitor cells
  - Stem/progenitor cells need to coopt regenerative programs

26

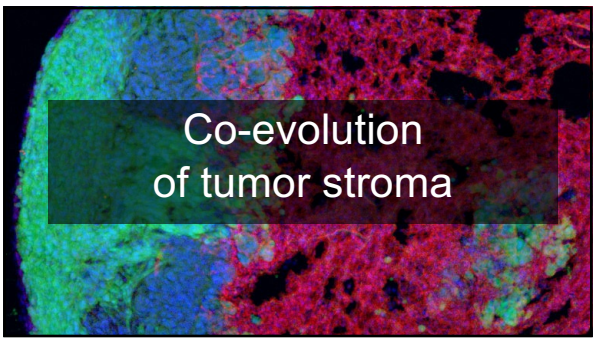
Why do we have stem cells?

- Maintenance of reserve proliferative potential and genome fidelity in a subset of cells lowers risk of transformation
- Conservation of "epigenetic potential energy" ensures ability to rapidly differentiate into one of multiple possible differentiation states (plasticity)
- Metabolic specialization
- Spatial organization



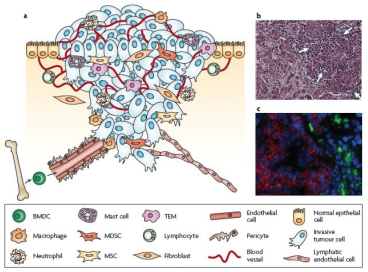
Waddington, The Epigenetics of Birds, 1953

27



28

Tumor evolution is accompanied by co-option of host cells (stroma)

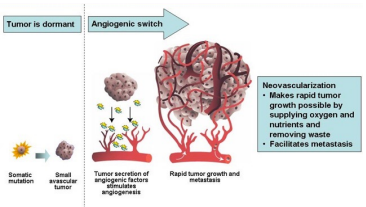


Joyce and Pollard, Nat Rev Cancer, 2009

29

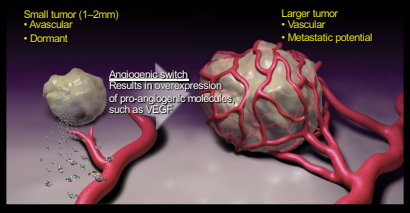
"The angiogenic switch" is required for tumor progression

Folkman et al., NEJM, 1971



30

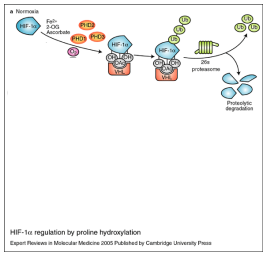
Vascular endothelial growth factor (VEGF) promotes the angiogenic switch



31

Cellular oxygen sensing

- HIF-1α = hypoxia-inducible factor
- HRE = hypoxia-responsive element
- PHD = proline-hydroxylase domain protein
- VHL = Von Hippel Lindau tumor suppressor



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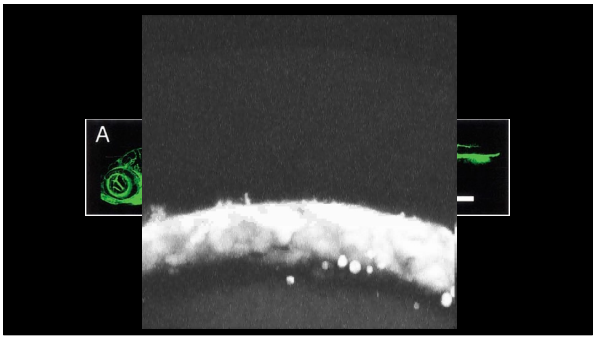

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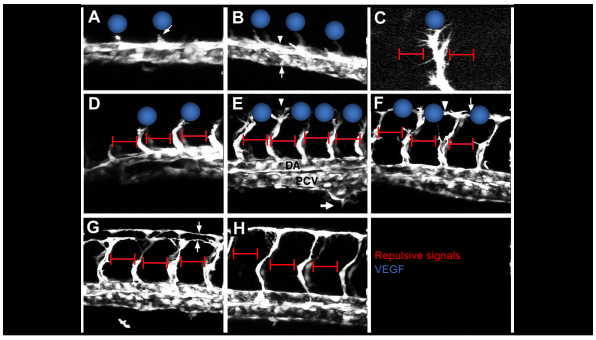

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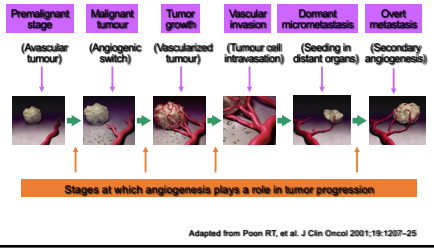
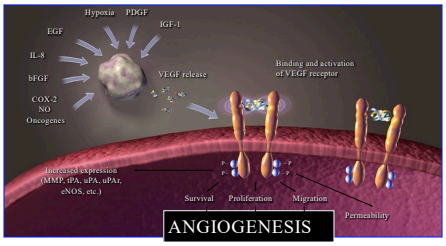
Angiogenesis is involved in tumor formation, growth and metastasis



35

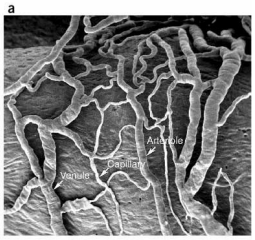
Multiple oncogenic processes promote VEGF expression in cancer cells



IGF-1 = insulin-like growth factor 1; EGF = epidermal growth factor; IL-8 = interleukin 8; bFGF = basic fibroblast growth factor

36

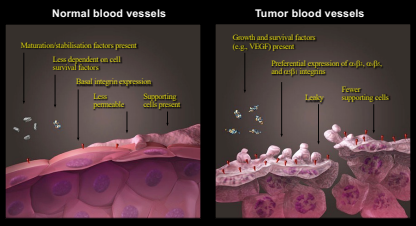
Tumor blood vessels are abnormal



McDonald and Choyke, Nature Medicine, 2003

37

Tumor blood vessels are abnormal



Jain RK. Semin Oncol 2002;29(Suppl. 16):3–9; Carmeliet P. Nat Med 2003;9:653–60; Lee TH, et al. J Biol Chem 2003;278:5277–84

38

Conclusions

- Cancer is a result of genetic mutations
- Multiple barriers exist to cellular transformation
  - Tumor suppressors
  - Cell state context
  - Microenvironmental context
- Cancers co-opt regenerative and embryonic growth programs, which are enabled by epigenetic remodeling and paracrine signaling cues
- Cancer evolution is an ordered process similar to organogenesis
- Tumor progression requires cooperative relationships with the host stroma
- Mouse models provide a flexible platform for investigating cancer evolution *in vivo*

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