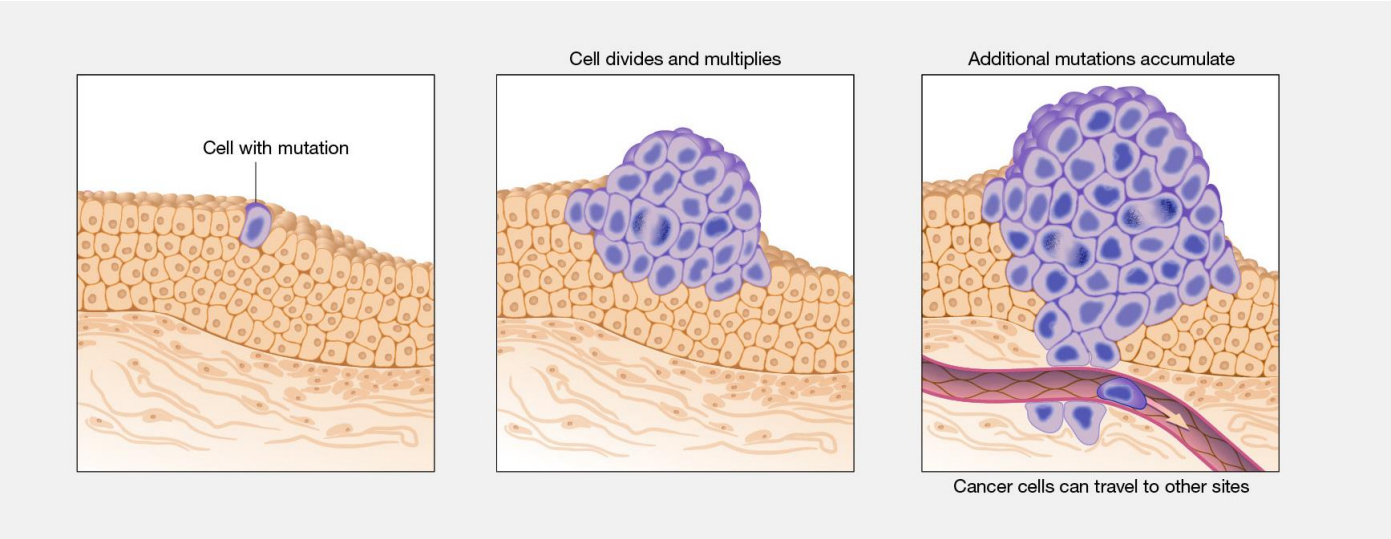
Karcinogeneze

MUNI | RECETOX

Mgr. Jan Kučera, Ph.D.
150663@mail.muni.cz

Co to je rakovina?

Rakovina je onemocnění, při kterém se některé buňky nekontrolovatelně množí a šíří do jiných částí těla.



Prekancerózy

- Hyperplázie
- Metaplázie
- Dysplázie

https://www.genome.gov/genetics-glossary/Cancer

Klasifikace

z histologického hlediska rozlišujeme několik hlavních typů

- **Karcinom** (80 – **90%**, z epitelií)
- **Sarkom** (pojivové tkáně)
- **Myelom** (plazmatická buňka)
- **Leukémie**
- **Lymfom**
- **Melanom**
- **Smíšené**

Klasifikace (TNM systém)

Staging

T-primární tumor: TX = nelze hodnotit, Tis = karcinom in situ, T0 = nádor není přítomen, T1 až T4 = popis rozsahu nádoru, jeho velikosti a/nebo vztahu k okolním strukturám

N-regionální lymfatické uzliny: NX = nelze hodnotit, N0 = uzliny nejsou postiženy nádorem, N1 až N3 = popis postižení lymfatických uzlin a rozsah takového postižení

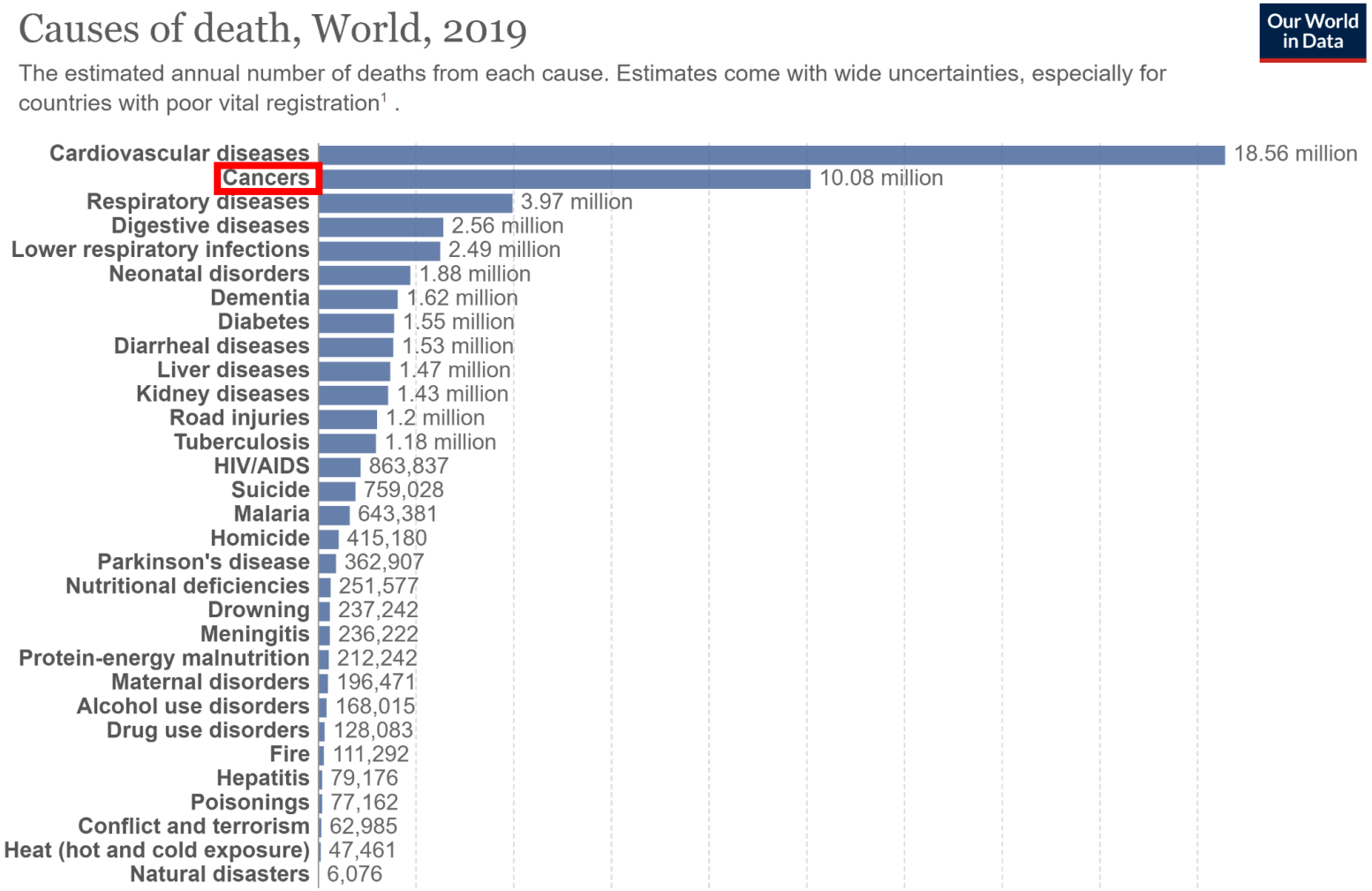
M-vzdálené metastázy (90% příčin úmrtí!): MX = nelze hodnotit, M0 vzdálené metastázy nepřítomny, M1 vzdálené metastázy přítomny, může být upřesněn orgán, do kterého nádor metastazoval, např. M1pul = přítomny metastázy v plicích

Grading

Grading je mikroskopické určení stupně diferencovanosti nádoru.

Gx (nelze stanovit stupeň diferenciace)
G1 (dobře diferencovaný nádor)
G2 (středně diferencovaný nádor)
G3 (málo diferencovaný nádor)
G4 (nediferencovaný nádor)

Proč se zabývat rakovinou?

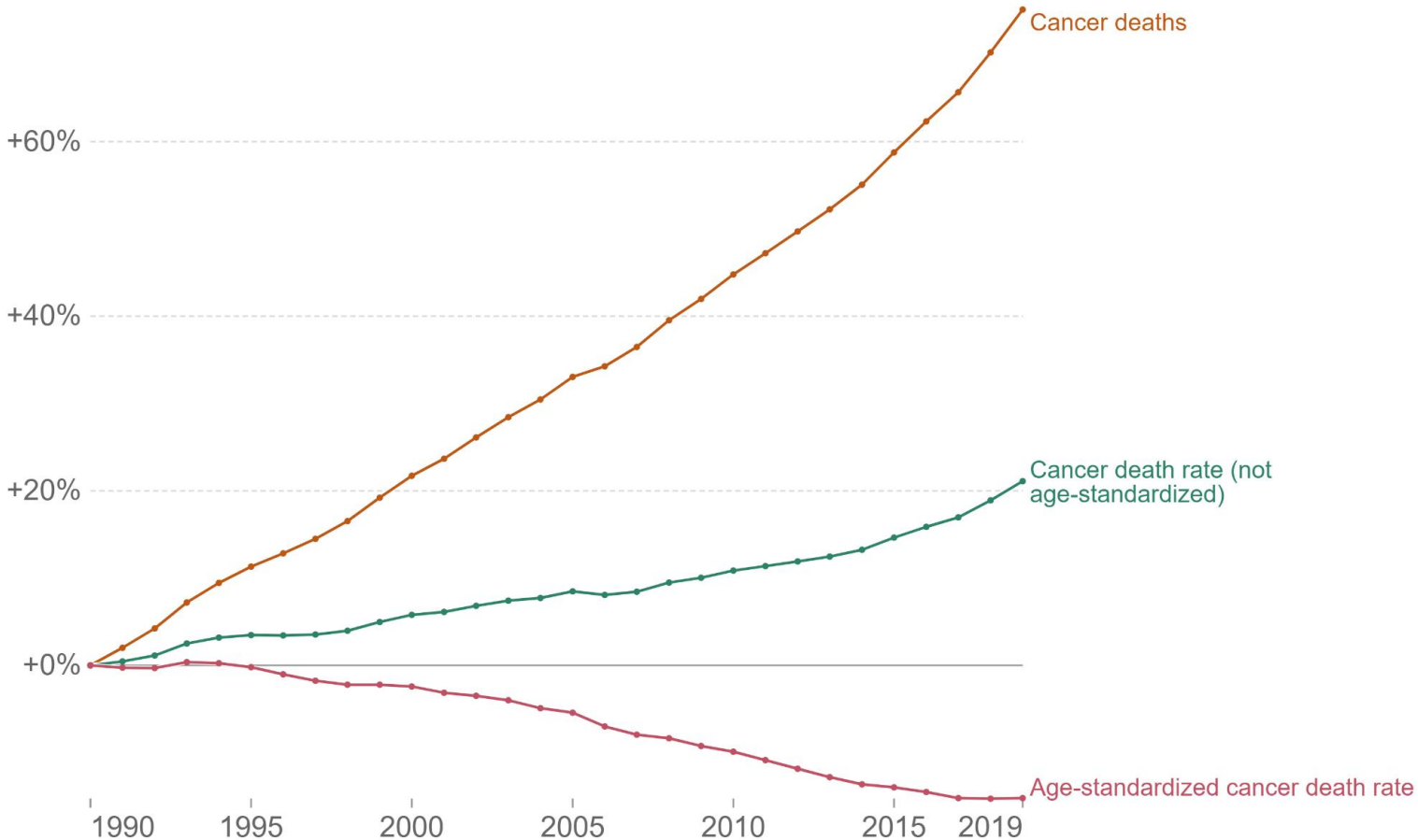


https://ourworldindata.org/cancer#cancer-is-one-of-the-leading-causes-of-death

Change in three measures of cancer mortality, World, 1990 to 2019

Our World in Data

This chart compares cancer deaths, crude cancer death rates, and age-standardized[1] death rates.



Data source: IHME, Global Burden of Disease (2019)

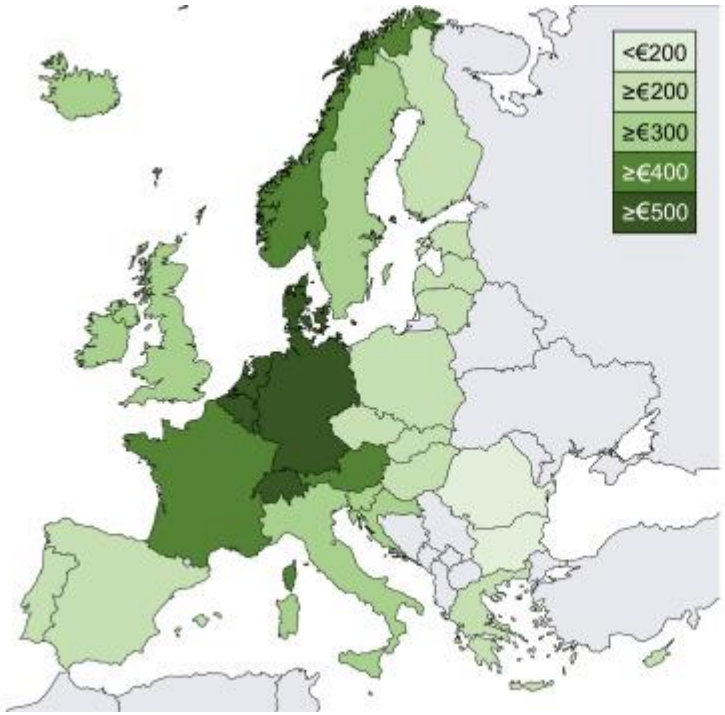
OurWorldInData.org/cancer | CC BY

1. Age standardization: Age standardization is an adjustment that makes it possible to compare populations with different age structures, by standardizing them to a common reference population. Read more: How does age standardization make health metrics comparable?

https://ourworldindata.org/cancer#cancer-is-one-of-the-leading-causes-of-death

Proč se zabývat rakovinou?

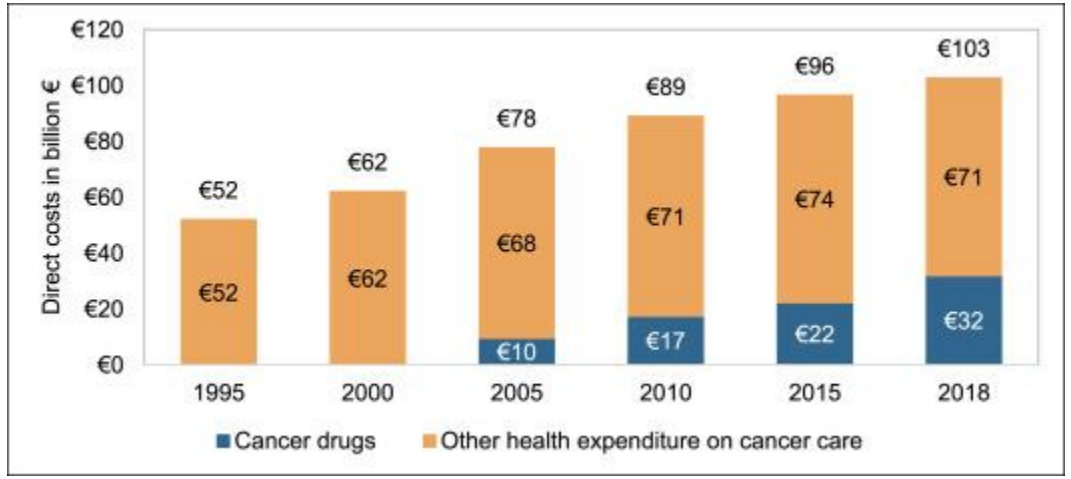
cena rakovina v Evropě za jeden rok (2018) => **200 miliard €**



Europe	€378	ITA	€348
AUT	€440	LVA	€201
BEL	€522	LTU	€235
BGR	€165	LUX	€510
HRV	€366	MLT	€282
CYP	€211	NLD	€524
CZE	€278	NOR	€406
DNK	€516	POL	€237
EST	€250	PRT	€256
FIN	€277	ROU	€160
FRA	€459	SVK	€248
DEU	€524	SVN	€362
GRC	€229	ESP	€285
HUN	€226	SWE	€336
ISL	€324	CHE	€578
IRL	€356	GBR	€310

https://www.ejcancer.com/article/S0959-8049(20)30026-5/fulltext

Proč to stojí tolik peněz?



https://www.ejcancer.com/article/S0959-8049(20)30026-5/fulltext

Proč ještě není „lék na rakovinu“?

- rakovina není to jedna nemoc (více než stovka nemocí)
- velká variabilita a heterogenita i v rámci „stejné nemoci“ (i uvnitř nádoru)
- vyvíjí se (léková rezistence)

Rakovina není nový problém…

THE LANCET
Oncology

PERSPECTIVES | HISTORY OF MEDICINE | VOLUME 21, ISSUE 8, P1021-1022, AUGUST 2020 Download Full Issue

First case of osteosarcoma in a dinosaur: a multimodal diagnosis

Seper Ekhtiari • Kentaro Chiba • Snezana Popovic • Rhianne Crowther • Gregory Wohl • Andy Kin On Wong • et al.
Show all authors

AUTHORS:
Edward J. Odes[1,2]
Patrick S. Randolph-Quinney[1,2*]
Maryna Steyn[1]
Zach Throckmorton[2,3]
Jacqueline S. Smilg[2,4,5]
Bernhard Zipfel[2,6]
Tanya N. Augustine[1]
Frikkie de Beer[7]
Jakobus W. Hoffman[7]
Ryan D. Franklin[8]
Lee R. Berger[2,6]

AFFILIATIONS:
[1]School of Anatomical Sciences, University of the Witwatersrand, Johannesburg, South Africa
[2]Evolutionary Studies Institute, School of Geosciences, University of the Witwatersrand, Johannesburg, South Africa
[3]De Busk College of Osteopathic Medicine, Lincoln Memorial University, Harrogate, Tennessee, USA

Earliest hominin cancer: 1.7-million-year-old osteosarcoma from Swartkrans Cave, South Africa

The reported incidence of neoplasia in the extinct human lineage is rare, with only a few confirmed cases of Middle or Later Pleistocene dates reported. It has generally been assumed that pre-modern incidence of neoplastic disease of any kind is rare and limited to benign conditions, but new fossil evidence suggests otherwise. We here present the earliest identifiable case of malignant neoplastic disease from an early human ancestor dated to 1.8–1.6 million years old. The diagnosis has been made possible only by advances in 3D imaging methods as diagnostic aids. We present a case report based on re-analysis of a hominin metatarsal specimen (SK 7923) from the cave site of Swartkrans in the Cradle of Humankind, South Africa. The expression of malignant osteosarcoma in the Swartkrans specimen indicates that whilst the upsurge in malignancy incidence is correlated with modern lifestyles, there is no reason to suspect that primary bone tumours would have been any less frequent in ancient specimens. Such tumours are not related to lifestyle and often occur in younger individuals. As such, malignancy has a considerable antiquity in the fossil record, as evidenced by this specimen.

PLOS ONE

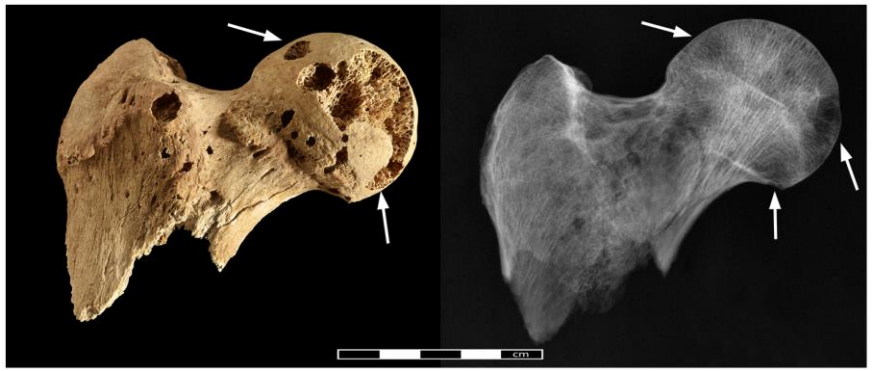
OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

On the Antiquity of Cancer: Evidence for Metastatic Carcinoma in a Young Man from Ancient Nubia (*c.* 1200BC)

Michaela Binder, Charlotte Roberts, Neal Spencer, Daniel Antoine, Caroline Cartwright

Published: March 17, 2014 • https://doi.org/10.1371/journal.pone.0090924



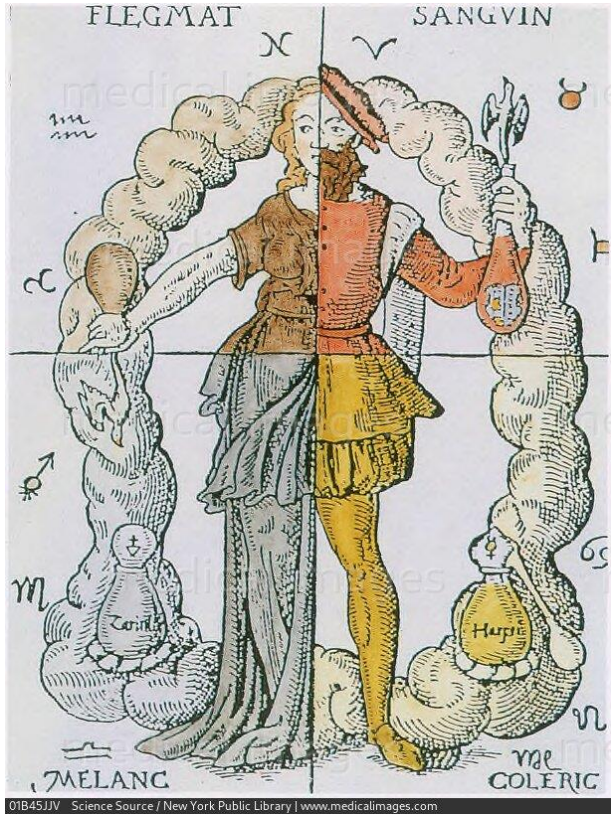
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30171-6/fulltext https://sajs.co.za/article/view/3566 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0090924

Papyrus Edwina Smitha

nejrozsáhlejší známý chirurgický text ze starověkého Egypta pocházející z doby kolem roku 1600 př. n. l (opis staršího díla 3000 př. n. l.)

Hippokratés (460 – 370 př. n. l.)

Hippokratovi je připisováno pojmenování "rakoviny" jako "karkinomu" (karcinomu), protože nádor vypadal jako krab ("karkinoma" je řecký výraz pro "kraba")



https://www.medicalimages.com/stock-photo-four-humors-hippocratic-medicine-image23594555.html

https://www.gavi.org/vaccineswork/funny-science-hippocratic-medicine-and-four-humours

Co způsobuje rakovinu?

Lymfatická teorie

Teorie blastemy

Teorie traumatu

Infekční teorie

Teorie chronického podráždění

The Nobel Prize in Physiology or Medicine 1926

Photo from the Nobel Foundation archive.

Johannes Andreas Grib Fibiger

Prize share: 1/1

The Nobel Prize in Physiology or Medicine 1926 was awarded to Johannes Andreas Grib Fibiger "for his discovery of the Spiroptera carcinoma"

https://www.nobelprize.org/prizes/medicine/1926/summary/

Je rakovina nakažlivá?

Je rakovina nakažlivá?

Veterinary and Comparative Oncology

Review Article

DOI: 10.1111/vco.12060

Canine transmissible venereal tumour: a review

B. Ganguly[1], U. Das[2] and A. K. Das[3]

[1]Animal Biotechnology Center, Department of Veterinary Physiology and Biochemistry, College of Veterinary and Animal Sciences, G. B. Pant University of Agriculture and Technology, Pantnagar, India
[2]Broad Street Pet Clinics, Kolkata, India
[3]Department of Surgery and Radiology, College of Veterinary and Animal Sciences, G. B. Pant University of Agriculture and Technology, Pantnagar, India

Abstract

Canine transmissible venereal tumour (CTVT) is a contagious venereal tumour of dogs, commonly observed in dogs that are in close contact with one another, or in stray and wild dogs that exhibit unrestrained sexual activity. CTVT represents a unique, naturally transmissible, contagious tumour, where the mutated tumour cell itself is the causative agent and perpetuates as a parasitic allograft in the host. Clinical history, signalment and cytological features are often obvious for establishing a diagnosis though biopsy and histological examination may be needed in atypical cases. Most cases are curable with three intravenous injections of vincristine sulphate at weekly intervals. The role of stray and wild dogs makes the disease difficult to control and necessitates sustained animal birth control in stray dogs along with prompt therapy of the affected dogs. This review captures the manifold developments in different areas embracing this fascinating tumour, including its biology, diagnosis and therapeutic alternatives.

Keywords
canine, diagnosis, immunity, transmissible venereal tumour, treatment

https://onlinelibrary.wiley.com/doi/10.1111/vco.12060

Tropical Medicine and Infectious Disease

MDPI

Review

A Devil of a Transmissible Cancer

Gregory M. Woods [1,*], A. Bruce Lyons [2] and Silvana S. Bettiol [2]

[1] Menzies Institute for Medical Research, College of Health and Medicine, University of Tasmania, Hobart, TAS 7000, Australia

[2] Tasmanian School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, TAS 7000, Australia; bruce.lyons@utas.edu.au (A.B.L.); s.bettiol@utas.edu.au (S.S.B.)

* Correspondence: G.M.Woods@utas.edu.au

Received: 28 November 2019; Accepted: 27 March 2020; Published: 1 April 2020

Abstract: Devil facial tumor disease (DFTD) encompasses two independent transmissible cancers that have killed the majority of Tasmanian devils. The cancer cells are derived from Schwann cells and are spread between devils during biting, a common behavior during the mating season. The Centers for Disease Control and Prevention (CDC) defines a parasite as "An organism that lives on or in a host organism and gets its food from, or at, the expense of its host." Most cancers, including DFTD, live within a host organism and derive resources from its host, and consequently have parasitic-like features. Devil facial tumor disease is a transmissible cancer and, therefore, DFTD shares one additional feature common to most parasites. Through direct contact between devils, DFTD has spread throughout the devil population. However, unlike many parasites, the DFTD cancer cells have a simple lifecycle and do not have either independent, vector-borne, or quiescent phases. To facilitate a description of devil facial tumor disease, this review uses life cycles of parasites as an analogy.

Figure 1. Gross facial deformities caused by (**A**) devil facial tumor disease 1 (DFT1) and (**B**) DFT2.

ORIGINAL ARTICLE BRIEF REPORT

Genetic Analysis of a Sarcoma Accidentally Transplanted from a Patient to a Surgeon

Hermine-Valeria Gärtner, M.D., Christian Seidl, M.D., Christine Luckenbach, Ph.D., Georg Schumm, M.D., Erhard Seifried, M.D., Horst Ritter, M.D., and Burkhard Bültmann, M.D.

Case Report

A 32-year-old man underwent emergency surgery to remove a malignant fibrous histiocytoma from his abdomen and died shortly thereafter of postoperative complications. During the operation the 53-year-old surgeon injured the palm of his left hand while placing a drain. The lesion was immediately disinfected and dressed. Five months later, the surgeon consulted a hand specialist because of a hard, circumscribed, tumor-like swelling, 3.0 cm (1.2 in.) in diameter, in his left palm at the base of the middle finger, where he had been injured during the operation. An extensive examination, including laboratory tests, did not reveal any signs of immune deficiency. The tumor was completely excised. Histologic examination revealed that it was a malignant fibrous histiocytoma. Two years later, the surgeon's condition was good, and there was no evidence of recurrence or metastasis of the tumor.

The pathologist who investigated both the patient's tumor and the surgeon's tumor raised the question whether the tumors were identical.

https://www.nejm.org/doi/full/10.1056/NEJM199611143352004

Journal of Clinical Oncology > List of Issues > Volume 21, Issue 11 >

PEDIATRIC ONCOLOGY

Metastatic Melanoma in Pregnancy: Risk of Transplacental Metastases in the Infant

April Alexander , Wolfram E. Samlowski , Douglas Grossman , Carol S. Bruggers , Ronald M. Harris , John J. Zone...

Show More

PNAS

Immunologically silent cancer clone transmission from mother to offspring

Takeshi Isoda[a,1], Anthony M. Ford[b,1], Daisuke Tomizawa[a], Frederik W. van Delft[b], David Gonzalez De Castro[b], Norkio Mitsuiki[a], Joannah Score[c], Tomohiko Taki[d], Tomohiro Morio[a], Masatoshi Takagi[a], Hiroh Saji[e], Mel Greaves[b,2,3], and Shuki Mizutani[a,2,3]

[a]Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 1138519, Japan; [b]Section of Haemato-Oncology, Institute of Cancer Research, Brookes Lawley Building, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom; [c]Wessex Regional Genetics Laboratory, University of Southampton, Salisbury District Hospital, Salisbury SP2 8BJ, United Kingdom; [d]Department of Molecular Laboratory Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Science, 465 Kajii Cho, Hirokoji-agaru, Kawaramachi, Kamigyo-ku, Kyoto 6028566, Japan; and [e]Human Leukocyte Antigen Laboratory, Ebis Building, 3-4F, 82 Shimo-Tsutsumimachi, Marutamachi-kudaru, Kawabata Dori, Sakyo-ku, Kyoto 606-8396, Japan

Edited by Janet D. Rowley, University of Chicago Medical Center, Chicago, IL, and approved July 28, 2009 (received for review April 28, 2009)

https://ascopubs.org/doi/full/10.1200/JCO.2003.12.149?role=tab https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2764945/pdf/zpq17882.pdf

ORIGINAL ARTICLE BRIEF REPORT

Malignant Transformation of *Hymenolepis nana* in a Human Host

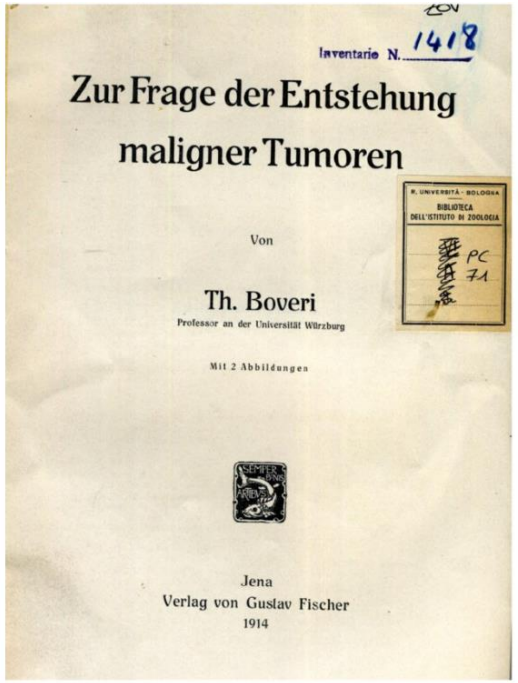
Atis Muehlenbachs, M.D., Ph.D., Julu Bhatnagar, Ph.D., Carlos A. Agudelo, M.D., Alicia Hidron, M.D., Mark L. Eberhard, Ph.D., Blaine A. Mathison, B.S.M.(A.S.C.P.), Michael A. Frace, Ph.D., Akira Ito, Ph.D., Maureen G. Metcalfe, M.S., Dominique C. Rollin, M.D., Govinda S. Visvesvara, Ph.D., Cau D. Pham, Ph.D., et al.

Summary

Neoplasms occur naturally in invertebrates but are not known to develop in tapeworms. We observed nests of monomorphic, undifferentiated cells in samples from lymph-node and lung biopsies in a man infected with the human immunodeficiency virus (HIV). The morphologic features and invasive behavior of the cells were characteristic of cancer, but their small size suggested a nonhuman origin. A polymerase-chain-reaction (PCR) assay targeting eukaryotes identified *Hymenolepis nana* DNA. Although the cells were unrecognizable as tapeworm tissue, immunohistochemical staining and probe hybridization labeled the cells in situ. Comparative deep sequencing identified *H. nana* structural genomic variants that are compatible with mutations described in cancer. Invasion of human tissue by abnormal, proliferating, genetically altered tapeworm cells is a novel disease mechanism that links infection and cancer.

https://www.nejm.org/doi/full/10.1056/nejmoa1505892

Theodor Boveri (1862 – 1915)



Rakovina může být spojena s chromozomálními abnormalitami

„When I published the results of my experiments on the development of double-fertilized sea-urchin eggs in 1902, I added the suggestion that malignant tumors might be the result of a certain abnormal condition of the chromosomes, which may arise from multipolar mitosis...So I have carried on for a long time the kind of experiments I suggested, which are so far without success, but my conviction remains unshaken“

https://pathsocjournals.onlinelibrary.wiley.com/doi/10.1002/path.4410 https://www.tandfonline.com/doi/pdf/10.4161/cbt.1.5.225

Poškození DNA

- mutageny

Mutace je změna v sekvenci DNA organismu. Mutace mohou vzniknout v důsledku chyb v replikaci DNA při dělení buněk, působením mutagenů nebo virovou infekcí. Zárodečné mutace (které se vyskytují ve vajíčkách a spermiích) se mohou přenášet na potomky, zatímco somatické mutace (které se vyskytují v tělesných buňkách) se nepřenášejí.

https://www.cancer.gov/about-cancer/understanding/what-is-cancer

Genetické změny potenciálně vedoucí k rakovině

https://www.genome.gov/genetics-glossary/Mutation

Postupné hromadění mutací nebo „single catastrophic event“?

Rakovina je způsobena somaticky získanými bodovými mutacemi a chromozomálními přestavbami, o nichž se obvykle předpokládá, že se v průběhu času postupně hromadí

ledaže…

Cell. 2011 Jan 7; 144(1): 27–40.
doi: 10.1016/j.cell.2010.11.055
PMCID: PMC3065307
PMID: 21215367

Massive Genomic Rearrangement Acquired in a Single Catastrophic Event during Cancer Development

Philip J. Stephens,[1] Chris D. Greenman,[1] Beiyuan Fu,[1] Fengtang Yang,[1] Graham R. Bignell,[1] Laura J. Mudie,[1] Erin D. Pleasance,[1] King Wai Lau,[1] David Beare,[1] Lucy A. Stebbings,[1] Stuart McLaren,[1] Meng-Lay Lin,[1] David J. McBride,[1] Ignacio Varela,[1] Serena Nik-Zainal,[1] Catherine Leroy,[1] Mingming Jia,[1] Andrew Menzies,[1] Adam P. Butler,[1] Jon W. Teague,[1] Michael A. Quail,[1] John Burton,[1] Harold Swerdlow,[1] Nigel P. Carter,[1] Laura A. Morsberger,[2] Christine Iacobuzio-Donahue,[2] George A. Follows,[3] Anthony R. Green,[3,4] Adrienne M. Flanagan,[5,6] Michael R. Stratton,[1,7] P. Andrew Futreal,[1] and Peter J. Campbell[1,3,4,*]

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

See editorial "Embracing the Landscape of Therapeutics" in *Cell*, volume 181 on page 1.

Associated Data

▸ **Supplementary Materials**

Summary

Go to: ▸

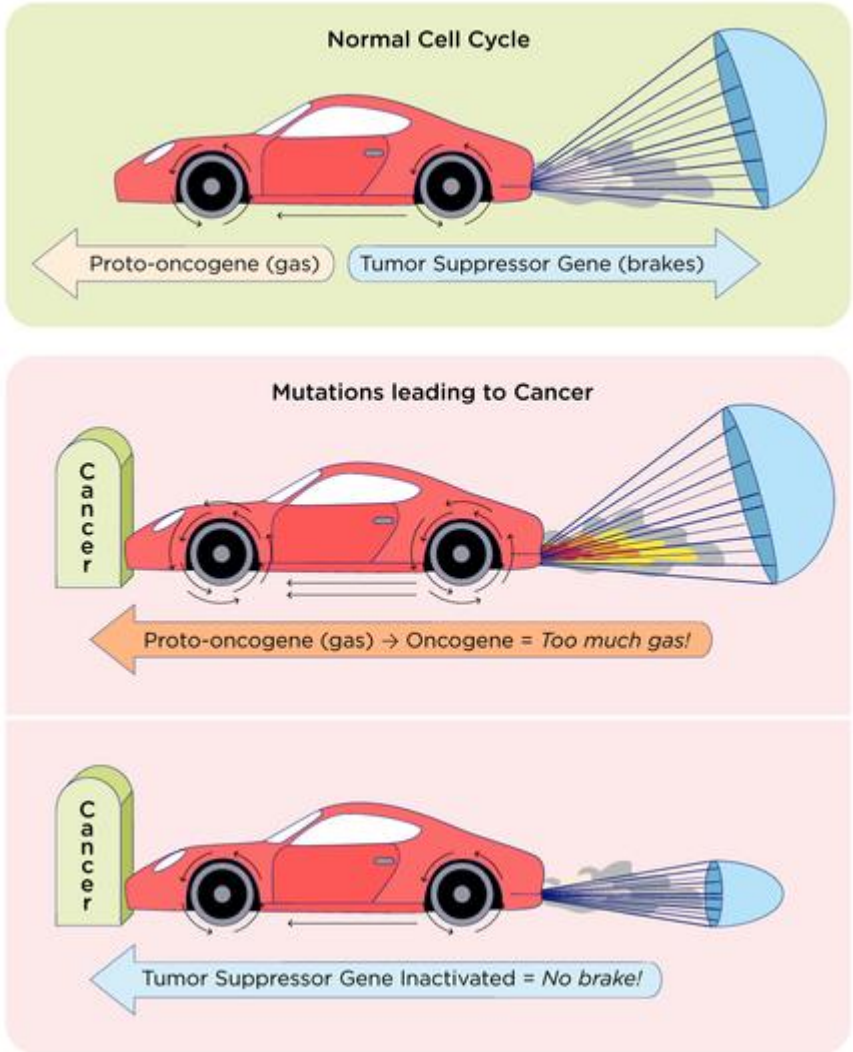
Cancer is driven by somatically acquired point mutations and chromosomal rearrangements, conventionally thought to accumulate gradually over time. Using next-generation sequencing, we characterize a phenomenon, which we term chromothripsis, whereby tens to hundreds of genomic rearrangements occur in a one-off cellular crisis. Rearrangements involving one or a few chromosomes crisscross back and forth across involved regions, generating frequent oscillations between two copy number states. These genomic hallmarks are highly improbable if rearrangements accumulate over time and instead imply that nearly all occur during a single cellular catastrophe. The stamp of chromothripsis can be seen in at least 2%–3% of all cancers, across many subtypes, and is present in ~25% of bone cancers. We find that one, or indeed more than one, cancer-causing lesion can emerge out of the genomic crisis. This phenomenon has important implications for the origins of genomic remodeling and temporal emergence of cancer.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065307/

Onkogeny a tumor supresorové geny

Proto-onkogeny

zrychlení/indukce buněčného cyklu
inhibice apoptózy

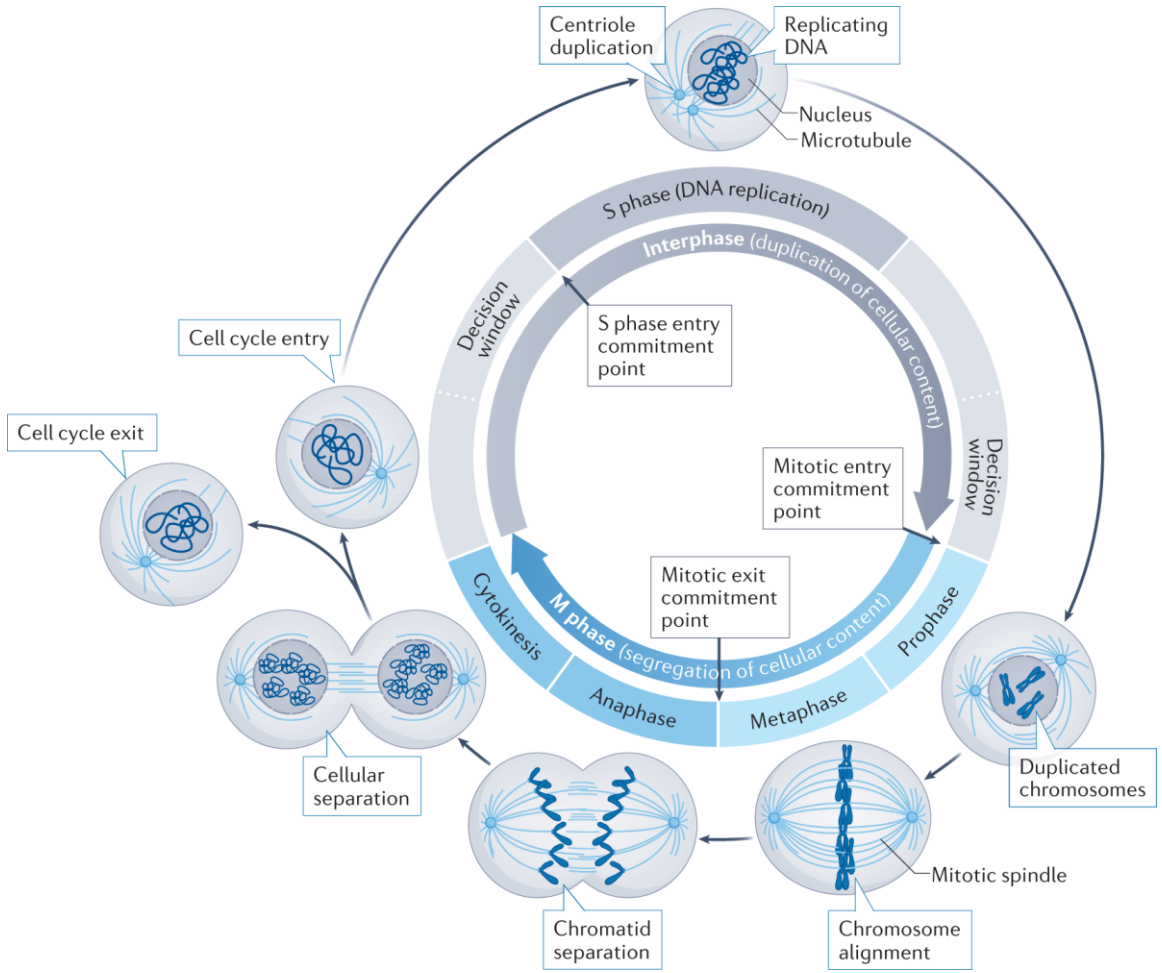


Tumor supresorové geny

zpomalení/zastavení buněčného cyklu
indukce apoptózy
opravy DNA

pravděpodobnost že za normálních získáte sadu mutací vedoucích k rakovině je velice nízká (je potřeba cca 5 mutací)
(ale jen do doby, než máte první mutaci co zrychlí b. cyklus nebo zastaví opravy DNA) => **Genetická nestabilita**

https://jackwestin.com/resources/mcat-content/control-of-gene-expression-in-eukaryotes/cancer-as-a-failure-of-normal-cellular-controls-oncogenes-tumor-suppressor-genes

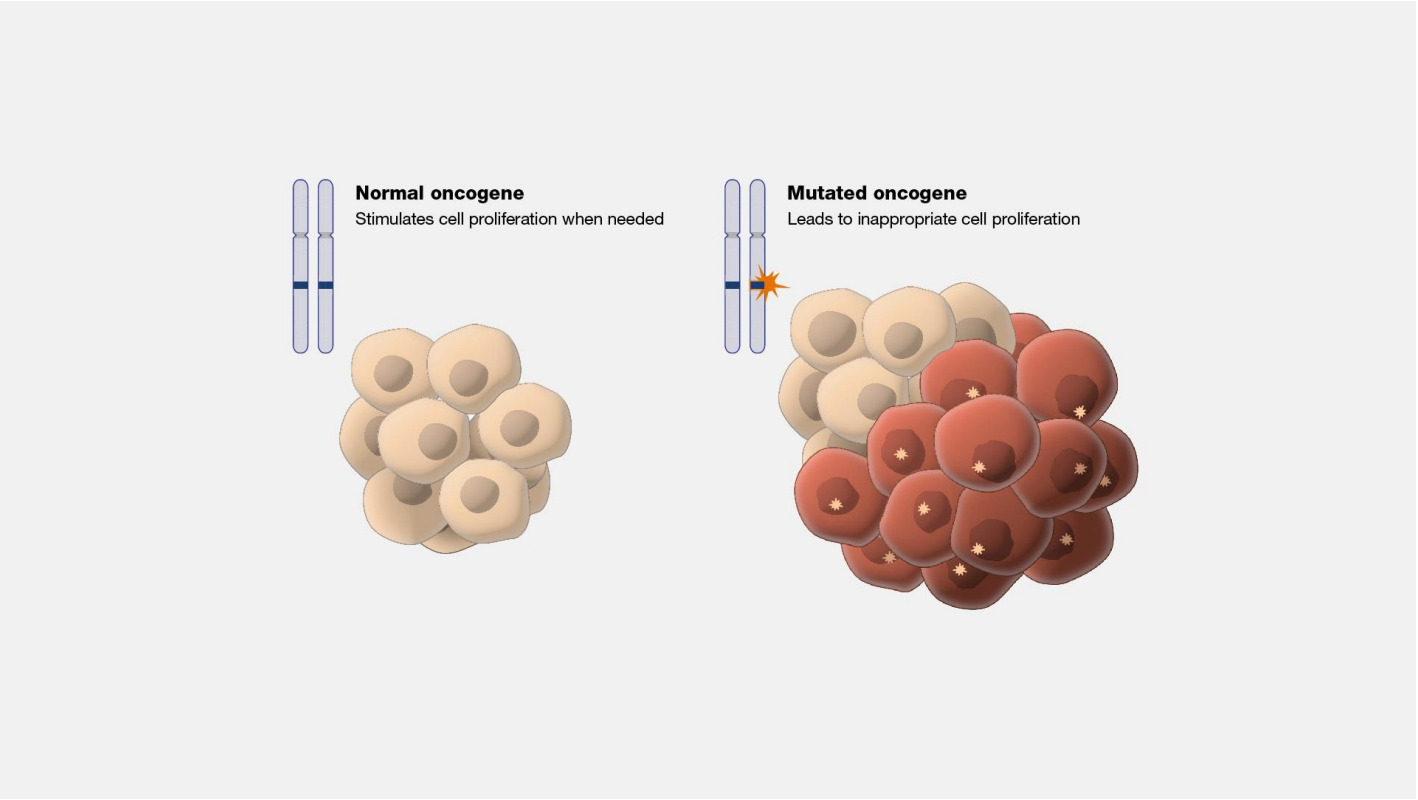


https://www.nature.com/articles/s41580-021-00404-3/figures/1

Onkogeny

Onkogen je mutovaný gen s potenciálem způsobit rakovinu. Předtím, než se gen stane mutovaným, nazývá se **protoonkogen** a má úlohu při **regulaci dělení buněk**. Rakovina může vzniknout, když je protoonkogen mutován, čímž se změní na onkogen a způsobí, že buňka začne dělit a množit se nekontrolovaně.

Mutace jsou obvykle získané a stačí mutace v jednom z páru (dominantní efekt).

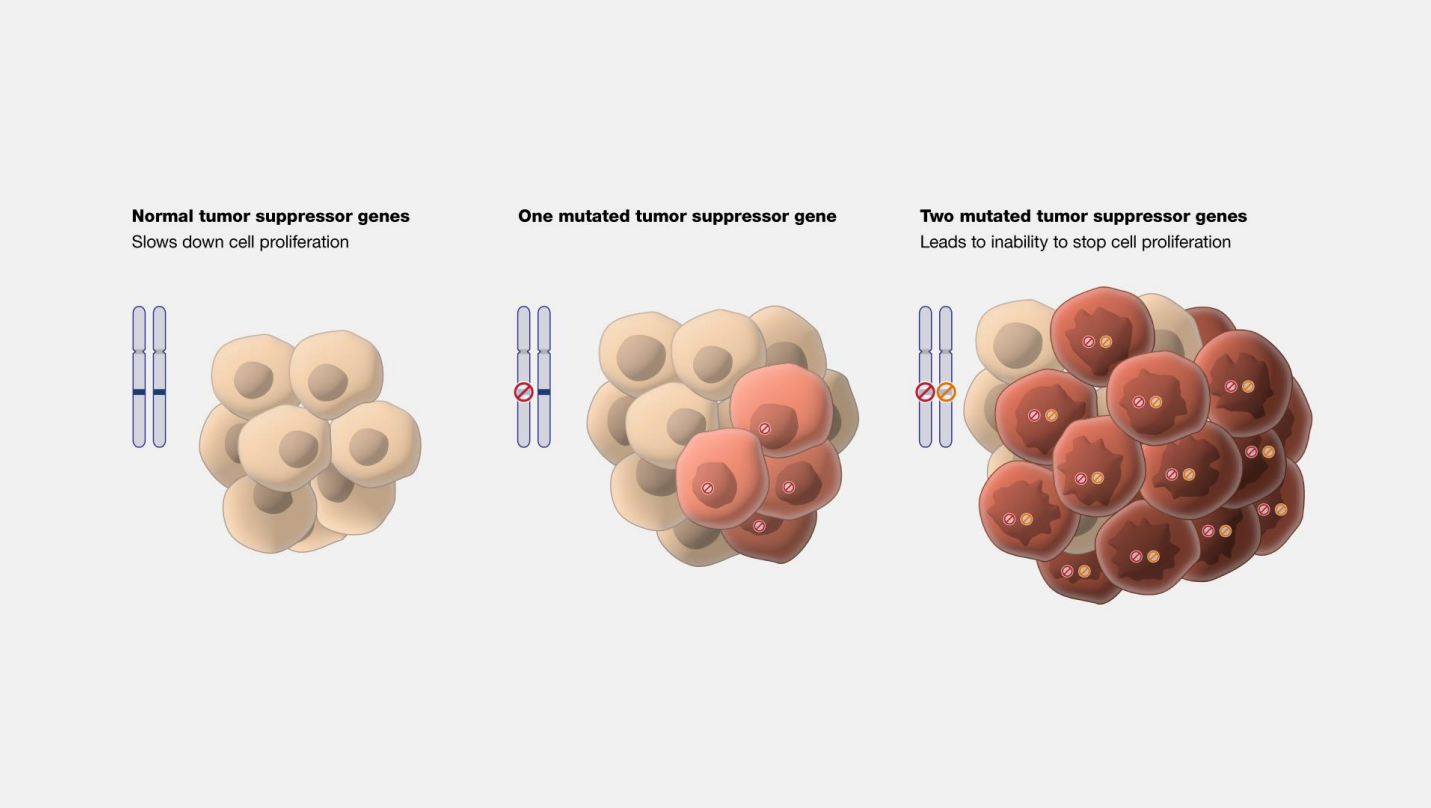


https://www.genome.gov/genetics-glossary/Oncogene

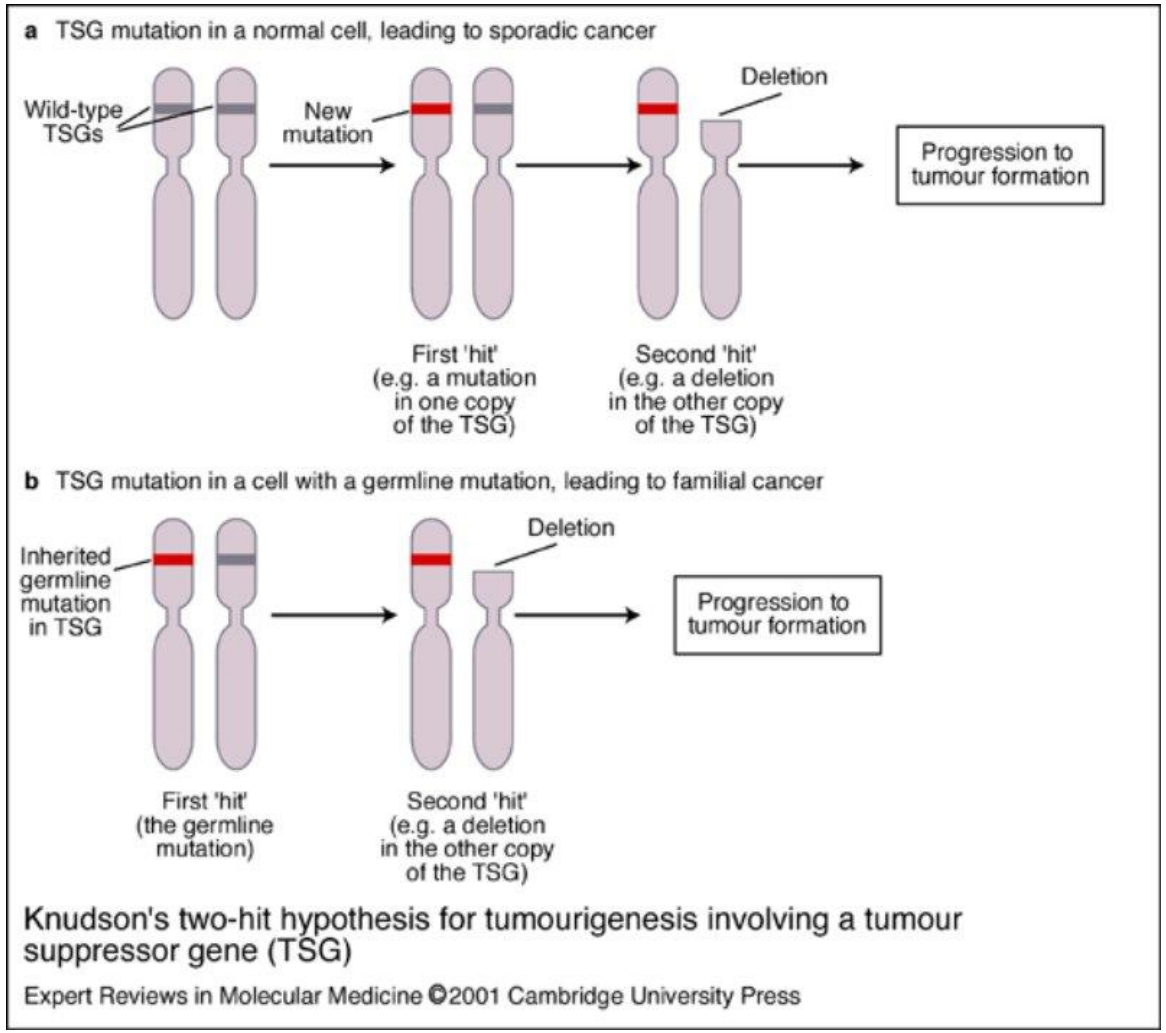
Tumor supresorové geny

Mutace v tumor supresorových genech jsou často získané. Mutace v obou kopiích páru genů potlačujících nádory se mohou vyskytnout jako výsledek stárnutí, vlivu životního prostředí nebo obojího.

Mutace může být také dědičná (např. retinoblastom, pRB). V těchto případech je mutace v jedné kopii páru genu předána od rodiče a je přítomna ve všech buňkách (germinální mutace). Mutace ve druhé kopii genu je získaná a obvykle se vyskytuje pouze v jediné buňce nebo v několika málo buňkách => **Two-hit hypothesis** (Knudson, 1971)



https://www.genome.gov/genetics-glossary/Tumor-Suppressor-Gene



Knudson's two-hit hypothesis for tumourigenesis involving a tumour suppressor gene (TSG)

https://theory.labster.com/heritable-cancer/

Representative Oncogenes and Tumor Suppressor Genes

Oncogenes			Tumor suppressor genes		
Class	Examples	Incidence	Class	Examples	Incidence
Growth factors	Sis/PDGF	Simian sarcoma	Phosphatase	PTEN	Breast, colon
Receptor tyrosine kinases	EGFR, HER2	Lung cancer, GBM, breast cancer	Cell–cell and extracellular matrix	APC, GP43/Merlin	Colon cancer, neurofibromatosis type 2
Cytoplasmic tyrosine kinases	Src, Syk, Abl	Colon cancer, head and neck cancer, CML	DNA repair and cell cycle checkpoints	BRCA1/2, pRb, p53	Breast and ovarian cancer, retinoblastoma; 70% of all
Cytoplasmic serine/threonine kinases	BRaf	Melanoma, colon	G-protein (ras) inhibitor	Neurofibromin 1	Neurofibromatosis type 1
21-kDa GTPases	H-Ras, N-Ras, K-Ras	Pancreatic cancer; 20% of all	Ubiquitin ligase	VHL	Renal cell cancer
Transcription factors	Myc	Burkitt's lymphoma; 20% of all	Dehydrogenases	Succinate dehydrogenases B and D	Pheochromocytoma

PDGF = platelet-derived growth factor; EGFR = epidermal growth factor receptor; GBM = glioblastoma multiforme; APC = adenomatosis polyposis coli; CML = chronic myelogenous leukemia; VHL = von Hippel–Lindau disease.

Shen et al. *Oncogenesis* (2018)7:25
DOI 10.1038/s41389-018-0034-x

Oncogenesis

ARTICLE Open Access

Double agents: genes with both oncogenic and tumor-suppressor functions

Libing Shen[1], Qili Shi[1] and Wenyuan Wang[1,2]

Abstract

The role of genetic components in cancer development is an area of interest for cancer biologists in general. Intriguingly, some genes have both oncogenic and tumor-suppressor functions. In this study, we systematically identified these genes through database search and text mining. We find that most of them are transcription factors or kinases and exhibit dual biological functions, e.g., that they both positively and negatively regulate transcription in cells. Some cancer types such as leukemia are over-represented by them, whereas some common cancer types such as lung cancer are under-represented by them. Across 12 major cancer types, while their genomic mutation patterns are similar to that of oncogenes, their expression patterns are more similar to that of tumor-suppressor genes. Their expression profile in six human organs propose that they mainly function as tumor suppressor in normal tissue. Our network analyses further show they have higher network degrees than both oncogenes and tumor-suppressor genes and thus tend to be the hub genes in the protein–protein interaction network. Our mutation, expression spectrum, and network analyses might help explain why some cancer types are specifically associated with them. Finally, our results suggest that the functionally altering mutations in "double-agent" genes and oncogenes are the main driving force in cancer development, because non-silent mutations are biasedly distributed toward these two gene sets across all 12 major cancer types.

Nádorová buňka

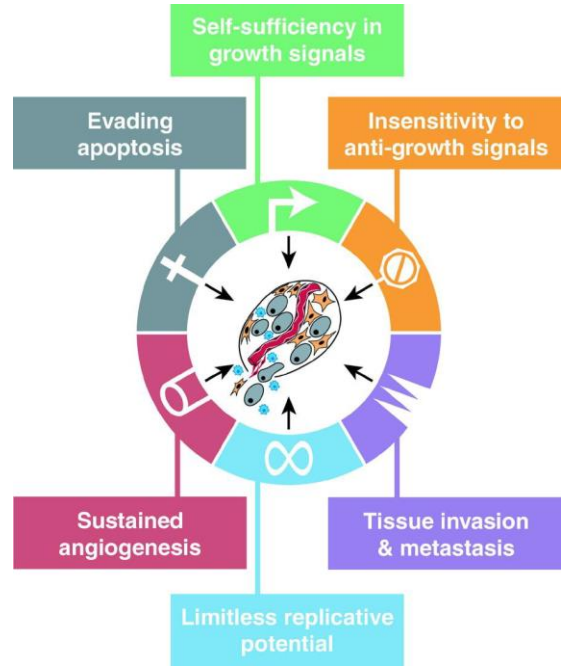
koncept tzv. "klíčových znaků rakoviny" byl poprvé navržen výzkumníky Douglasem Hanahanem a Robertem Weinbergem v roce 2000

- **růst bez přítomnosti růstových faktorů**
- **neschopnost odpovídat na signály pro ukončení růstu**
- **omezená citlivost vůči indukci programované buněčné smrti**
- **neomezená schopnost dělení (nenaráží na Hayflickův limit)**
- **stimulace růstu krevních kapilár zásobujících nádor**
- **schopnost šířit se do vzdálených tkání**

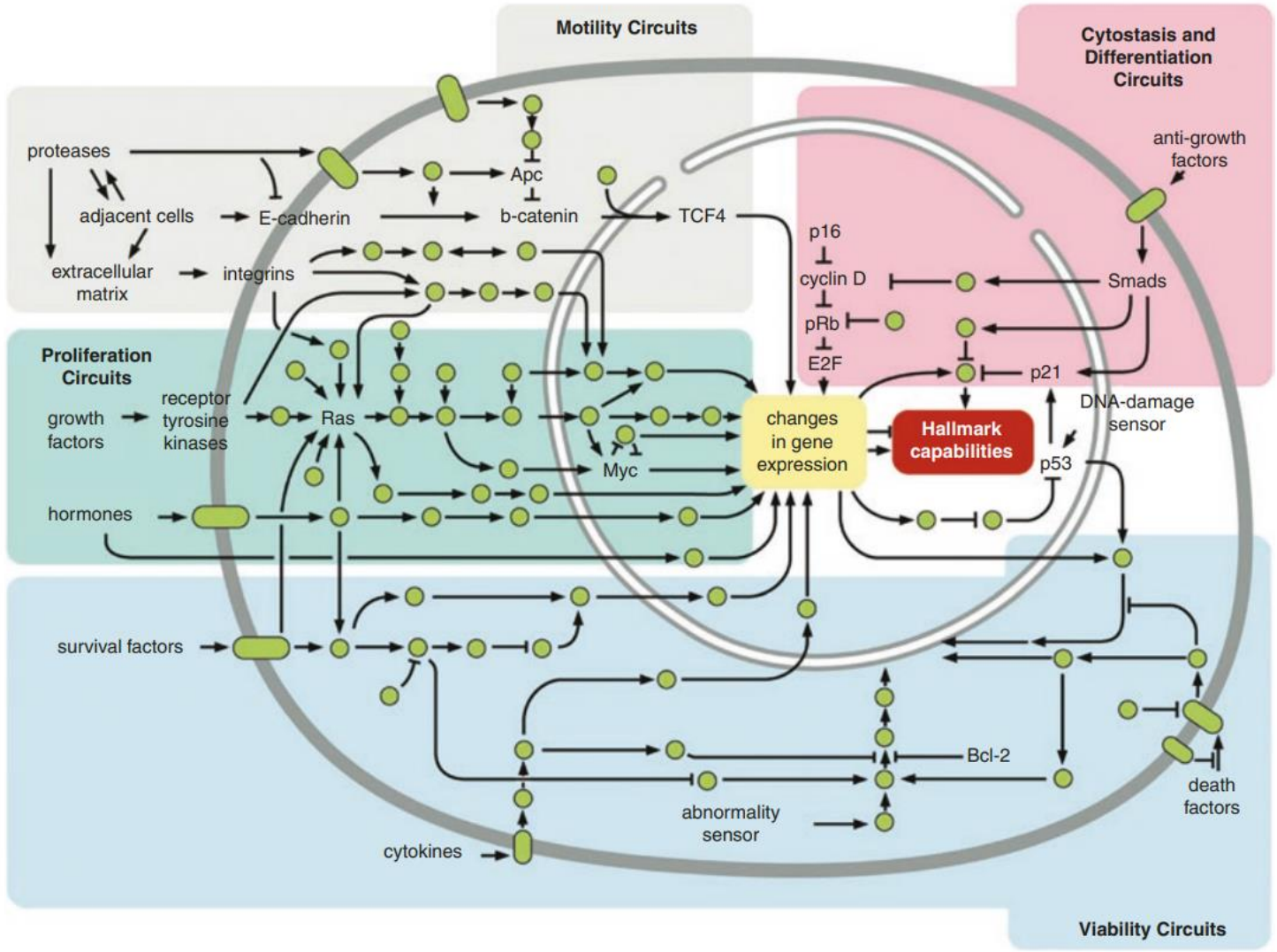
Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

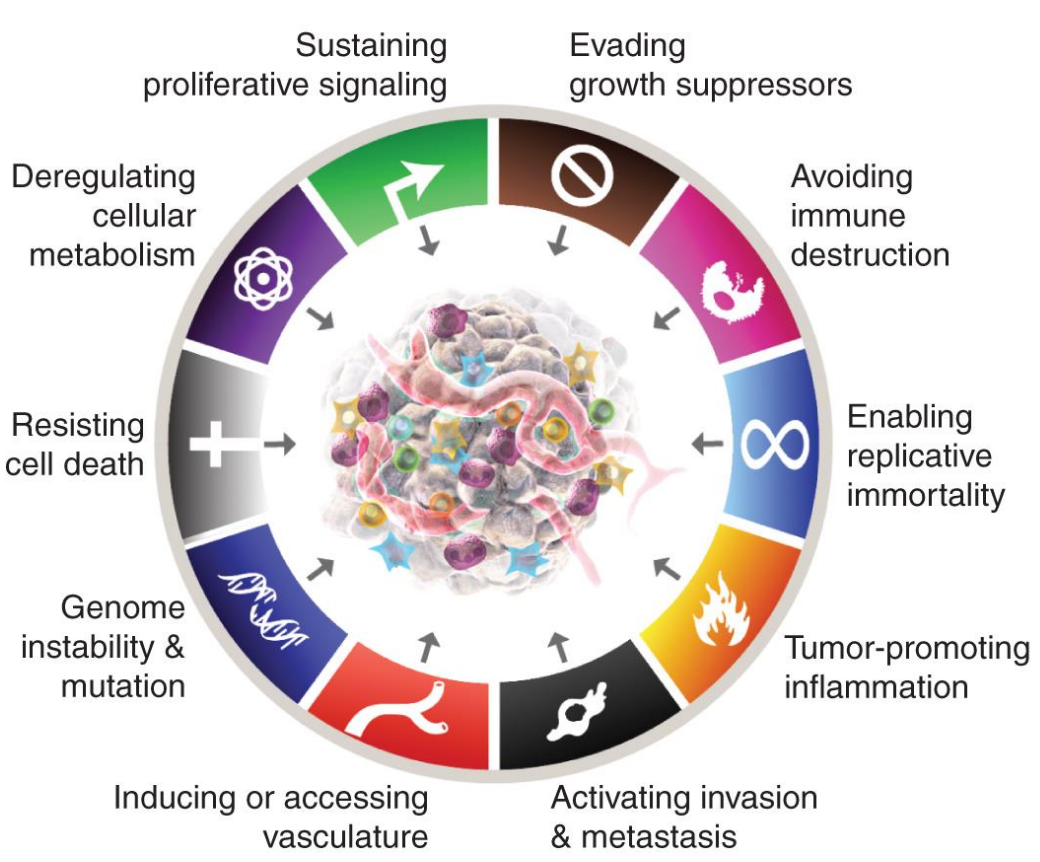
Douglas Hanahan* and Robert A. Weinberg†
*Department of Biochemistry and Biophysics and Hormone Research Institute
University of California at San Francisco
San Francisco, California 94143
†Whitehead Institute for Biomedical Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02142

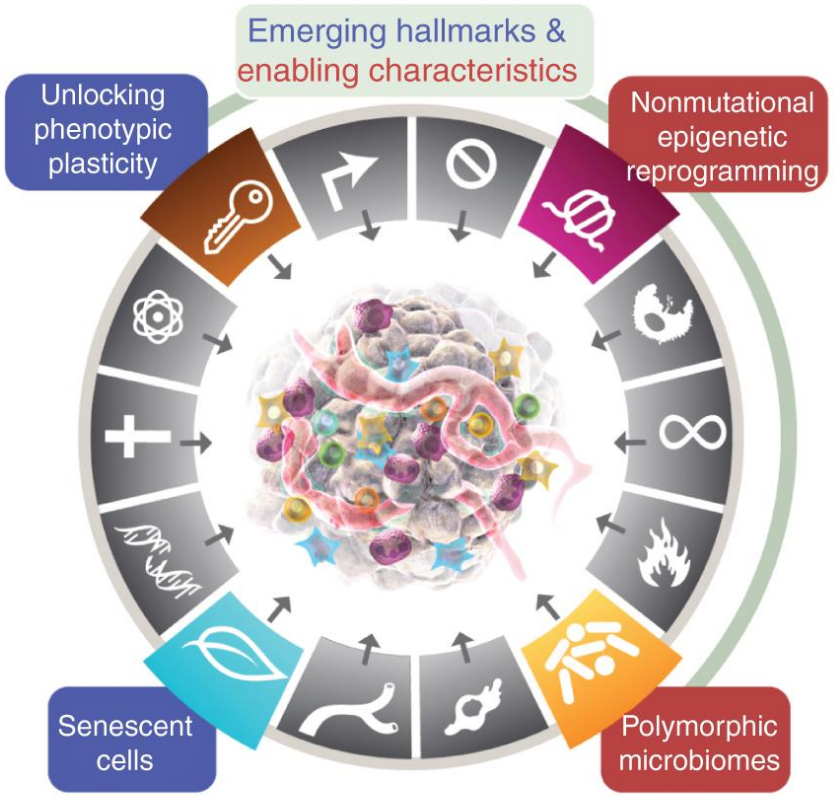


https://www.cell.com/fulltext/S0092-8674(00)81683-9

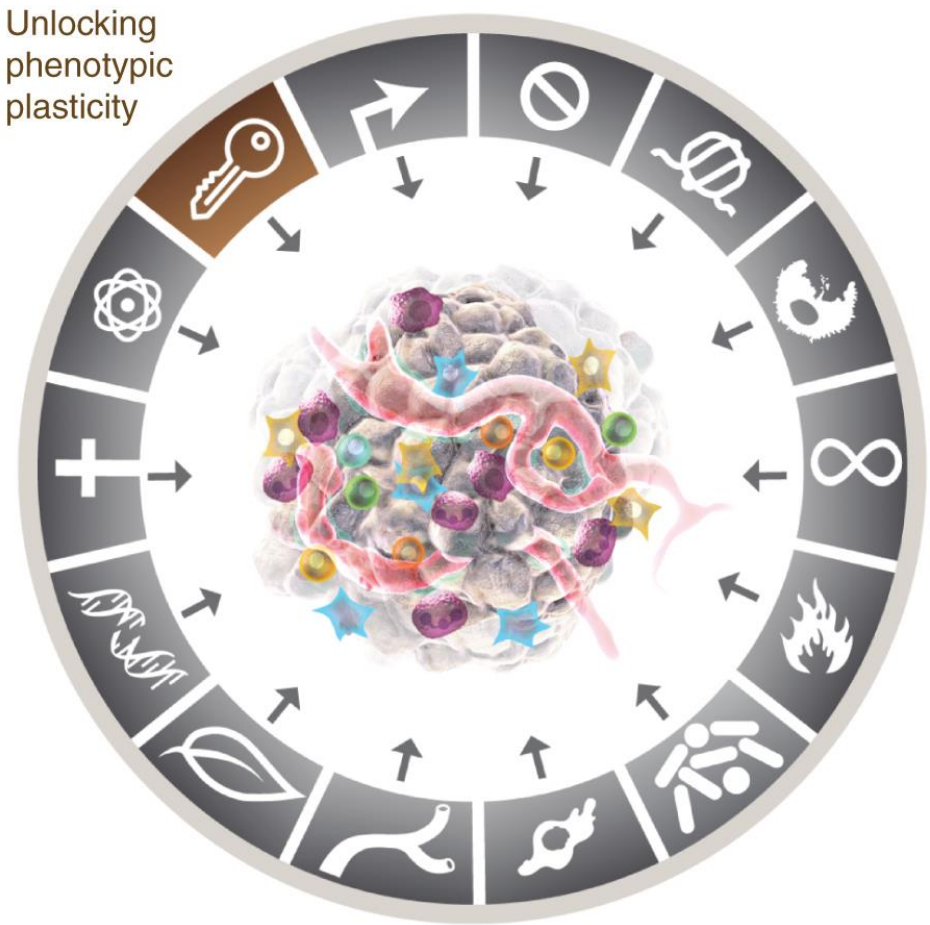


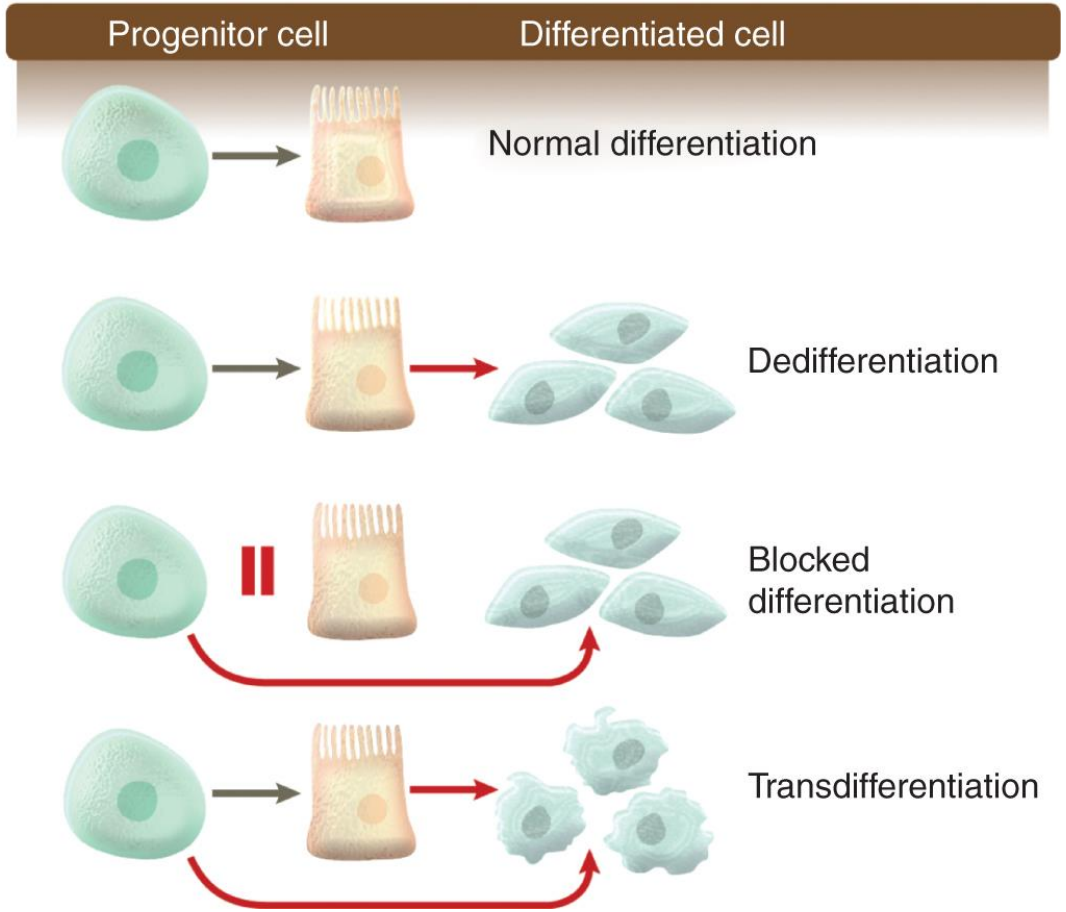
https://link.springer.com/chapter/10.1007/978-3-319-95228-4_12 https://www.cell.com/fulltext/S0092-8674(00)81683-9

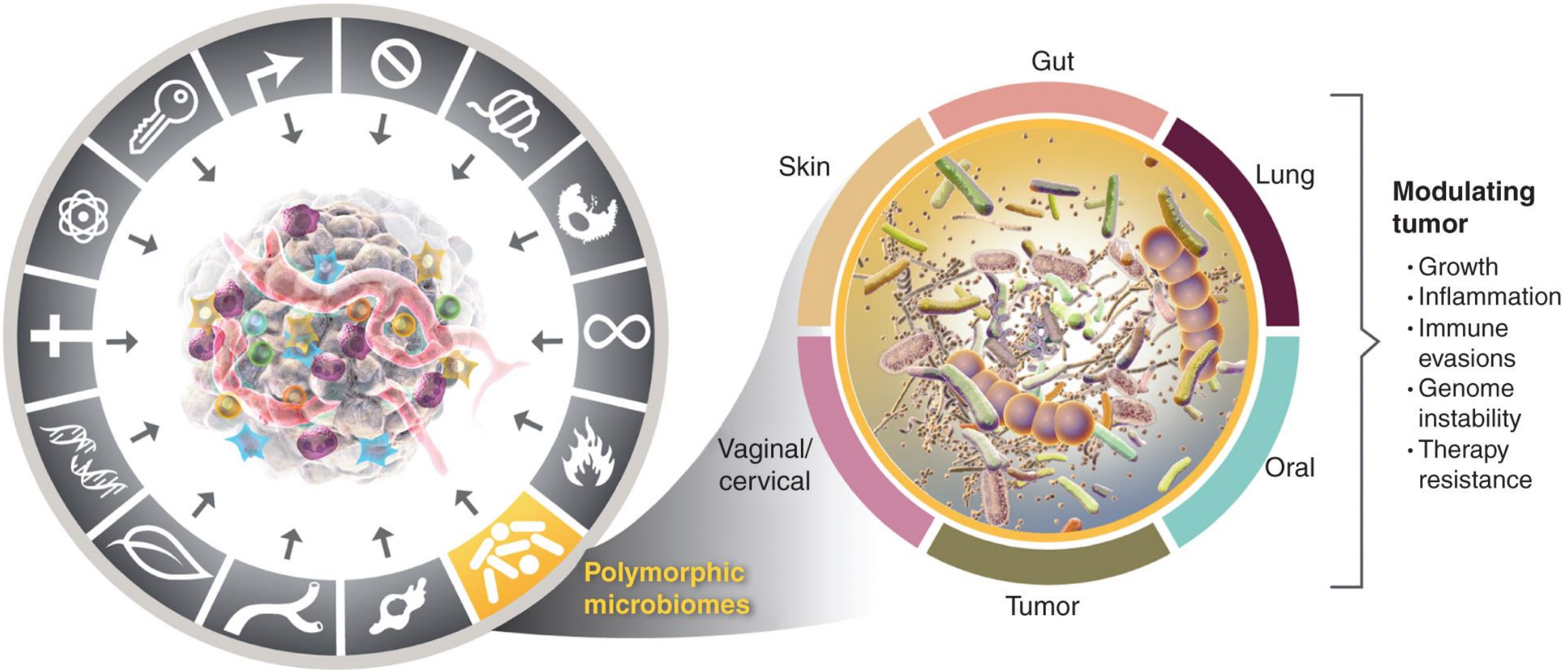


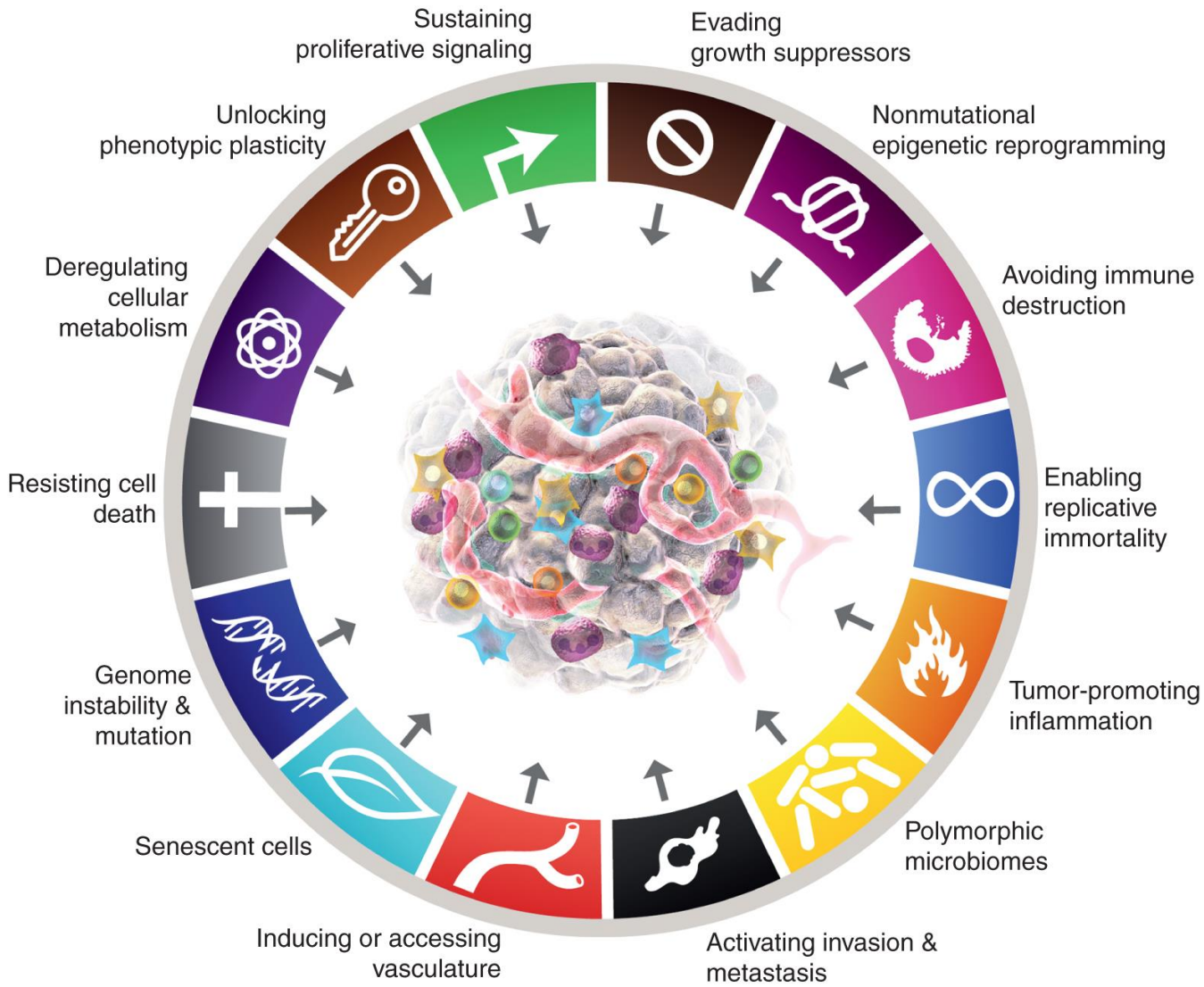


https://aacrjournals.org/view-large/figure/13775671/31fig1.jpeg


Unlocking
phenotypic
plasticity

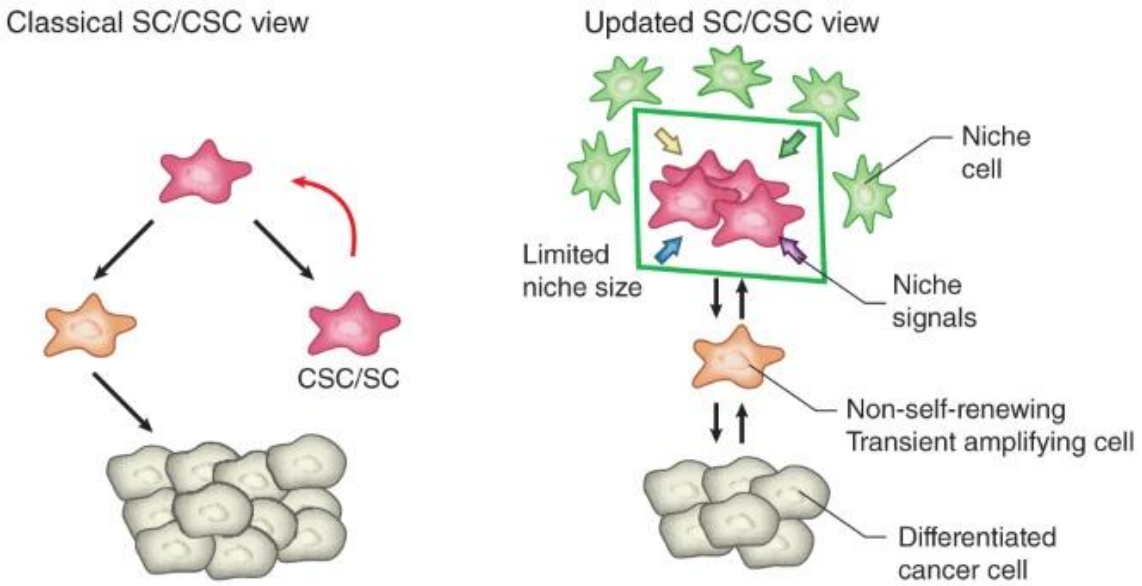

Progenitor cell
Differentiated cell
Normal differentiation
Dedifferentiation
Blocked
differentiation
Transdifferentiation


Gut
Skin
Lung
Vaginal/
cervical
Oral
Tumor
Polymorphic
microbiomes
Modulating
tumor
• Growth
• Inflammation
• Immune
evasions
• Genome
instability
• Therapy
resistance

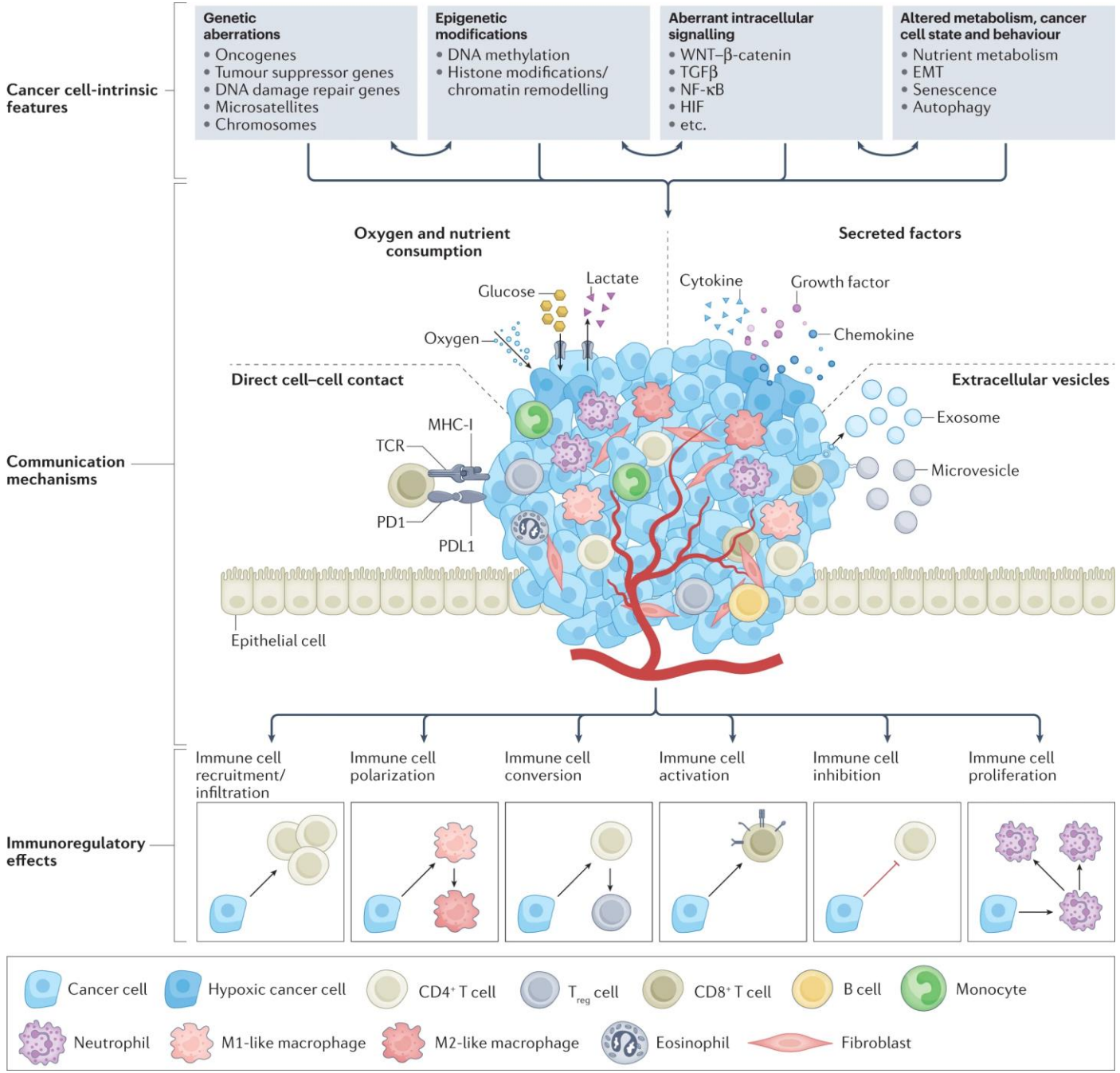

Sustaining proliferative signaling
Evading growth suppressors
Unlocking phenotypic plasticity
Nonmutational epigenetic reprogramming
Deregulating cellular metabolism
Avoiding immune destruction
Resisting cell death
Enabling replicative immortality
Genome instability & mutation
Tumor-promoting inflammation
Senescent cells
Polymorphic microbiomes
Inducing or accessing vasculature
Activating invasion & metastasis

Nádorové kmenové buňky (Cancer stem cells)

subpopulace buněk nádoru zodpovědná za jeho vznik, rezistenci a rozvoj?

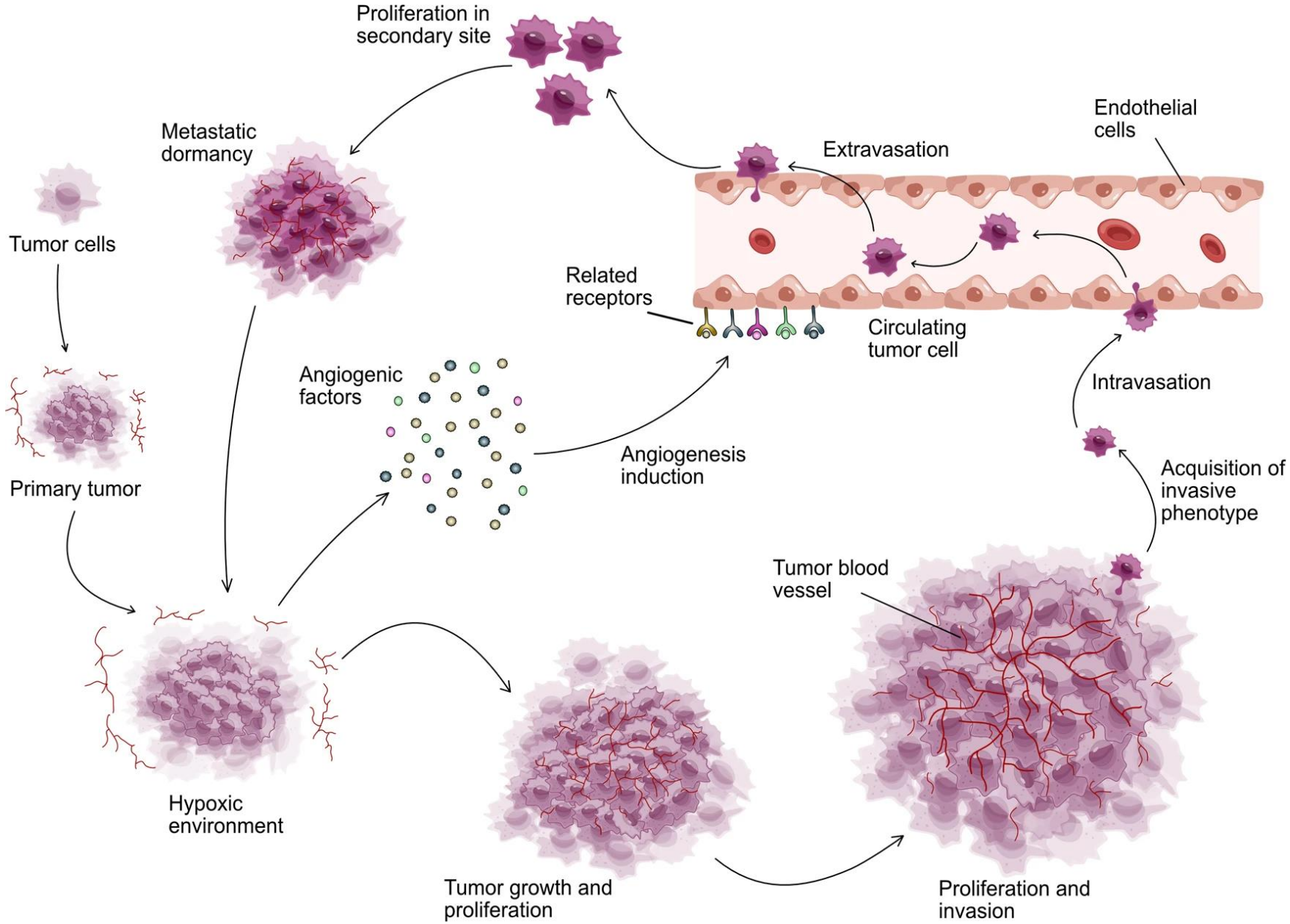


https://www.nature.com/articles/nm.4409



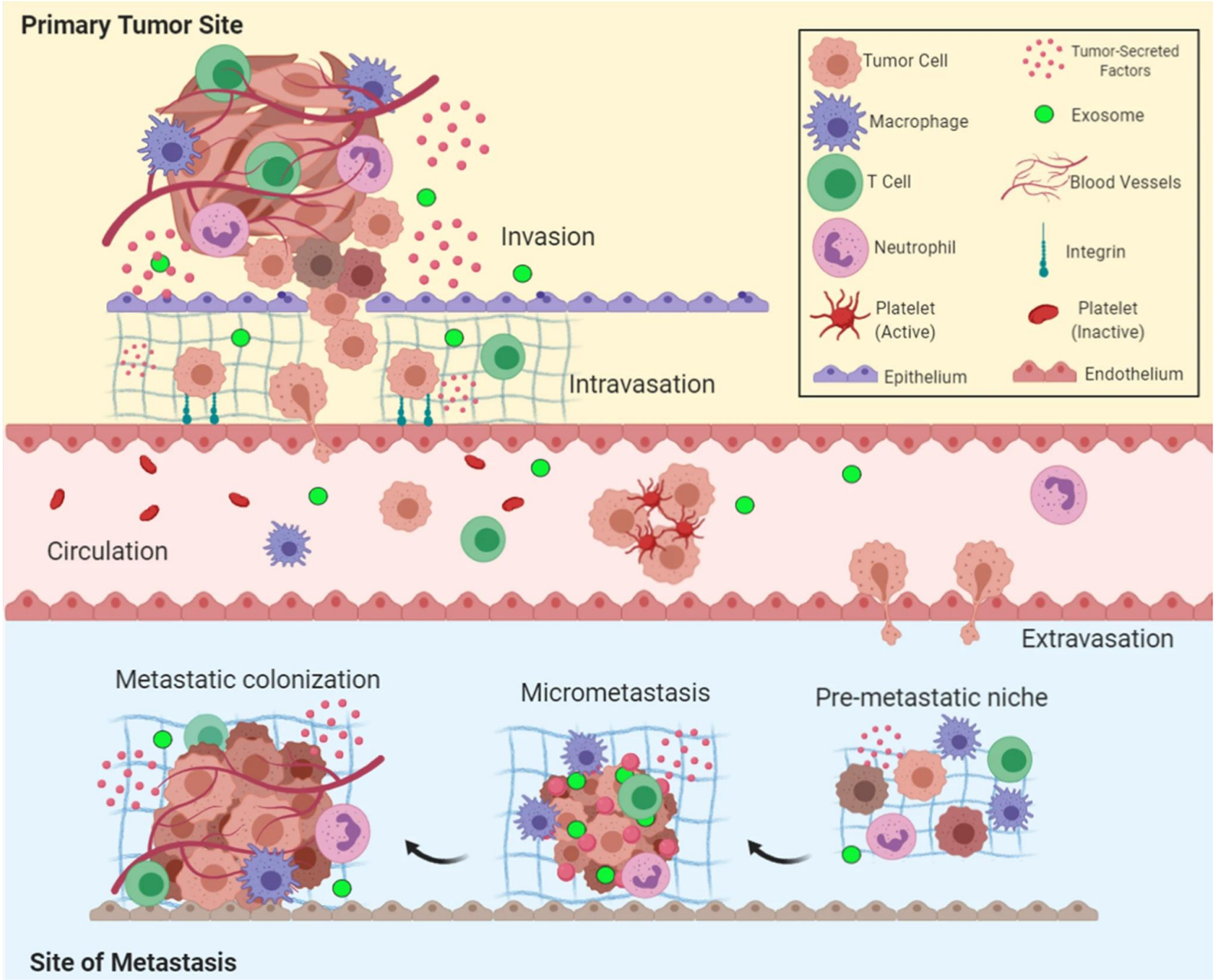
https://www.nature.com/articles/s41568-022-00544-4/figures/1

Angiogeneze

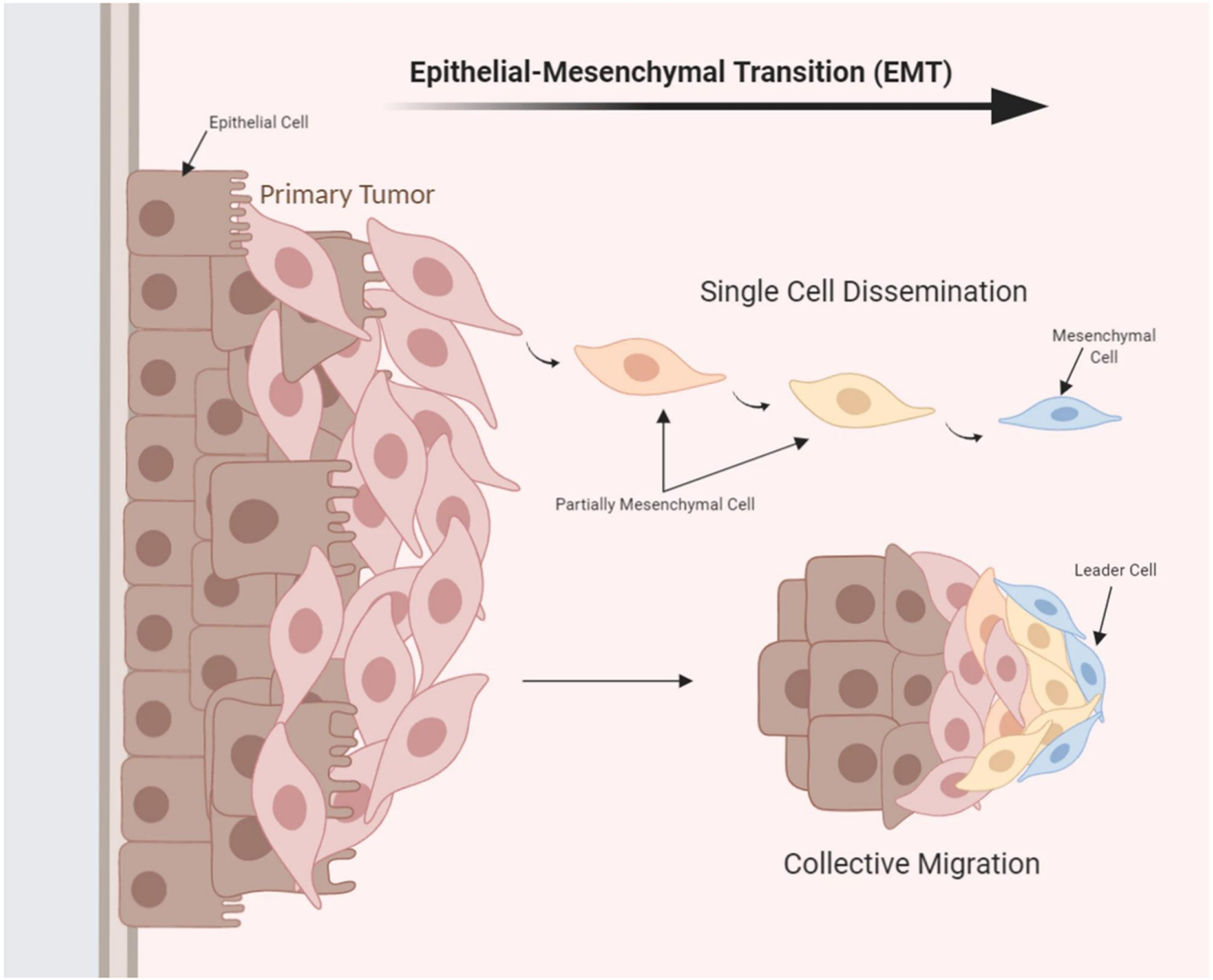


https://www.nature.com/articles/s41392-023-01460-1

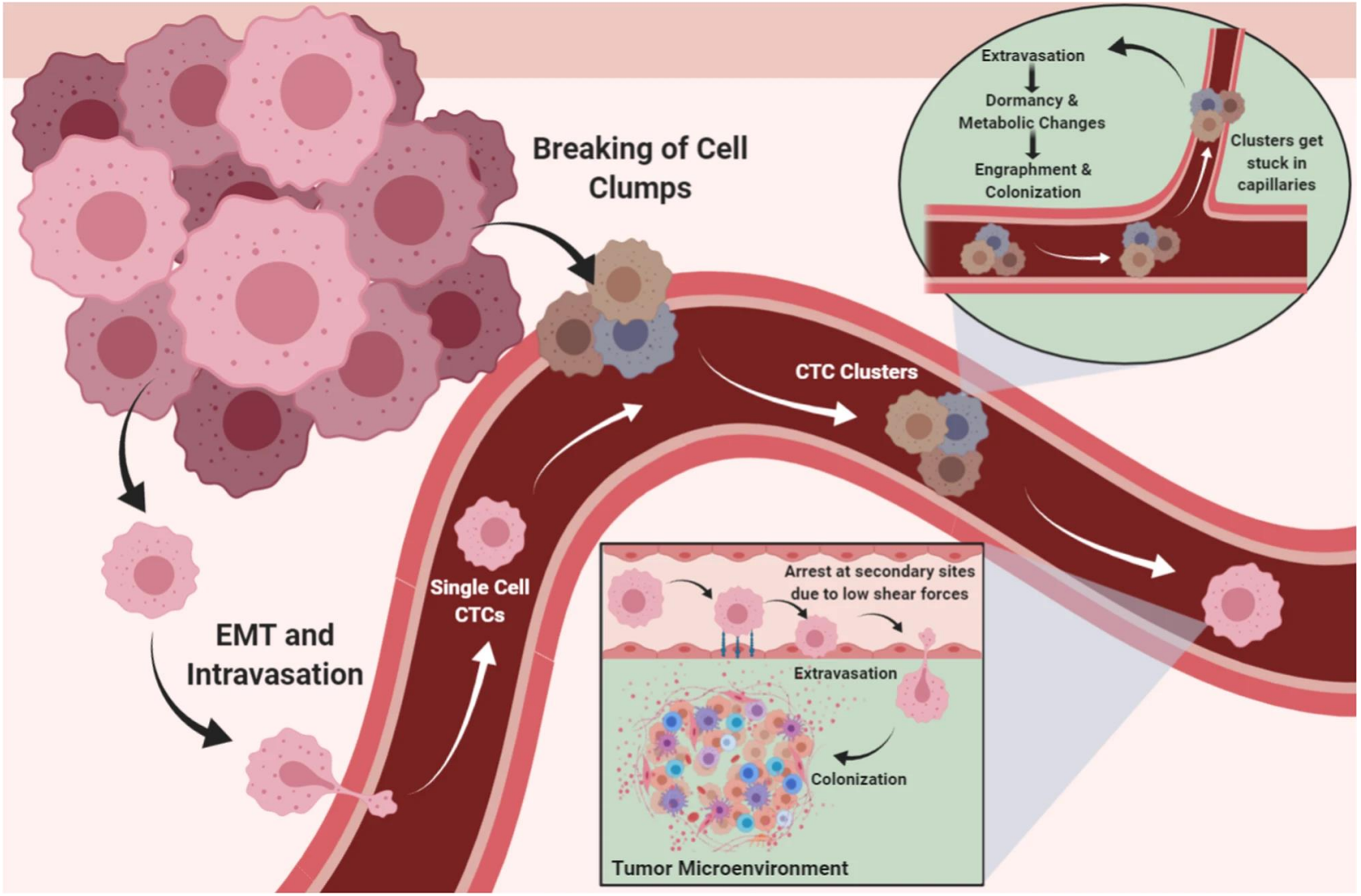
Metastáze



https://www.nature.com/articles/s41392-020-0134-x



https://www.nature.com/articles/s41392-020-0134-x



https://www.nature.com/articles/s41392-020-0134-x

Rakovina a environmentální expozice

Percival Pott (1714 – 1788)

THE

CHIRURGICAL WORKS

OF

PERCIVALL POTT, F.R.S.

AND

SURGEON to St. BARTHOLOMEW's HOSPITAL.

A certis potius et exploratis petendum esse præsidium; id ipsi, his quæ Experientia in ipsis curationibus docuerit; sicut in cæteris omnibus artibus: nam ne Agricolam quidem aut Gubernatorem Disputatione, sed Usu fieri.

A. CORN. CELSUS.

LONDON:

Printed for HAWES, W. CLARKE, and R. COLLINS, in Pater-noster Row.

M DCC LXXV.

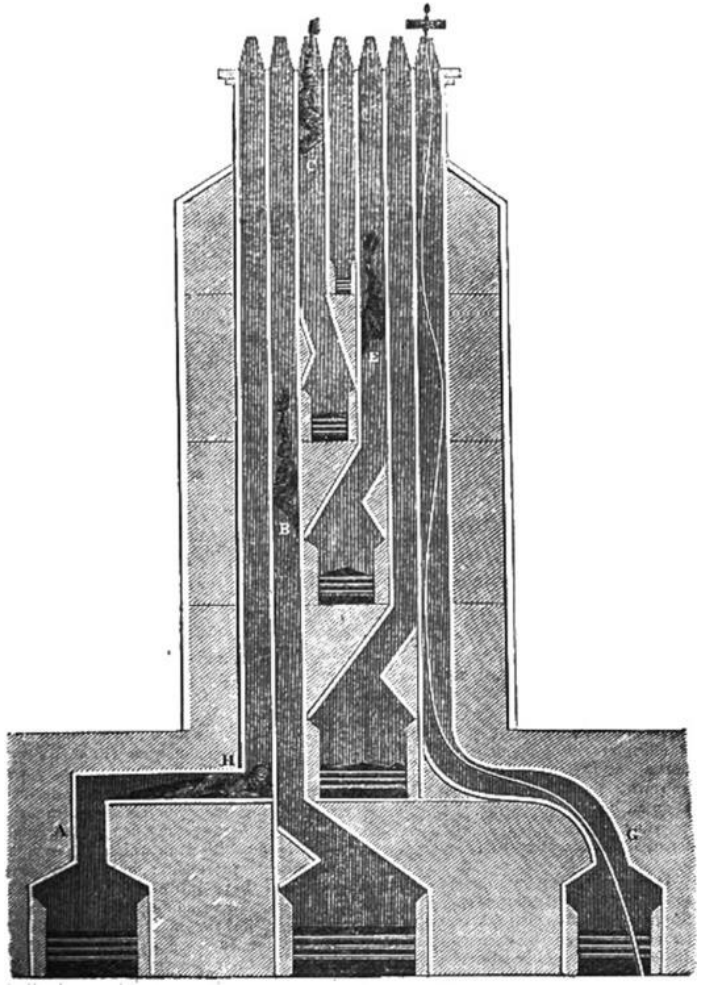
[734]

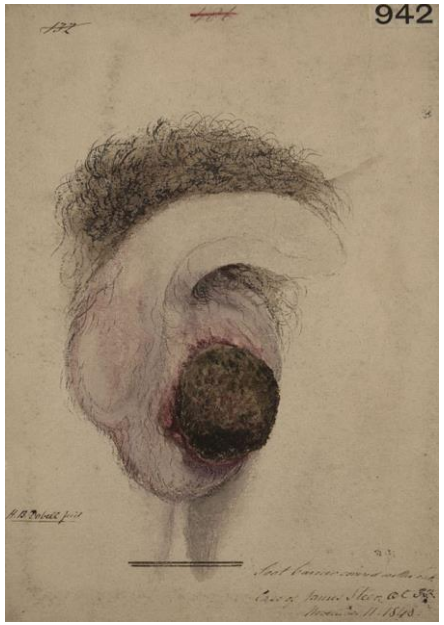
CANCER

SCROTI.

RAMAZINI has written a book de morbis artificum; the Colic of Poictou is a well-known distemper; and every body is acquainted with the disorders to which painters, plummers, glaziers, and the workers in white lead, are liable: but there is a disease as peculiar to a certain set of people, which has not, at least to my knowledge, been publickly noticed; I mean the chimney-sweepers' cancer.

It is a disease which always makes its first attack on, and its first appearance in, the inferior part of the scrotum; where it produces a superficial, painful, ragged, ill-looking sore, with hard and rising edges: the trade call it the soot-wart. I never saw it under the age of puberty, which is, I suppose, one reason, why it is generally taken, both by



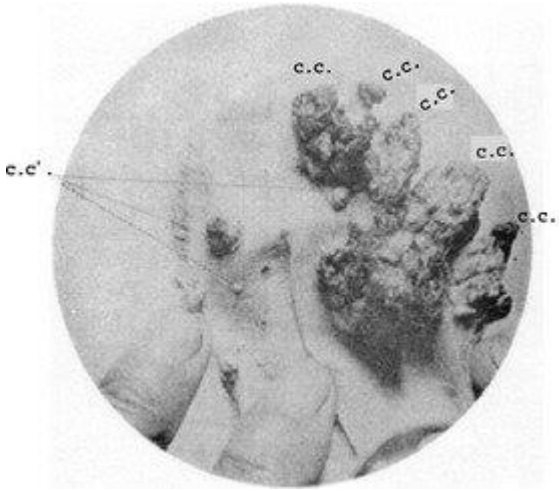


https://www.sciencedirect.com/science/article/pii/S0738081X21002601 https://www.sciencedirect.com/science/article/pii/S0738081X21002601

Rakovina a environmentální expozice

indukce karcinogeneze u králíka (vnitřní strana ucha potírána dehtem, první experimentální rakovina u zvířecího modelu, 1915)

K. Yamagiwa a A. Fujinami



https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.28005

https://www.researchgate.net/publication/259244349_Gist_of_Dr_Katsusaburo_Yamagiwa%27s_papers_entitled_Experimental_study_on_the_pathogenesis_of_epithelial_tumors_I_to_VI_reports/figures?lo=1

International Agency for Research on Cancer
World Health Organization

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

Agents Classified by the IARC Monographs, Volumes 1–134

Group 1	Carcinogenic to humans	127 agents
Group 2A	Probably carcinogenic to humans	95 agents
Group 2B	Possibly carcinogenic to humans	323 agents
Group 3	Not classifiable as to its carcinogenicity to humans	500 agents

https://monographs.iarc.who.int/agents-classified-by-the-iarc/

THE IARC CLASSIFICATION OF CARCINOGENS

The IARC classification, which was adopted in 1987–1988 on the basis of more than 15 years of experience in evaluating potentially carcinogenic agents, constitutes one of the first evidence-based systems in biomedicine. At about the same time (in the early 1990s), the term "evidence-based medicine" was introduced in clinical research. The classification as it is used today is based on the following five elements.

(a) The evidence of carcinogenicity from studies in humans is evaluated and classified into one of four categories: sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity (which also covers agents for which there are no data), or evidence suggesting lack of carcinogenicity.

(b) The evidence of carcinogenicity in experimental animals is evaluated separately and is classified into one of the same four categories as in (a).

(c) Mechanistic and other relevant data are described.

(d) The body of evidence in (a), (b), and (c) is considered as a whole to reach an overall evaluation in one of the following categories.

Group 1: The agent is *carcinogenic to humans*.

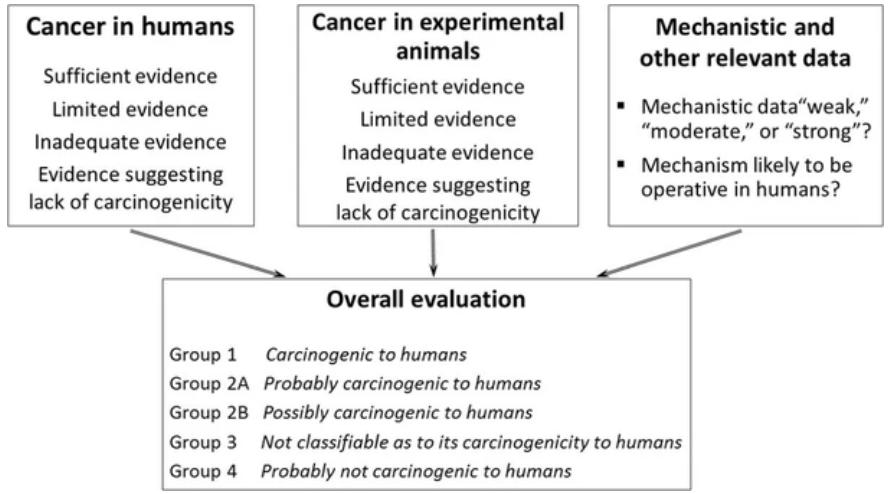
Group 2A: The agent is *probably carcinogenic to humans*.

Group 2B: The agent is *possibly carcinogenic to humans*.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.

Group 4: The agent is *probably not carcinogenic to humans*.

(e) A Rationale section explains the main lines of reasoning that the Working Group used to reach its evaluation and classification. Should significant differences of scientific interpretation occur among Working Group members, a summary of the alternative interpretations is provided.



https://monographs.iarc.who.int/agents-classified-by-the-iarc/

https://link.springer.com/article/10.1007/s12550-016-0265-7/figures/1

Cancer Health Effects

- RoC Latest Edition
- RoC Process & Listing Criteria
- RoC Handbook
- Completed Evaluations
- Ongoing Evaluations
- Environmental Factors Under Consideration

15th Report on Carcinogens

https://ntp.niehs.nih.gov/go/roc15

The U.S. Department of Health and Human Services (HHS) released the 15th Report on Carcinogens on December 21, 2021. The Report on Carcinogens is a congressionally mandated, science-based public health document that NTP prepares for the HHS Secretary. This cumulative report now includes 256 listings of substances — chemical, physical, and biological agents; mixtures; and exposure circumstances — that are known or reasonably anticipated to cause cancer in humans.

Discover more details about the report and its new listings below. Also, check out the Data Exploration Dashboard, which provides an easy-to-understand visual breakdown of all substances listed in the document and their associated cancers.

- Table of Contents
- Press Release
- Fact Sheet on the 15th Report on Carcinogens
- Federal Register notice
- Journal Publication
  - Cancer Hazard Evaluations for Contemporary Needs: Highlights from New National Toxicology Program Evaluations and Methodological Advancements

Methods for Identifying Human Carcinogens

Epidemiology studies	Experimental animal studies	Mechanistic and related studies	Emerging mechanistic data
Occupational exposure General population: • Environmental exposures • Lifestyle exposures (e.g., tobacco smoking) • Exposure scenarios Patients receiving medical treatments (e.g., chemotherapeutic drugs)	Typically rodents Exposure to multiple doses for most of their lifetimes Doses: Relatively high but not toxic, chosen to increase the sensitivity of the assay, because a small number of animals are used to predict the effects in millions of people	Genomic data/mutational signatures Key characteristics of carcinogens: Biological effects common to many different carcinogens Hallmarks of cancer: Common traits by which a normal cell transforms to a cancer cell Adverse outcome pathway: Modeling of the sequence of molecular and cellular events that result in cancer following exposure to a carcinogen	High-throughput screening: • Tox21 • ToxCast *in vitro* assays NextGen approaches, including grouping chemicals, and "read-across" approaches, such as quantitative structure-activity relationship models

https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria

Chronický zánět asociovaný s rakovinou

více než 20% malignit je asociováno s chronickým zánětem a infekcemi

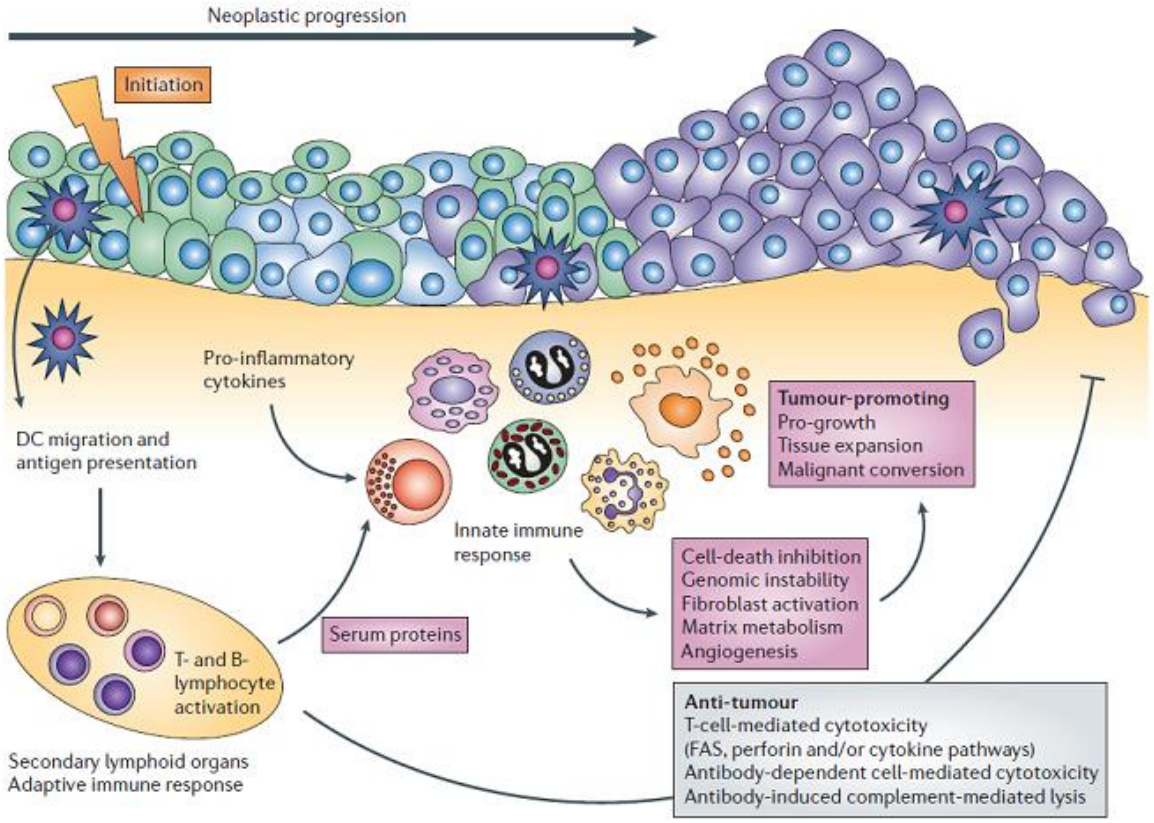


Table 1 **Chronic inflammatory conditions associated with neoplasms**

Pathologic condition	Associated neoplasm(s)	Aetiologic agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibres, silica particles
Bronchitis	Lung carcinoma	Silica, asbestos, smoking (nitrosamines, peroxides)
Cystitis, bladder inflammation	Bladder carcinoma	Chronic indwelling, urinary catheters
Gingivitis, lichen planus	Oral squamous cell carcinoma	
Inflammatory bowel disease, Crohn's disease, chronic ulcerative colitis	Colorectal carcinoma	
Lichen sclerosus	Vulvar squamous cell carcinoma	
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma	Alcholism, mutation in trypsinogen gene on Ch. 7
Reflux oesophagitis, Barrett's oesophagus	Oesophageal carcinoma	Gastric acids
Sialadenitis	Salivary gland carcinoma	
Sjögren syndrome, Hashimoto's thyroiditis	MALT lymphoma	
Skin inflammation	Melanoma	Ultraviolet light
Cancers associated with infectious agents		
Opisthorchis, Cholangitis	Cholangiosarcoma, colon carcnoma	Liver flukes (*Opisthorchis viverrini*), bile acids
Chronic cholecystitis	Gall bladder cancer	Bacteria, gall bladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Mononucleosis	B-cell non-Hodgkin's lymphoma, Burkitts lymphoma,	Epstein-Barr Virus
AIDS	Non-Hodgkin's lymphoma, squamous cell carcinomas, Kaposi's sarcoma	Human immunodeficiency virus, human herpesvirus type 8
Osteomyelitis	Skin carcinoma in draining sinuses	Bacterial infection
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonnorrhoea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen	Schistosomiasis

https://www.nature.com/articles/nature01322
https://www.astro.org/Patient-Care-and-Research/Research/Professional-Development/Research-Primers/Tumor-Immune-Interactions

Viry asociované s rakovinu

Virus	Genetic Material	Route of Transmission	Associated Cancer Types
EBV	dsDNA	Oral transmission *via* saliva, transfusion (reported)	Burkitt lymphoma, classic Hodgkin's lymphoma (especially mixed-cellular subtypes), Lymphomas in immunosuppressed individuals (post-transplant and HIV-associated lymphoproliferative disorders), Extra-nodal Natural Killer/T-cell lymphoma (nasal type), Nasopharyngeal carcinoma, Gastric cancer (LD), Diffuse large B-cell lymphoma of the elderly (LD), Lymphoepithelioma-like carcinoma (LD)
HBV	partially dsDNA	Percutaneous and permucosal exposure to infected body fluids, sexual contact, blood and blood product transfusion, solid organ transplantation from an infected donor, unsafe needle practices, vertical transmission	Hepatocellular carcinoma, Cholangiocarcinoma (LD), Hodgkin's lymphoma (LD), non-Hodgkin's lymphoma (LD), Pancreatic Carcinoma (LD)
HCV	ssRNA(+)	Blood and blood product transfusion, solid organ transplantation from an infected donor, unsafe needle practices, perinatal and sexual transmission (less effectively)	Hepatocellular carcinoma, non-Hodgkin's lymphoma (especially B-cell), Biliary tract and Gallbladder carcinoma (LD), Myeloid Leukemia (LD), Thyroid carcinoma (LD)
HHV-8	dsDNA	Oral transmission *via* saliva, parenteral transmission (possible), transplantation (reported)	Kaposi's sarcoma, Primary effusion lymphoma, Multicenter Castleman's Disease
HPV	dsDNA	Skin-to-skin contact, skin-to-mucosa contact, perinatal transmission (rare)	Cervical Cancer (HPV:16,18, 31,33,35,39,45,51,52,56,58,59), HPV16: cancer of the vulva, vagina, penis and anus, oral cancer, oropharyngeal carcinoma, tonsillar carcinoma, cancer of the larynx
MCPyV	dsDNA	Skin contact (Not clarified)	Merkel Cell Carcinoma, chronic lymphocytic leukemia (reported)
HTLV-1	ssRNA(+)	Sexual transmission, vertical transmission (mostly through breastfeeding), transfusion of cellular blood products, unsafe needle practices (rare)	Adult T-cell leukemia/lymphoma
HIV-1	ssRNA(+)	Sexual transmission, parenteral transmission (blood and blood product transfusion, unsafe needle practices), vertical transmission (placental, child delivery, breastfeeding)	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma, Cervical and anogenital carcinoma, Cancer of the conjunctiva, Cancer of the vulva, vagina, and penis (LD), Skin carcinoma (LD), Lung and Hepatocellular carcinoma (LD)

"IARC monographs on the evaluation of carcinogenic risks to humans, volume 100 B, biological agents" (4) is the source of the information in this table.
LD, Limited Data.

https://www.frontiersin.org/files/Articles/687631/fonc-11-687631-HTML/image_m/fonc-11-687631-t001.jpg

https://www.cancer.org/cancer/risk-prevention/infections/infections-that-can-lead-to-cancer/viruses.html

infikované buňky více hynou, je nutno je nahrazovat => více dělení
+ toxické produkty imunitního systému indukující mutace (**Hepatitida C**)

integrace do genomu, produkty virových genů nepřímo ničící tumor supresorové geny (p53) (**HPV**)
(transformace HPV je vzácná, záleží na subtypu, virovém loadu, stavu imunitního systému)

často projev pouze v imunosuprimovaných jedincích (**HHV-8**)

Léčba

Stem cell therapy

- Pluripotent stem cells- iPSC (sipuleucel-T)
- Adult stem cells- MSC-INFβ
- Cancer stem cells- Venetoclax

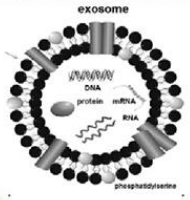
Gene therapy

✓ Oncolytic Virotherapy (OV)

- Directly lyses tumor cells and introduces wild-type tumor suppressor genes into cells
- Gendicine, Oncorine (rAd5-H101), Imlygic, Rexin-G, Kymriah, Zalmoxis

Exosome based therapy

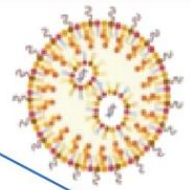
- Tumor-released exosomes
- Dendritic cell-derived exosomes
- T lymphocyte cell-derived exosomes
- B lymphoma cell-derived exosomes
- Natural killer cell-derived exosomes
- Myeloid-derived suppressor CD exosomes
- Mast cell-derived exosomes
- Neutrophil-derived exosomes



Nanoparticle based therapy

Liposome

- Polymer based nanocarriers
- Lipid based nanocarriers
- Drug conjugates
- Viral nanoparticles
- Inorganic nanoparticle

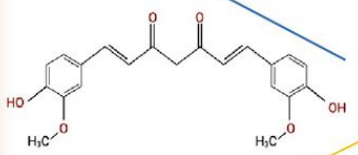


Dendrimer

Natural Product therapy

✓ Plant based secondary metabolites

- Natural anti-cancer compound: Curcumin, genistein, 3,3 diindolylmethane, lycopene, piperine, epigallocatechin-3-gallate, vitamin D, resveratrol, selenium, fisetin, dammarane type triterpene, sapogenin, tannic acid and quercetin



https://link.springer.com/article/10.1007/s11033-023-08809-3