An Introduction to Cancer Cell Biology and Genetics

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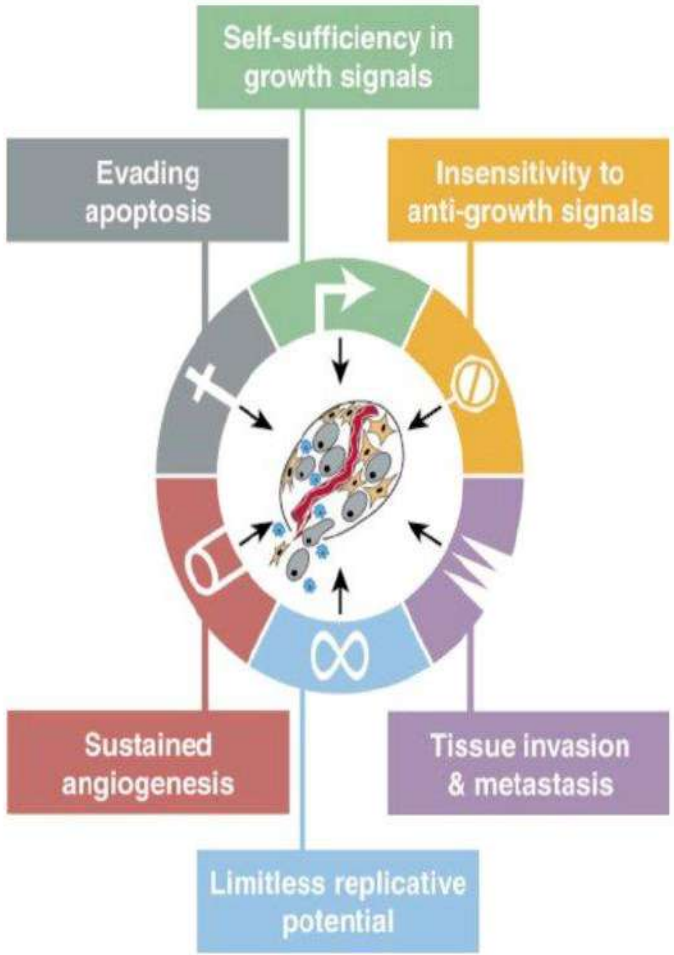
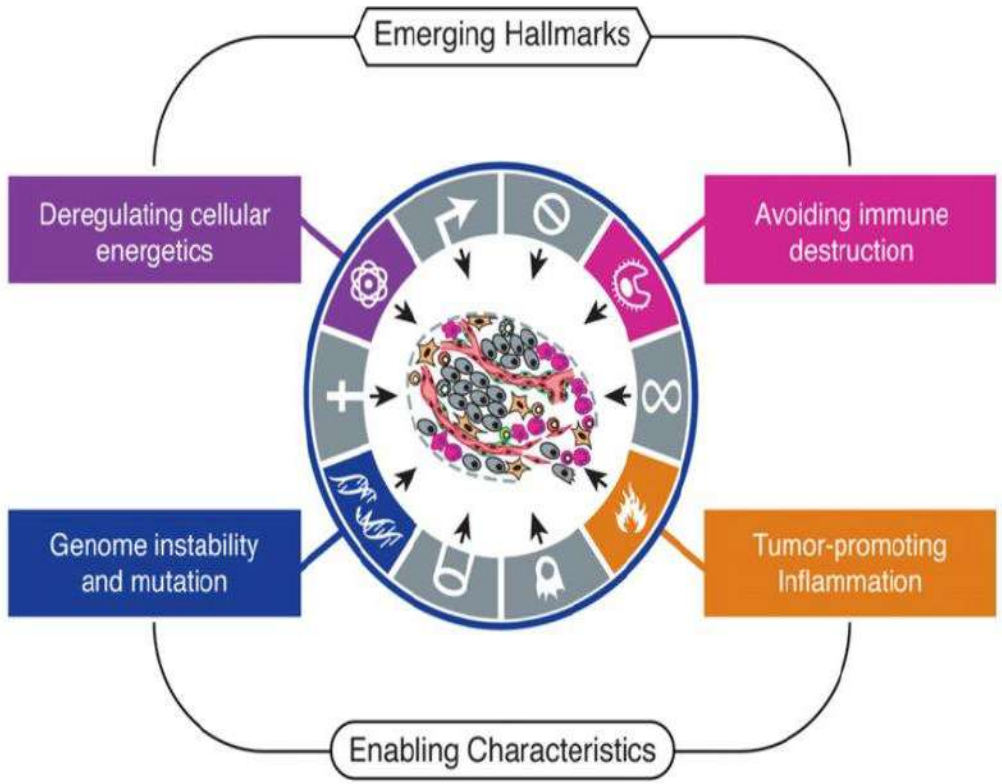
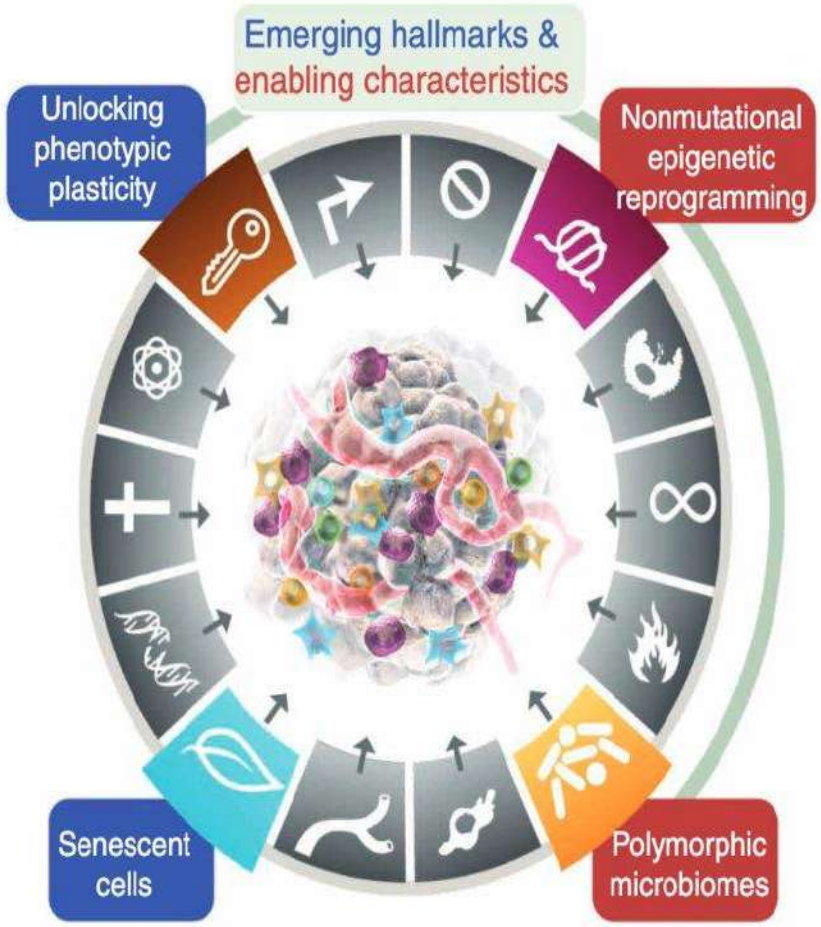
Evolution of Hallmarks of Cancer



Hanahan and Weinberg. Cell (2000).

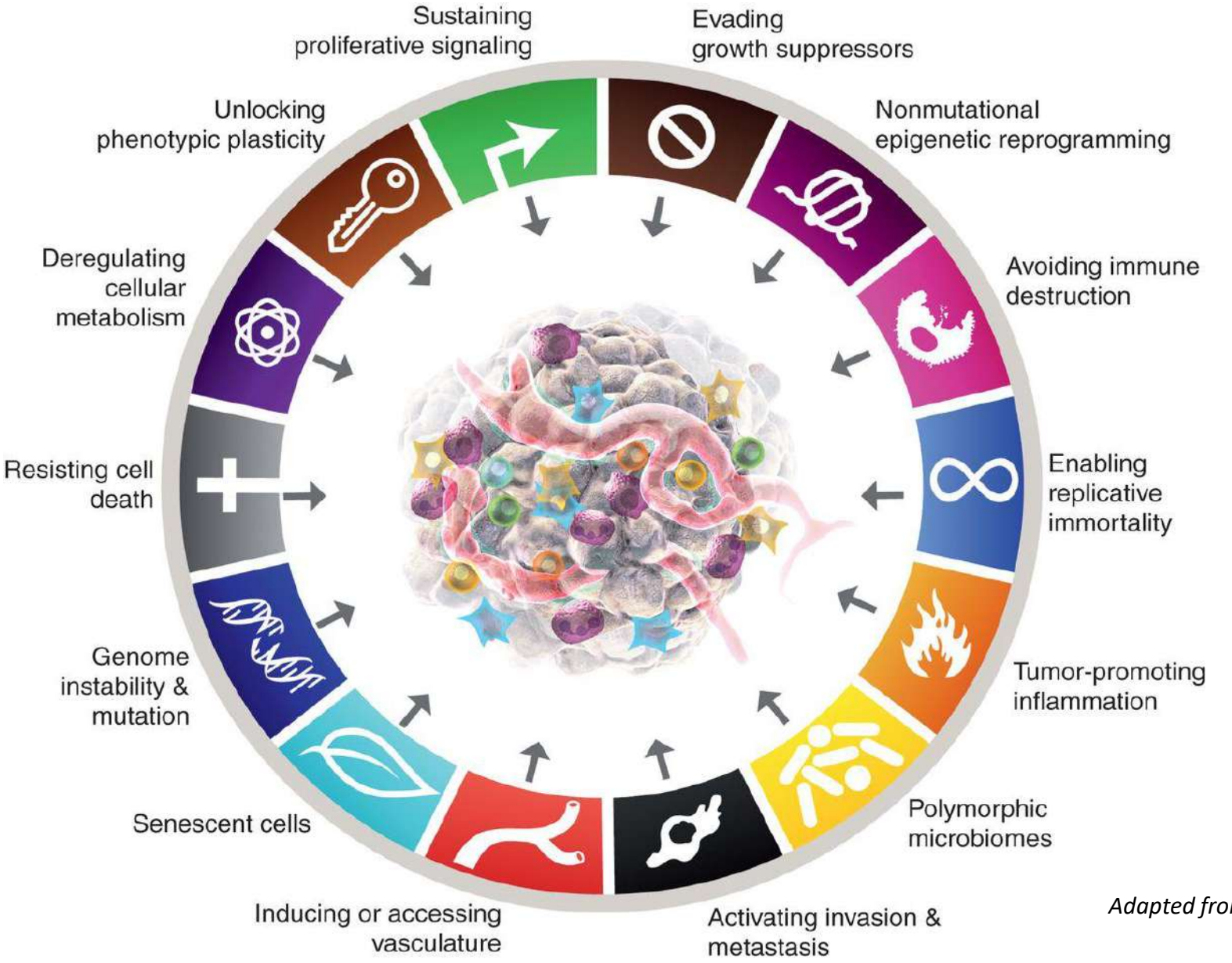


Hanahan and Weinberg. Cell (2011).



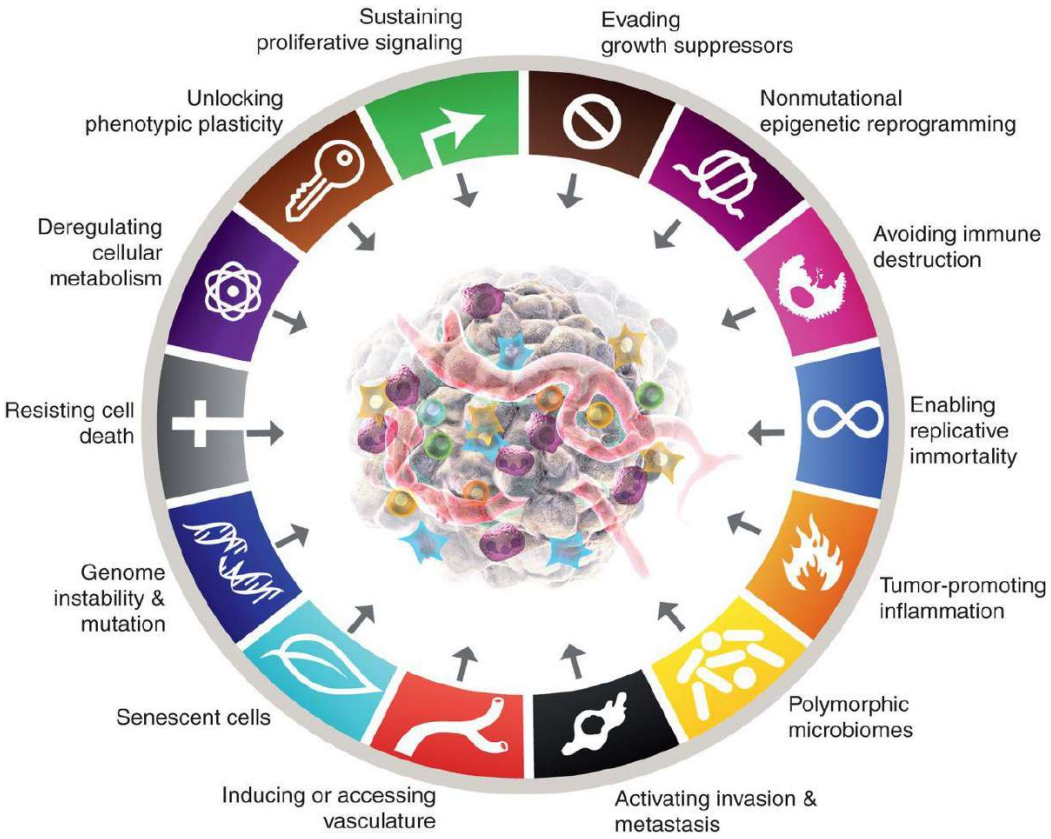
Hanahan. Cancer Disc (2022).

A more complicated picture



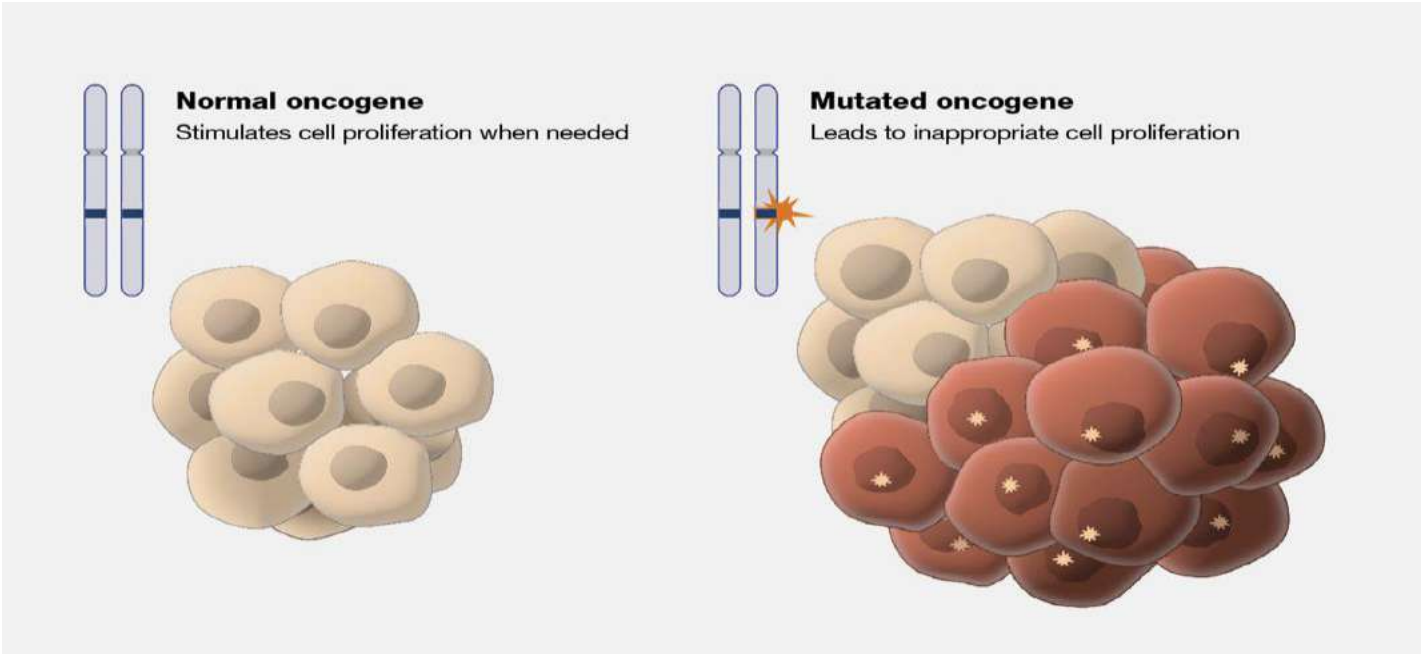
Adapted from Hanahan D et al Cancer Disc 2022

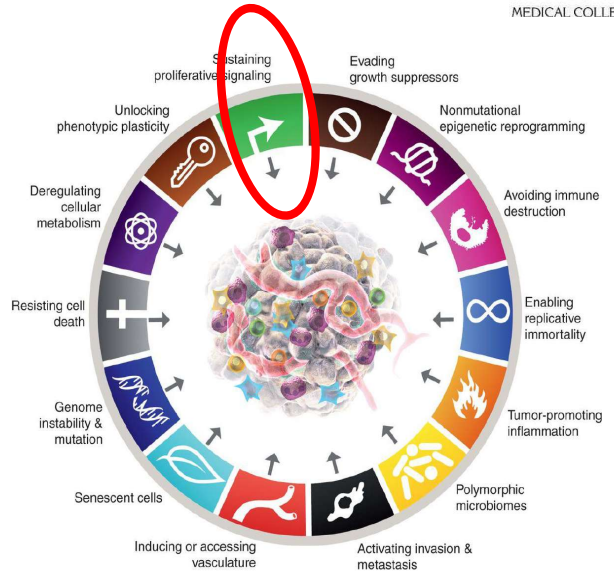
Sustaining proliferative signaling



Sustaining proliferative signaling

- An *oncogene* is a *mutated gene* that has the potential to cause cancer.
- *Before an oncogene becomes mutated*, it is called a *proto-oncogene*, and it plays a role in regulating normal cell division.

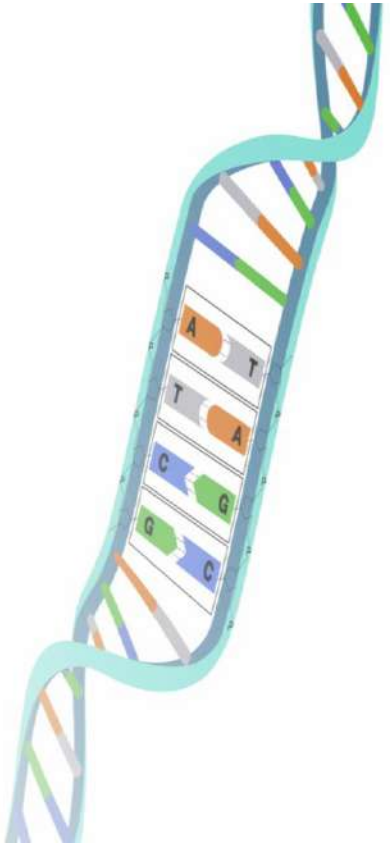




https://www.genome.gov/genetics-glossary/Oncogene

Carcinogen and Mutagen

- A carcinogen is a substance, organism or agent capable of causing cancer.
- Carcinogens may occur naturally in the environment (such as ultraviolet rays in sunlight and certain viruses) or may be generated by humans (such as automobile exhaust fumes and cigarette smoke).
- Most carcinogens work by interacting with a cell's DNA to produce mutations.

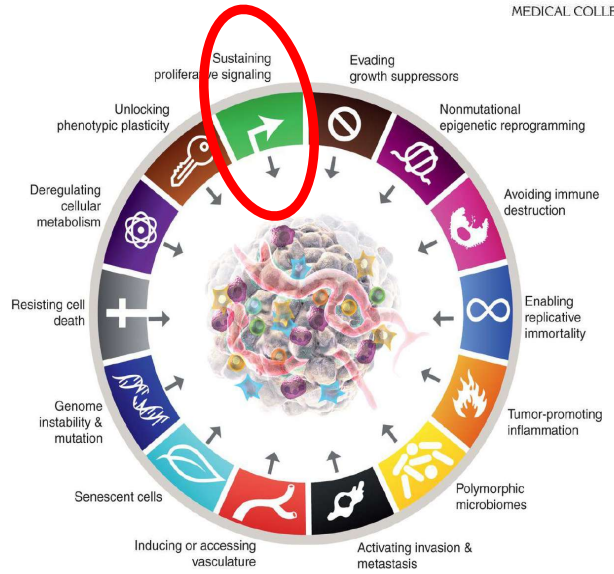


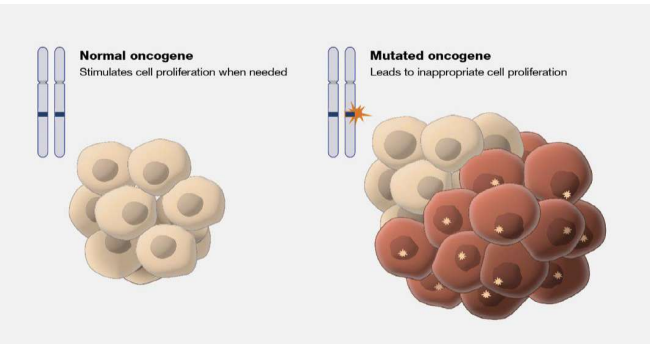
- A mutagen is a chemical or physical agent capable of inducing changes in DNA called mutations.
- Exposure to a mutagen can produce DNA mutations that cause or contribute to certain diseases, not only cancer.
- Examples of mutagens include tobacco products, radioactive substances, x-rays, ultraviolet radiation and a wide variety of chemicals.

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

Oncogenes

Cellular oncogene	Location	Protein function	Type of cancer
ABL	9q34.1	Protein tyrosine kinase	Chronic myeloid leukemia
BCL1	11q13.3	G_1/S-specific cyclin D1	Breast cancer, squamous cell carcinoma of the head and neck, bladder cancer
CDK4	12q14	Cyclin-dependent kinase	Sarcomas
EGFR/ERBB1	7p12	Epidermal growth factor receptor	Glioblastoma multiforme, epidermoid carcinoma, bladder cancer, breast cancer
ERBB2(NEU)	17q12-q21	Growth factor receptor	Breast cancer, ovarian cancer, stomach cancer, renal adenocarcinoma, adenocarcinoma of salivary gland, colon carcinoma
HSTF1	11q13.3	Fibroblast growth factor	Breast cancer, esophageal carcinoma
INT1/WNT1	12q13	Probably growth factor	Retinoblastoma
INT2	11q13.3	Fibroblast growth factor	Breast cancer, esophageal carcinoma, melanoma, squamous cell carcinoma of the head and neck
MDM2	12q14.3-q15	p53-binding protein	Sarcomas
MET	7q31	Hepatocyte growth factor receptor	Amplified in cell lines from human tumors of nonhematopoietic origin, particularly gastric tumors
MYB	6q22-q23	DNA-binding protein (essential for normal hematopoiesis)	Leukemias, colon carcinoma, melanoma
MYC (c-MYC)	8q24.12-q24.13	DNA-binding protein	Small-cell lung cancer, giant cell carcinoma of lung, breast cancer, colon carcinoma, acute promyelocytic leukemia, cervical cancer, gastric adenocarcinoma, chronic granulocytic leukemia
MYCN (NMYC)	2p24.3	DNA-binding protein	Neuroblastoma, small-cell lung cancer, retinoblastoma, medulloblastoma, glioblastoma, rhabdomyosarcoma, adenocarcinoma of lung, astrocytoma
MYCL1 (LMYC) MYCLK1	1p32 7p15	DNA-binding protein	Small-cell lung cancer
RAF1 (c-RAF)	3p25	Serine/threonine protein kinase	Non-small-cell lung cancer
HRAS1	11p15.5	GTPase	Bladder cancer
KRAS2	12p12.1	GTPase	Adrenocortical tumor, giant cell carcinoma of lung
NRAS	1p13	GTPase	Breast cancer
REL	2p12–p13	DNA-binding protein	Non-Hodgkin lymphomas





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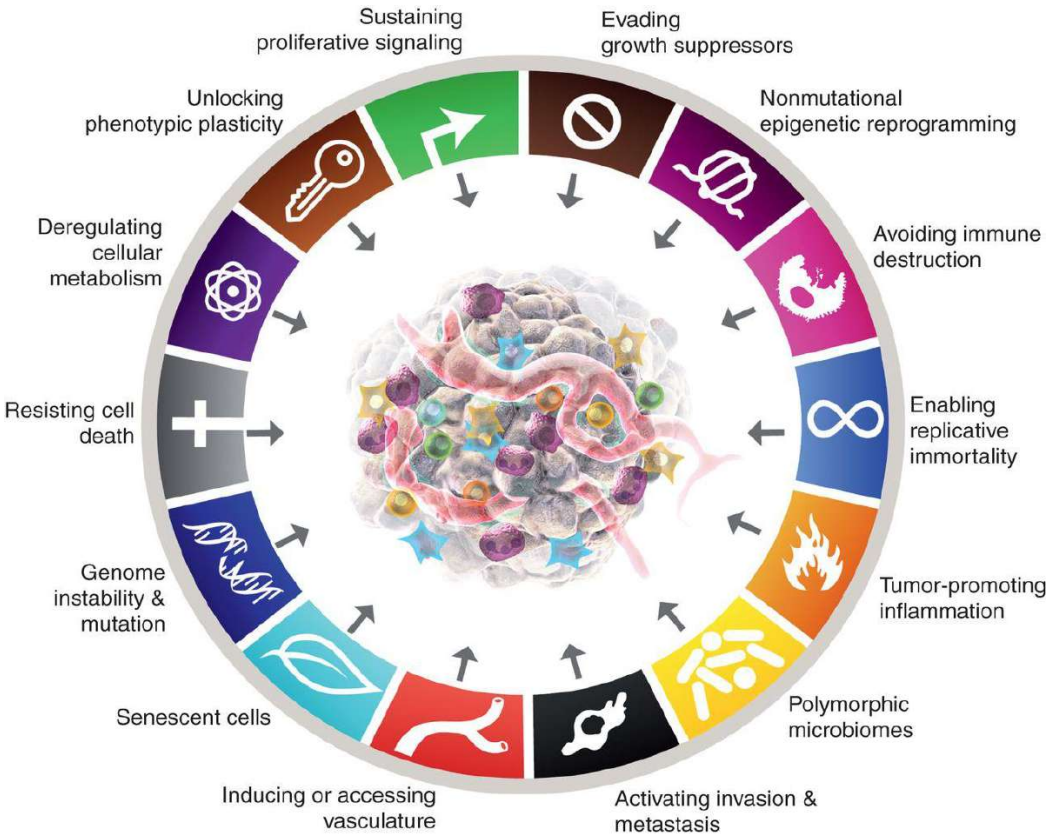
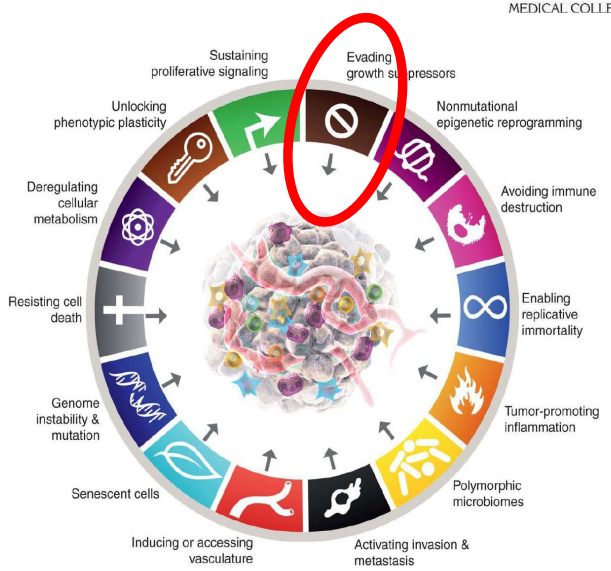
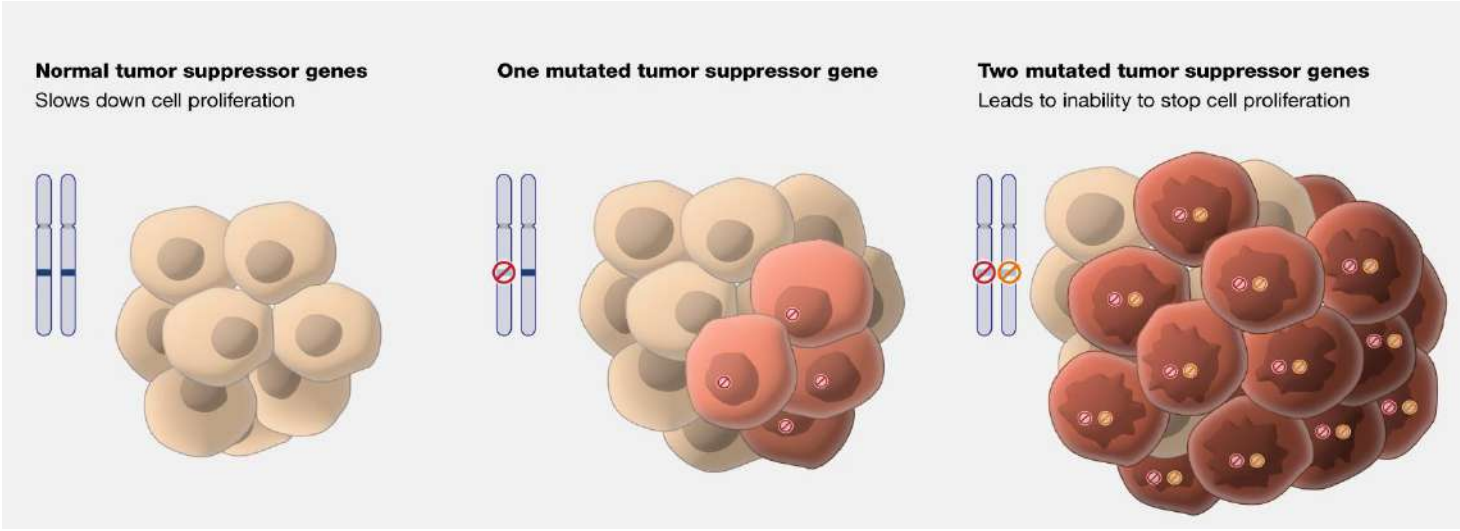
Evading growth supressors



Tumour suppressor genes

- A *tumor suppressor gene* encodes a protein that acts to regulate cell division, keeping it in check.
- When a tumor suppressor gene is *inactivated by a mutation*, the protein it encodes is not produced or does not function properly, and as a result, *uncontrolled cell division may occur*.
- Such mutations may contribute to the development of a cancer.





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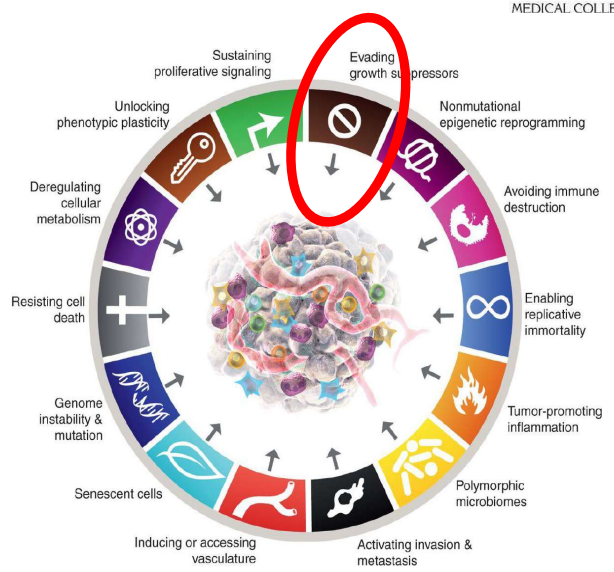
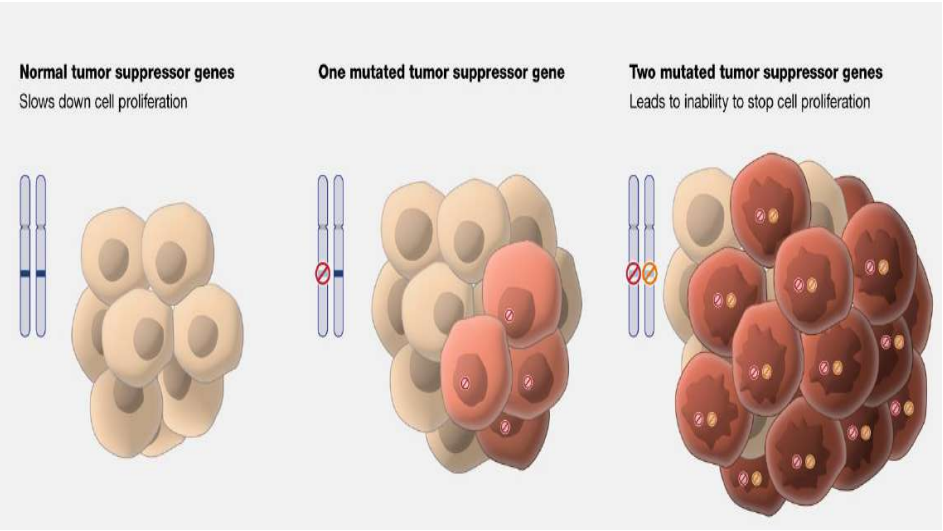
Tumour suppressor genes

Gene	Chromosomal location	Cellular location	Mode of action	Neoplasm associated with somatic mutation	Neoplasm associated with inherited mutation
Rb	13 q 14	Nucleus	Transcriptional regulator	Retinoblastoma, osteosarcoma, carcinomas of breast, prostate, bladder and lung	Retinoblastoma, osteosarcoma
p53	17 p 13.1	Nucleus	Transcriptional factor/regulator	Most human cancers breast, brain, sarcomas, leukemias	Li-Fraumeni syndrome, carcinomas of oral cavity
APC	5 q 21	Cytoplasm	Unknown	Carcinomas of colon, stomach and pancreas	Familial adenomatosis polyposis coli, carcinoma of colon
WT 1	11 p 13	Nucleus	Transcriptional factor	Nephroblastoma	Wilms' tumor
DCC	18 q 21	membrane	cell adhesion molecule	Carcinomas of colon and stomach	Unknown
NF-1	17 q 11	Cytoplasm	p 21, ras. GTPase activator	Schwannomas	Neurofibromatosis type 1
NF-2	22 q 12	Inner membrane	Cytoskeleton membrane link	Schwannomas, meningiomas	Neurofibromatosis type-2 schwannomas, meningiomas
VHL	3 p 25	Cytoplasm	Inhibits transcriptional elongation	Renal cell carcinoma	Von Hippel-Lindau disease, angiomas and cysts of various visceral organs





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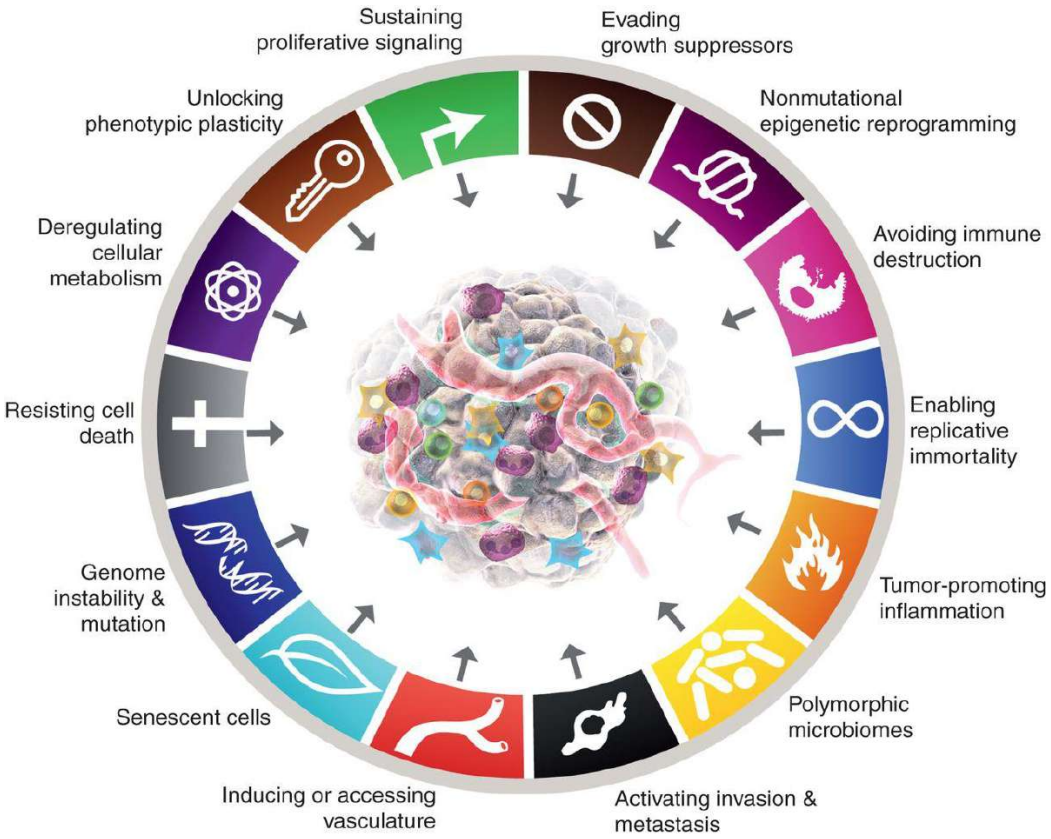
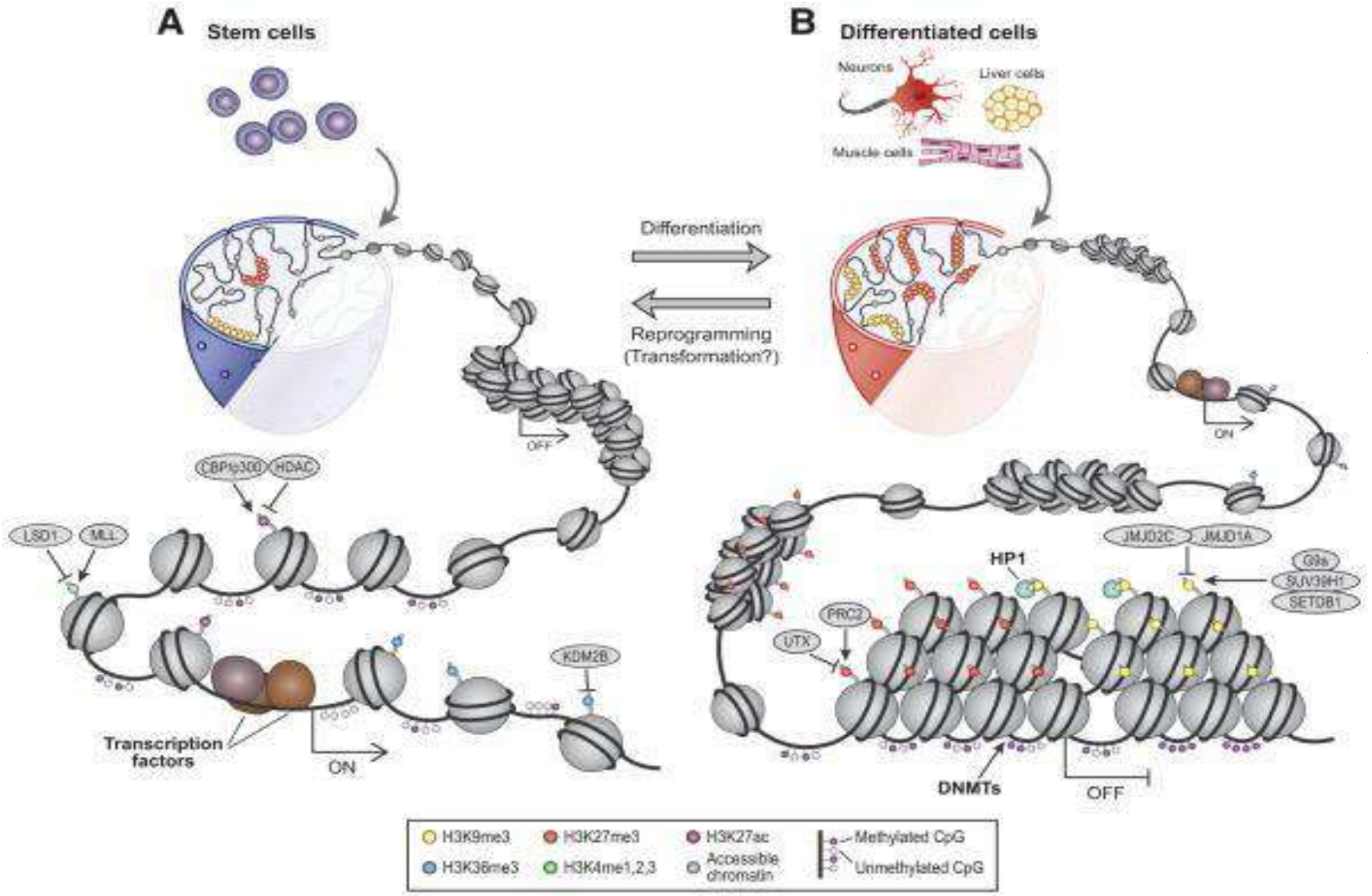
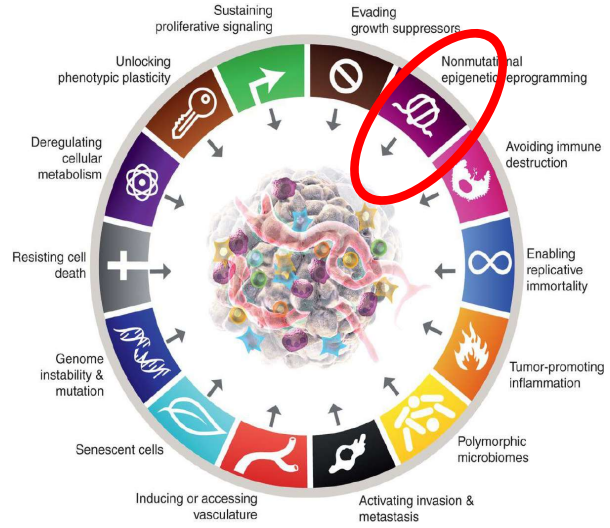
Non-mutational epigenetic reprogramming



Epigenetic reprogramming





Feng et al, 2021

A

Transcription factors

SOX2
Esophageal squamous cell carcinoma
Lung carcinoma
Glioblastoma
Breast carcinoma
Ewing sarcoma

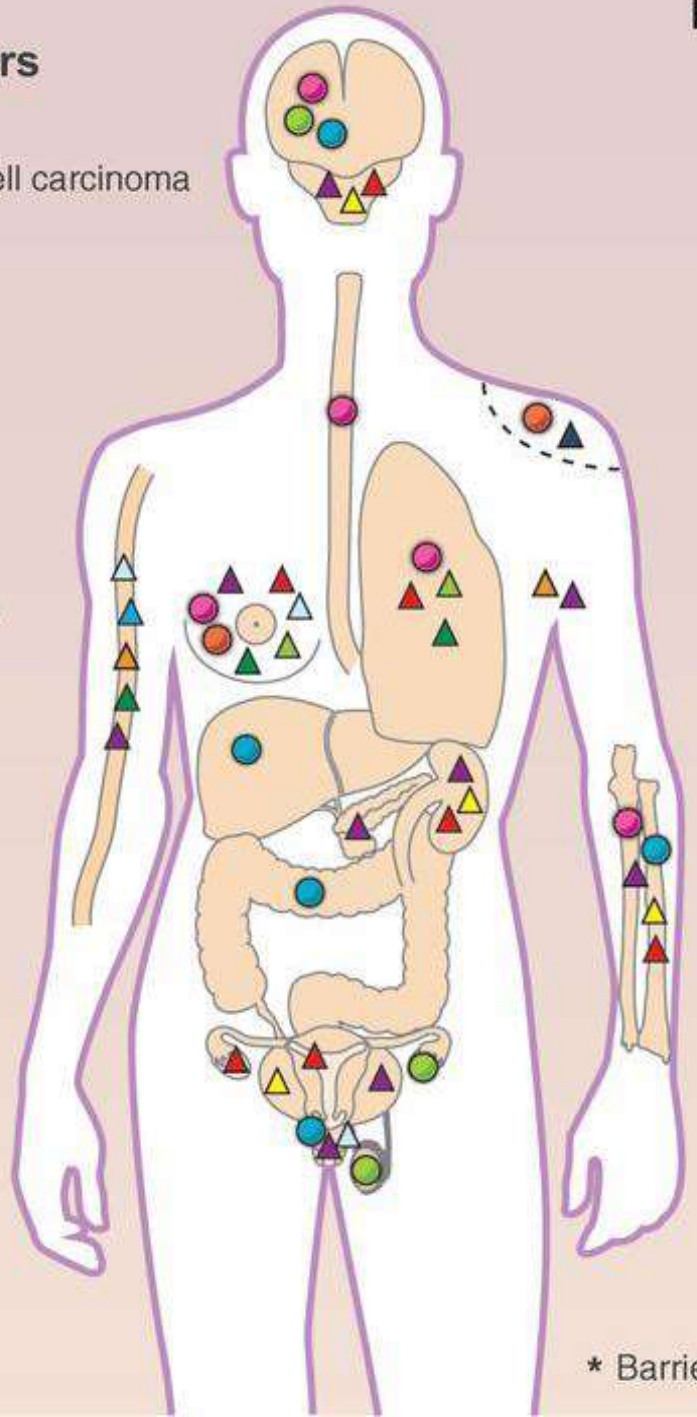
KLF4
Breast carcinoma
Skin malignancies

NANOG
Hepatocellular carcinoma
Glioblastoma
Colon carcinoma
Prostate carcinoma
Ewing sarcoma

OCT4
Germ cell tumors

C-MYC
Multiple malignancies

LIN28
Multiple malignancies



B

Chromatin regulators

SUV39H1*
Acute promyelocytic leukemia (APL)

SETDB1*
Melanoma

G9a*
Lung carcinoma
Breast carcinoma

UTX
Multiple myeloma
Clear cell renal cell carcinoma
Transitional cell carcinoma of bladder
Medulloblastoma

PRC2
Follicular and large B-cell lymphomas
Myelodysplastic syndromes
T-cell acute lymphoblastic leukemia
Overexpressed in multiple malignancies

ARID1A
Ovarian clear cell carcinoma
Endometriod carcinoma
Renal cell carcinoma
Neuroblastoma
Medulloblastoma
Lung carcinoma
Breast carcinoma

MLL1
Acute myeloid leukemia (AML)
Acute lymphoblastic leukemia (ALL)
Transitional cell carcinoma of bladder

MLL2
Large B cell and follicular lymphoma
Medulloblastoma
Prostate carcinoma
Renal carcinoma

MLL3
Medulloblastoma
Transitional cell carcinoma of bladder
Breast carcinoma
Pancreatic adenocarcinoma

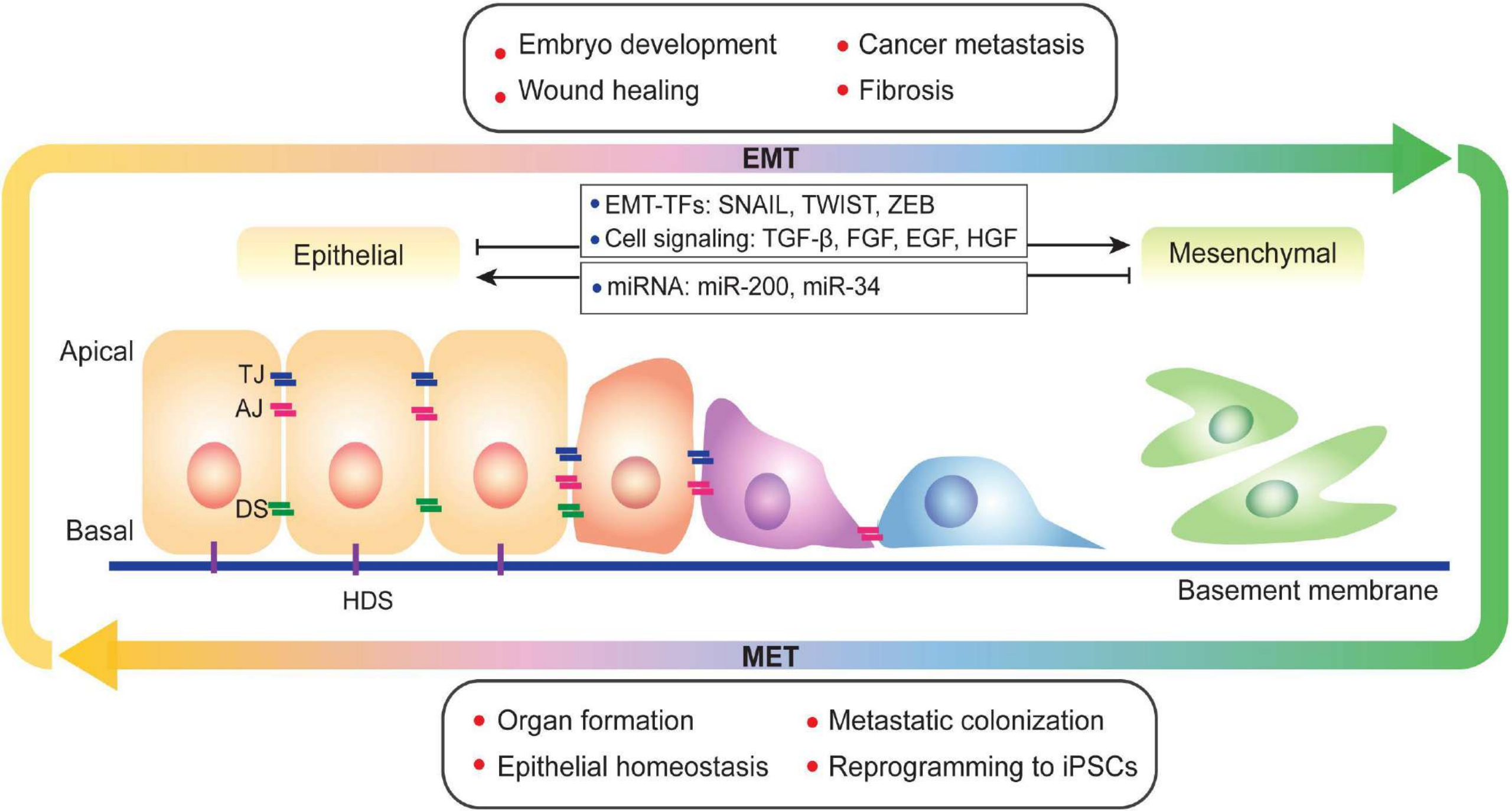
LSD1
Acute myeloid leukemia (AML)
Breast carcinoma
Prostate carcinoma

DOT1L*
Mixed lineage leukemia (MLL)

KDM2B
Acute myeloid leukemia (AML)

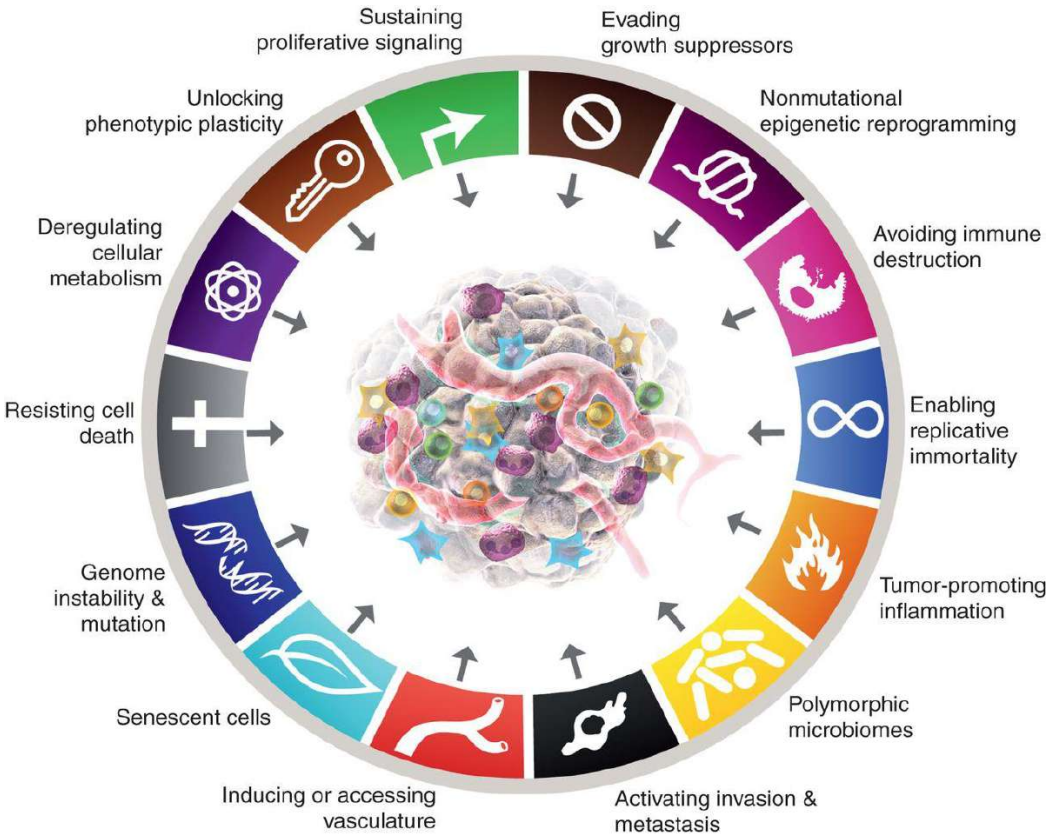
DNMT3A/B
Acute myeloid leukemia (AML)
Breast carcinoma
Lung carcinoma

* Barrier to reprogramming.

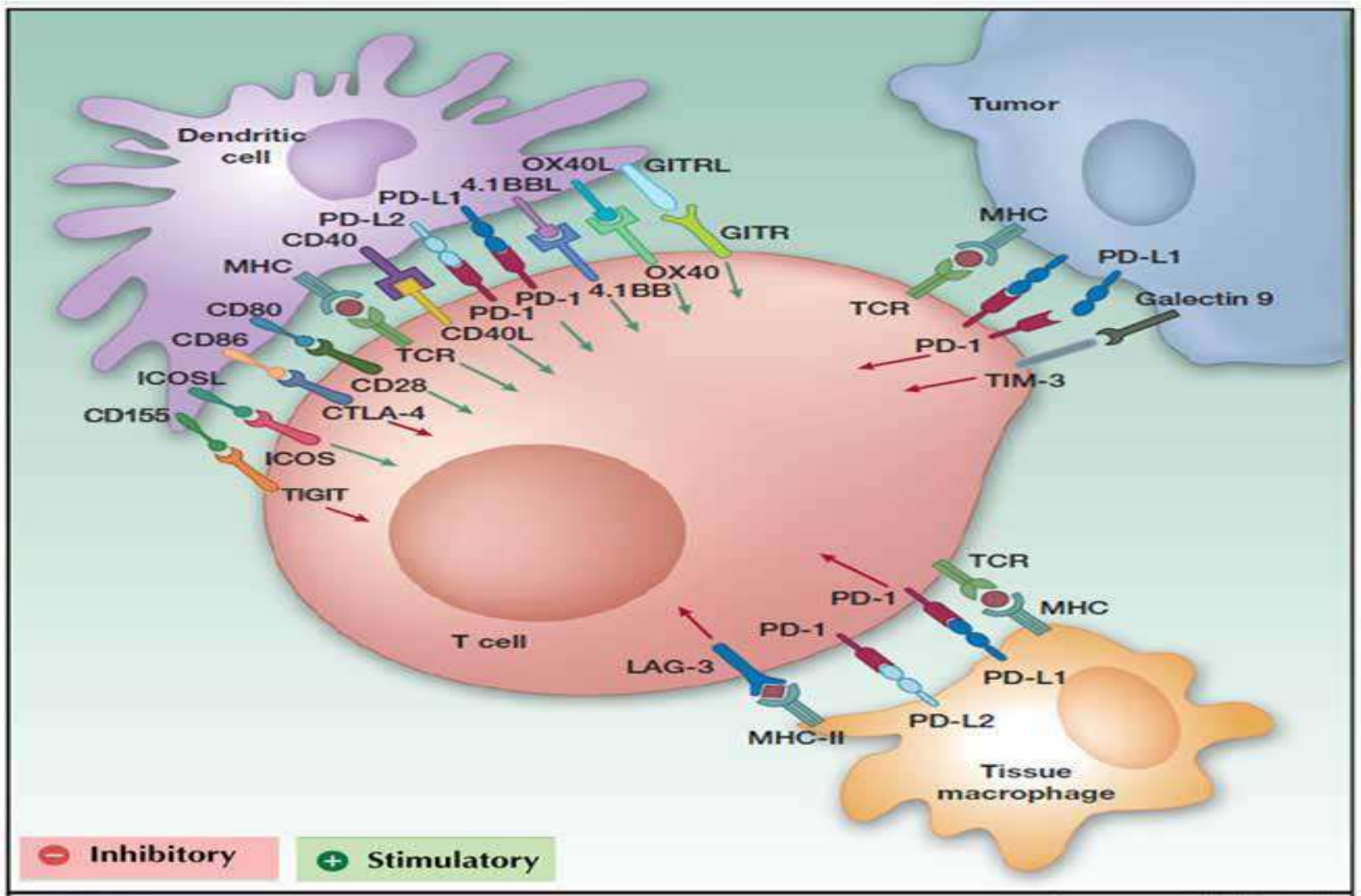

Embryo development
Wound healing
Cancer metastasis
Fibrosis
EMT
EMT-TFs: SNAIL, TWIST, ZEB
Cell signaling: TGF-β, FGF, EGF, HGF
miRNA: miR-200, miR-34
Epithelial
Mesenchymal
Apical
TJ
AJ
DS
Basal
HDS
Basement membrane
MET
Organ formation
Epithelial homeostasis
Metastatic colonization
Reprogramming to iPSCs

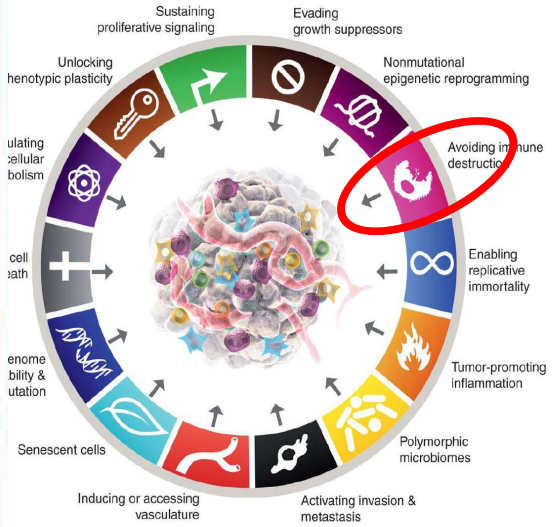
Wu et al, 2020

Avoiding immune destruction



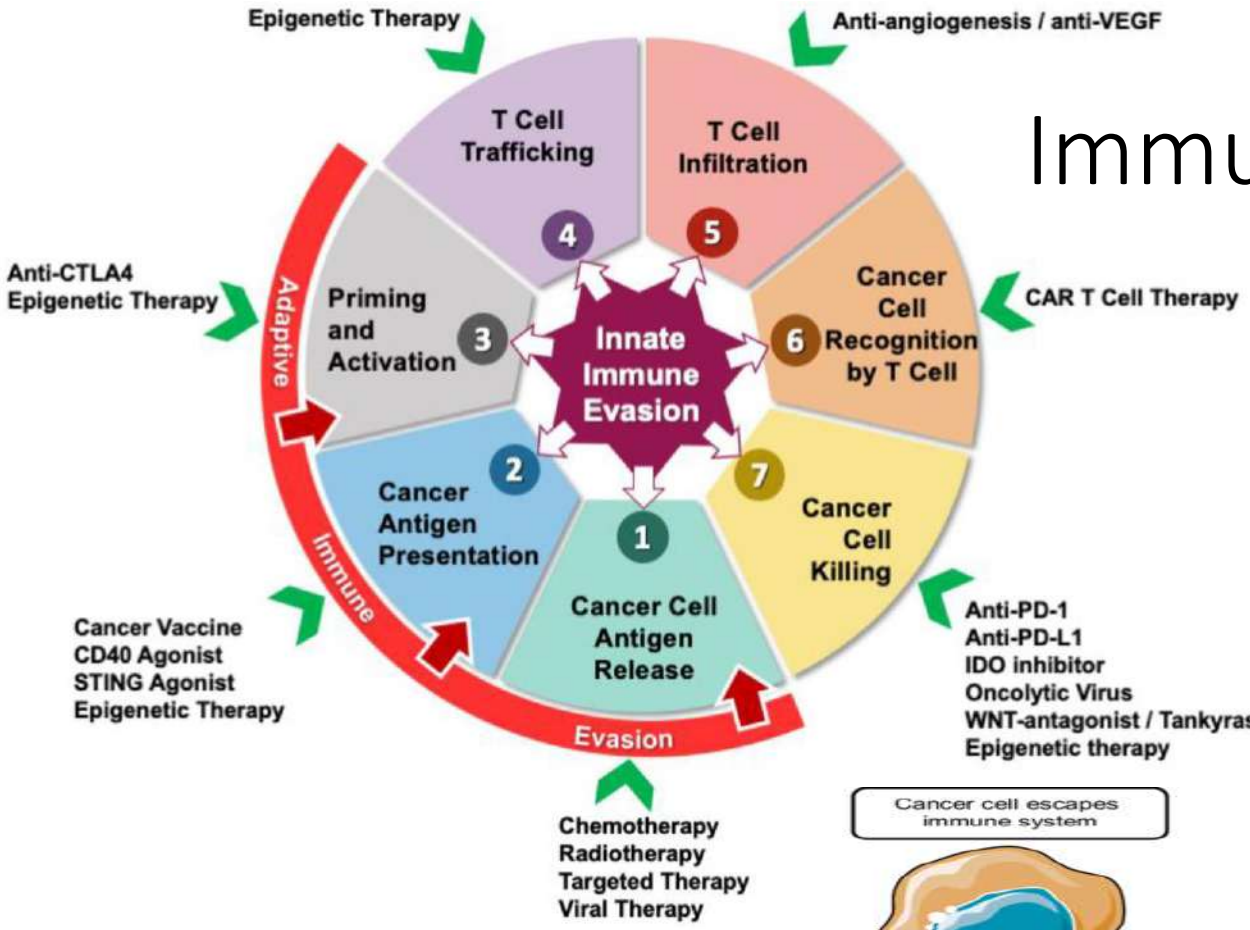
Immune evasion

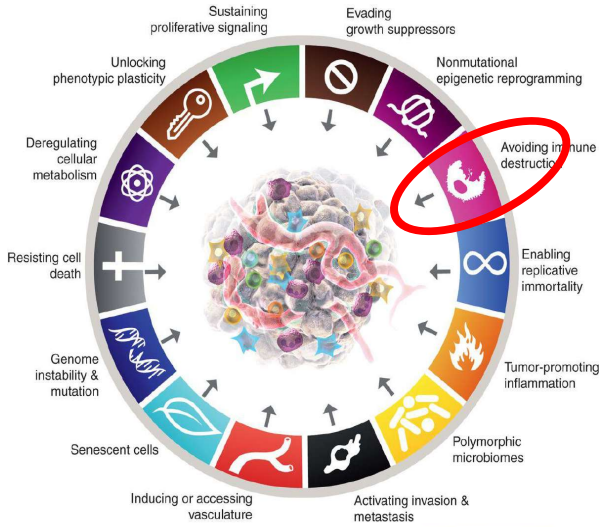


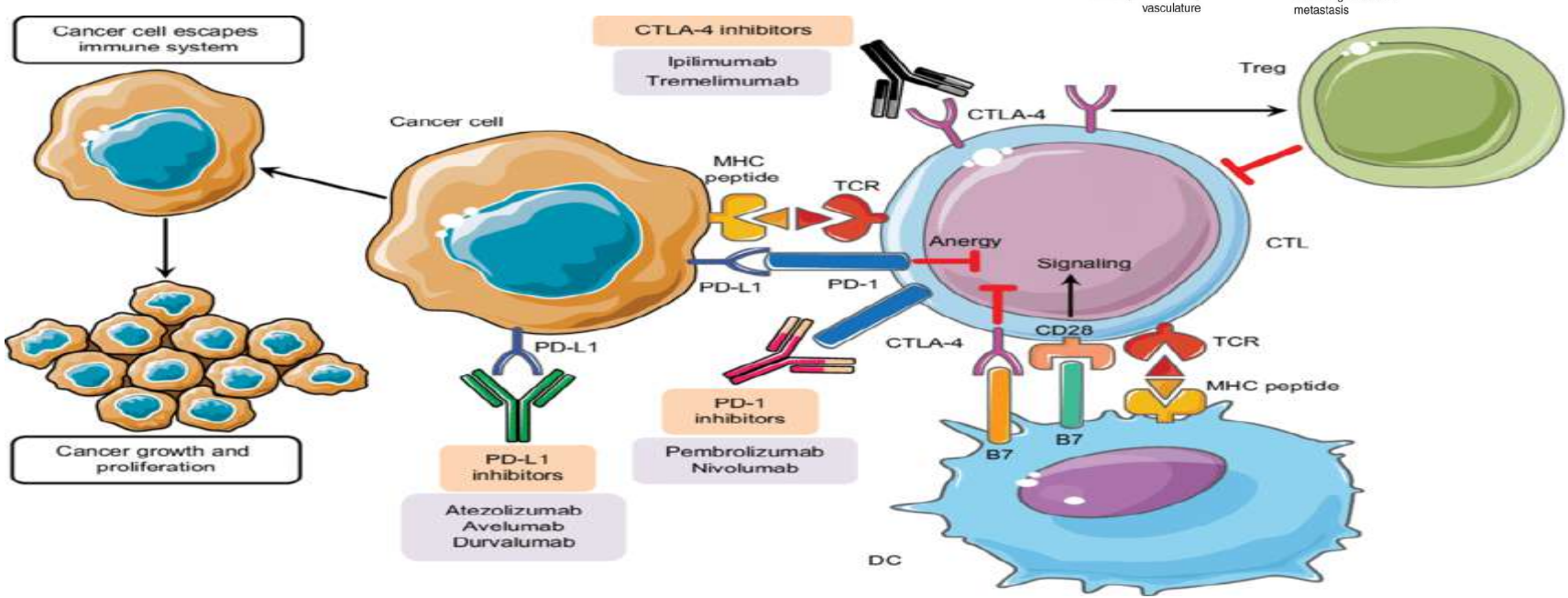


Vinay et al, Semin Radiat Oncol 2015

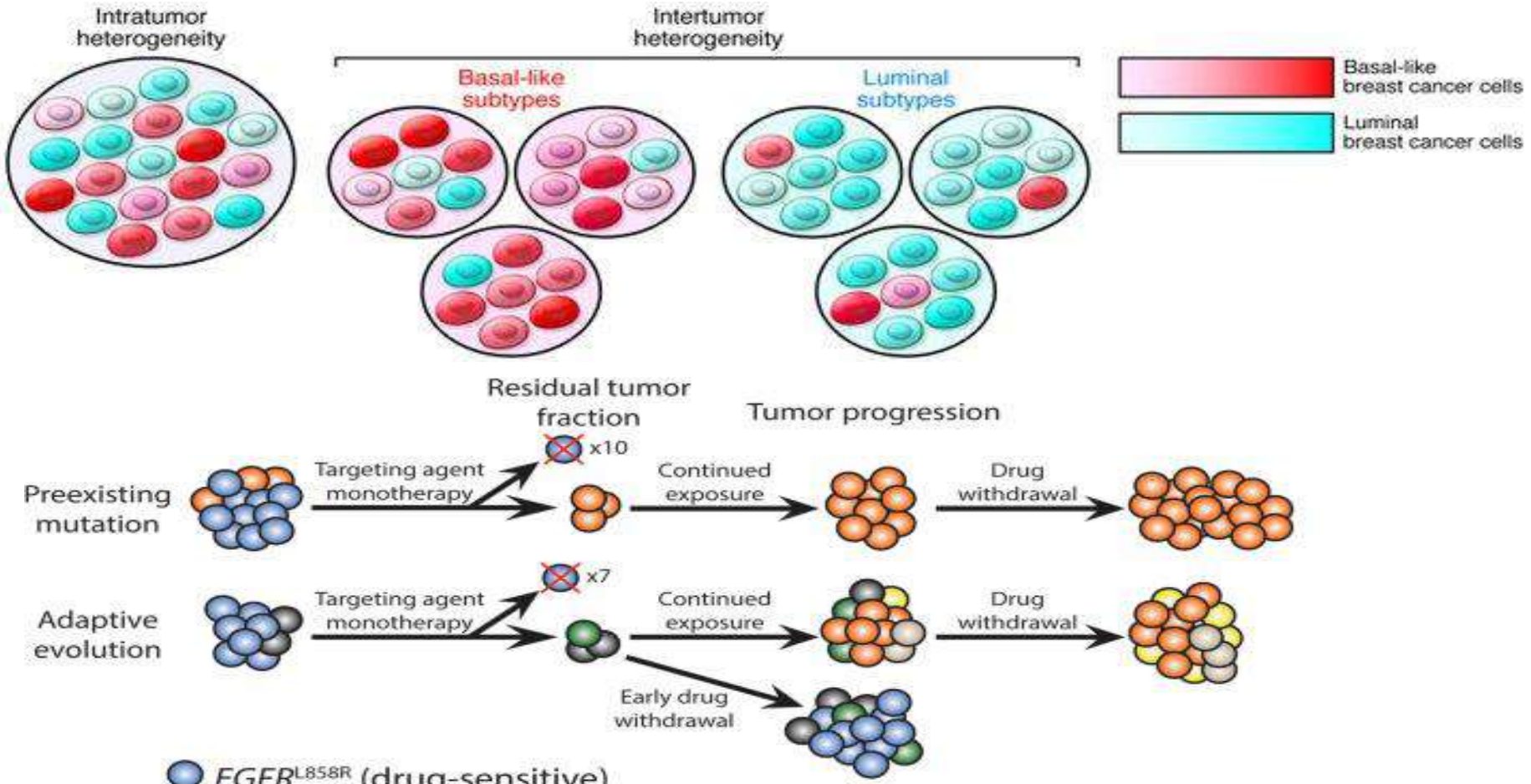
Immune evasion

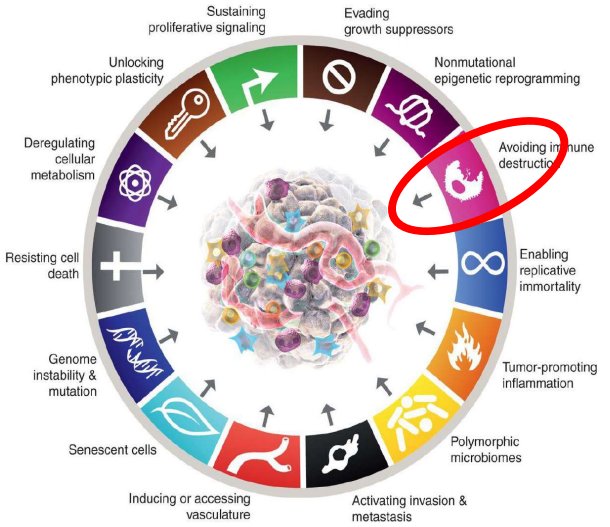






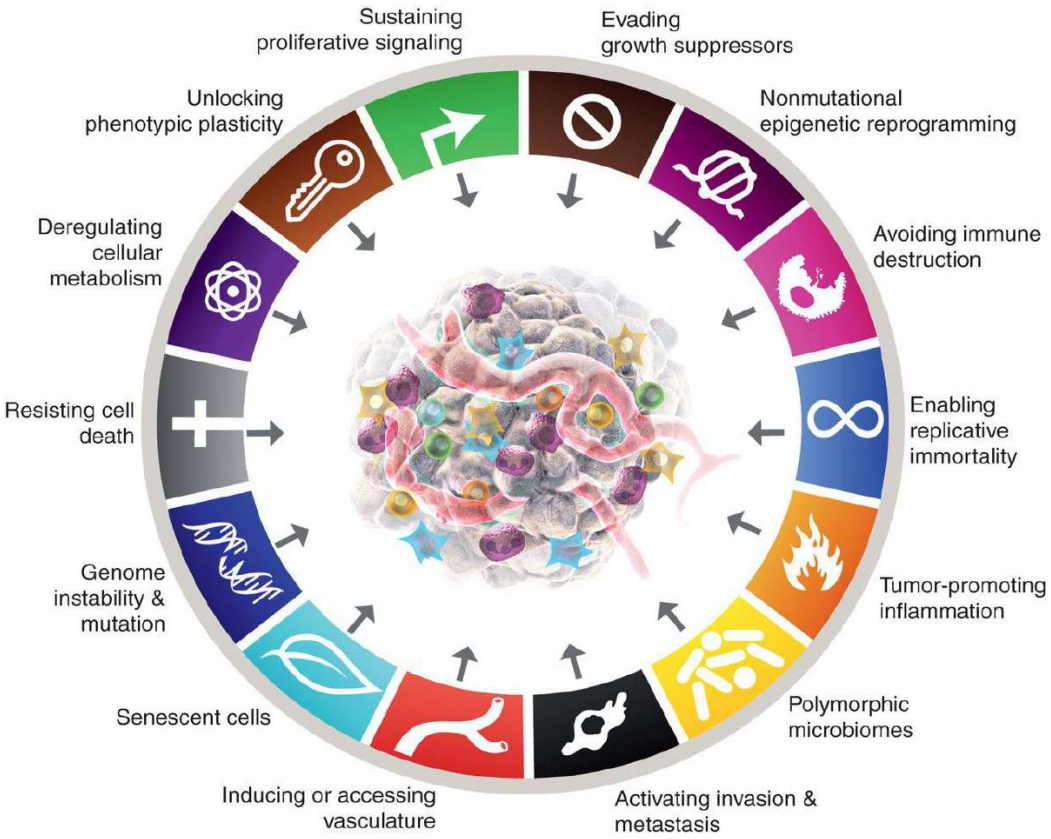
Intratumour heterogeneity

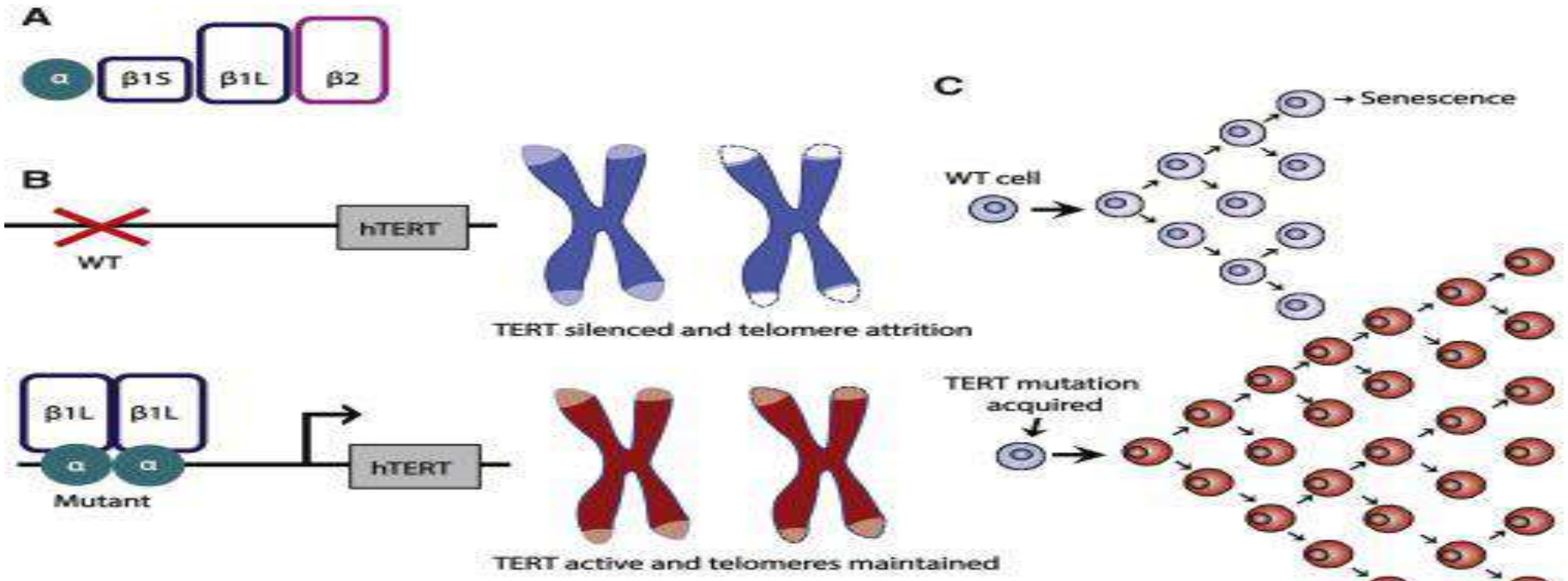


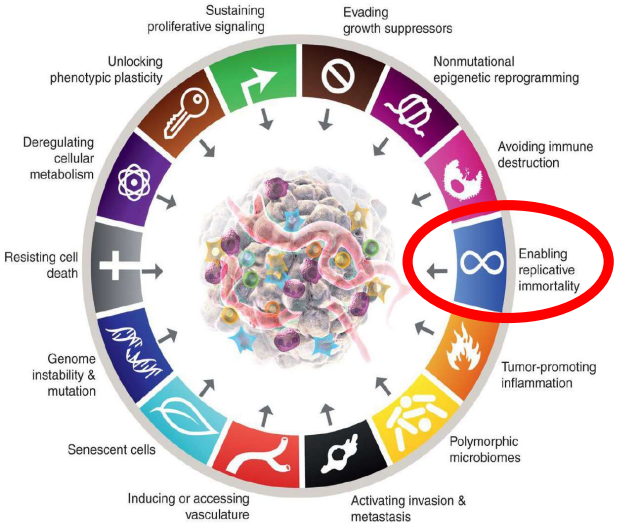


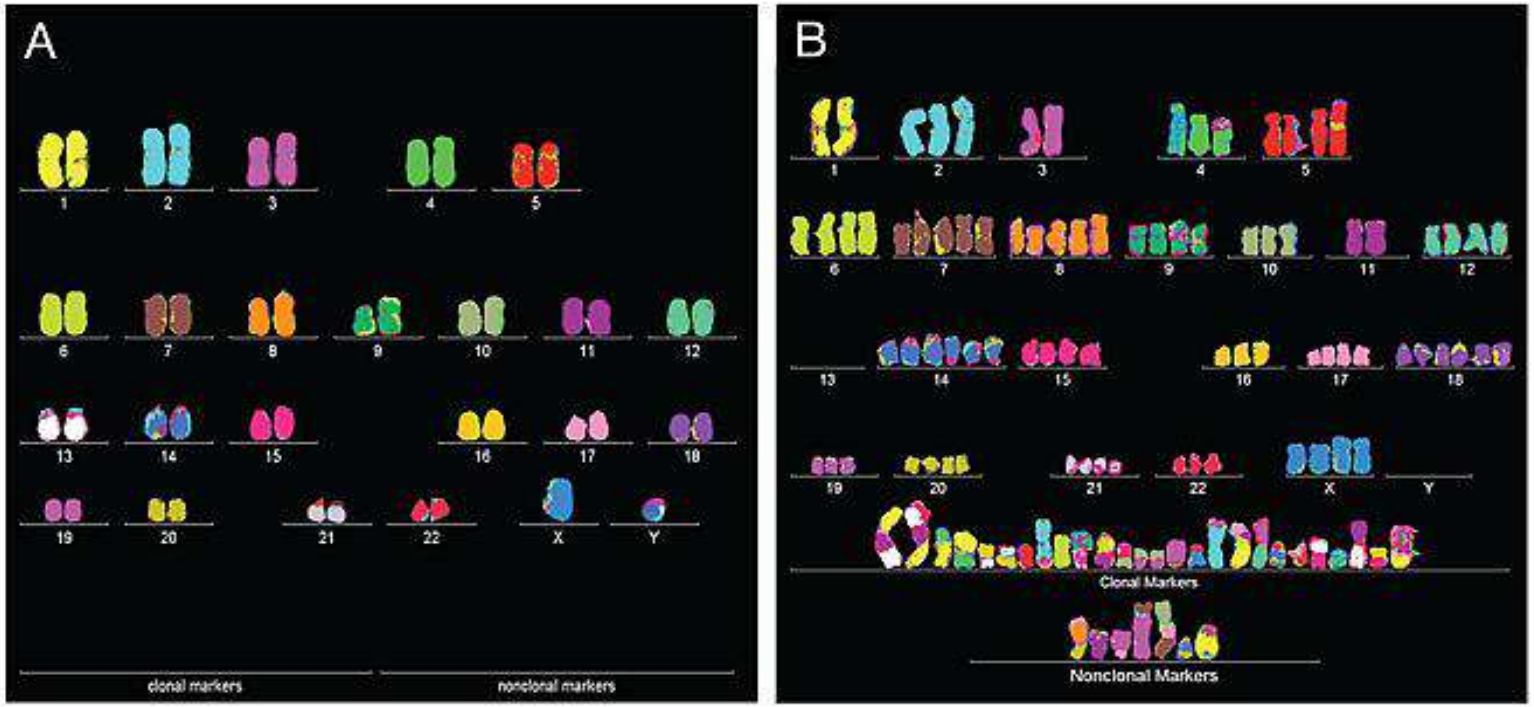
Polyak et al, 2011
Lim et al, 2019

Enabling replicative immortality



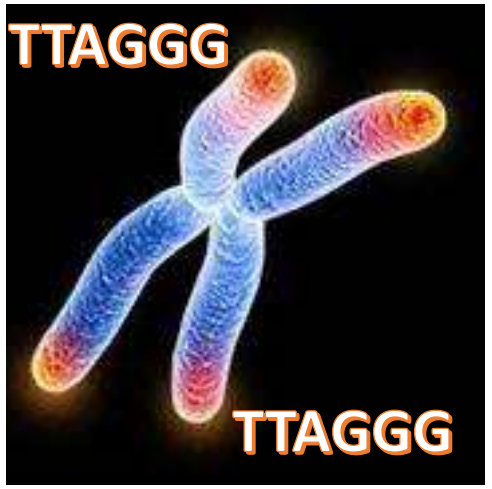






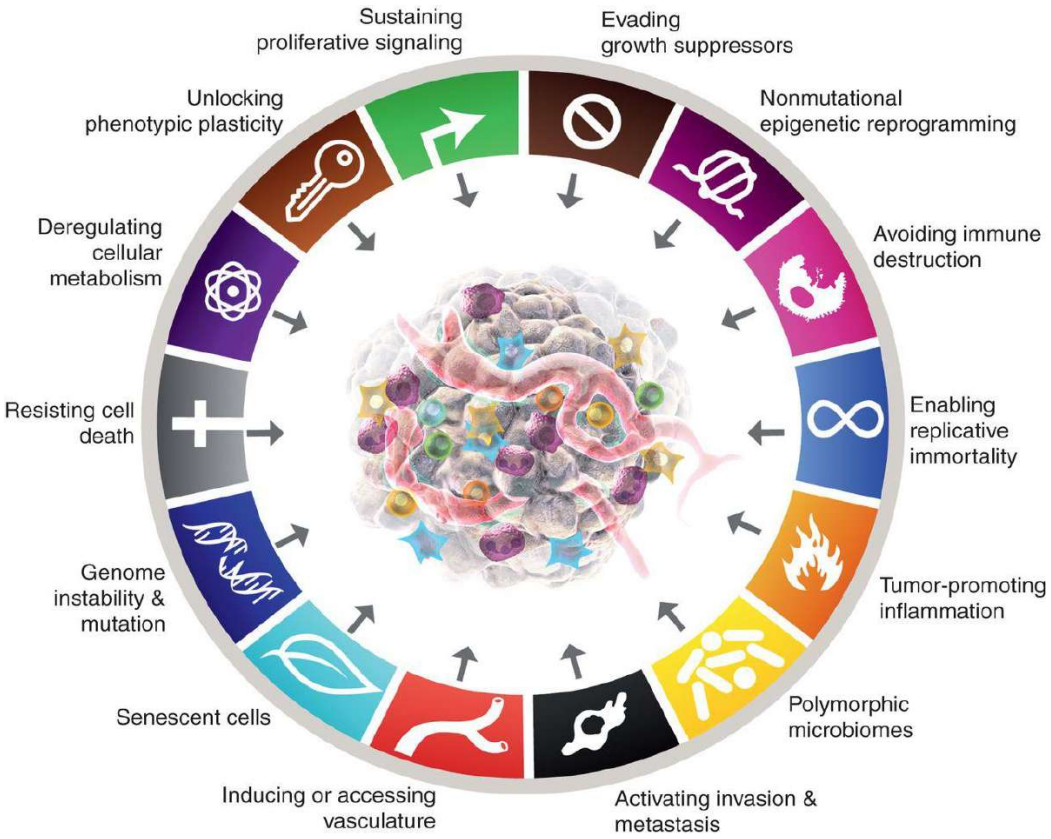
dynamic
variation
roductive

of cancer

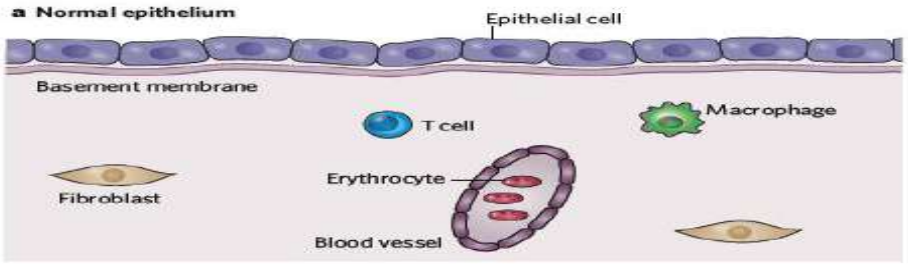


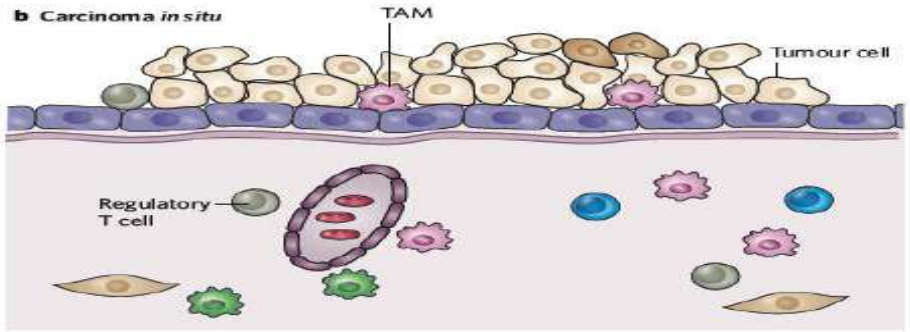
Jafri et al, 2016
Duesberg et al, 2013

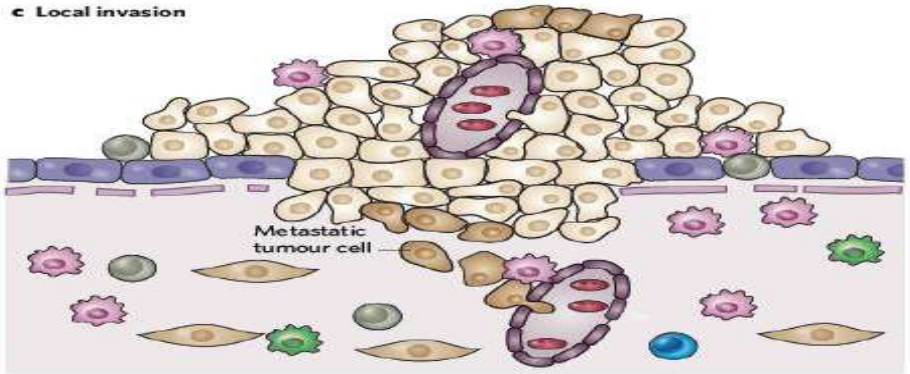
Tumour promoting inflammation

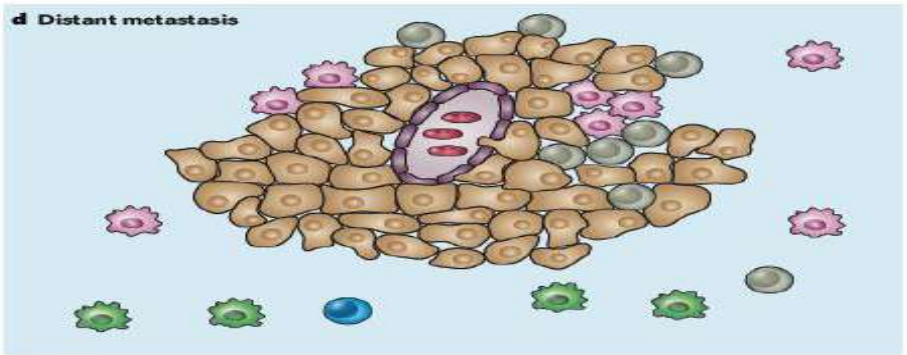


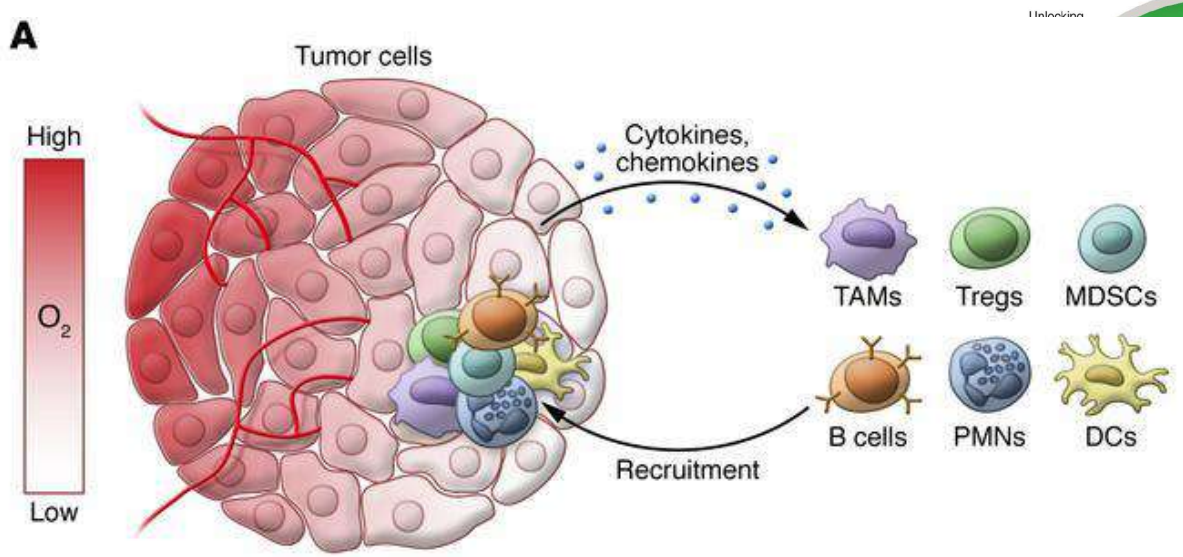
Tumour promoting Inflammation

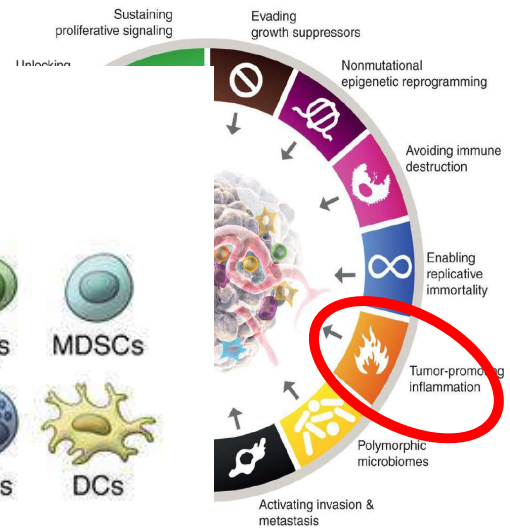


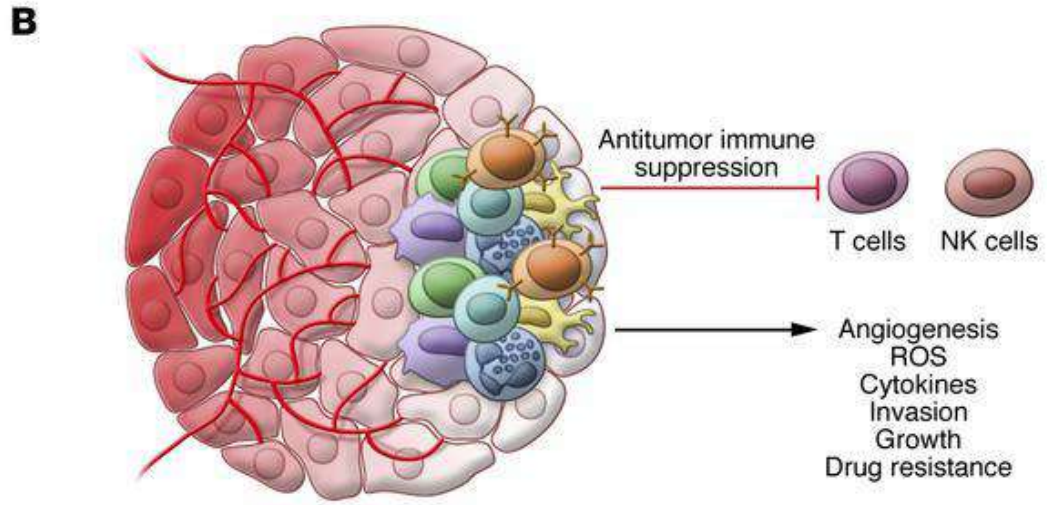






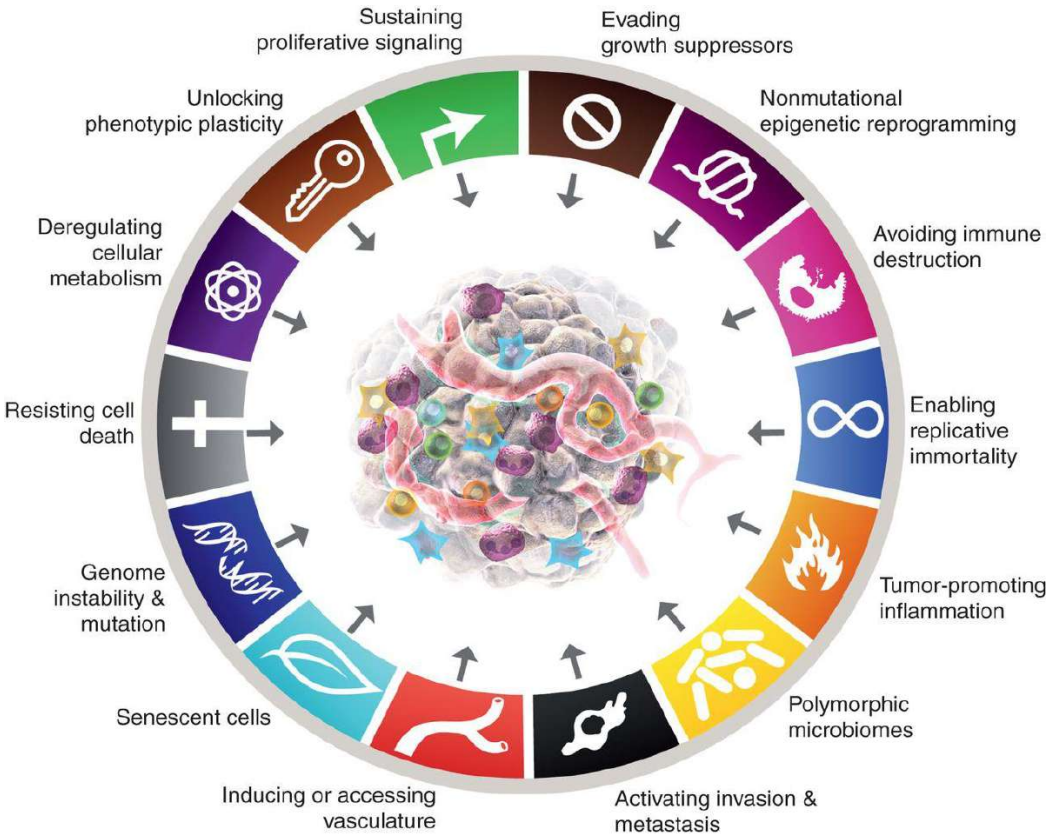




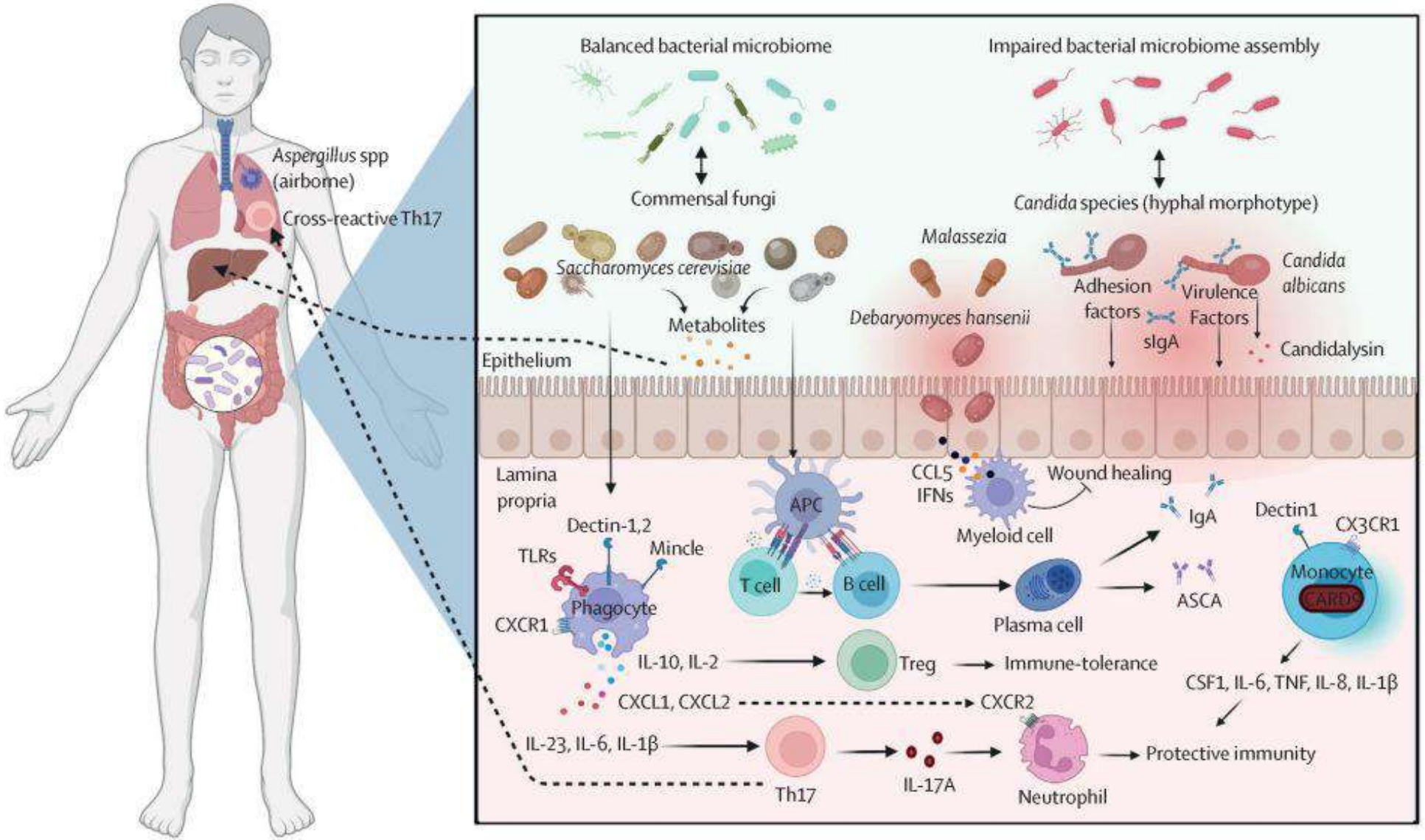


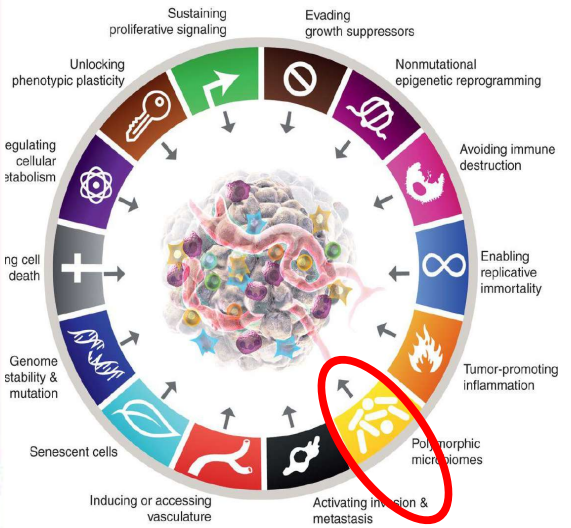
et al, J Clin Invest. 2016
Mantovani et al, 2008

Polymorphic microbiome



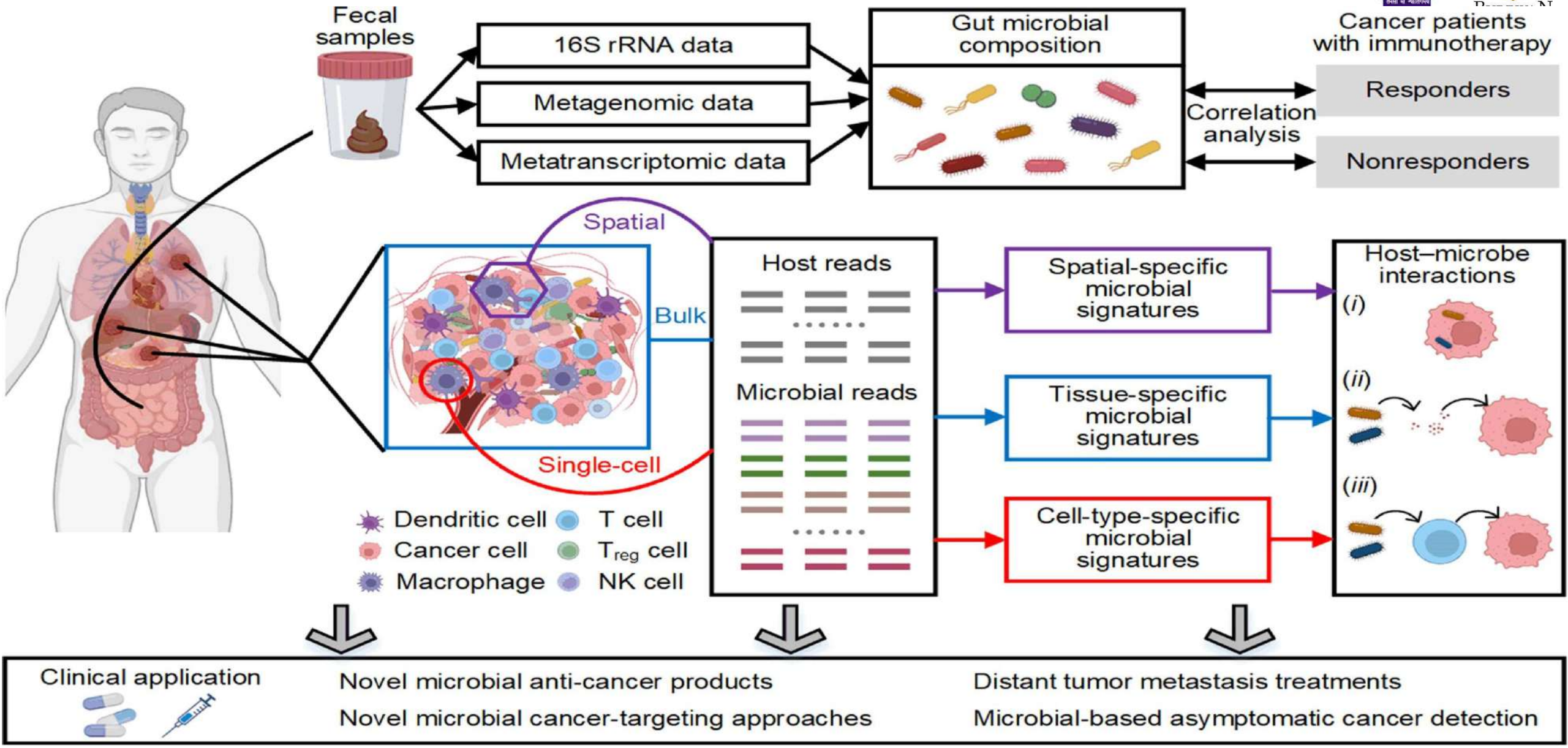
Polymorphic microbiome





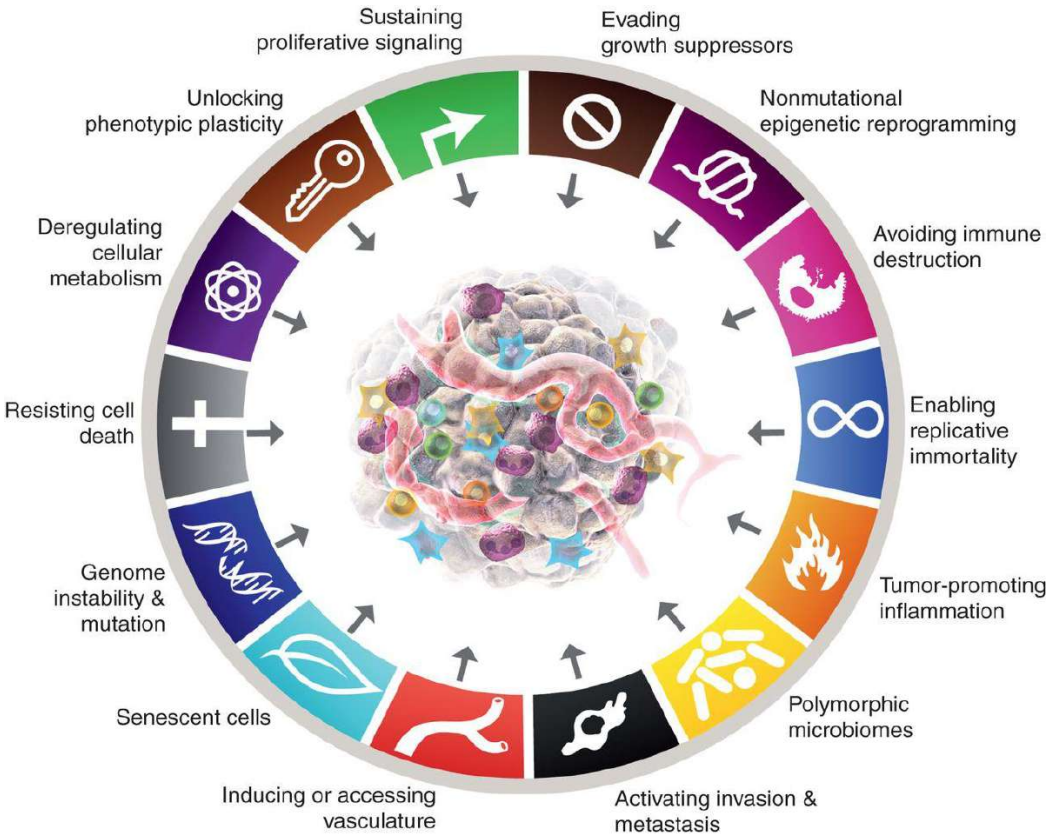
Hanahan D et al Cancer Disc 2022
Zhang et al, Lancet Microbe 2022

Polymorphic microbiome

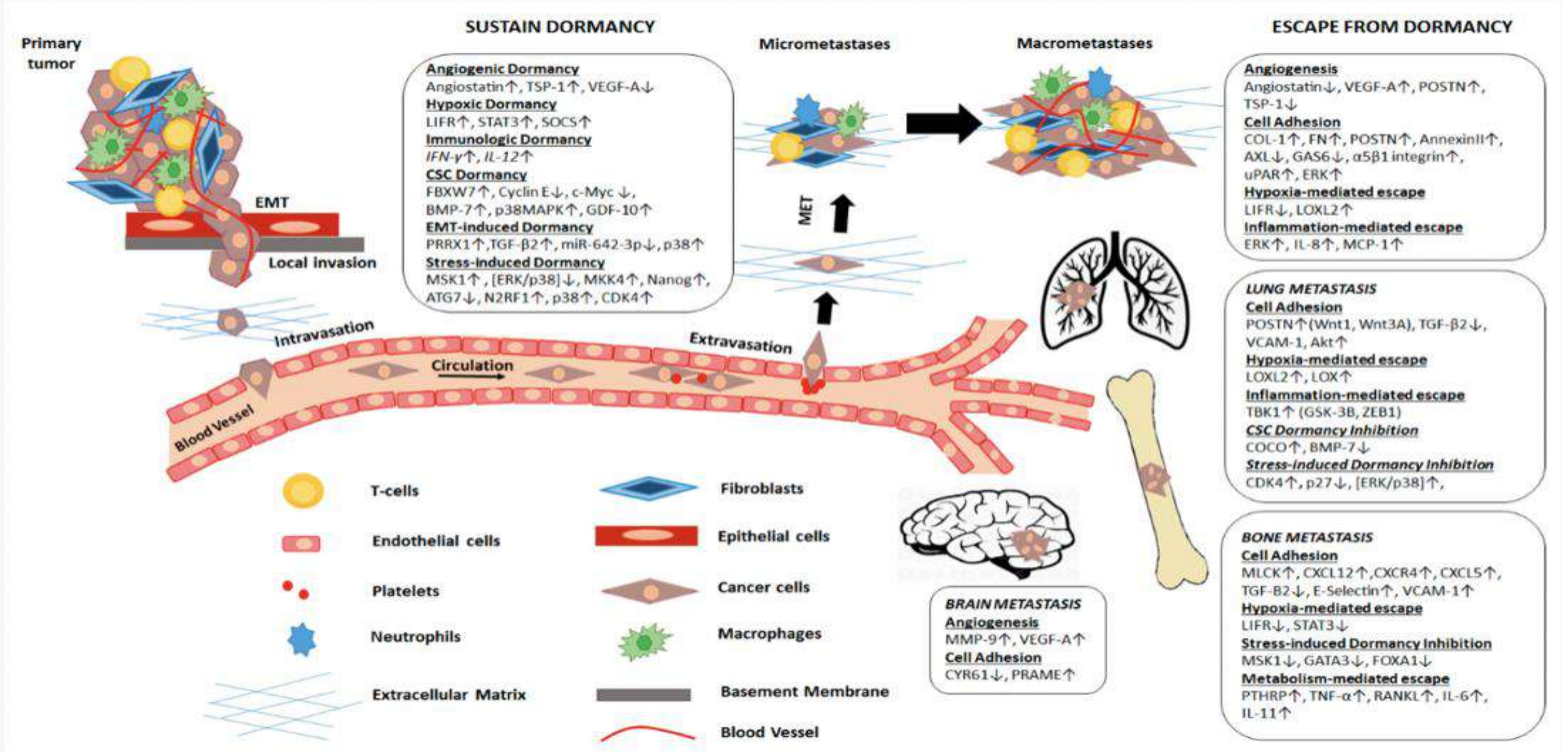


Trends in Microbiology

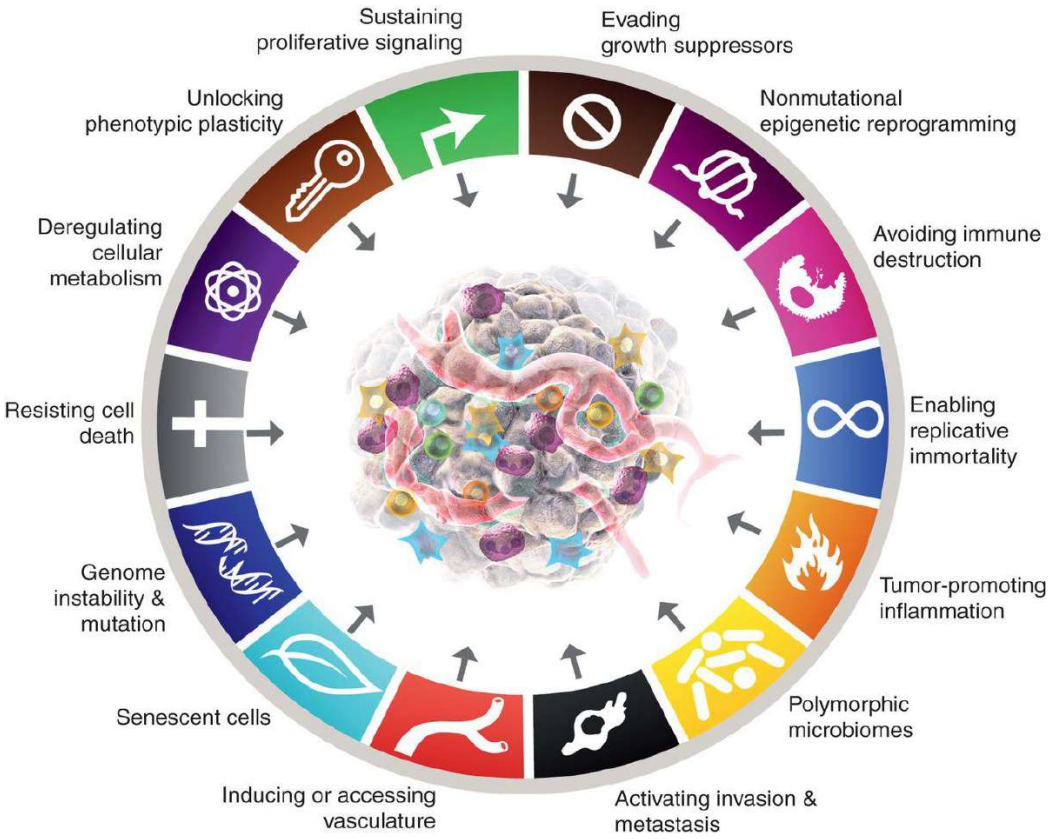
Activating invasion and metastasis



Activating invasion and metastasis

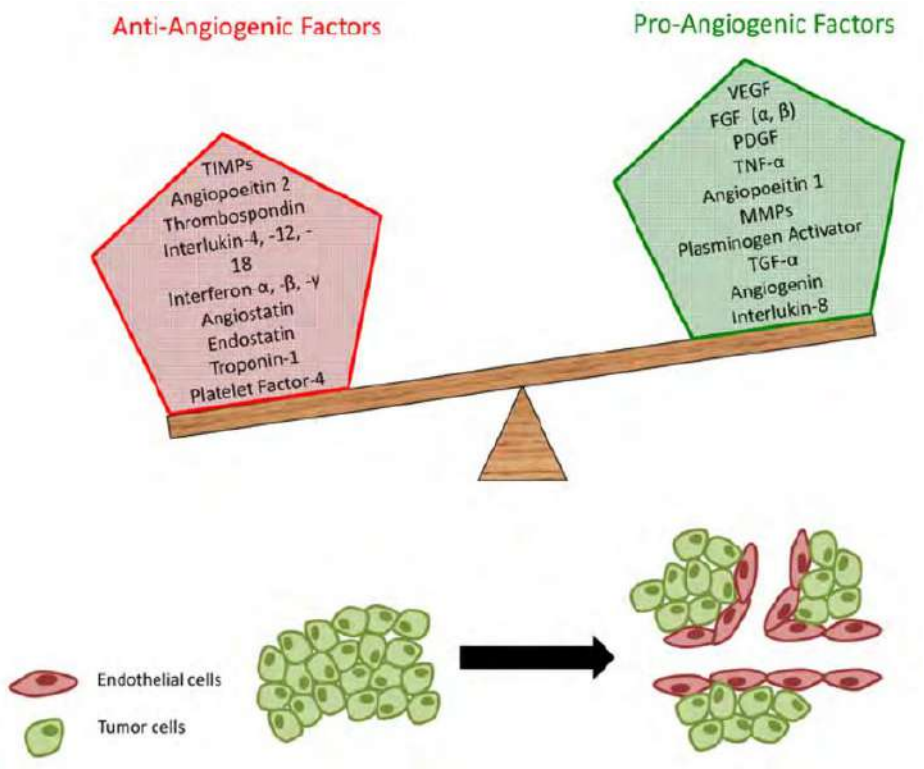


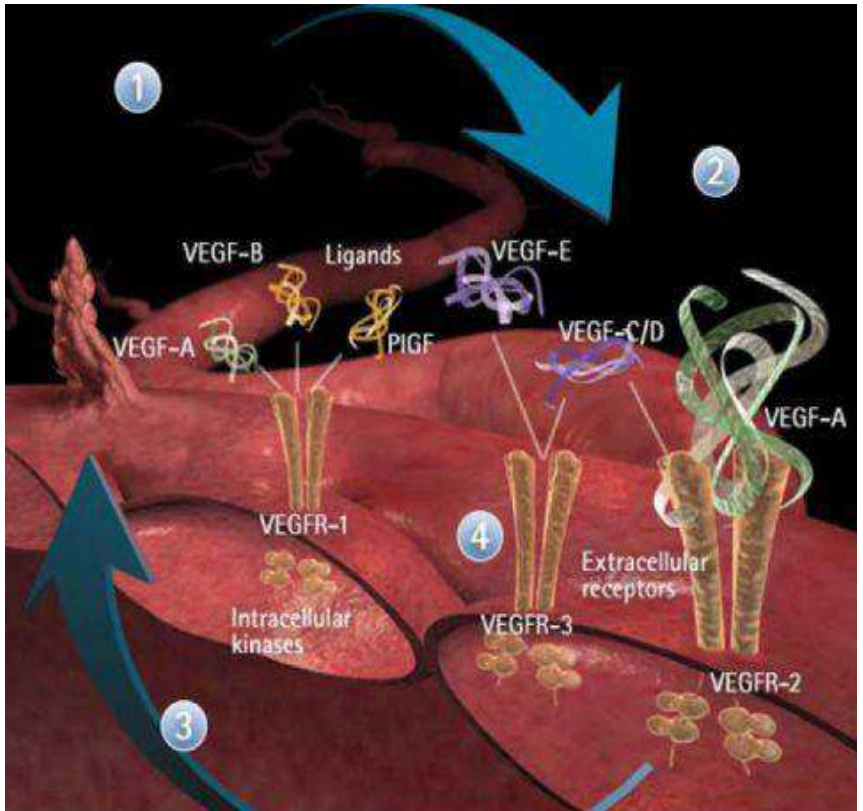
Inducing or accessing vasculature

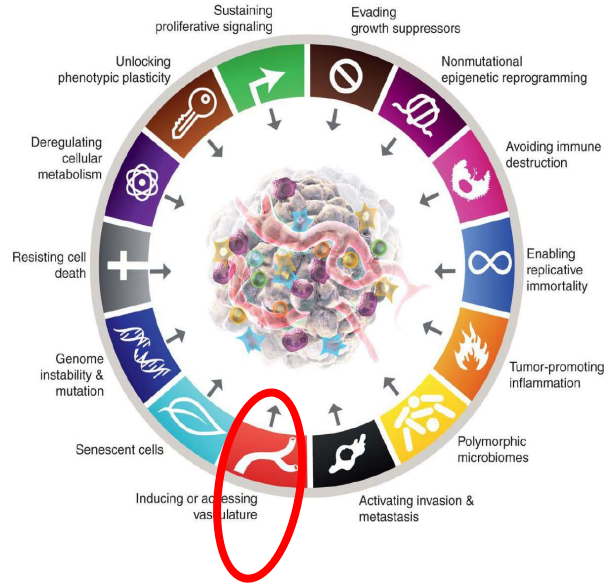


Inducing or accessing vasculature

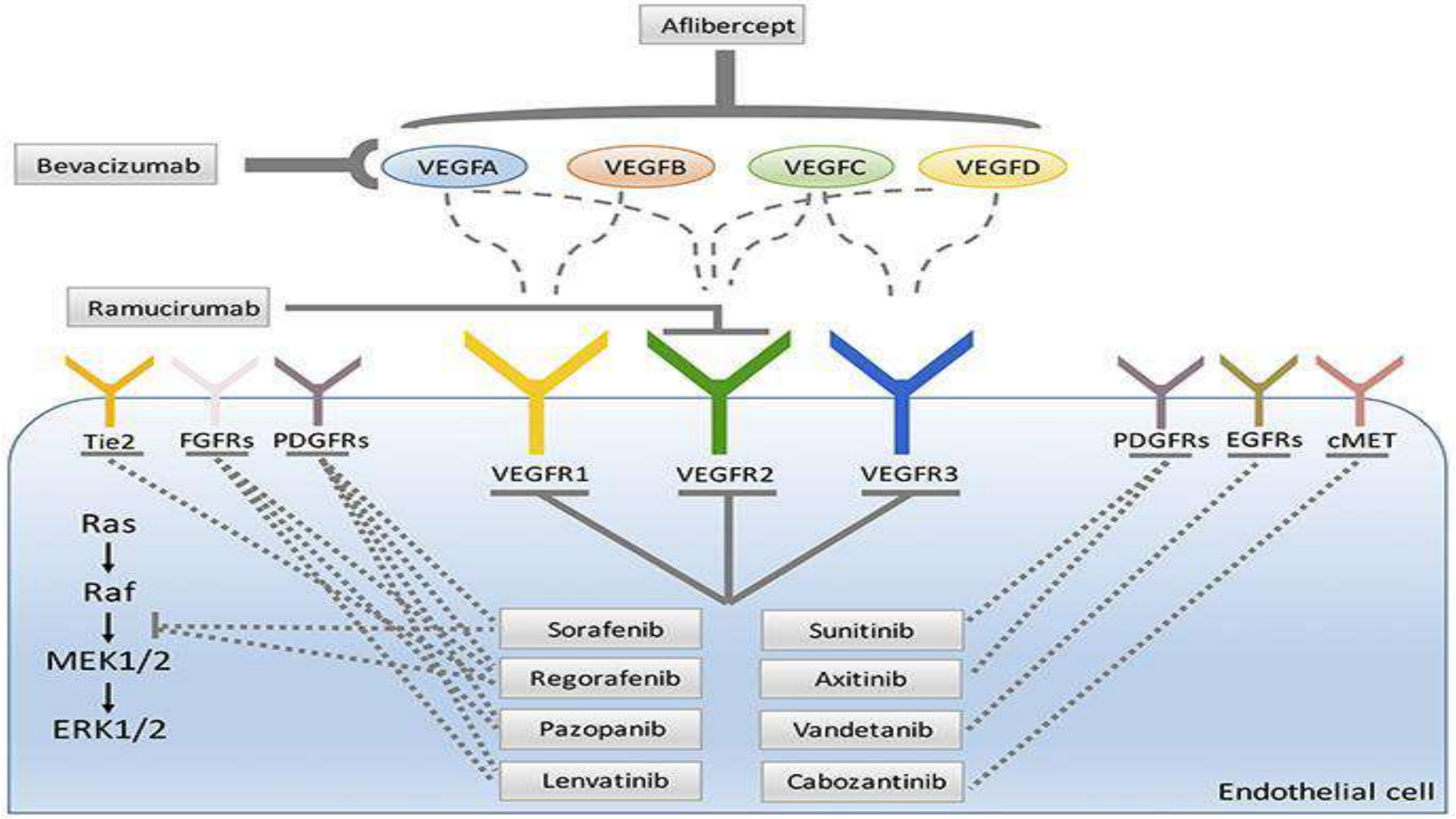
- Angiogenic switch - the point where the number or activity of the pro-angiogenic factors exceeds that of the anti-angiogenic factors, giving rise to new blood vessels accompanied by increased tumour growth, metastasis, and potential drug resistance.



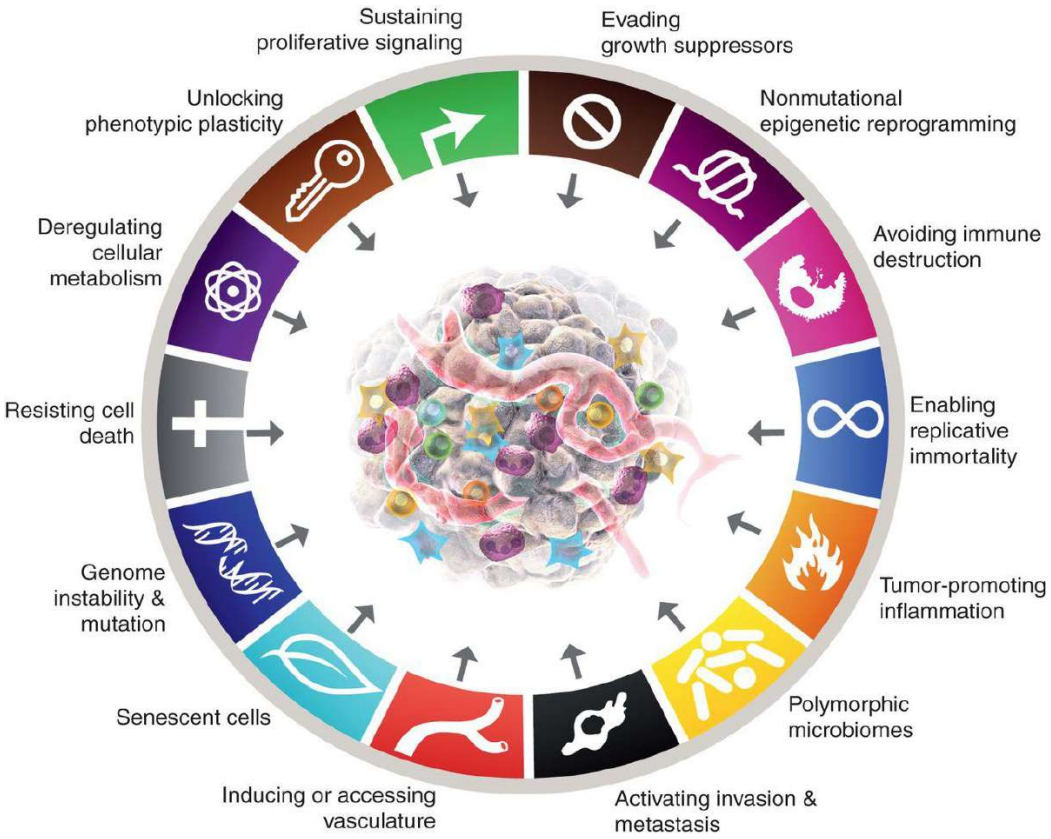




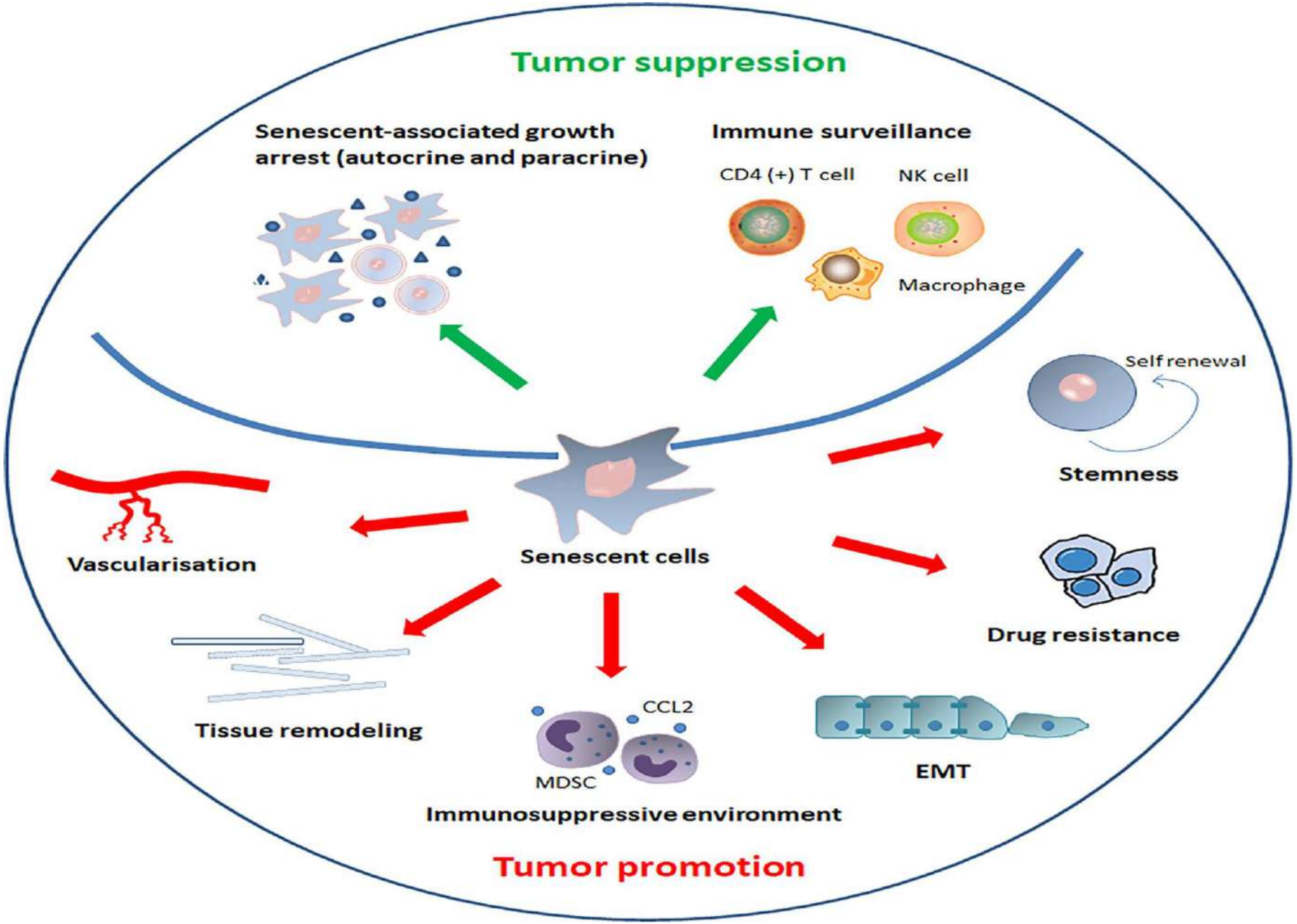
Mabeta et al, 2022

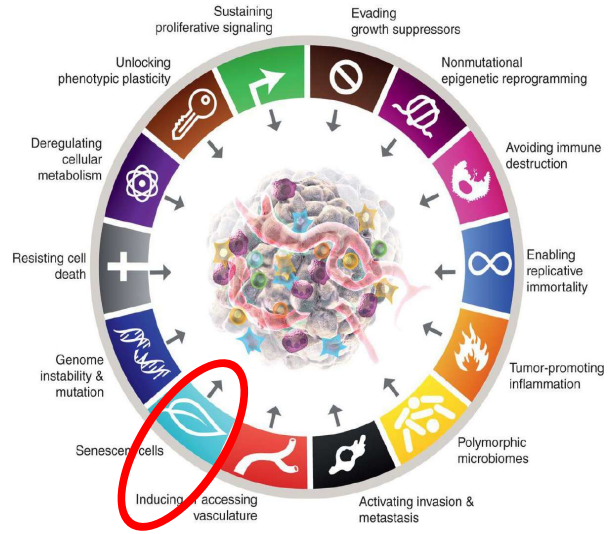

Aflibercept
Bevacizumab
VEGFA
VEGFB
VEGFC
VEGFD
Ramucirumab
Tie2
FGFRs
PDGFRs
VEGFR1
VEGFR2
VEGFR3
PDGFRs
EGFRs
cMET
Ras
Raf
MEK1/2
ERK1/2
Sorafenib
Regorafenib
Pazopanib
Lenvatinib
Sunitinib
Axitinib
Vandetanib
Cabozantinib
Endothelial cell

Senescent cells



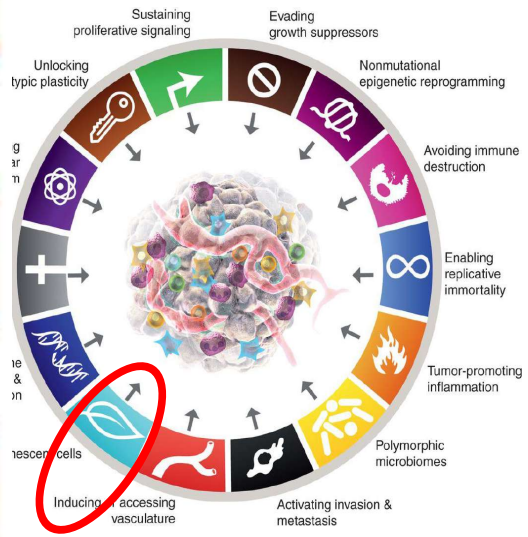
Senescent cells





Campisi, 2000
Schmitt et al, Nature 2022

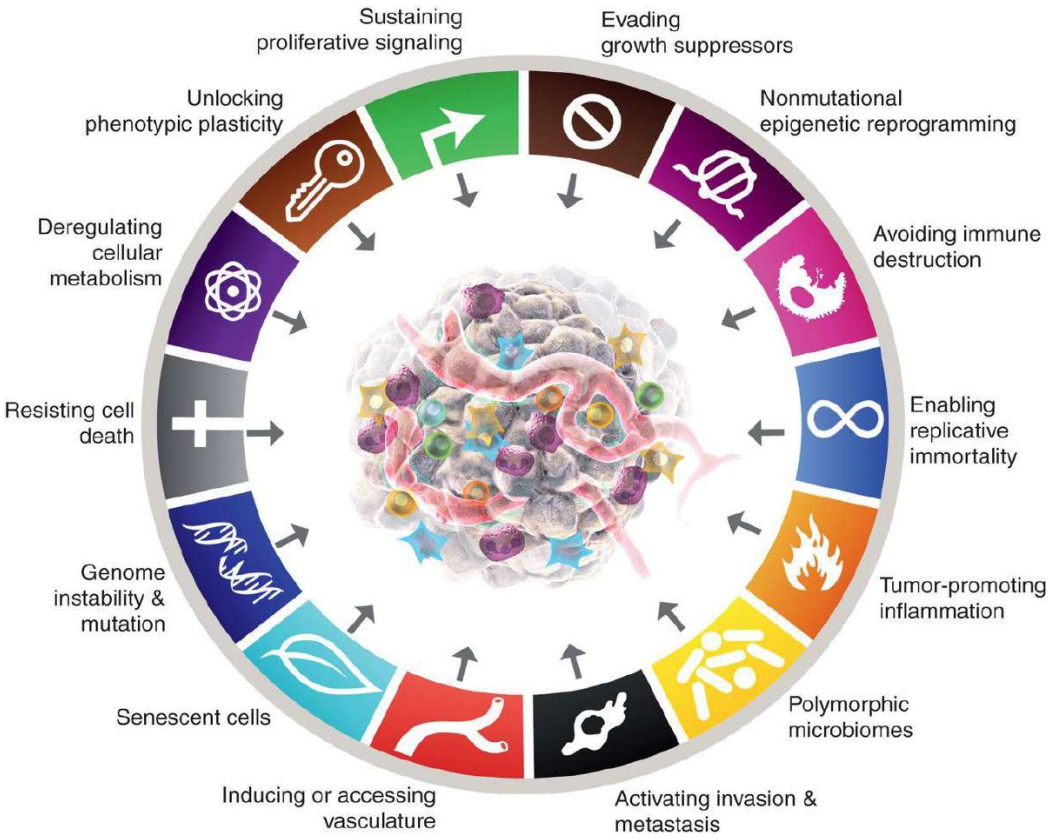
Senescent cells



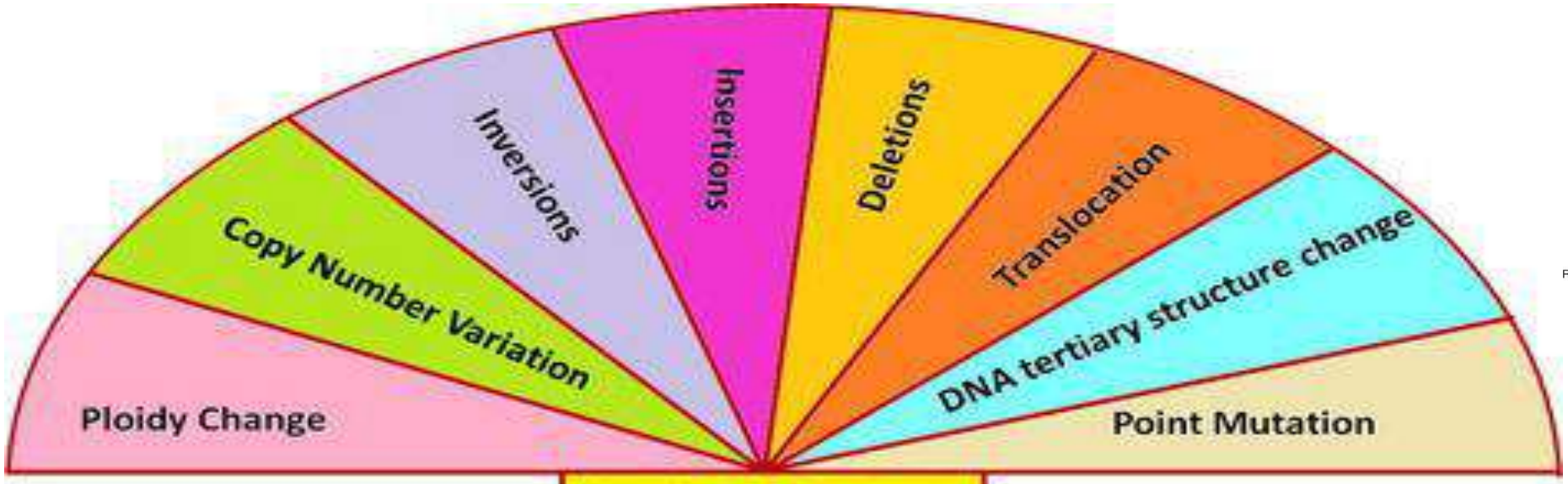
- **Senotherapies** – drugs that interact with senescent cells to interfere with their pro-aging impacts. Two main categories: **senolytic drugs** (selectively destroy senescent cells) and **senostatic** drugs, (inhibit their function).
  - **Navitoclax** interacts with the BCL-2 pathway and prevents it from inhibiting apoptosis.
  - **Quercetin / Fisetin** (a flavonoid) may act in part via senescence induction.
  - **Metformin** has senostatic properties and reduces the stimulatory effect of SASP.

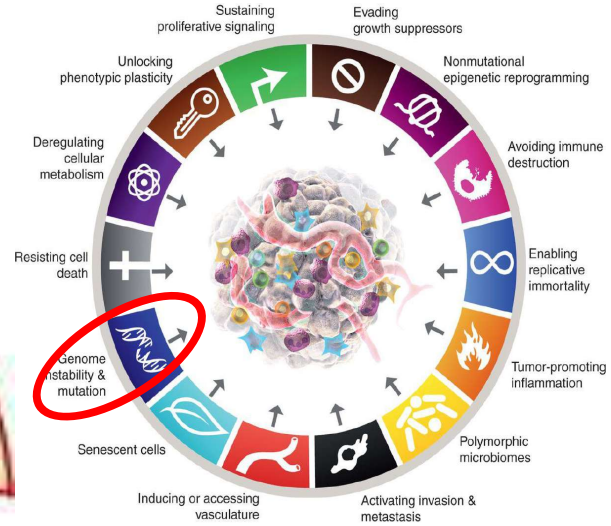
Campisi, 2000
Schmitt et al, Nature 2022

Genomic instability and mutation



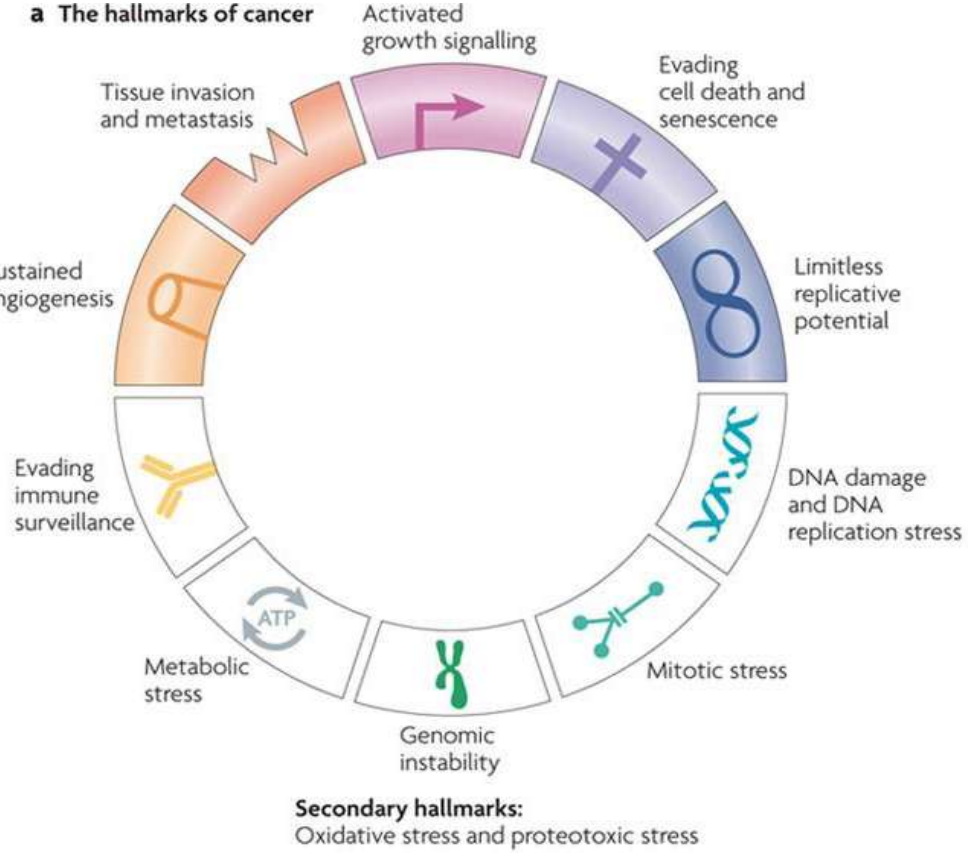
Genomic instability and mutations

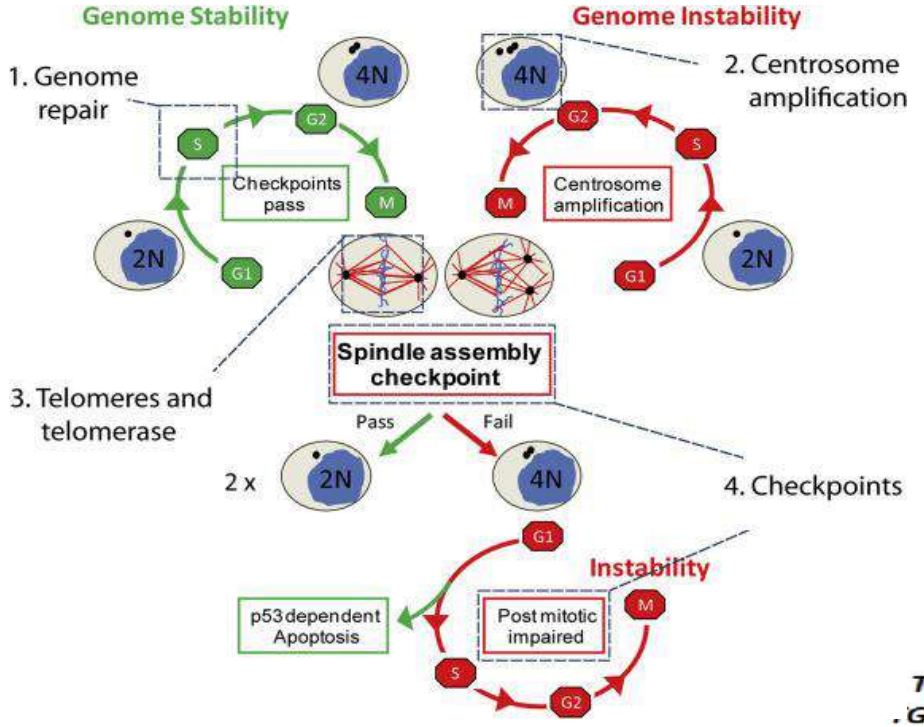


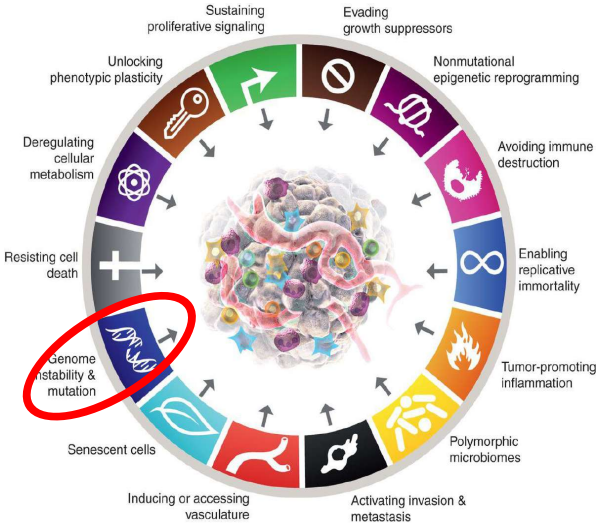


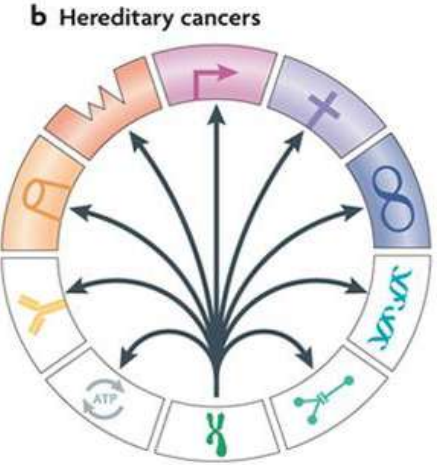
Charames et al, Nature 2003

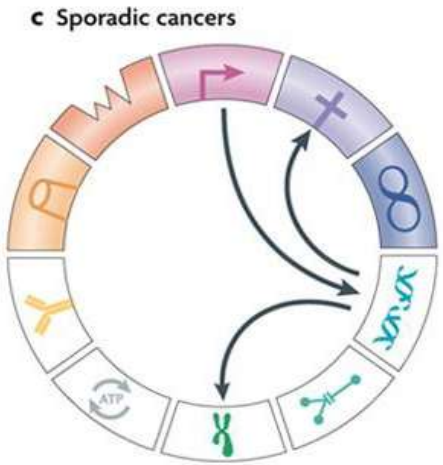
Genomic instability

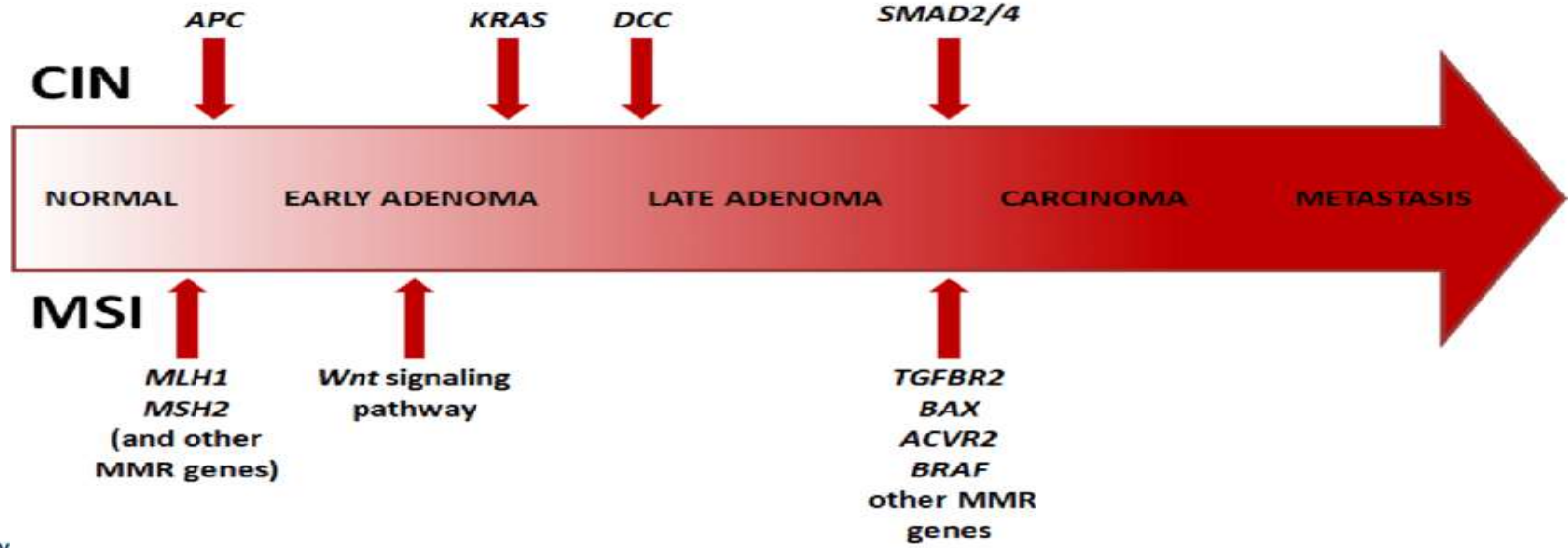






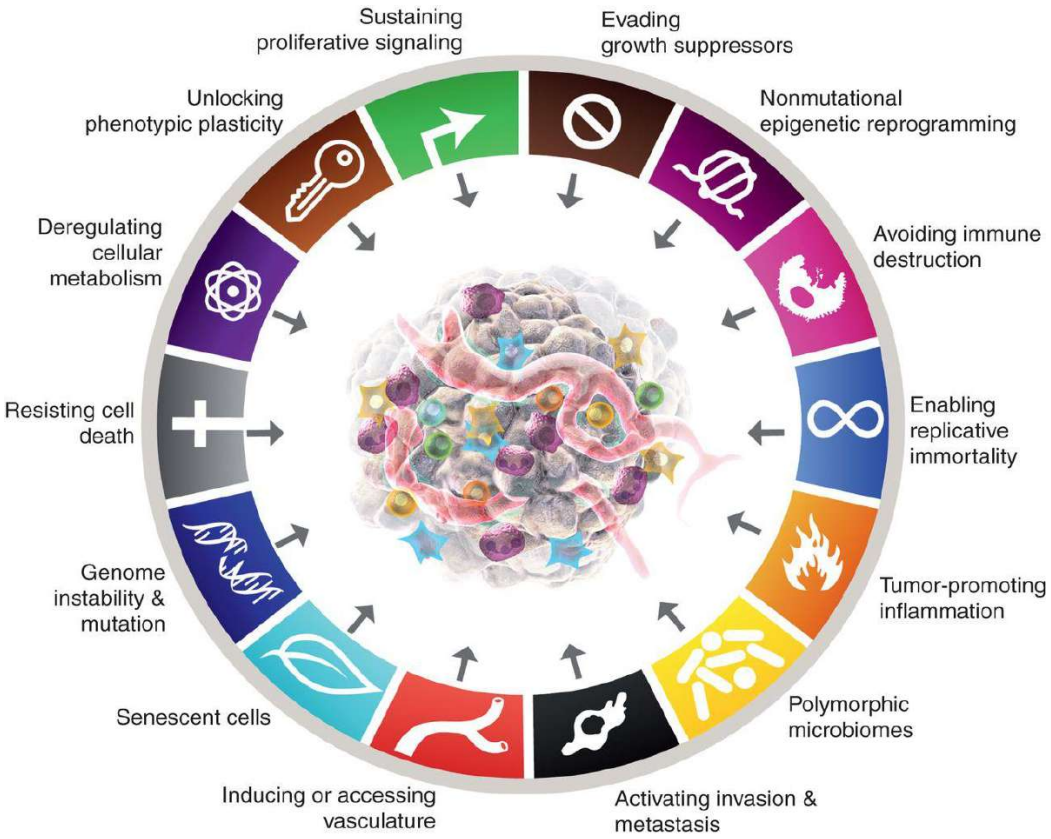


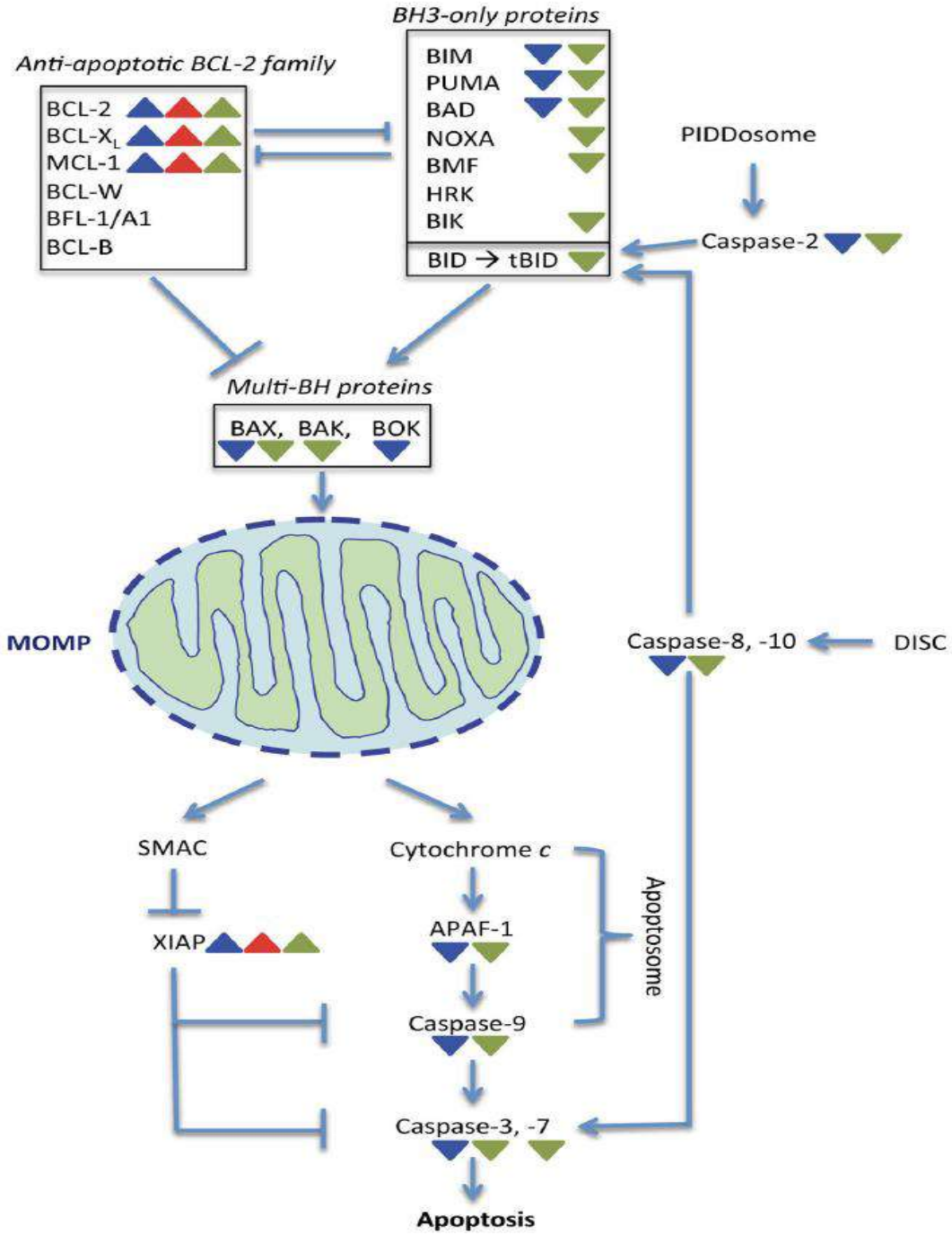


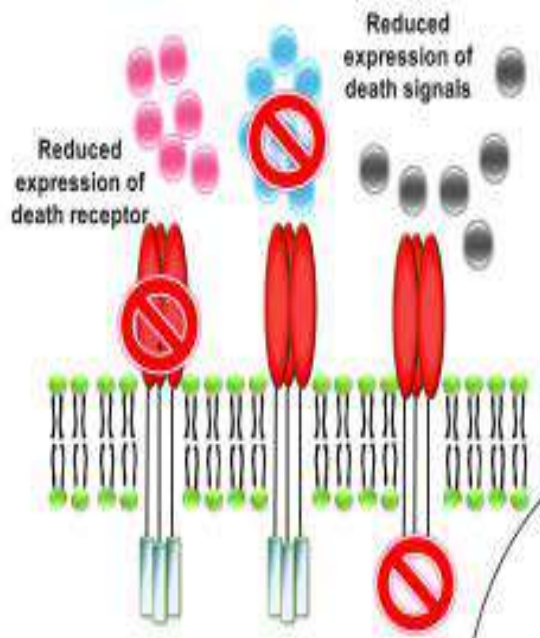


Nature Reviews | Molecular Cell Biology

Resisting cell death

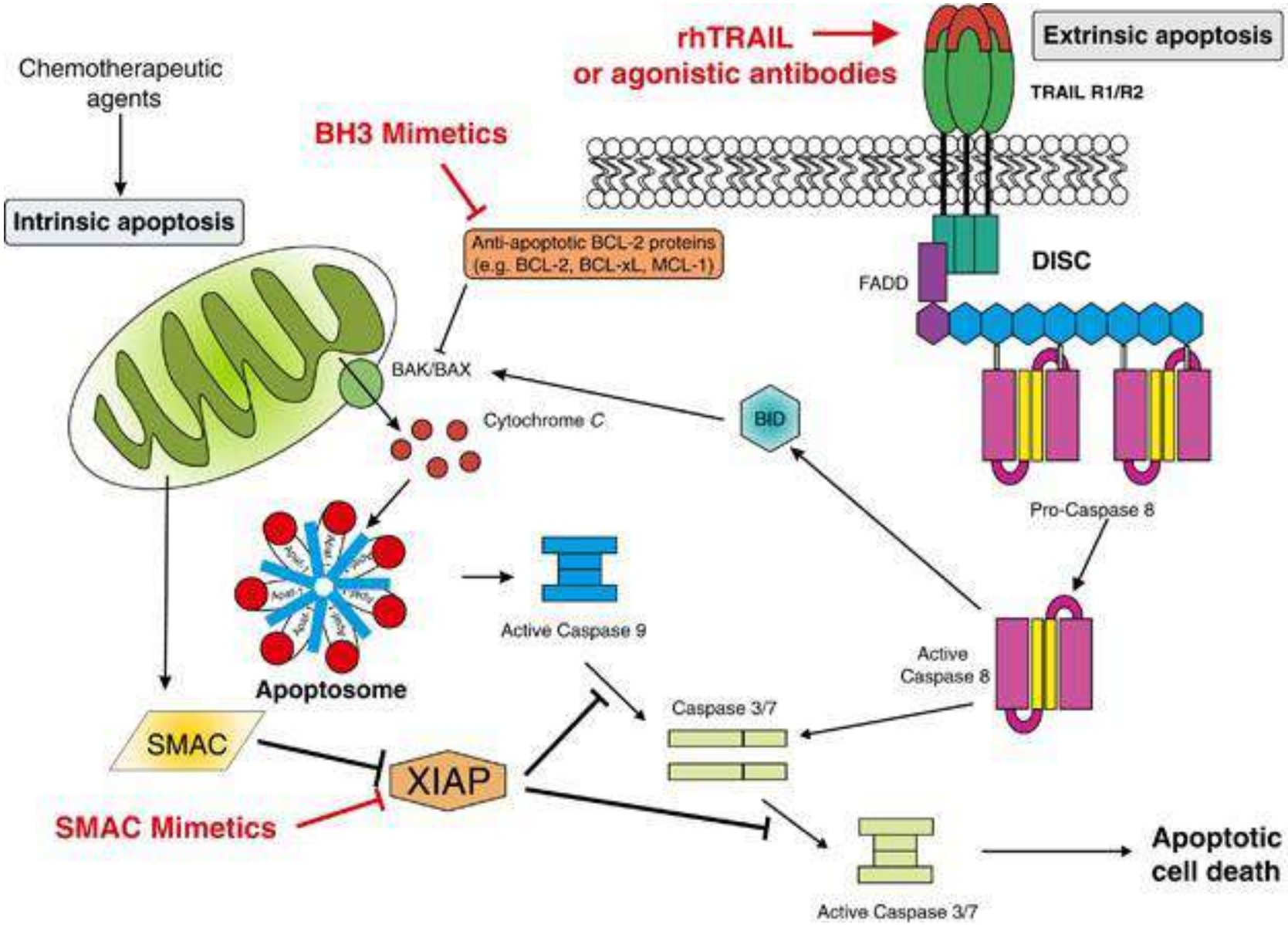


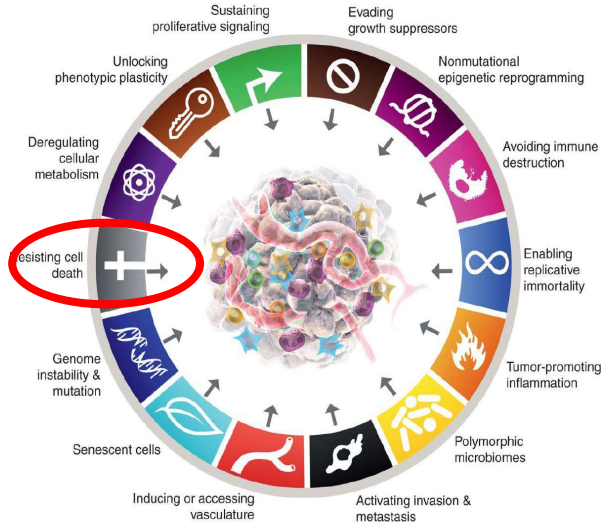

BH3-only proteins
Anti-apoptotic BCL-2 family
BCL-2
BCL-XL
MCL-1
BCL-W
BFL-1/A1
BCL-B
BIM
PUMA
BAD
NOXA
BMF
HRK
BIK
BID → tBID
PIDDosome
Caspase-2
Multi-BH proteins
BAX, BAK, BOK
MOMP
Caspase-8, -10
DISC
SMAC
XIAP
Cytochrome c
APAF-1
Caspase-9
Apoptosome
Caspase-3, -7
Apoptosis


Reduced expression of death signals
Reduced expression of death receptor
Expression of decoy receptor without death domain
Impaired receptor signaling pathway

Overexpression of antiapoptotic proteins
Group I
Bcl-2, Bcl-xL, Mcl-1, Bcl-w, A1/BF-1, BclB/Bcl2L10
Underexpression of proapoptotic proteins
Group II
Bid, Bim, Puma, Noxa,Bad, Bmf, Hrk, Bik
Group III
Bax, Bak, Bok/Mtd
Dysregulated Apoptosis & Cancer
Disrupted balance of Bcl-2 family of proteins
Defects/ mutations in p53
Reduced expression of caspases
Increased expression of IAPs

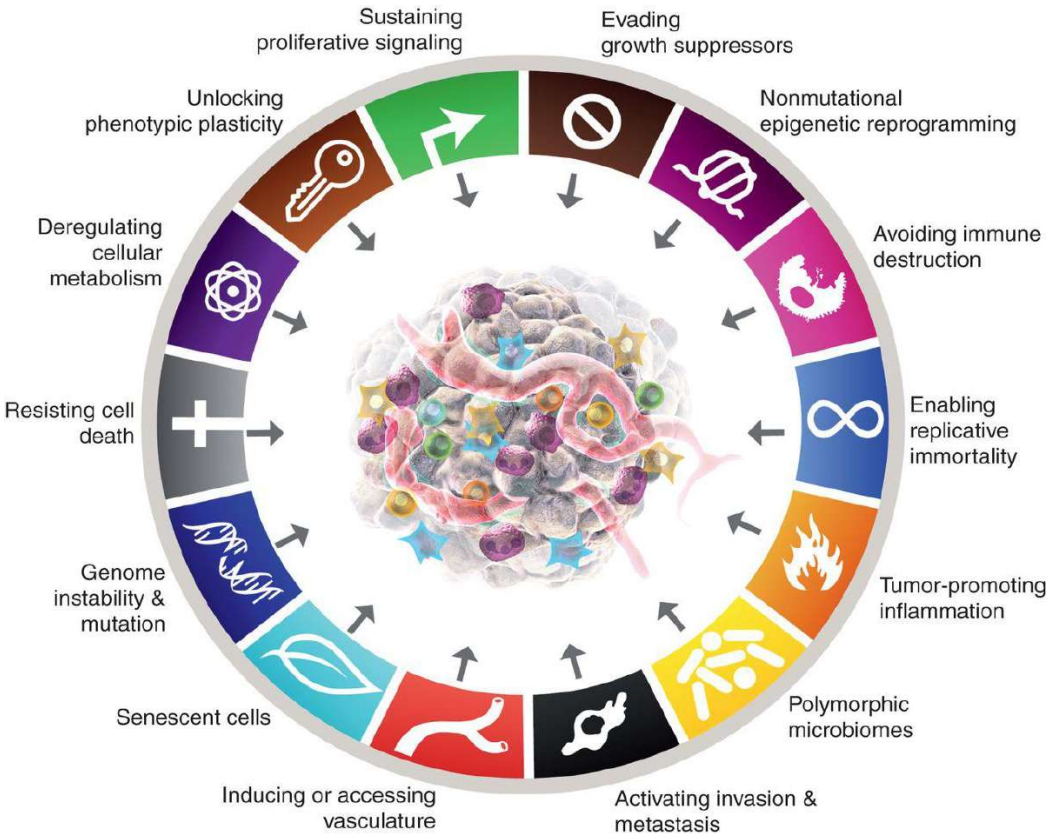
Resisting cell death

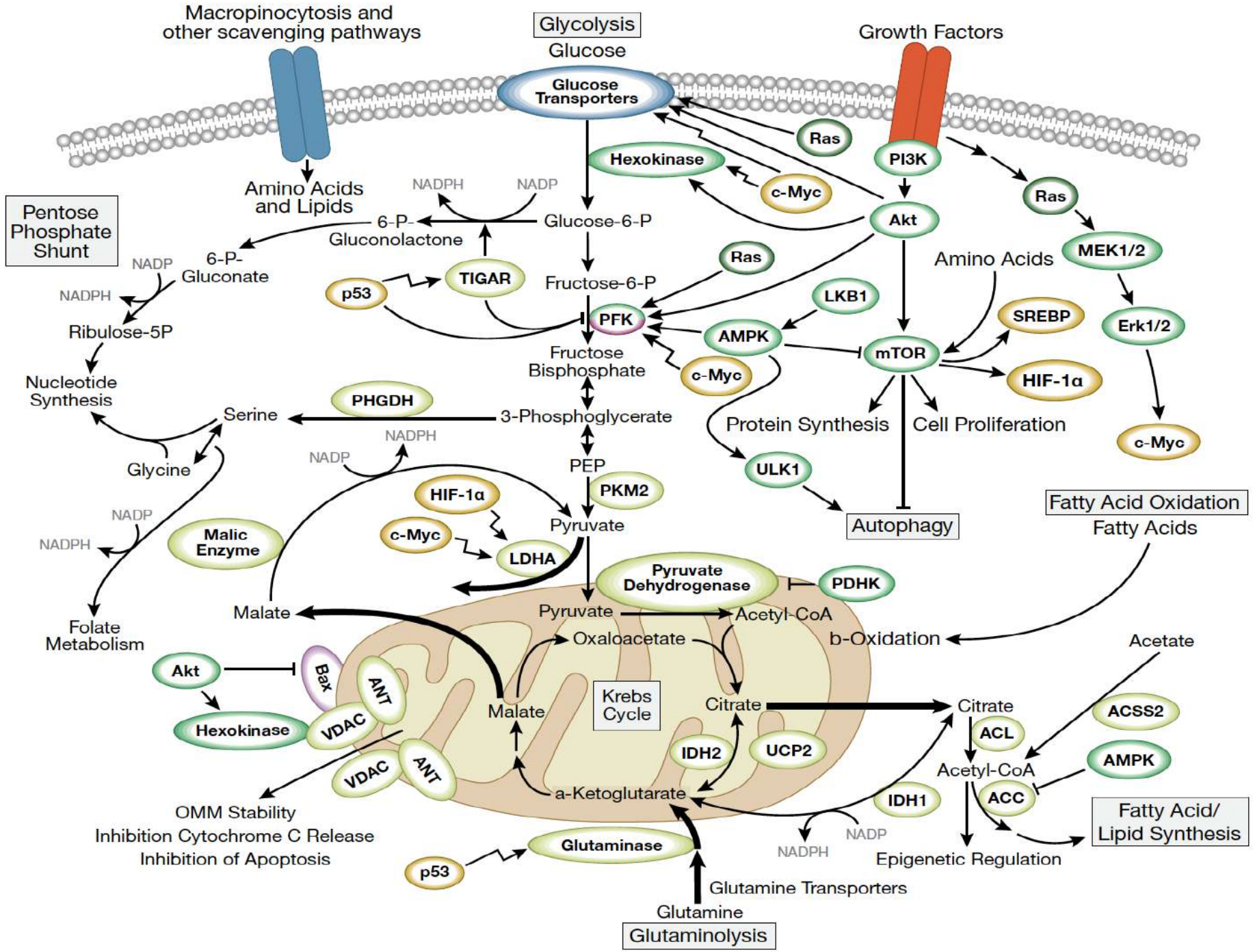


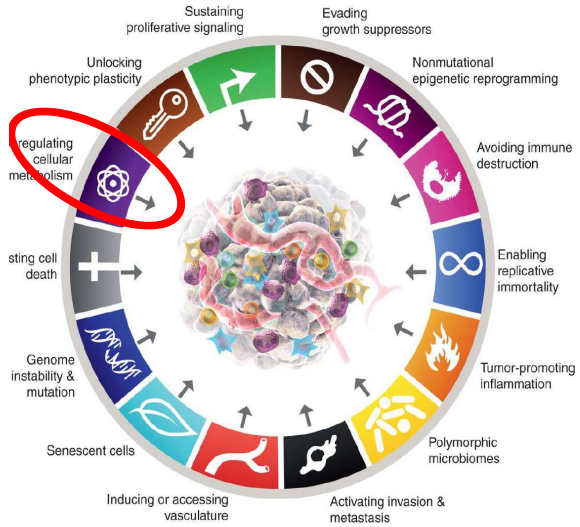


Schmitt et al, Nature 2022

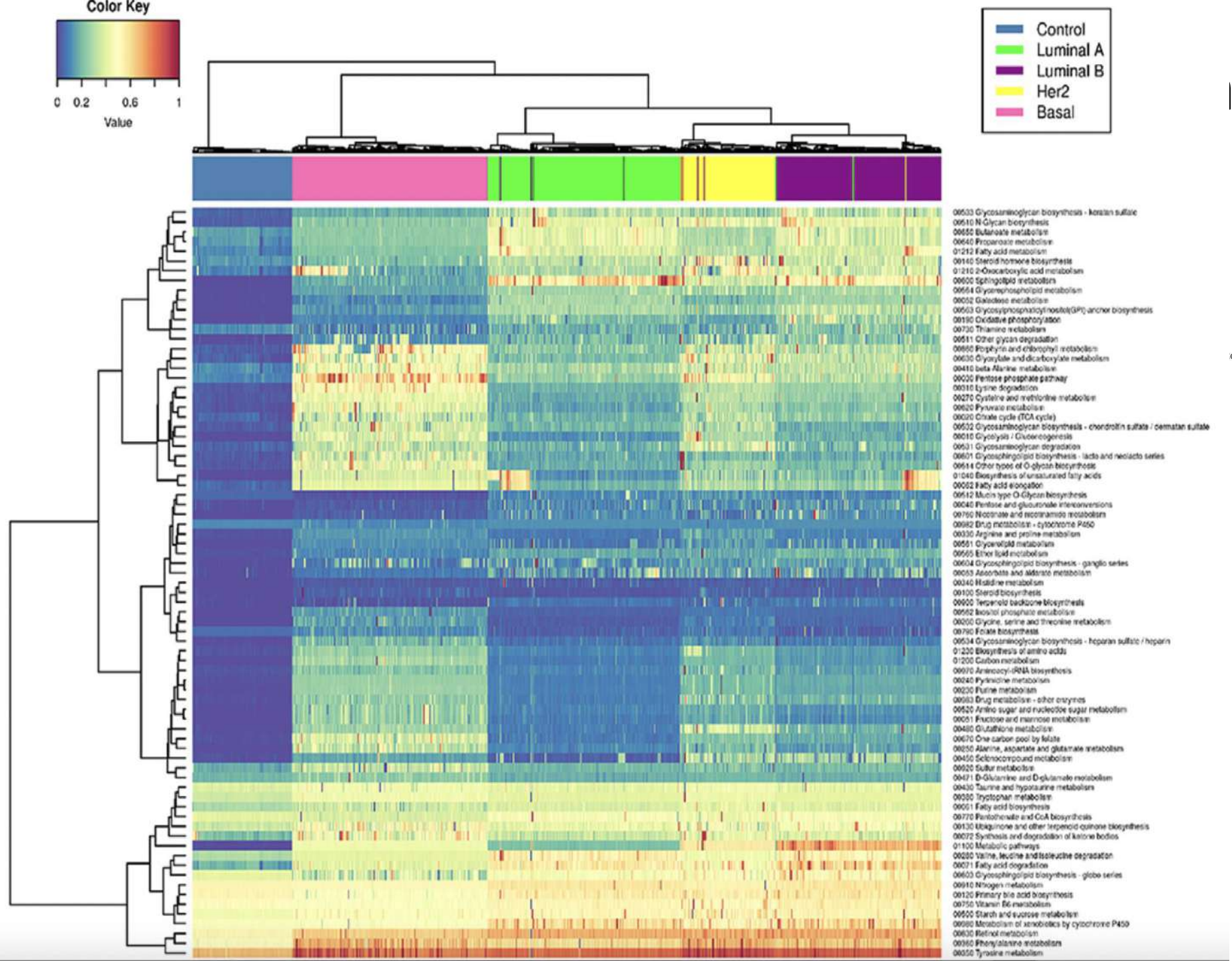
Deregulating cellular metabolism

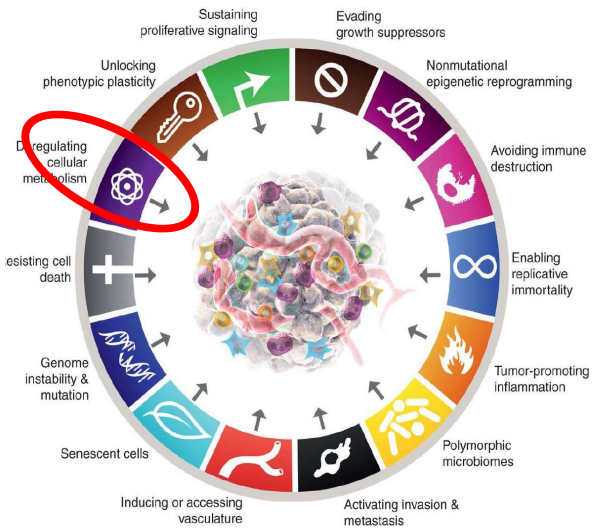






Serrano-Carbajal et al, Front Oncol 2020





BURDWAN MEDICAL COLLEGE

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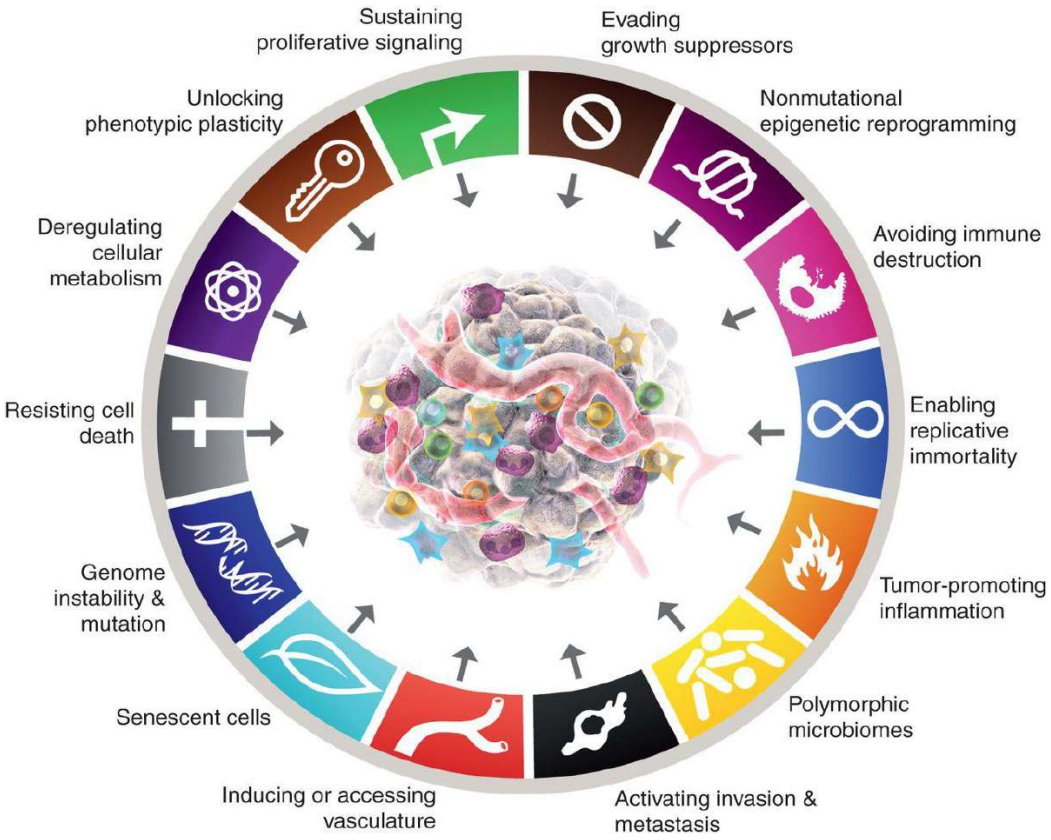
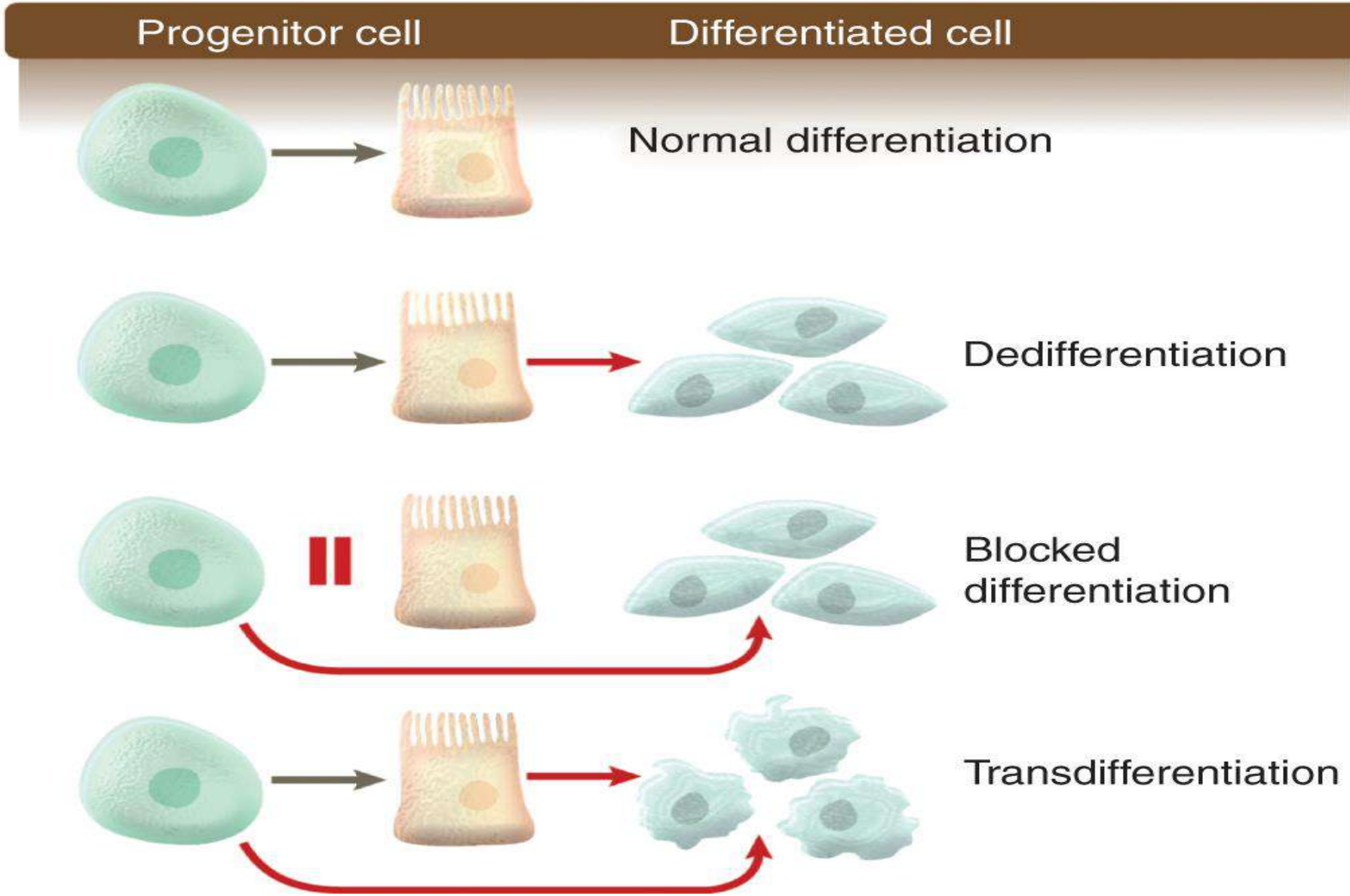
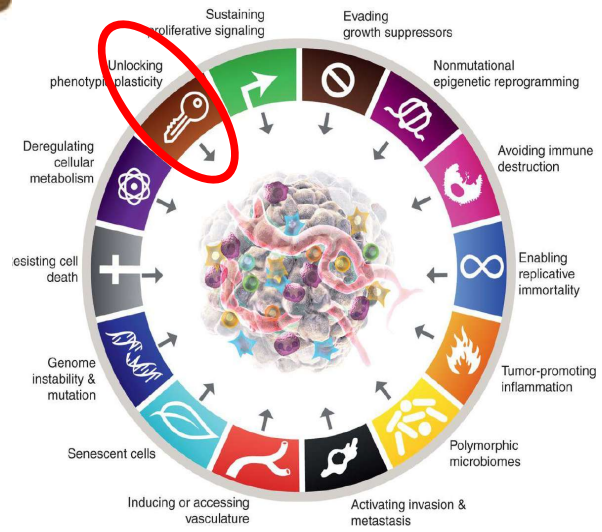
Unlocking phenotypic plasticity



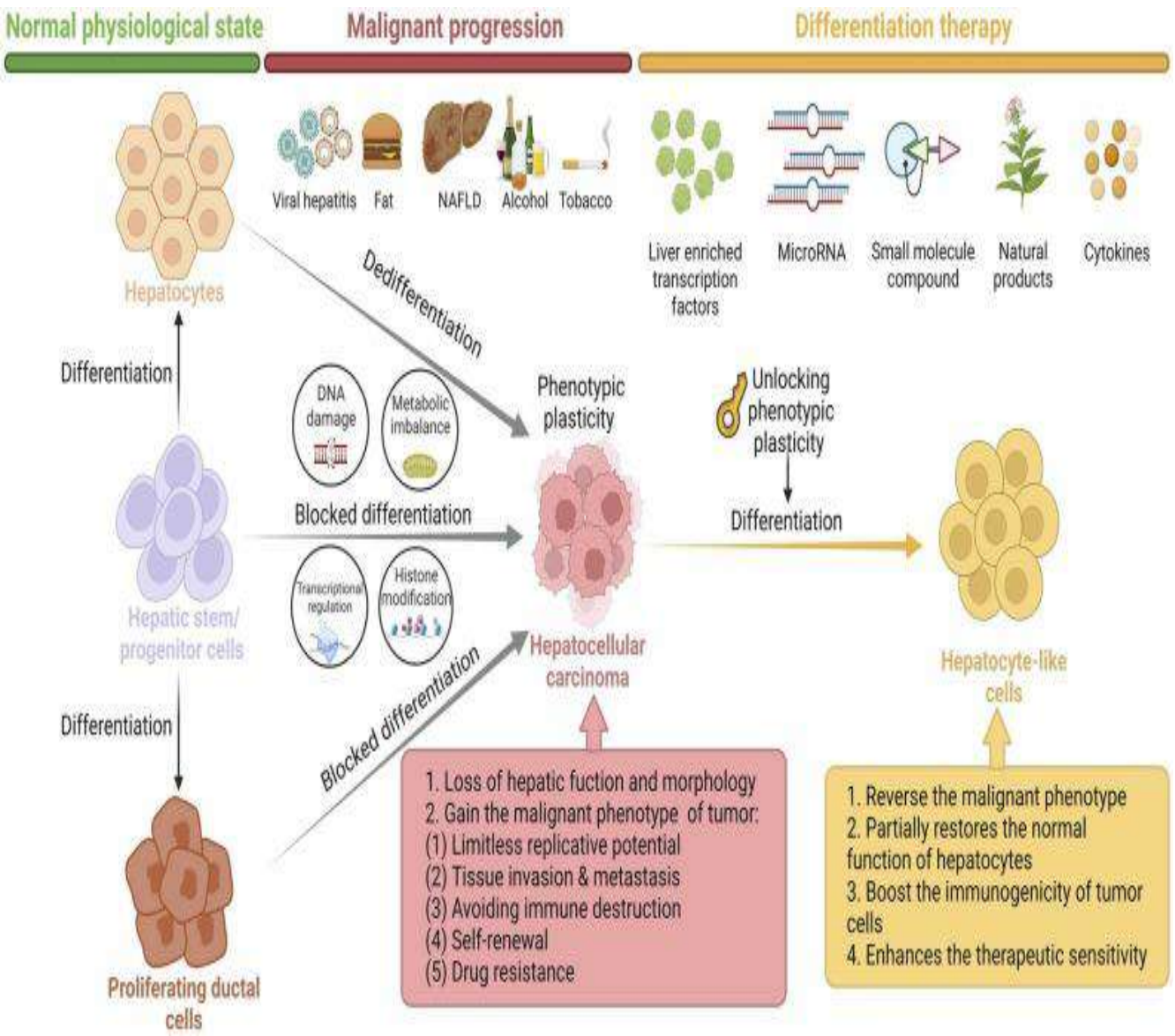
Unlocking phenotypic plasticity

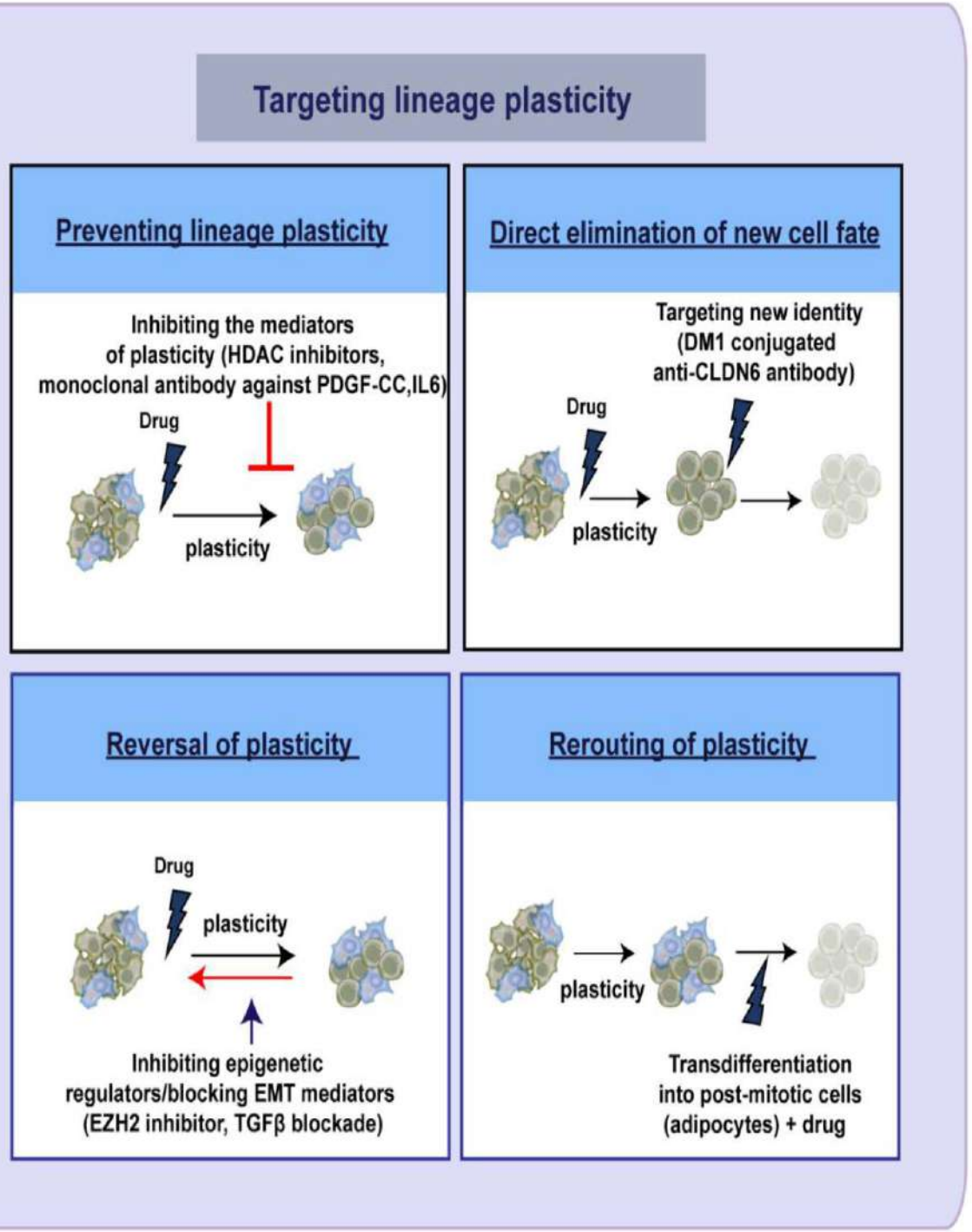




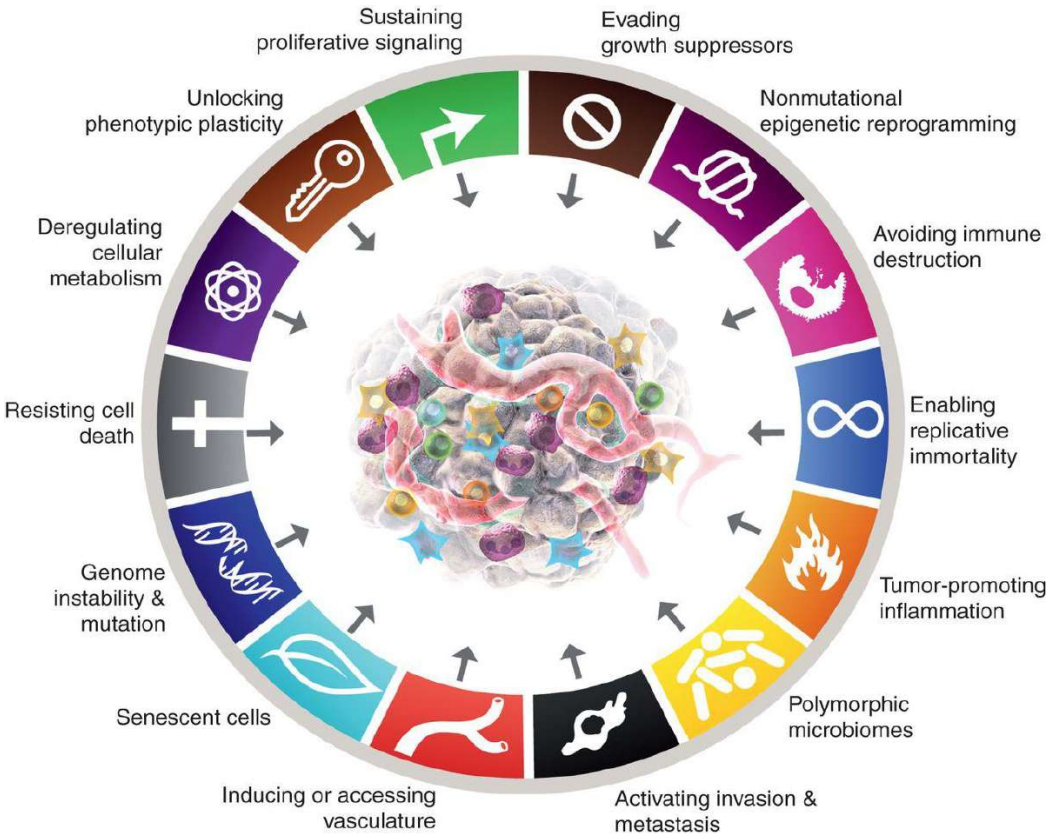
Serrano-Carbajal et al, Front Oncol 2020

Unlocking phenotypic plasticity

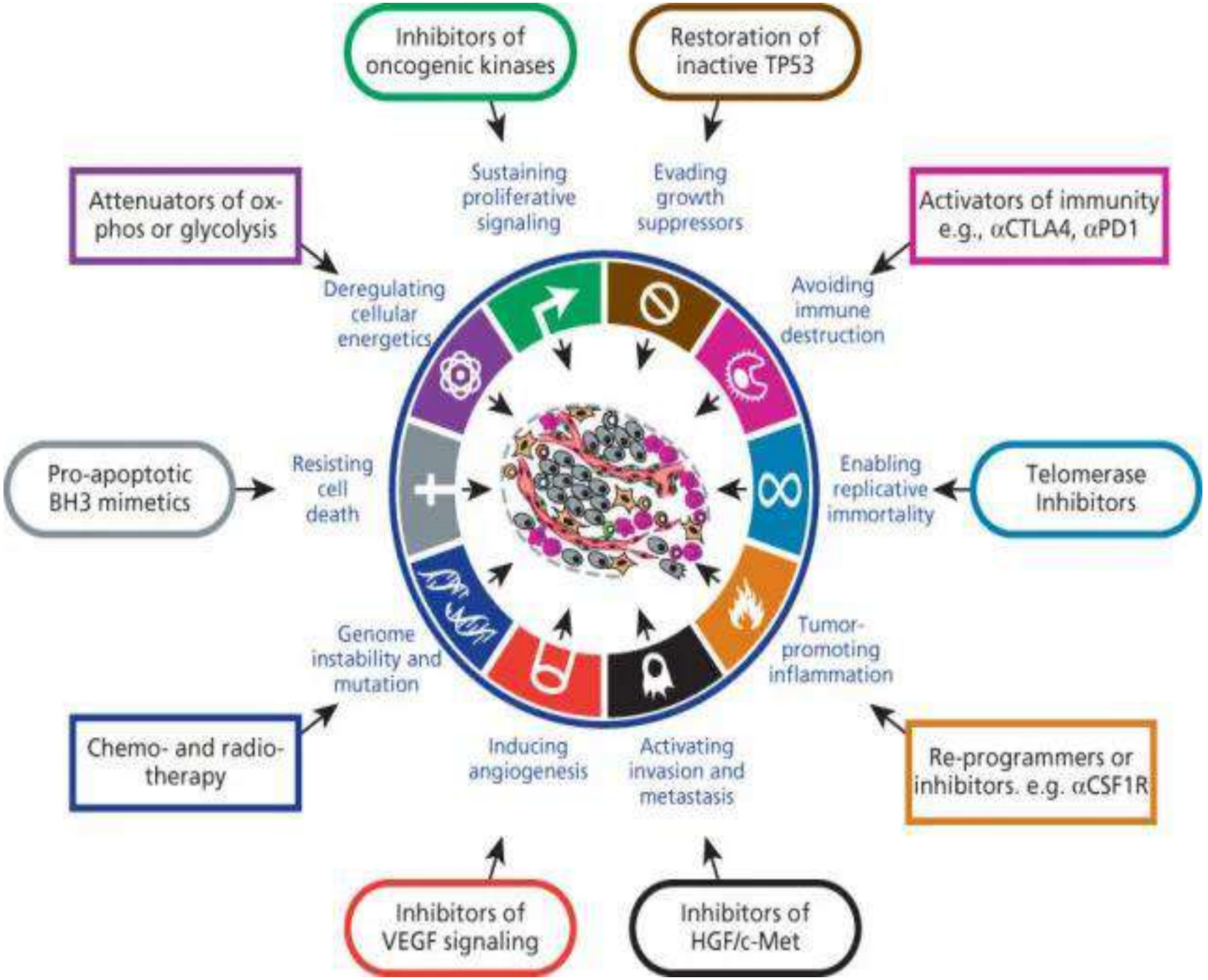




Summary


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

How can we target cancer?



Thank You!

drabhishekbasu@yahoo.com