

Stem cells, Organogenesis and Cancer

An OLD & NEW Dimension of Tumorigenesis

Stem Cells and Organogenesis GMB-305

Arafath (Rafa) Najumudeen

FIMM-EMBL, Group Leader

Research Fellow, Institute of Biotechnology

HiLIFE

University of Helsinki

Learning goals and Intended Outcomes

Basics principles of organogenesis and cancer formation

- What is homeostasis?
- How do stem cells lead to cancer formation?
- What is the link between cancer cells and stem cell and organogenesis?

Cancer and stem cell biology

- Cancer and its hallmarks
- Stem Cells and role in cancer formation and progression
- Stem cell signaling pathways that contribute to cancer development
- How stem cell targeting applications are explored in cancer therapy?

Reflect on GMB-305

What have you learned so far about stem cells and organogenesis?

Pathways that you have come across throughout the whole course

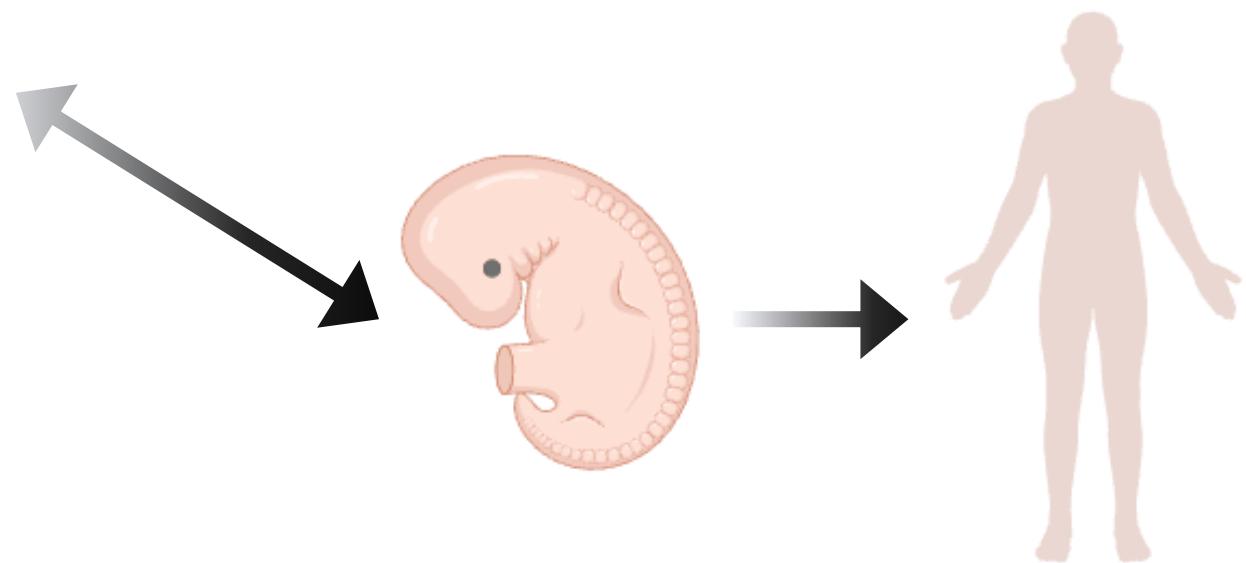
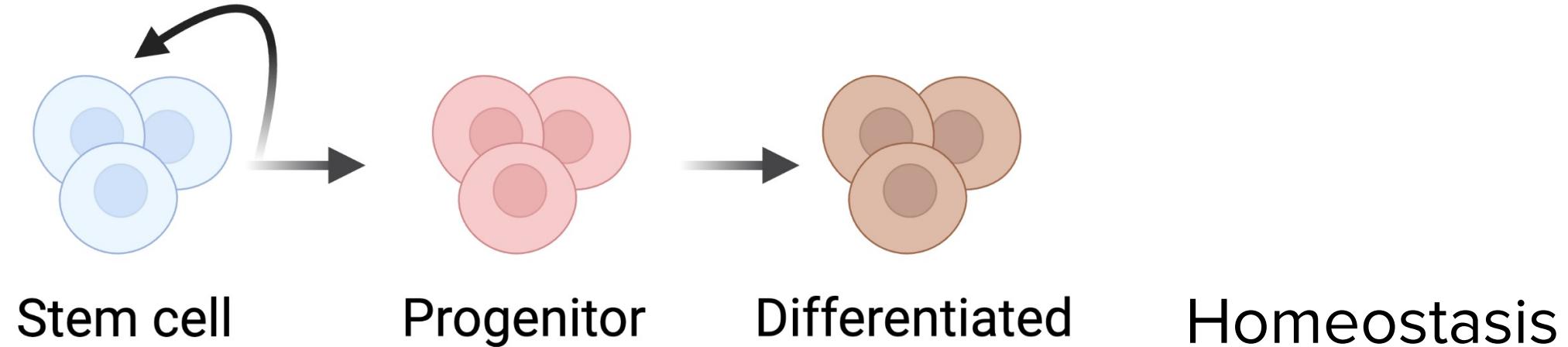
Any specific tissue or organs that stand out?

Remember: There are no wrong answers

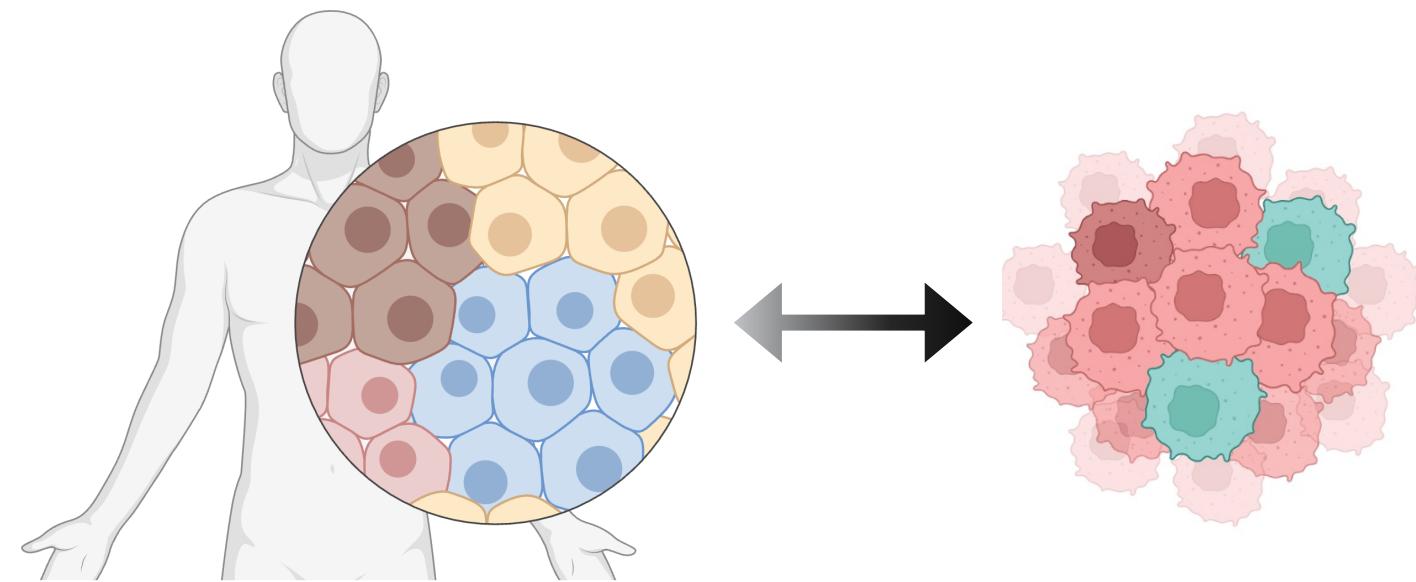
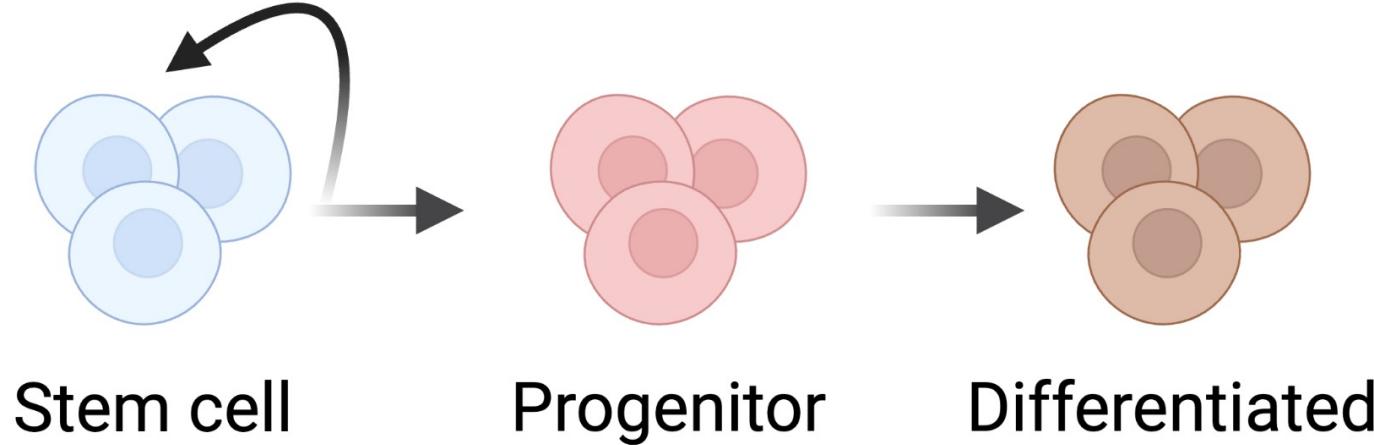
Peyton Rous – Nobel Lecture, December 13, 1966
The Challenge to Man of the Neoplastic Cell

Tumors destroy man in a unique and appalling way, as flesh of his own flesh which has somehow been rendered proliferative, rampant, predatory and ungovernable.

Stem cells maintain organ function



Stem cells maintain organ function



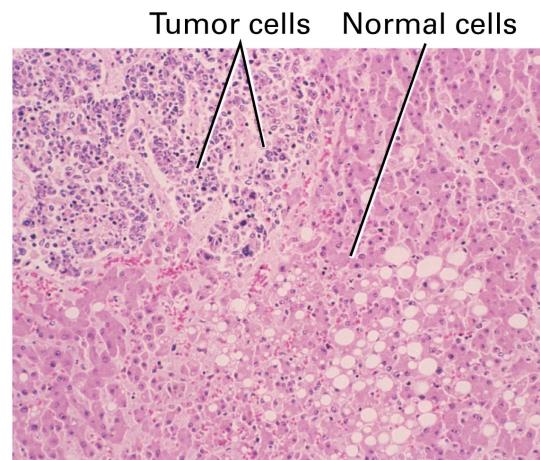
Cancer cells hijack the organogenesis pathways

Cancer occurs when **cellular fitness** becomes dominant over **organismal fitness**.

To get fitness, cancer cells hijack existing organogenesis pathways

This lets them grow beyond homeostatic constraints.

This hijacking leads to cancer formation, metastasis, and response to anti-cancer drugs.



Embryonal rest theory of cancer

Proposed in 1829 by Joseph Claude Anhelme Récamier, after a clinical observation on a patient with breast cancer

- similarities seen between samples of tumour and embryonic tissue

This theory states that adult tissues contain residues of embryonic cells which, under certain conditions, can reactivate and give rise to tumor masses

Cancer could originate from a residual of embryonic cells still present within the adult organism

‘Developmental processes gone awry’

What do you think?

Why do adult cells go back to having embryonic features in cancers?

- Form groups of around 3 people
- Discuss for a couple minutes
- Present to everyone

Remember: There are no wrong answers

Evolution and cancer development

Human cells accumulate mutations throughout their lifetime.

A subset of these, so-called driver mutations, are associated with neoplastic transformation.

Ongoing mutation and selection cause subclonal divergence within the tumour clone.

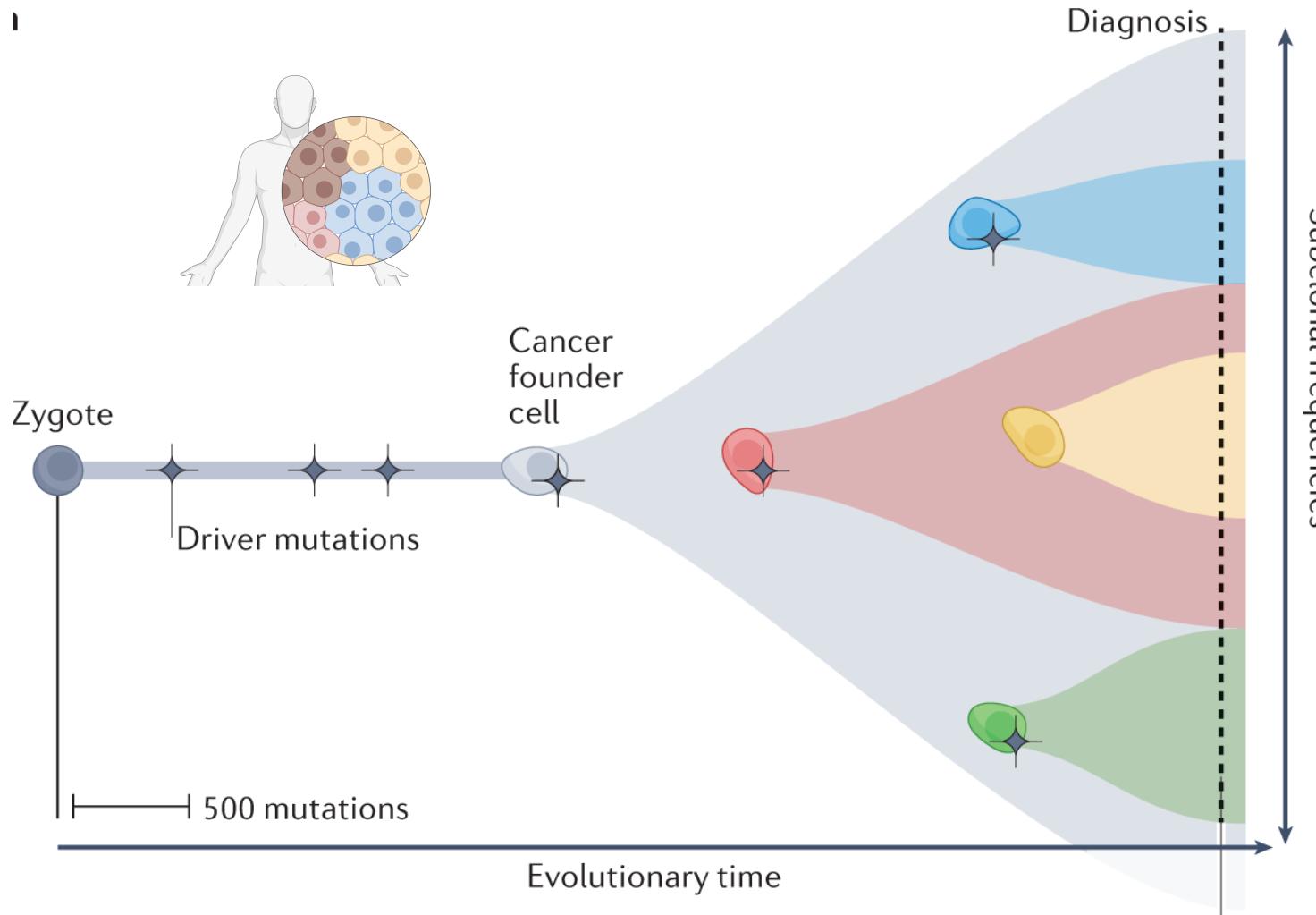


TABLE 24-1**Classes of Genes Implicated in the Onset of Cancer**

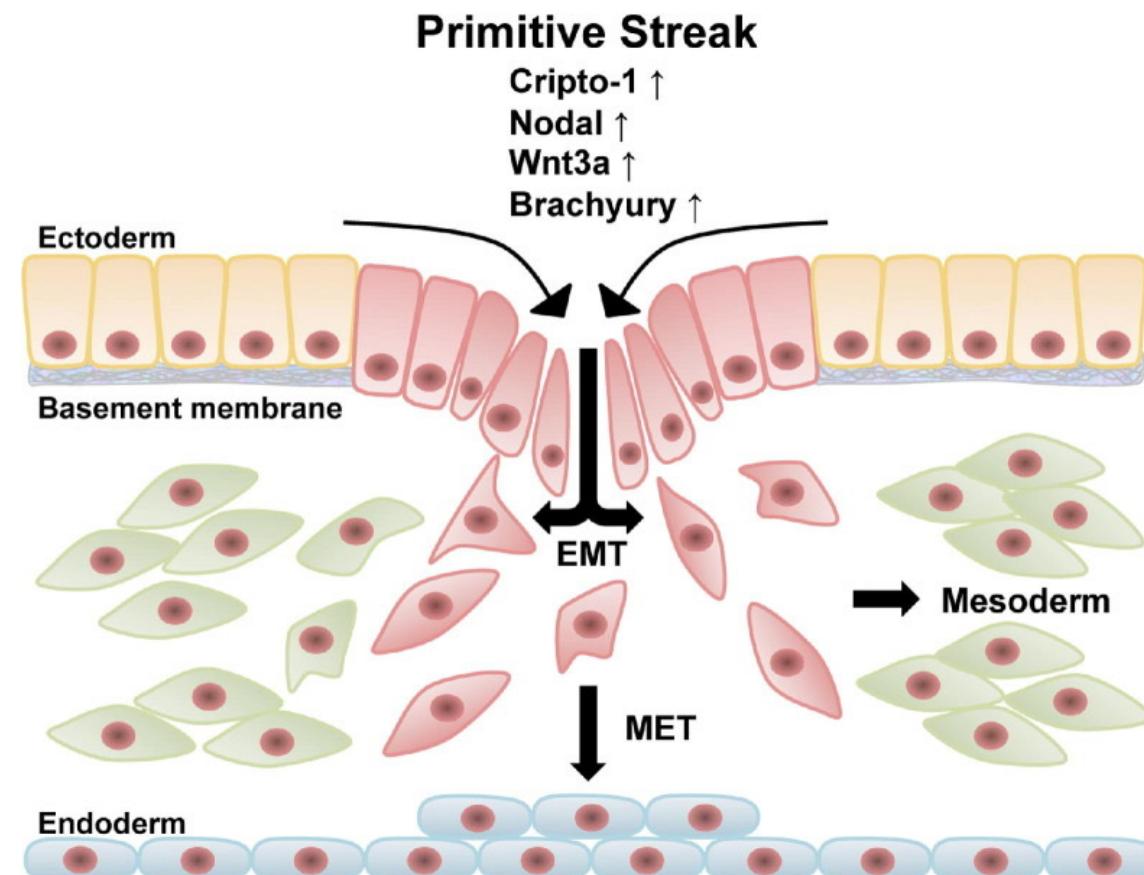
	Normal Function of Genes	Examples of Gene Products	Effect of Mutation	Genetic Properties of Mutant Gene	Origin of Mutations
Proto-oncogenes	Promote cell survival or proliferation	Anti-apoptotic proteins, components of signaling and signal transduction pathways that result in proliferation, transcription factors	Gain-of-function mutations allow unregulated cell proliferation and survival	Mutations are genetically dominant	Arise by point mutation, chromosomal translocation, amplification
Tumor-suppressor genes	Inhibit cell survival or proliferation	Apoptosis-promoting proteins, inhibitors of cell-cycle progression, checkpoint-control proteins that assess DNA/chromosomal damage, components of signal pathways that restrain cell proliferation	Loss-of-function mutations allow unregulated cell proliferation and survival	Mutations are genetically recessive	Arise by deletion, point mutation, methylation
Caretaker genes	Repair or prevent DNA damage	DNA-repair enzymes	Loss-of-function mutations allow mutations to accumulate	Mutations are genetically recessive	Arise by deletion, point mutation, methylation

Epithelial-mesenchymal transition (EMT)

Elizabeth Hay - conducted pioneering research

EMT - epithelial cells typically organized in sheets undergo a series of molecular changes that enable them to acquire characteristics of mesenchymal cells.

During gastrulation, for example, EMT allows epithelial cells in the primitive streak of the embryo to undergo a transition to a mesenchymal phenotype, enabling them to migrate and contribute to the formation of various tissues and organs.



Elizabeth Hay

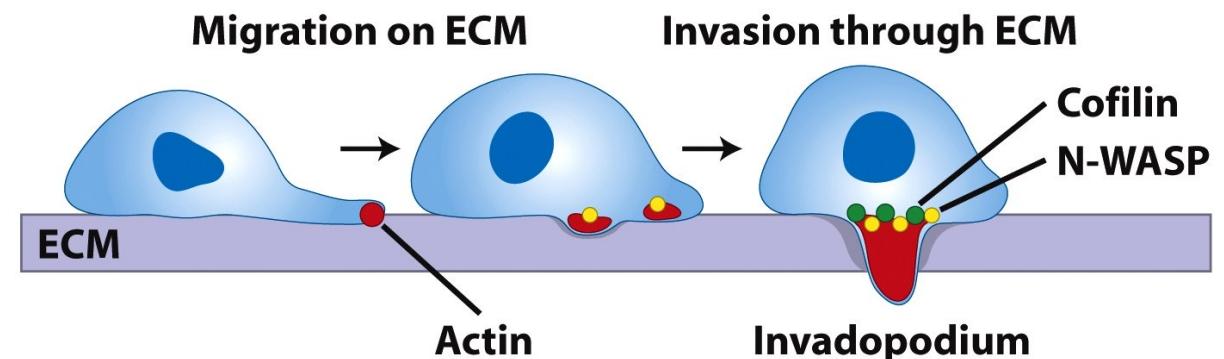
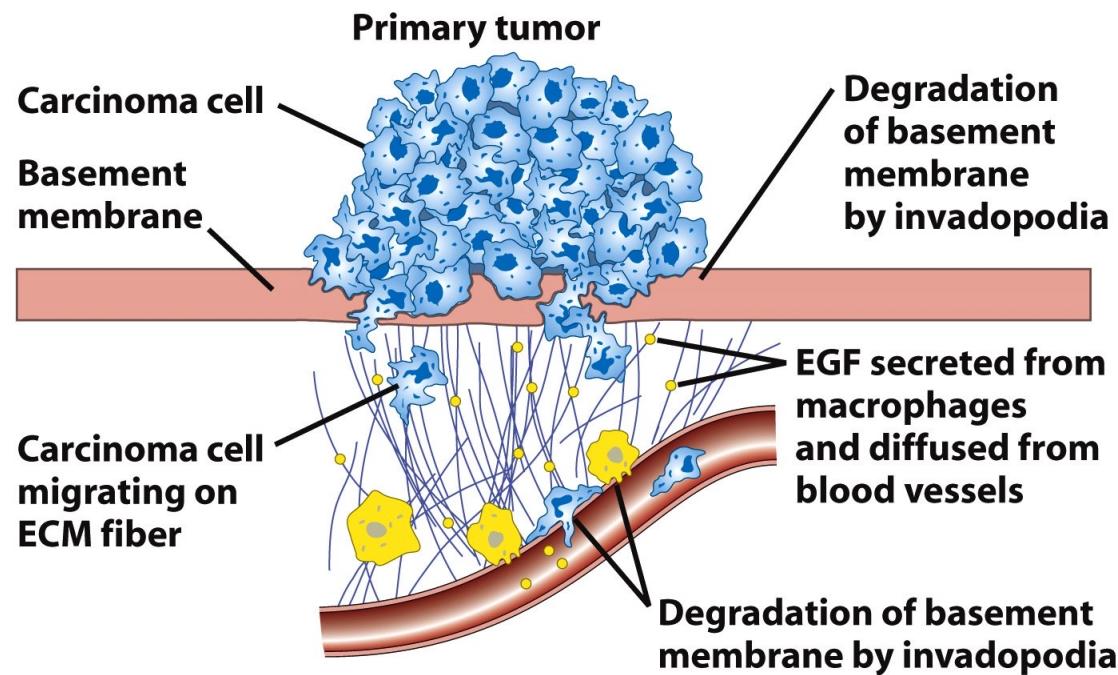
Metastasis

Most malignant tumor cells eventually acquire the ability to metastasize.

To do so they must degrade the basement membranes of connective tissue underlying epithelial cells and surrounding the endothelial cells of blood.

This can be accomplished by secretion of plasminogen activator, which activates the blood protease, plasmin.

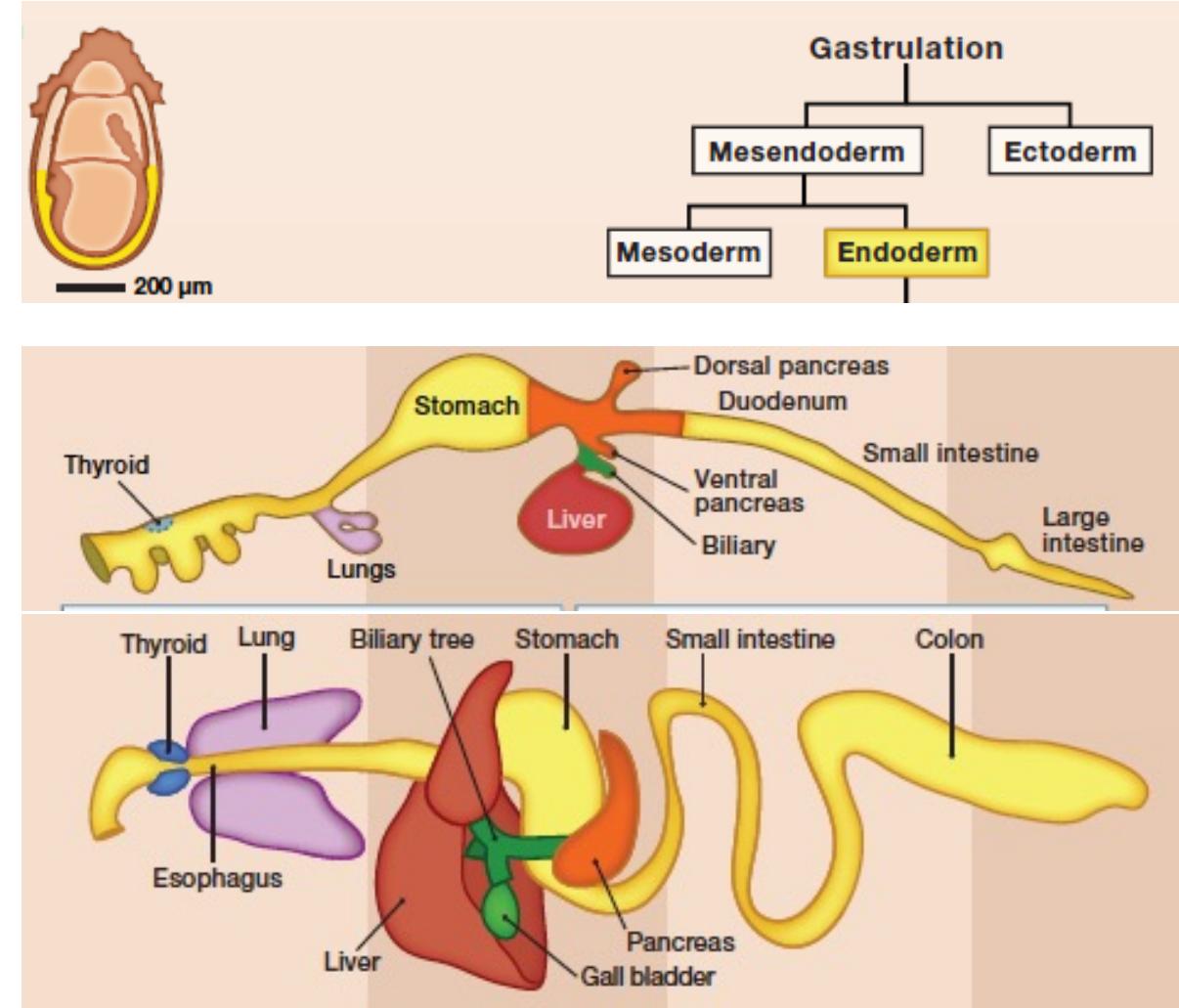
Malignant cells form structures called invadopodia which contain protein components needed for crossing basement membranes.



Cellular origin, nomenclature of tumors and link to embryology

Sometimes a distinction is made between solid tumors and those tumors of the hemopoietic and immune system in which there is an increase in circulating abnormal cells.

A neoplasm is termed a **carcinoma** if it arises from tissue derived from embryonic ectoderm or endoderm. Those tumors of epithelial cells may be distinguished from tumors of connective tissue which are described as **sarcomas**. Most human neoplasms are carcinomas.

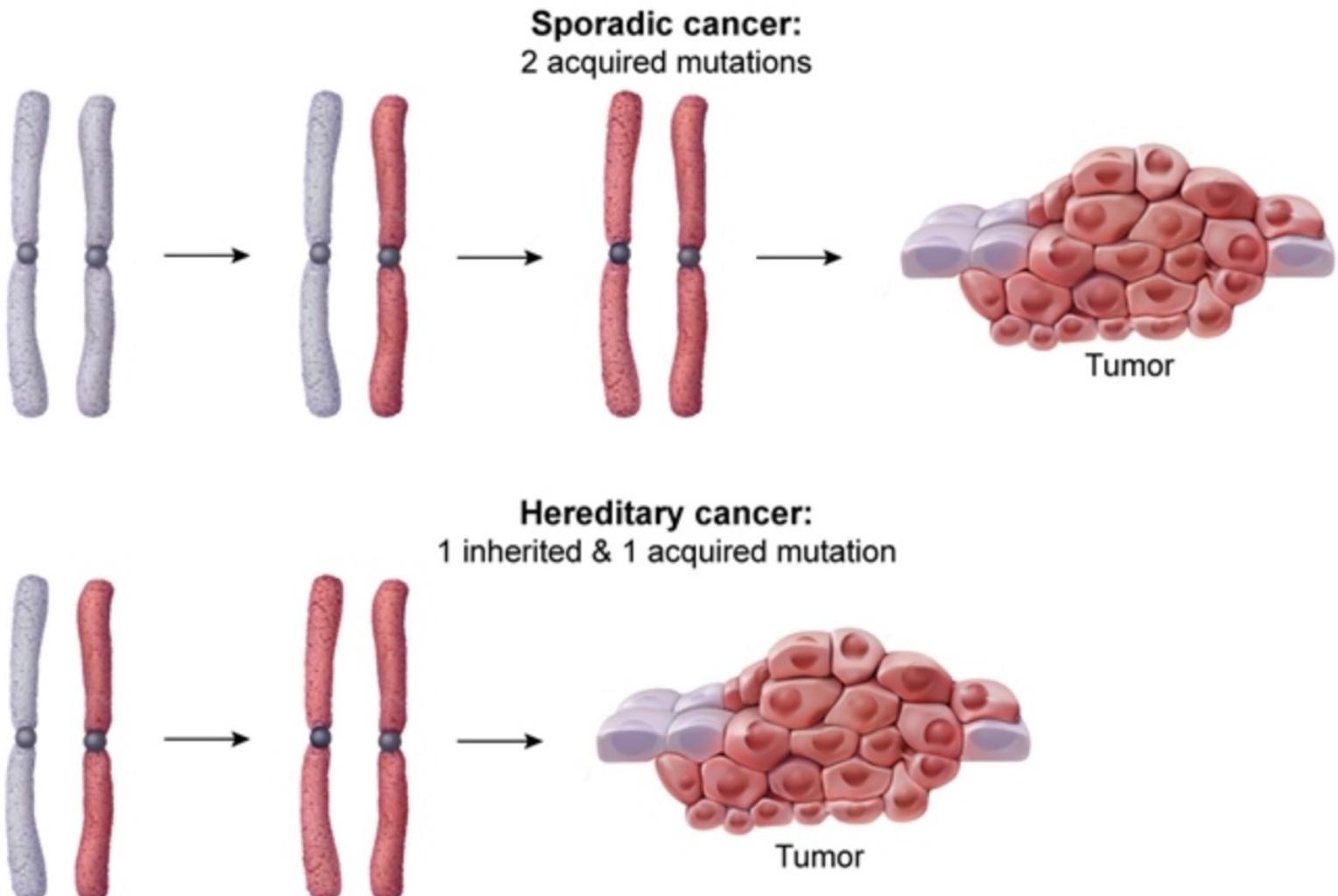


From: Cell, 2015, McGrath and Wells

Knudson's "Two-Hit" Theory of Cancer Causation



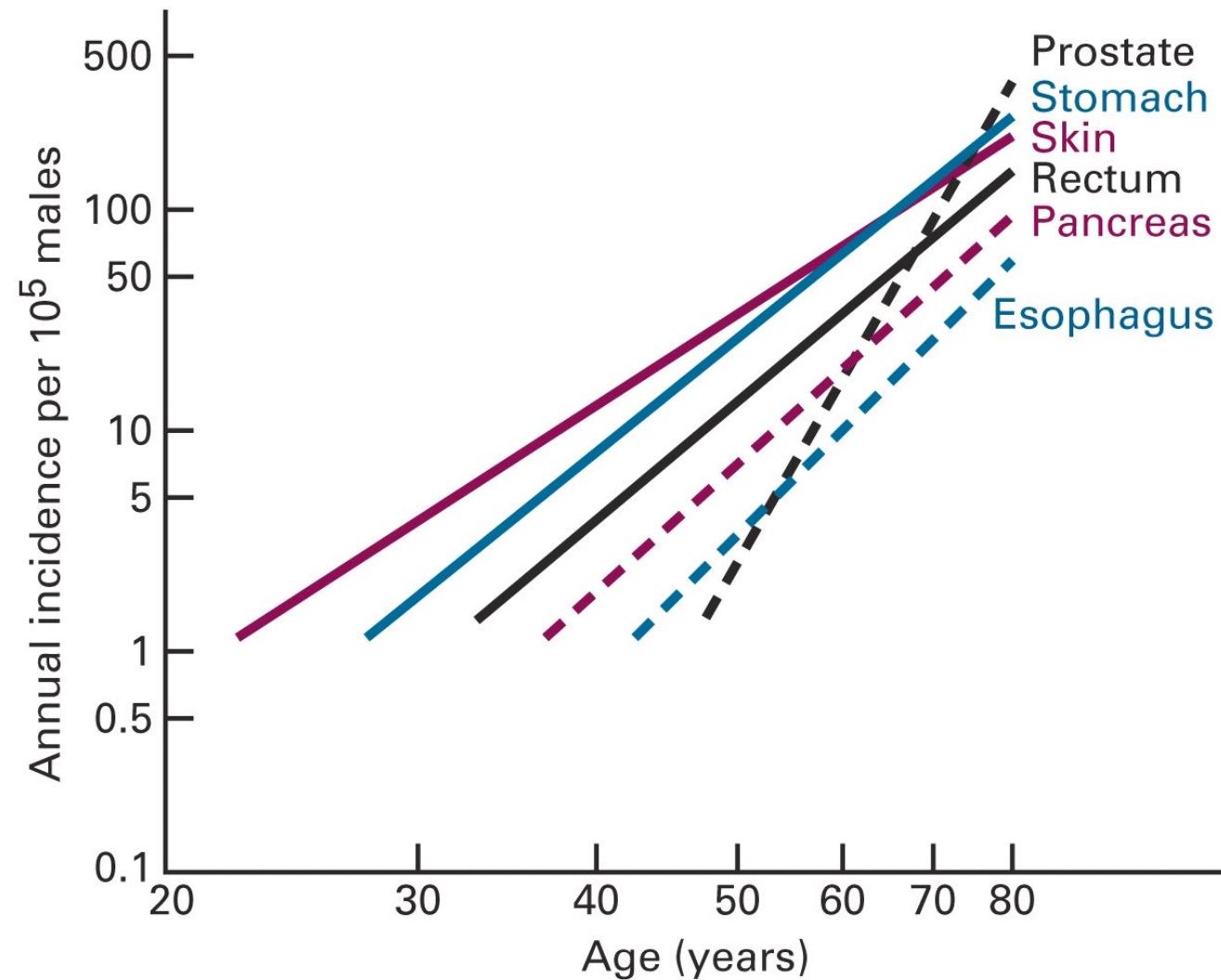
Alfred G. Knudson Jr., MD, PhD
Geneticist and physician
Pediatric oncology



Multi-hit Model for Cancer Causation

The "multi-hit" model for cancer induction theorizes that metastatic tumor cells evolve from an original transformed cell via the accumulation of multiple mutations that increase its survivability and invasion potential.

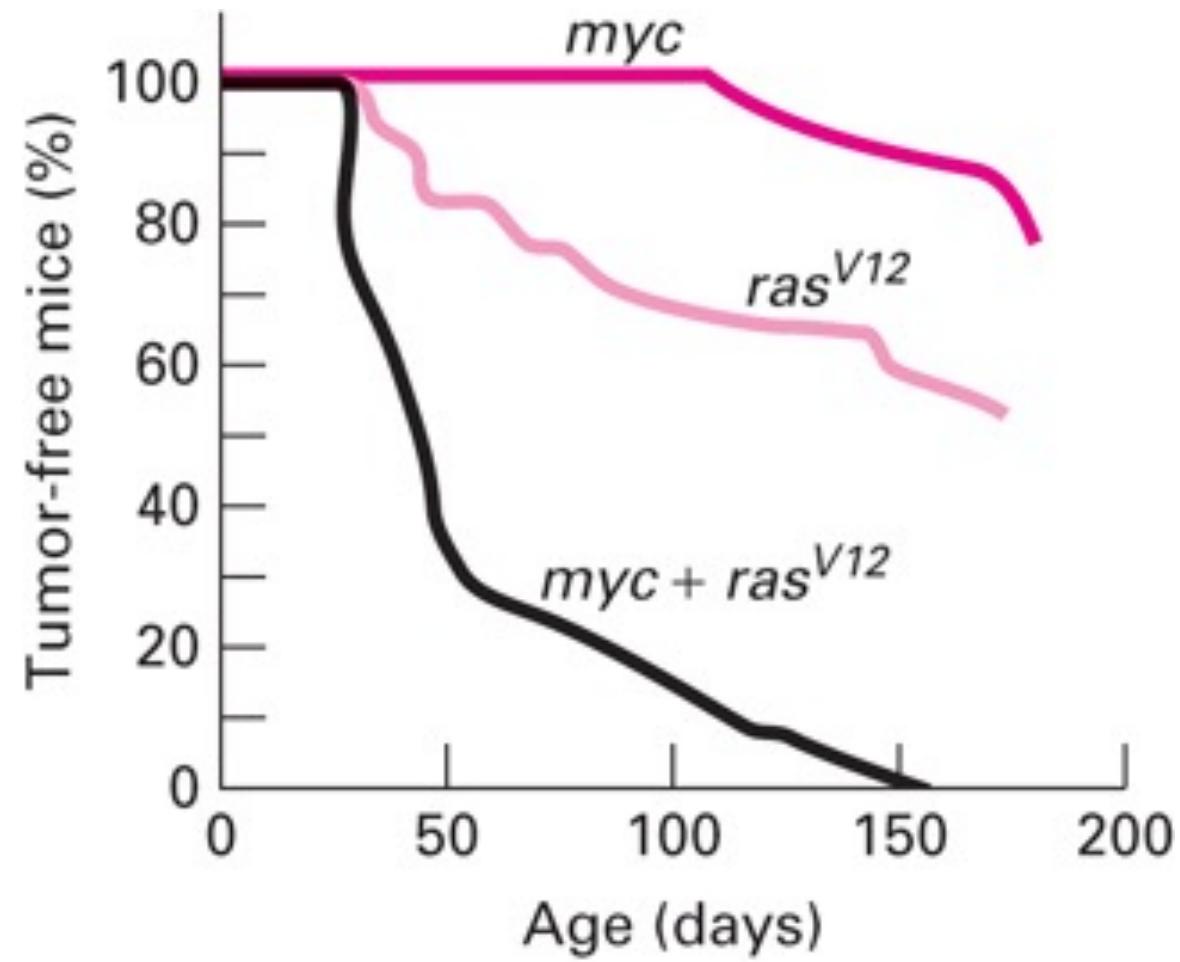
The multiple mutation theory is supported by the fact that the incidence of contracting most cancers increases steadily with age.



Multi-hit Model for Cancer Causation

Compelling evidence for the multi-hit model comes from the study of the progression of lesions in the development of human breast and colon cancer

Combined expression of the ras^{V12} oncogene and over-expression of the myc proto-oncogene causes a higher frequency of tumors in mice than when either gene is expressed alone.



Similarities in organogenesis and Hallmarks of Cancer

a process crucial for eliminating abnormal or damaged cells during development

to ensure a nutrient supply, facilitating their growth

similar to the rapid proliferation seen in embryonic tissues during development

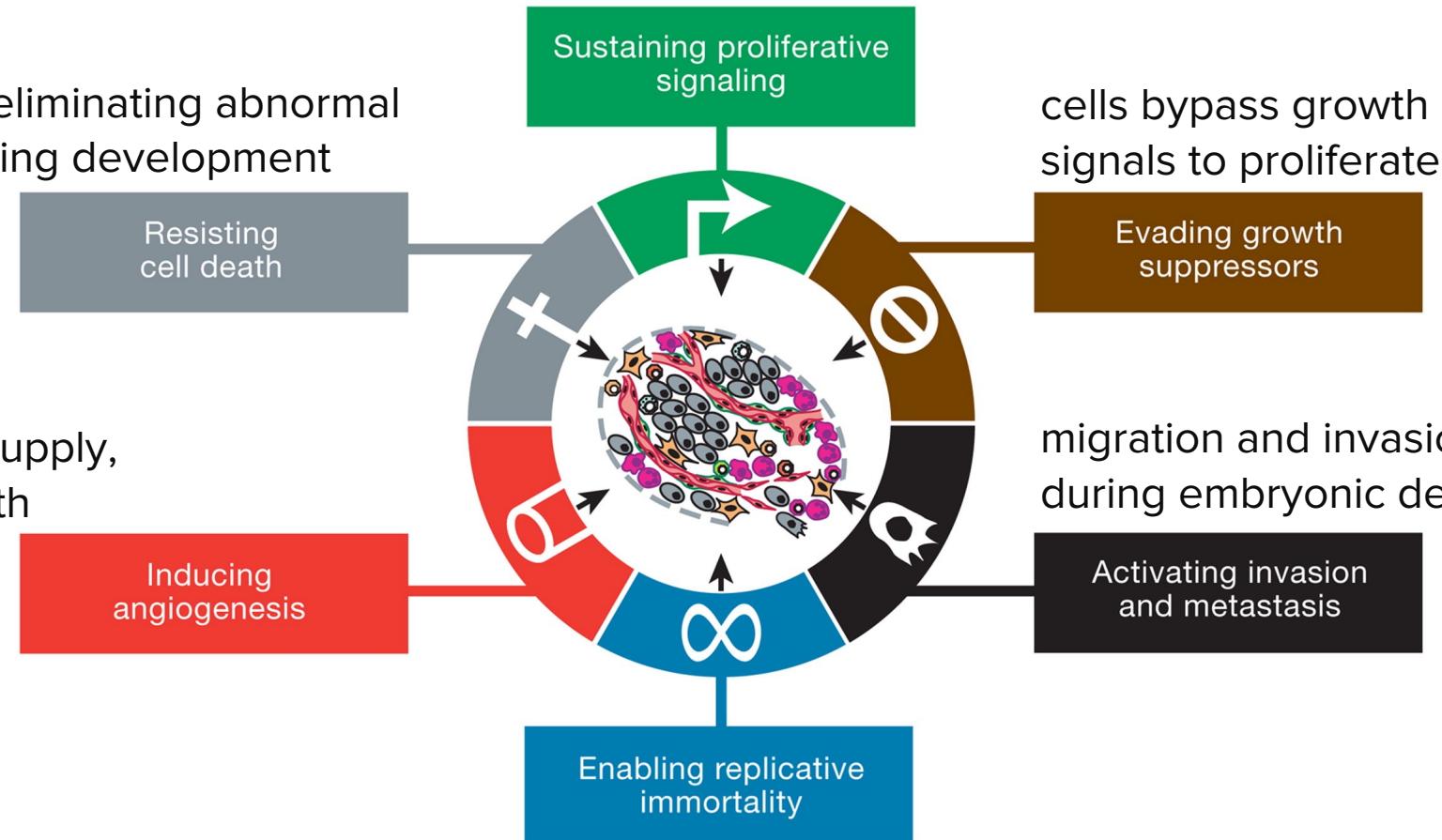
cells bypass growth inhibitory signals to proliferate rapidly

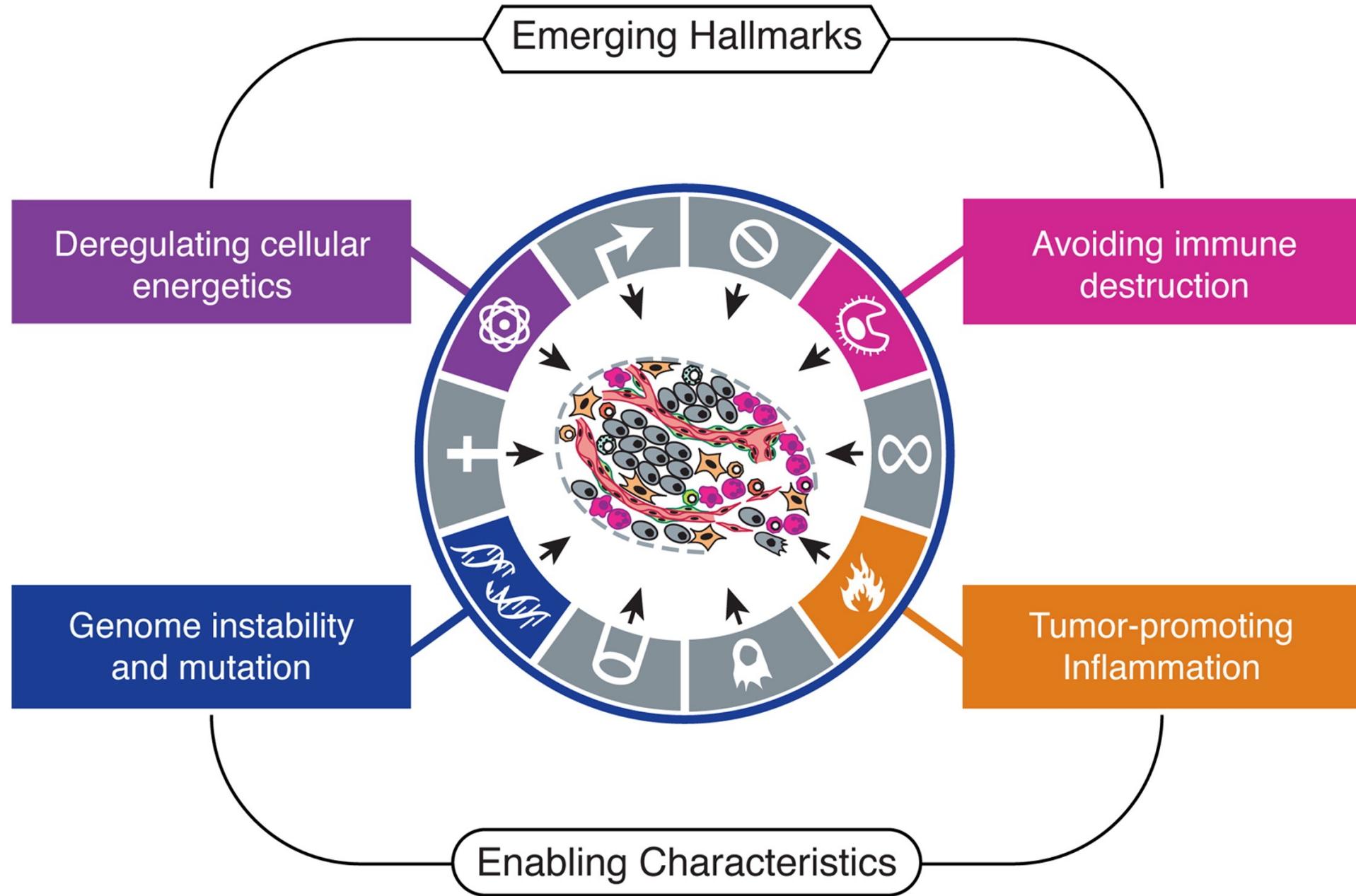
Evading growth suppressors

migration and invasion of cells during embryonic development

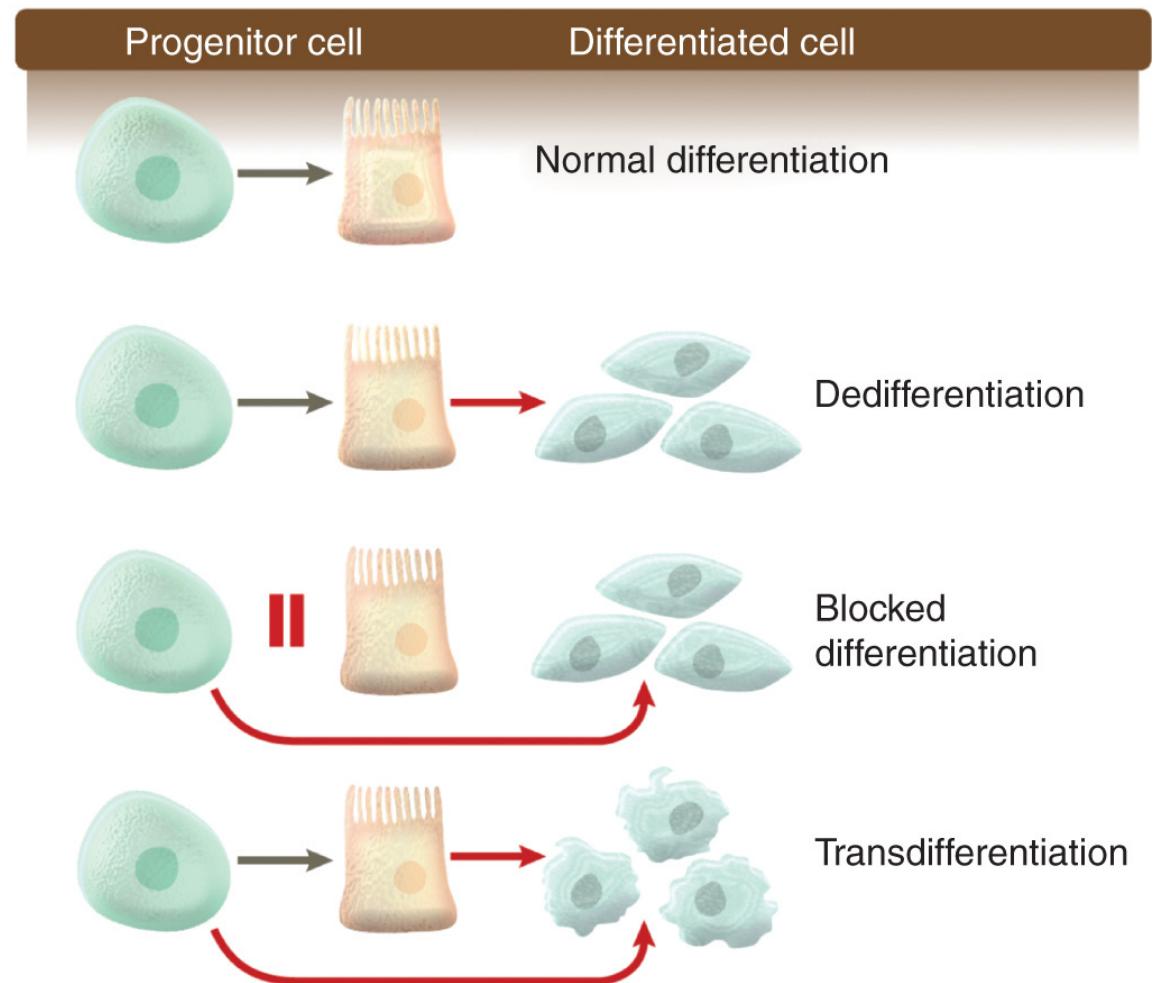
Activating invasion and metastasis

Enabling replicative immortality





Hallmarks of Cancer: New Dimension



From: **Hallmarks of Cancer: New Dimensions**

Cancer Discov. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059

Paediatric Cancer – Wilms Tumours

Renal pediatric cancer

- Fifth most common pediatric cancer
- associated with other developmental syndromes
- Young age
- Genetic predisposition

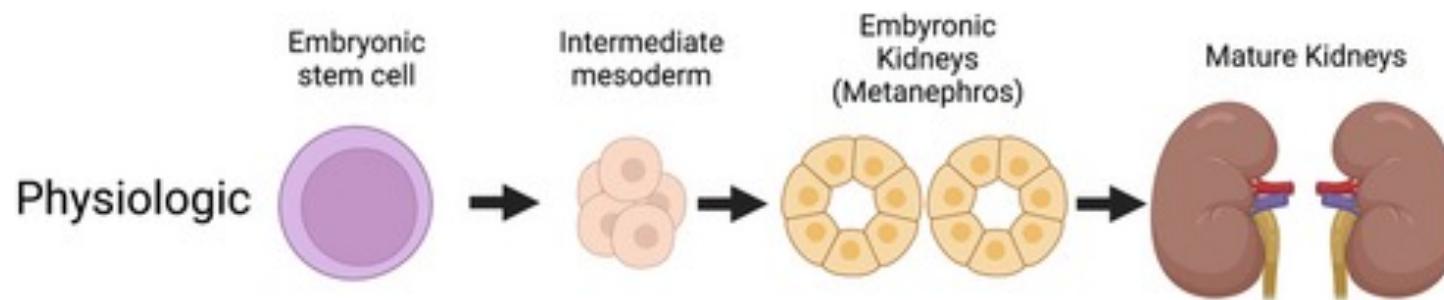
Article | [Open access](#) | Published: 18 December 2023

Genetic and epigenetic features of bilateral Wilms tumor predisposition in patients from the Children's Oncology Group AREN18B5-Q

Andrew J. Murphy , Changde Cheng, Justin Williams, Timothy I. Shaw, Emilia M. Pinto, Karissa Dieseldorf-Jones, Jack Brzezinski, Lindsay A. Renfro, Brett Tornwall, Vicki Huff, Andrew L. Hong, Elizabeth A. Mullen, Brian Crompton, Jeffrey S. Dome, Conrad V. Fernandez, James I. Geller, Peter F. Ehrlich, Heather Mulder, Ninad Oak, Jamie Maciezsek, Carolyn M. Jablonowski, Andrew M. Fleming, Prahalathan Pichavaram, Christopher L. Morton, ... Xiang Chen  [+ Show authors](#)

[Nature Communications](#) 14, Article number: 8006 (2023) | [Cite this article](#)

Cancer cells arise from the embryonic mesoderm



From: Welter et al., [Pediatric Blood & Cancer](#), 2022

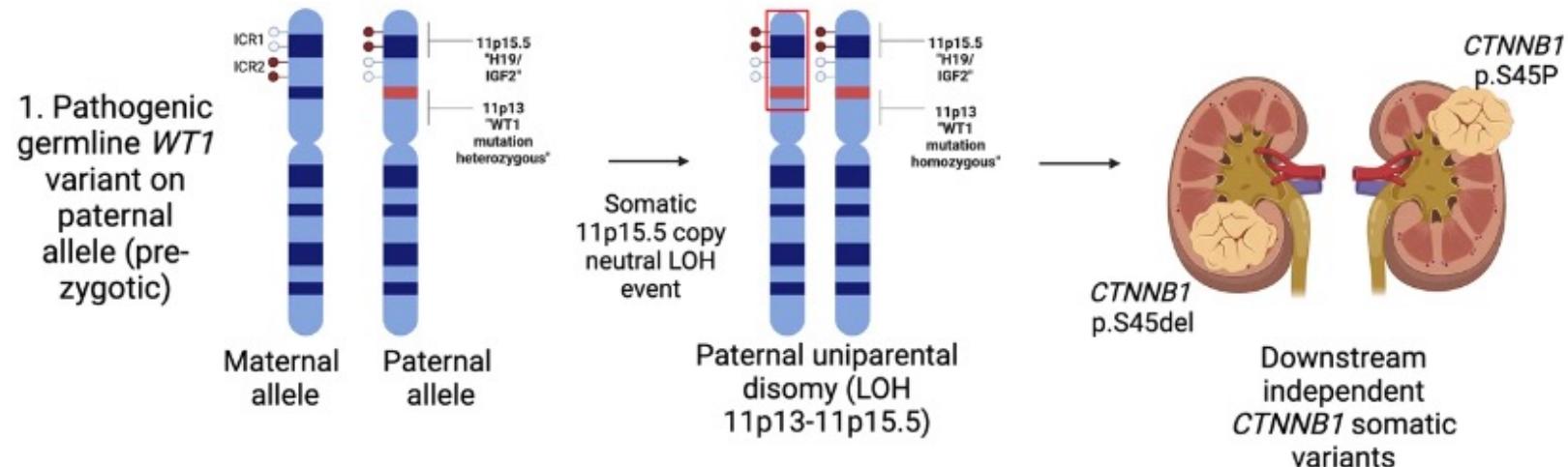
Tumorigenesis of Wilms Tumours

Tumorigenesis in *WT1*-associated WT follows the Knudson two-hit model

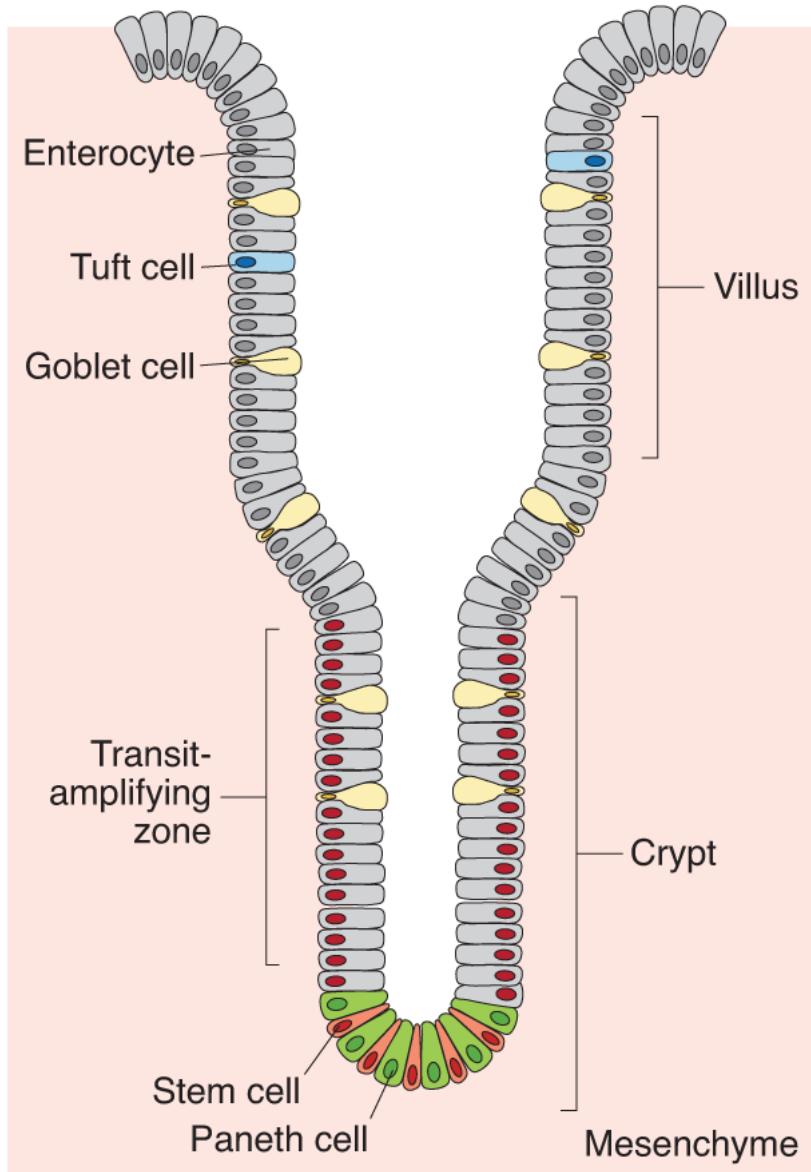
WT1 gene, located on chromosome 11p13, encodes a transcription factor with four DNA-binding zinc-finger domains.

WT1, a transcription factor critical for normal renal development (acts as a tumour suppressor)

Inactivating pathogenic germline variants in *WT1*



Intestine is the major nutrient sensing organ



It is the nexus for cellular, metabolic, and biosynthetic processes

Active from embryogenesis and throughout adulthood

Nutrient absorption is essential for life

Sugars, fatty acids and minerals

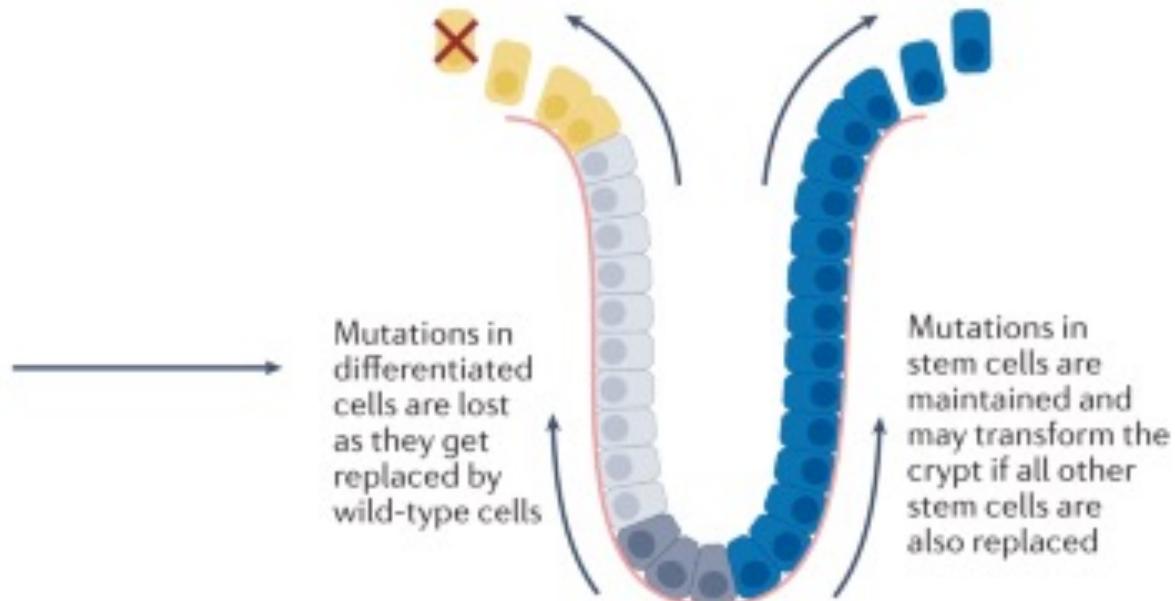
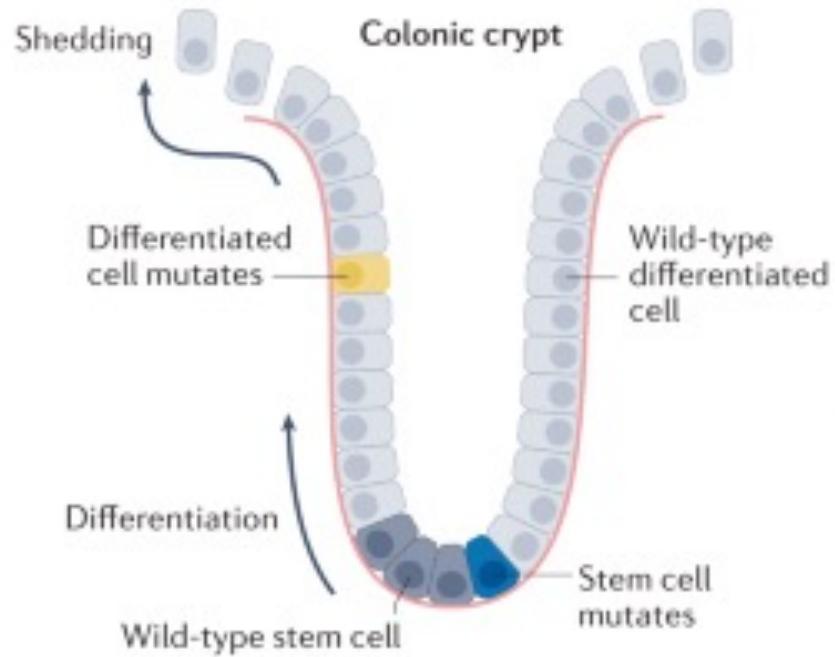
Maintenance and healthy homeostasis of the intestine is critical for organismal survival

Encounters various tissue insults everyday (microbes, toxins, drugs..)

Stem cell hierarchy limits tumorigenesis

a Normal tissue organization

Population structure constraints



The differentiation hierarchy in the colonic crypt limits the number of cells with tumorigenic potential, this reduces the chances of malignant transformation

Familial Adenomatous Polyposis

Hereditary colorectal cancer (CRC). Runs in the family

Hundreds of polyps in colon.

Highly penetrant. Germline mutation in APC gene.
Other mutations may occur.

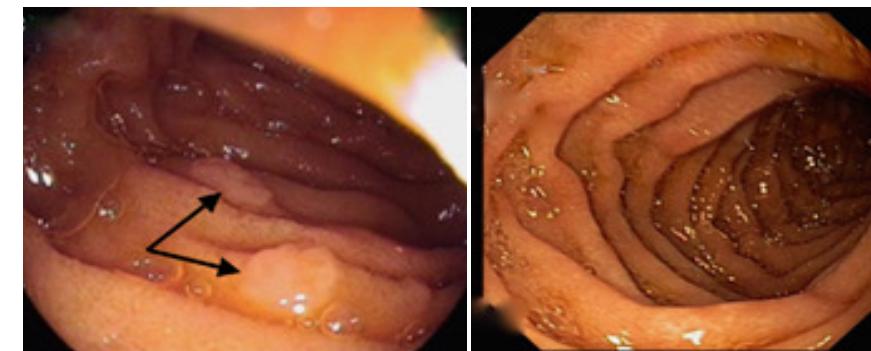
Malignant if untreated.



FAP patient with numerous adenomatous polyps in the colon

Familial Adenomatous Polyposis: Successful Use of Sirolimus

Hasan Yuksekkaya, MD¹, Aylin Yucel, MD¹,
Meltem Gumus, MD², Hasan Esen, MD³ and
Hatice Toy, MD³



Before

6 months later

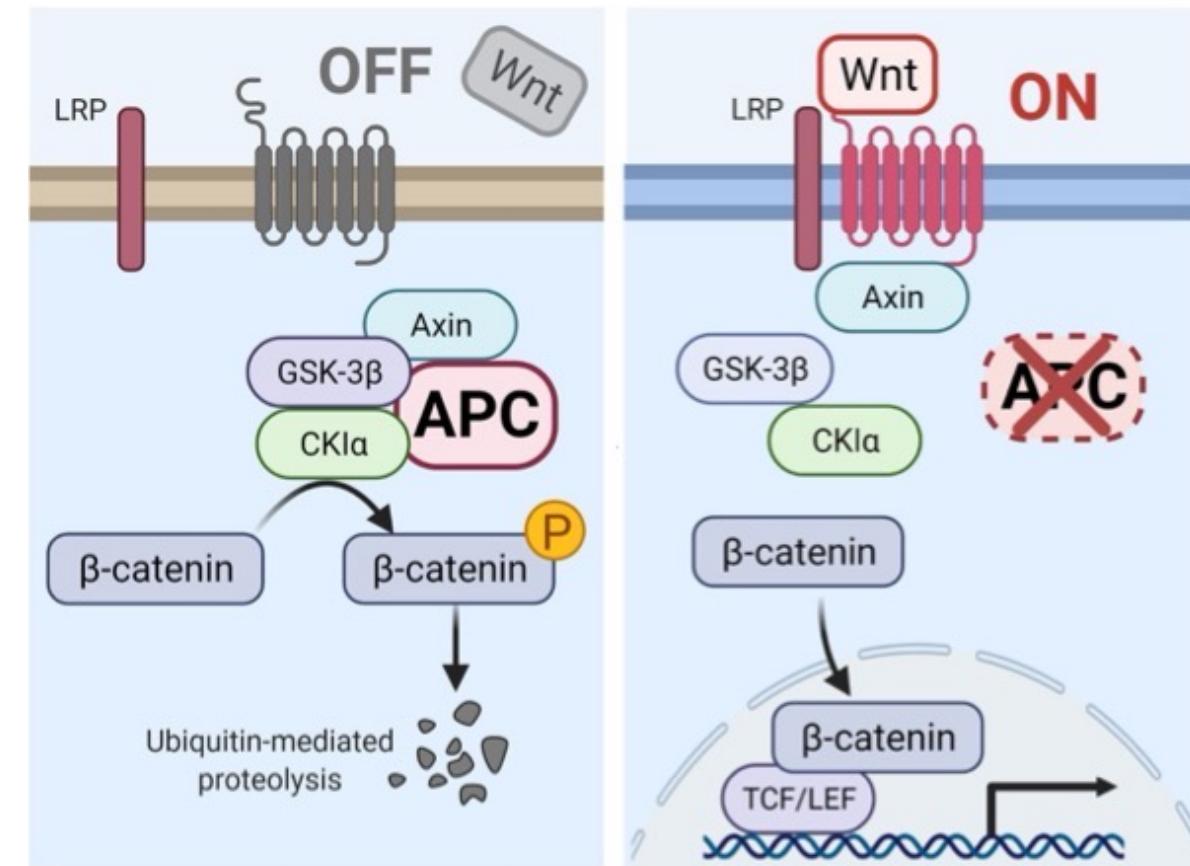
WNT signalling activation in CRC

Same pathways governing endodermal patterning are reactivated during CRC



Without a Wnt signal, β -catenin in the cell is firstly phosphorylated by the destruction complex composed by APC, glycogen synthase kinase 3 β (GSK3 β), Axin and casein kinase 1 (CK1), then ubiquitinated and targeted for proteosomal degradation

APC mutations can lower the levels of destruction complex, causing the high β -catenin content to translocate into the nucleus and cause tumorigenesis

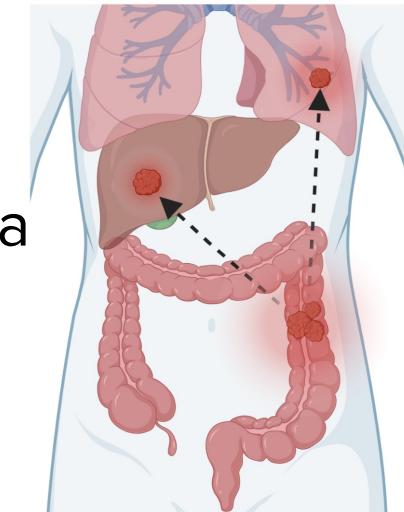
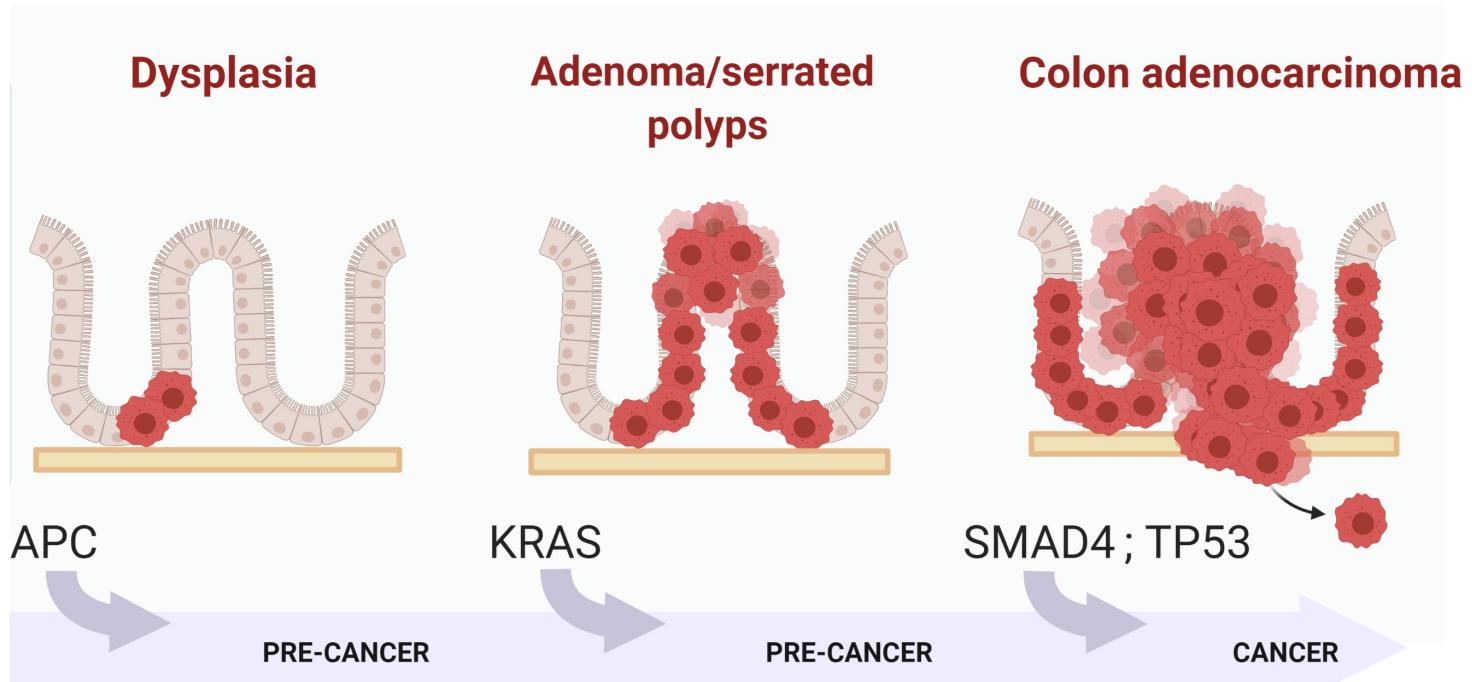


Colorectal cancer, multi-hit model

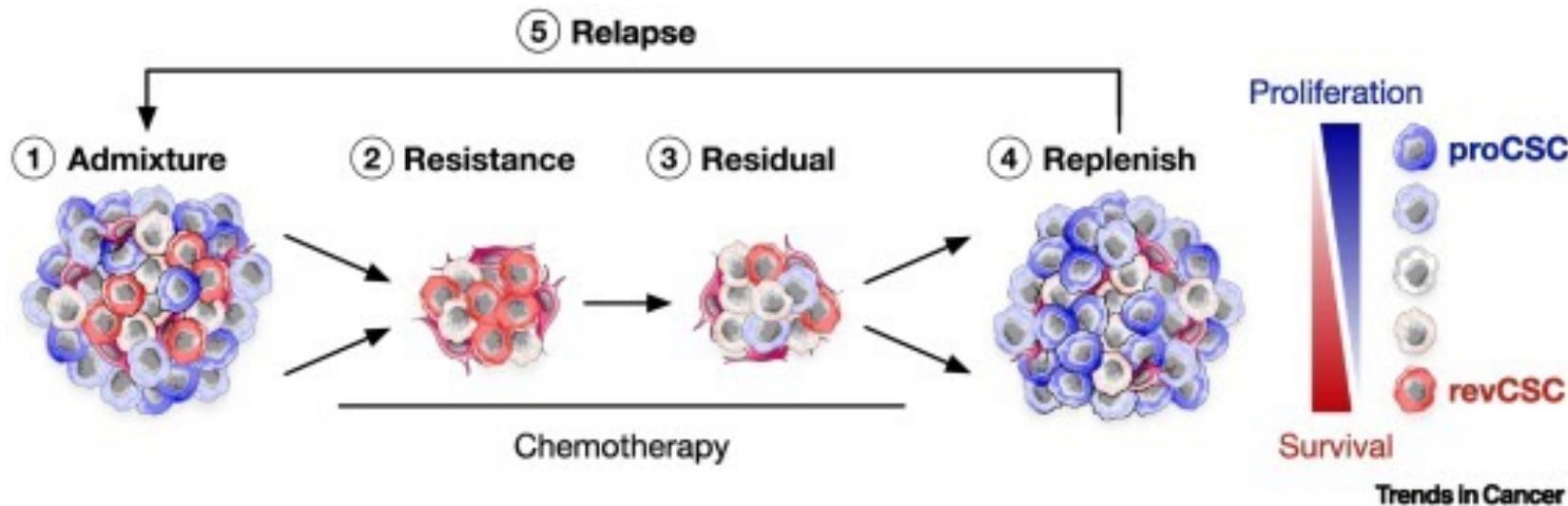
CRC begin as a benign polyp that grows and becomes a benign adenoma.

Genetic analysis of cells from each stage shows that loss-of-function mutations in the *APC* tumor-suppressor gene (*APC*, adenomatous polyposis coli) occur in all polyps.

APC and *KRAS* mutations occur in the benign adenoma stage. Later, loss-of-function of the *p53* tumor-suppressor gene results in a malignant carcinoma with metastatic properties.



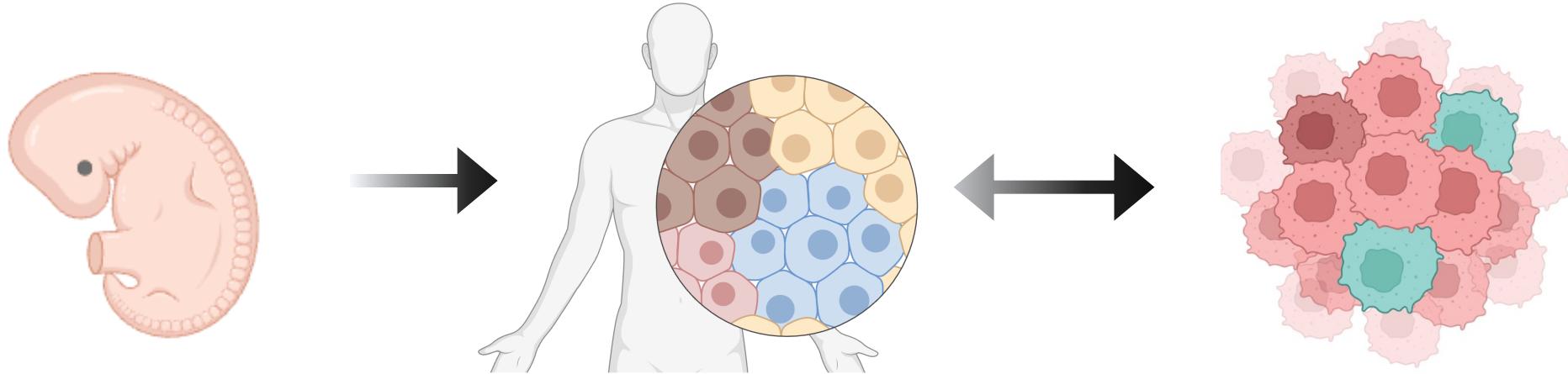
Drug resistance and cancer stem cell model



1. CRC tumours comprise an admixture of proliferative colonic stem cells (proCSCs) and revival colonic stem cells (revCSCs).
2. Chemotherapy eliminates mitotic proCSCs and enriches a slow-cycling revCSC polarised resistant population.
3. Residual disease can withstand chemotherapy in a revCSC-dominant state.
4. Once treatment is complete, CRC cells can polarise to proCSCs to replenish tumours.
5. Relapsed CRC tumours can restore the proCSC–revCSC admixture.

RECAP

Cancers - cells taking over fitness of the tissue over organismal fitness



Genetic and nongenetic mechanisms drive cancer initiation, maintenance, metastasis, and therapy resistance.

Foetal-like or developmental pathways activated broadly in cancers.

Questions?

Now or later at arafath.najumudeen@helsinki.fi

Background Material

- Overview of Cancer
 - Hannahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation, Cell 14(5), 2011.
- Overview of Molecular Biology
 - Kimball's Biology Pages
 - <http://home.comcast.net/~john.kimball1/BiologyPages>