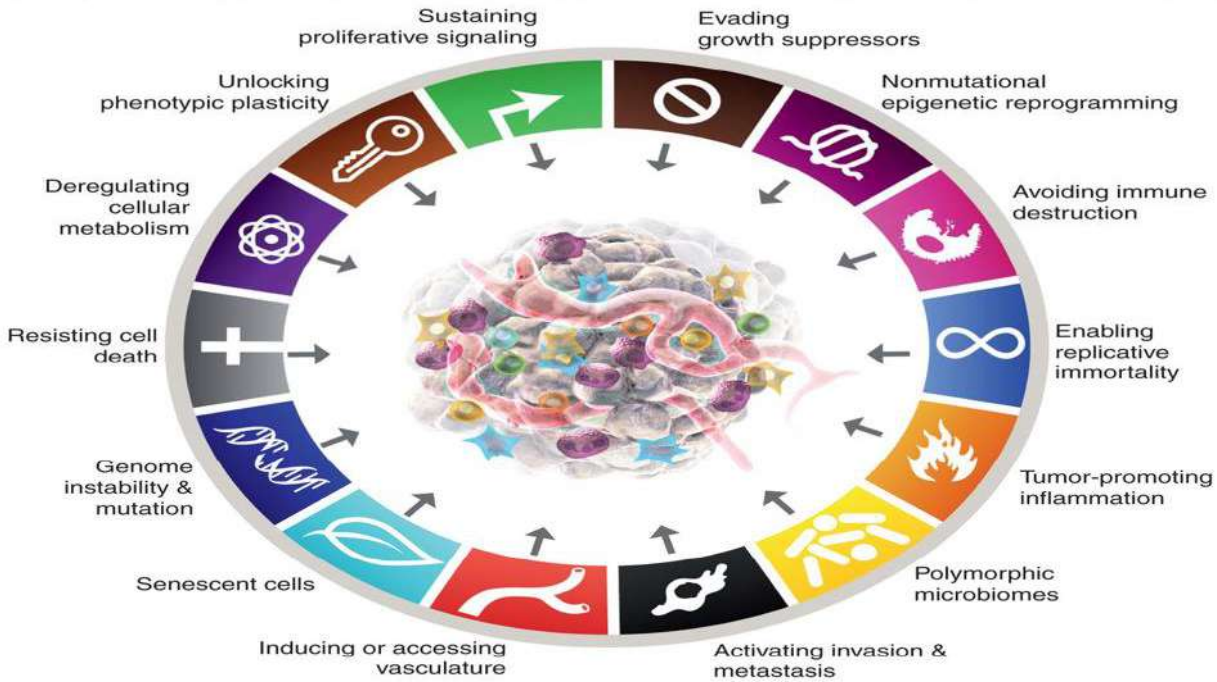
AN INTRODUCTION TO CANCER CELL BIOLOGY AND GENETICS



Dr. SURENDRA NATH SENAPATI

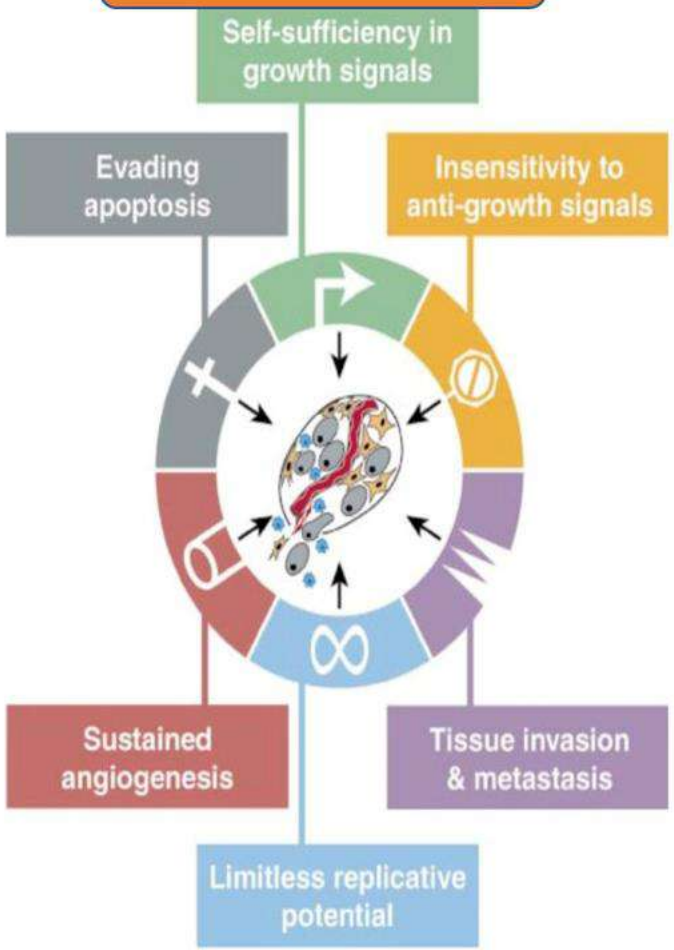
PROFESSOR, DEPARTMENT OF RADIATION ONCOLOGY,

AH POST GRADUATE INSTITUTE OF CANCER,

CUTTACK,ODISHA

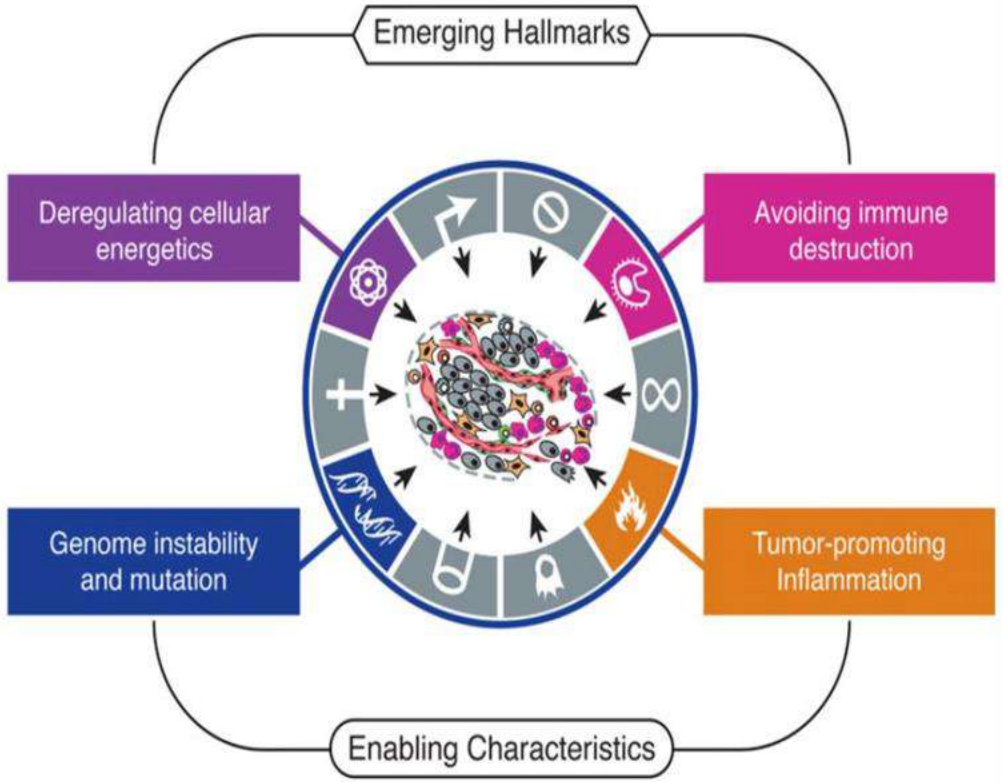
Evolution of Hallmarks of Cancer

6 HALL MARKS



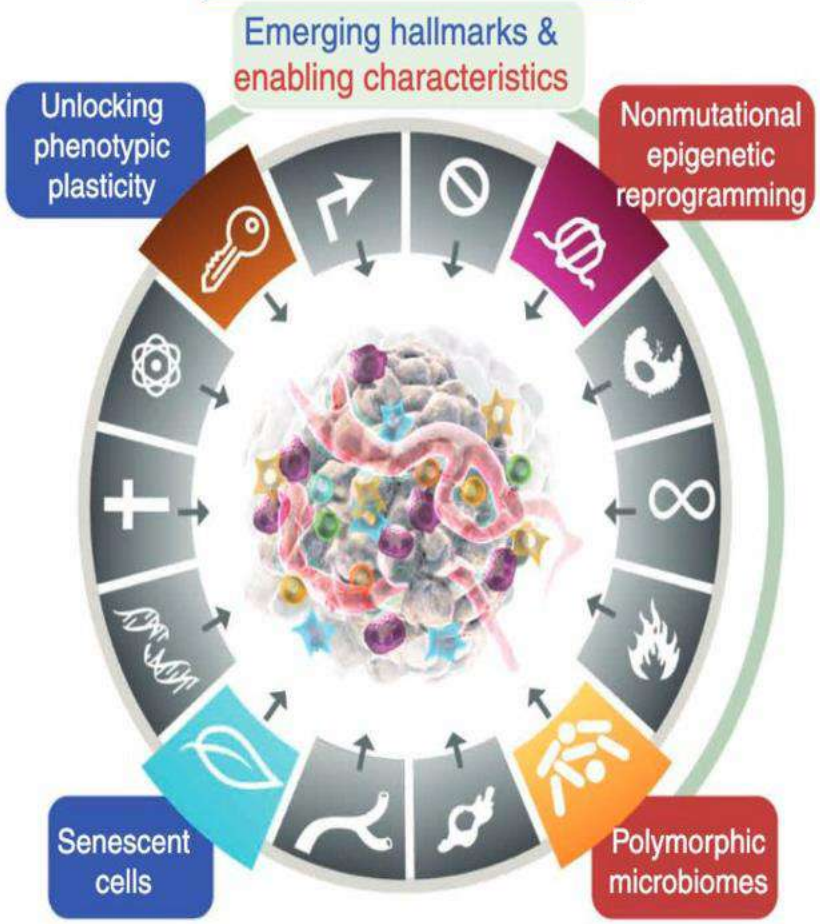
Hanahan and Weinberg. Cell (2000).

10 HALL MARKS



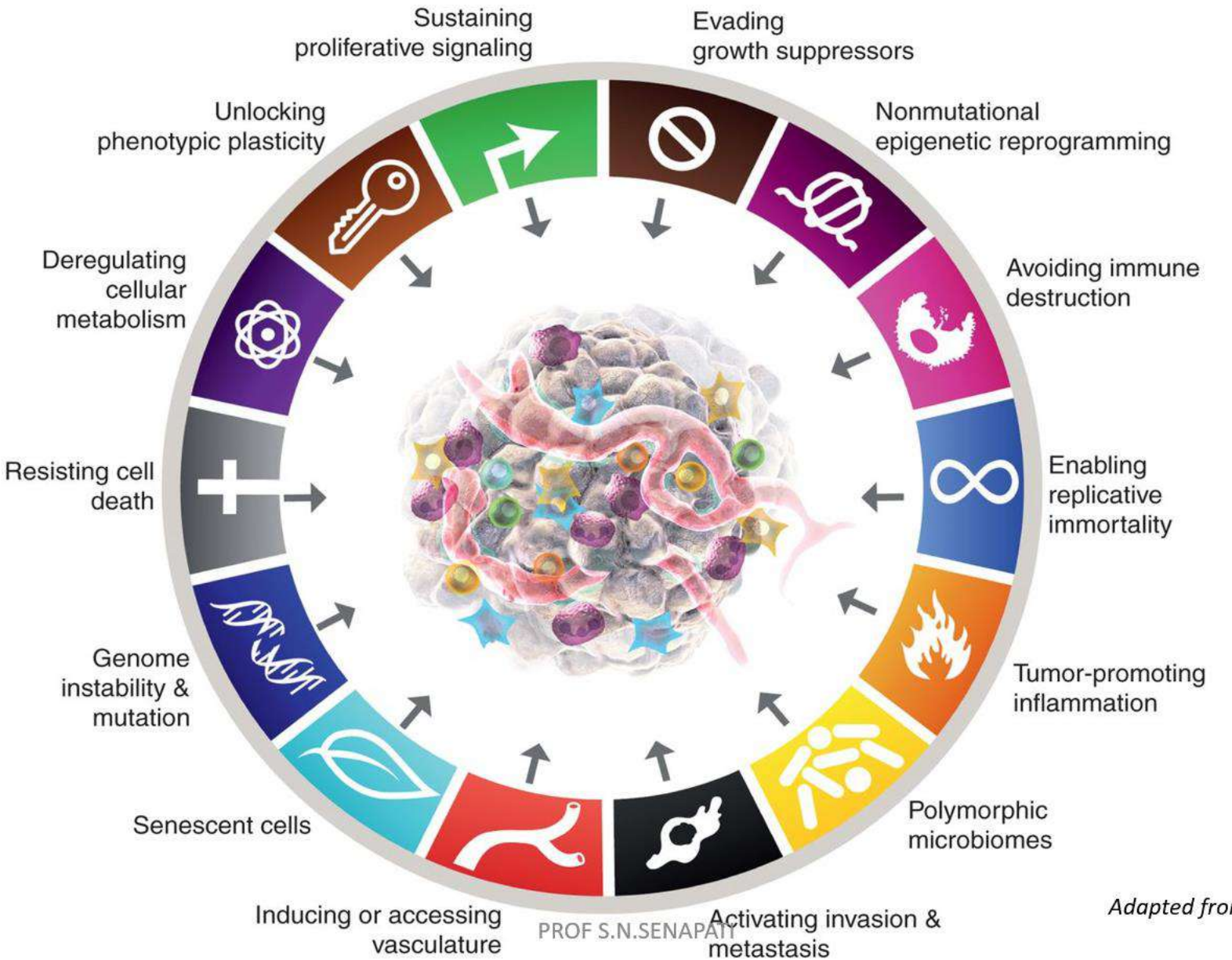
Hanahan and Weinberg. Cell (2011).

14 HALL MARKS



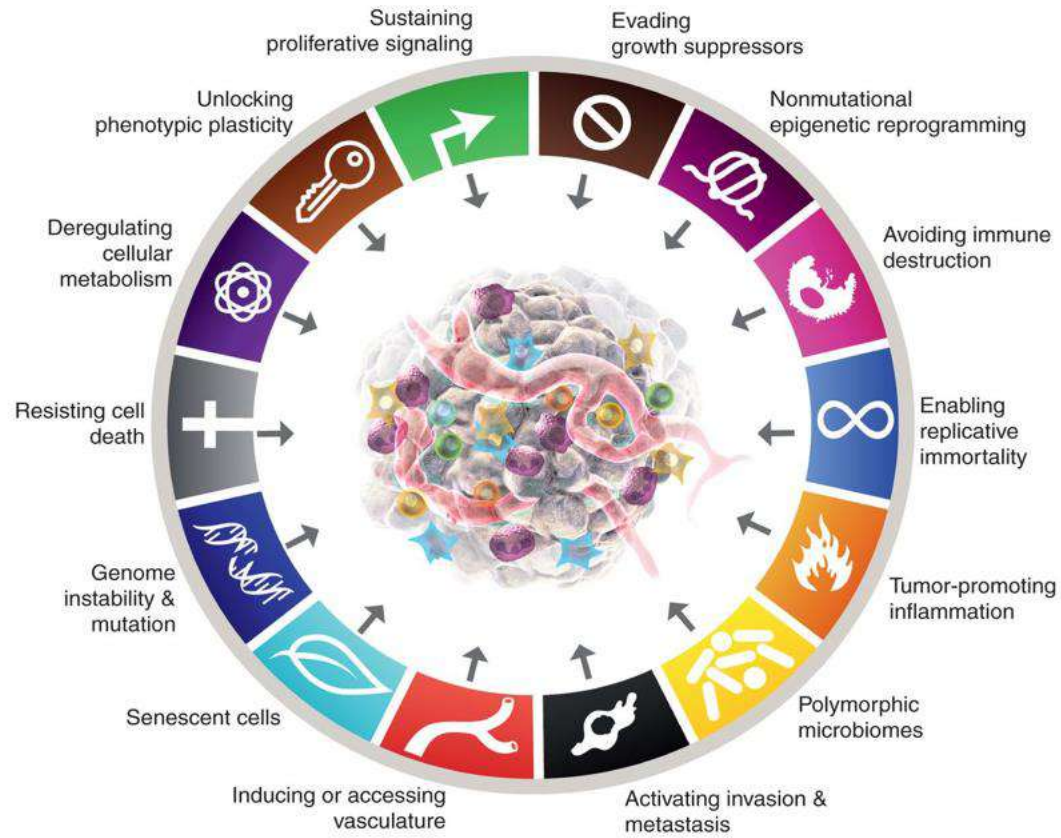
Hanahan. Cancer Disc (2022).

A more complicated picture



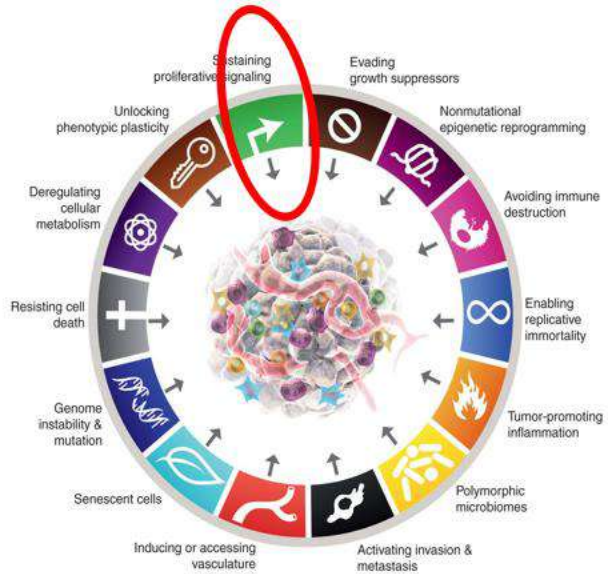
Adapted from Hanahan D et al Cancer Disc 2022

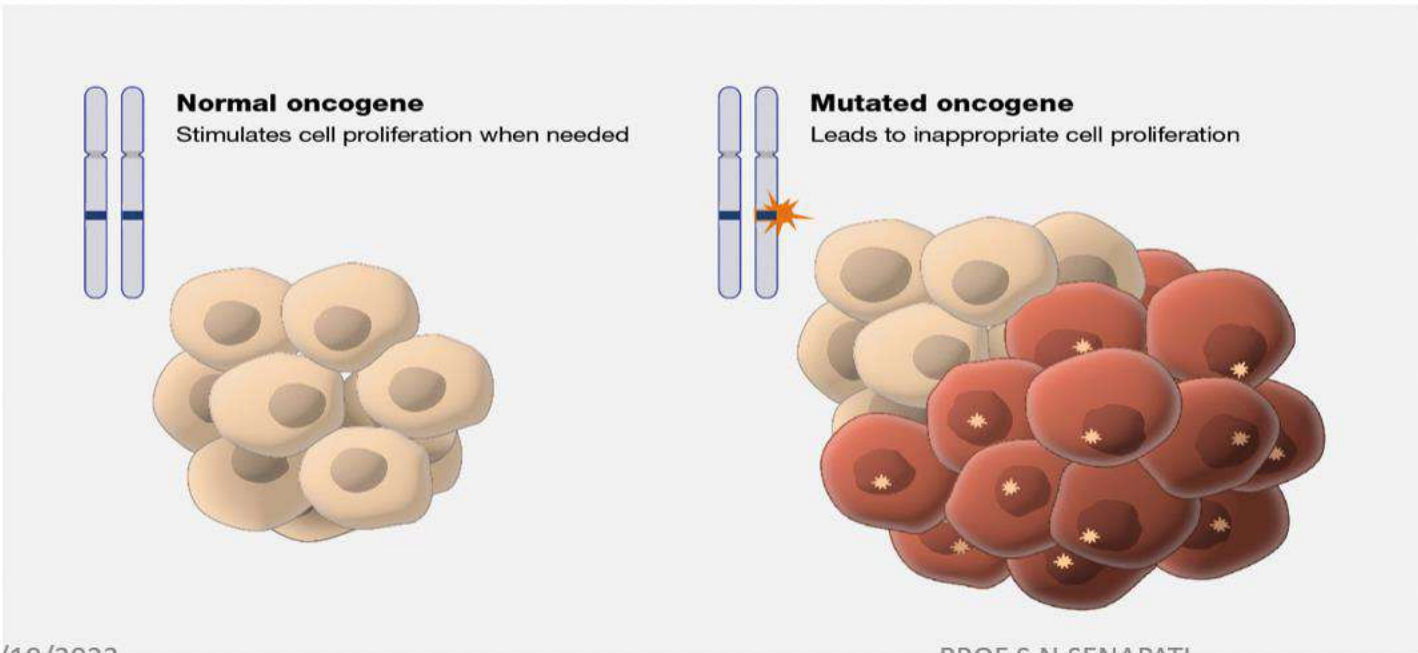
SUSTAINING PROLIFERATIVE SIGNALING



Sustaining proliferative signaling

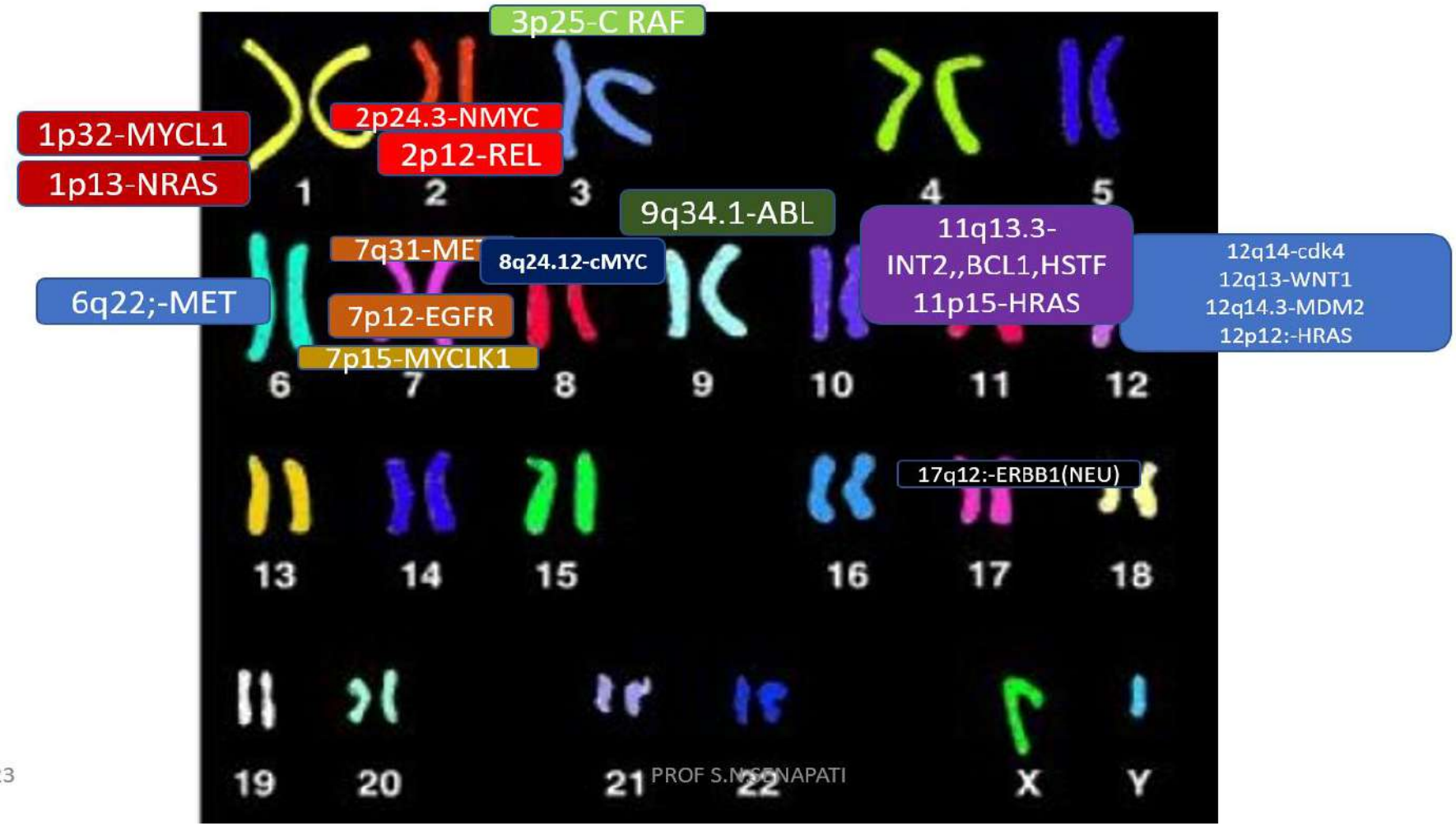
- An *oncogene* is a *mutated gene* that has the potential to cause cancer.
- *Before an oncogene becomes mutated*, it is called a *proto-oncogene*, and it plays a role in regulating normal cell division.





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

CHROMOSOME AND ONCOGENES

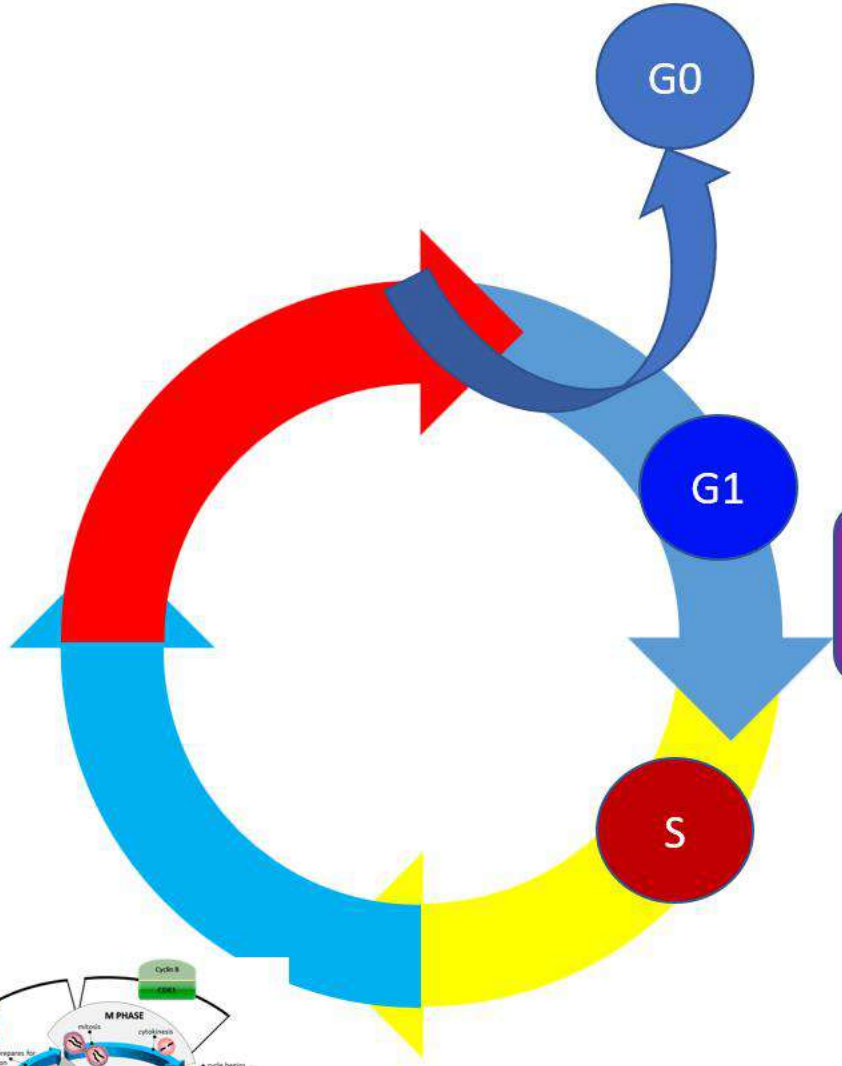


Oncogenes

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

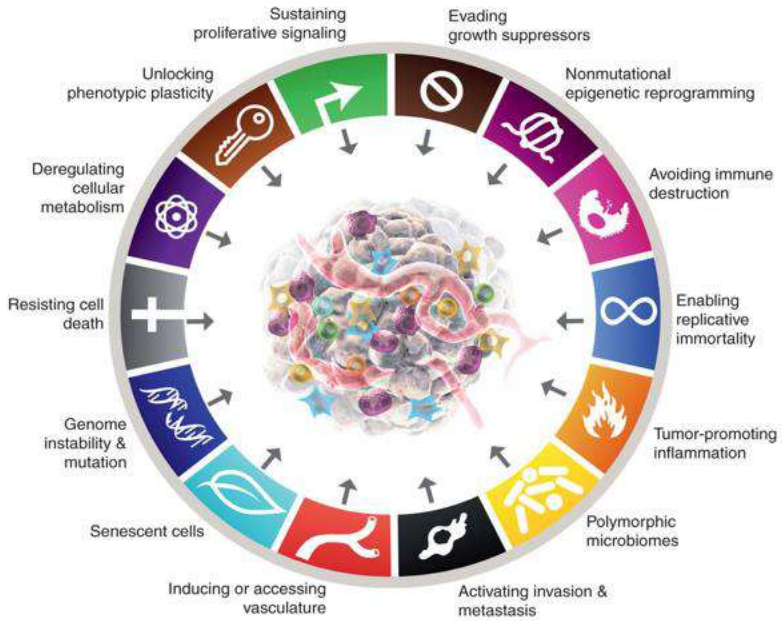
Signaling molecule	Activation	Cancer
H-RAS	Point mutations	Thyroid and bladder carcinoma
K-RAS	Point mutations	Pancreatic, lung and colon adenocarcinomas, non-small-cell lung carcinoma, myeloid leukemia, thyroid carcinomas
N-RAS	Point mutations	Melanoma, myeloid leukemia, thyroid carcinomas
B-RAF	Point mutations	Melanoma, colorectal carcinoma, small-cell lung cancer
SRC	Overexpression	Gastrointestinal cancers, lung, breast, ovary
BCR–ABL	Translocation	Chronic myelogenous leukemia
CYCLIN D1	Amplification/overexpression	Breast cancer, head and neck squamous carcinoma, esophageal cancer, lymphoma
PI3K P110	Amplification/overexpression	Ovarian and cervical cancer
STAT3		Melanoma

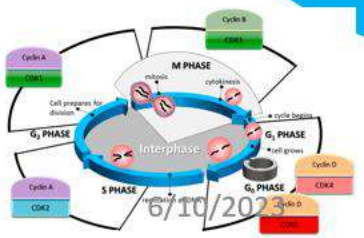
EVADING GROWTH SUPRESSORS

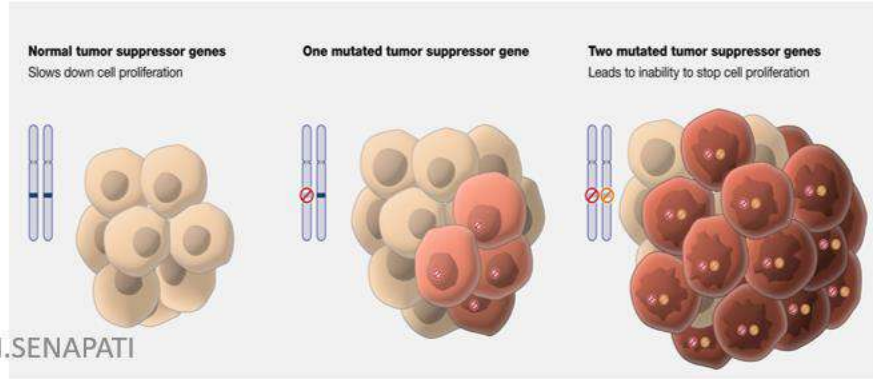


MUTATION OF RB
LOSS OF TP53

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

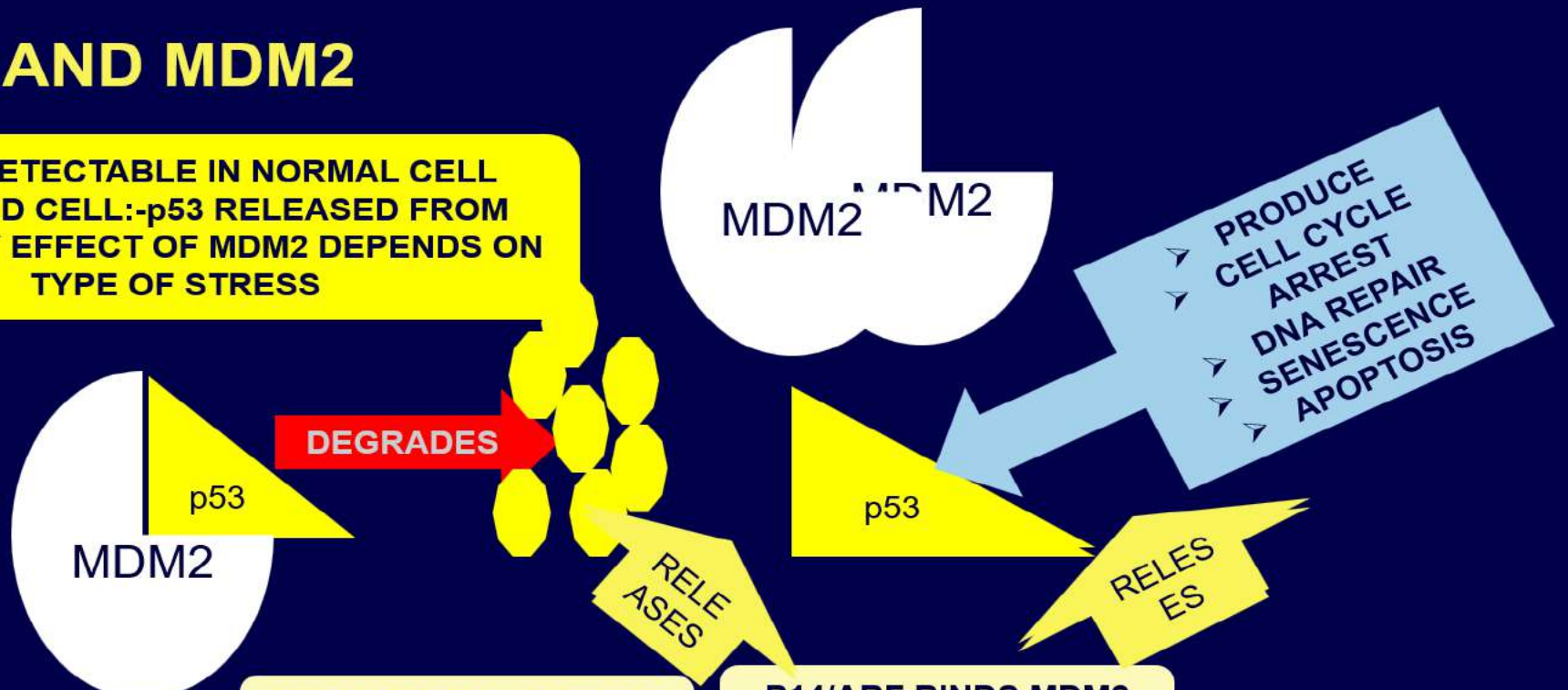






P53 AND MDM2

P53 UNDETECTABLE IN NORMAL CELL STRESSED CELL:-p53 RELEASED FROM INHIBITORY EFFECT OF MDM2 DEPENDS ON TYPE OF STRESS



RELEASE OF p53 FROM MDM2

P14/ARF BINDS MDM2 AND RELEASES p53

PHOSPHORYLATION OF p53 &MDM2

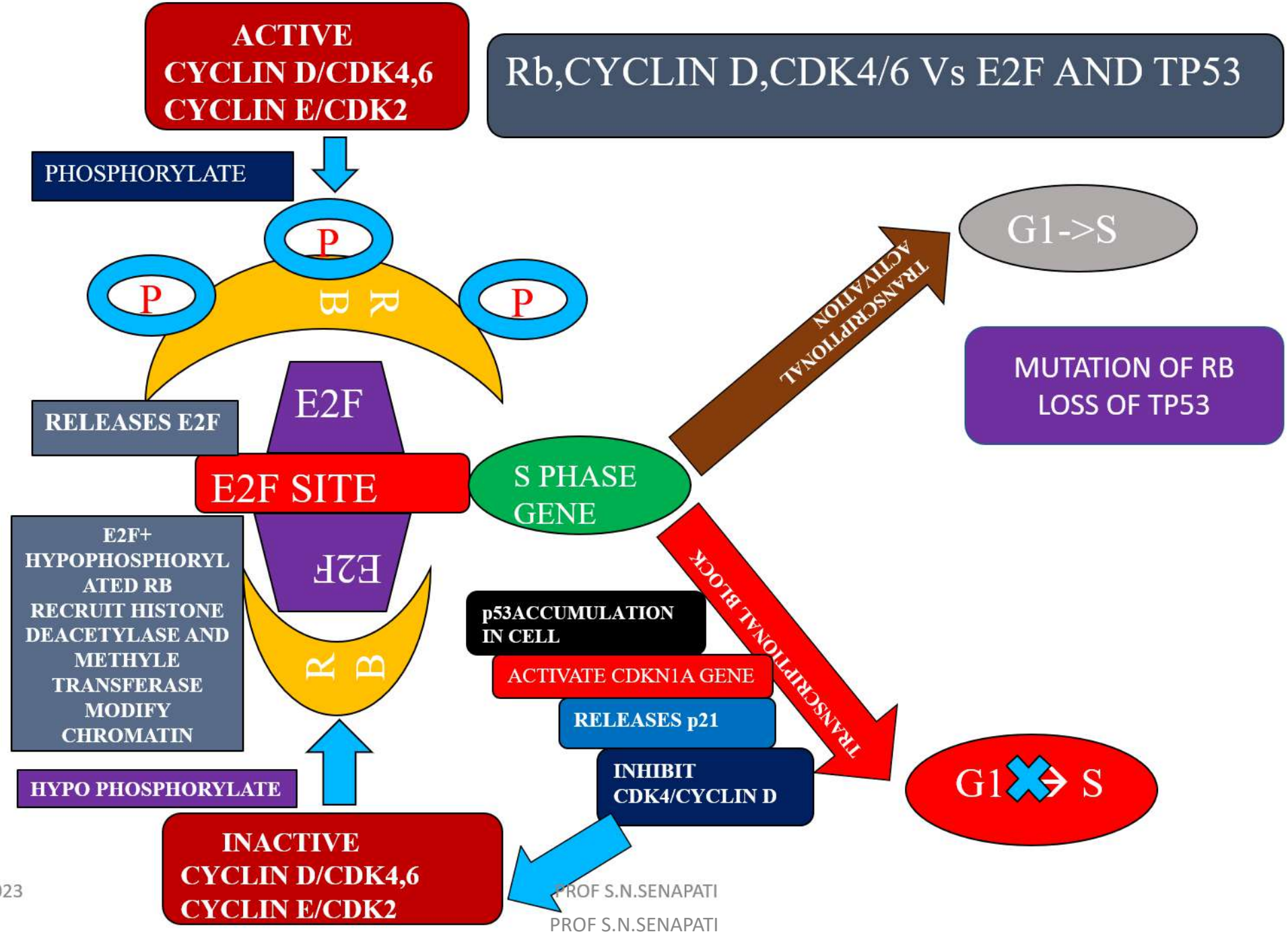
INCREASED EXPRESSION OF p14/ARF,ENCODED BY CDKN2A

PROTEINE KINASE ATM,ATR

ACTIVATION OF RAS,MPAK,PI3K/AKT

DNA DAMAGE/HYPOXIA

ONCOGENIC STRESS



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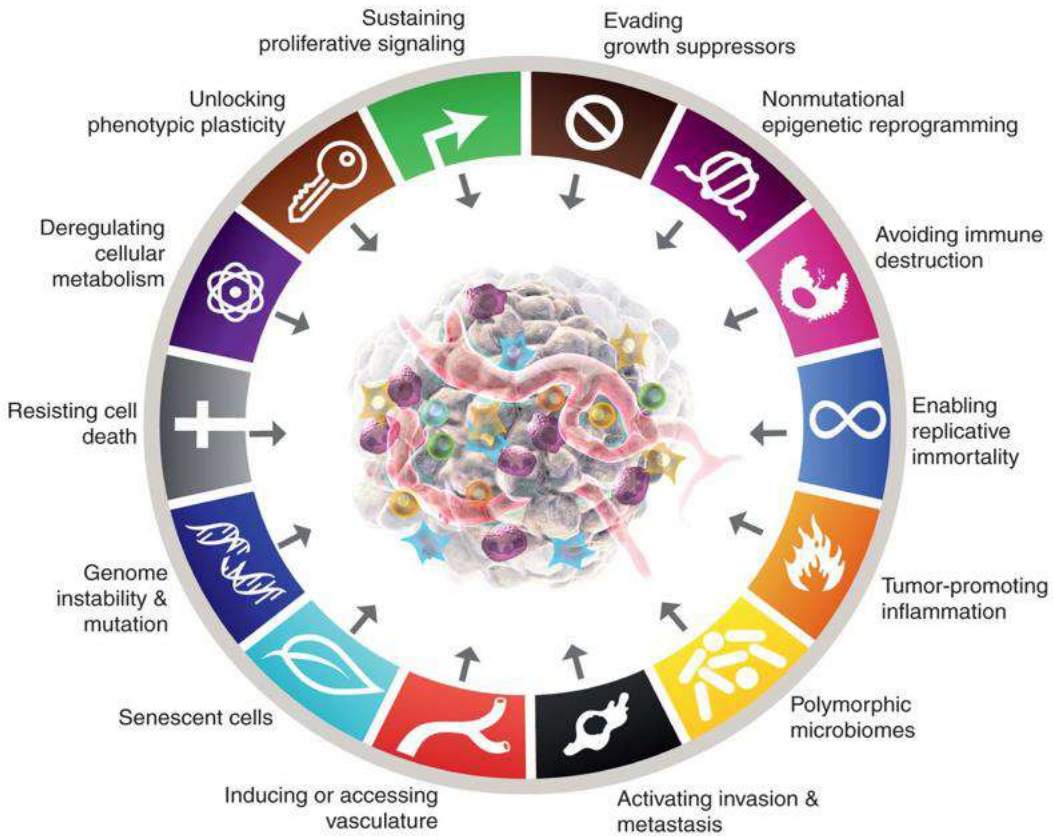
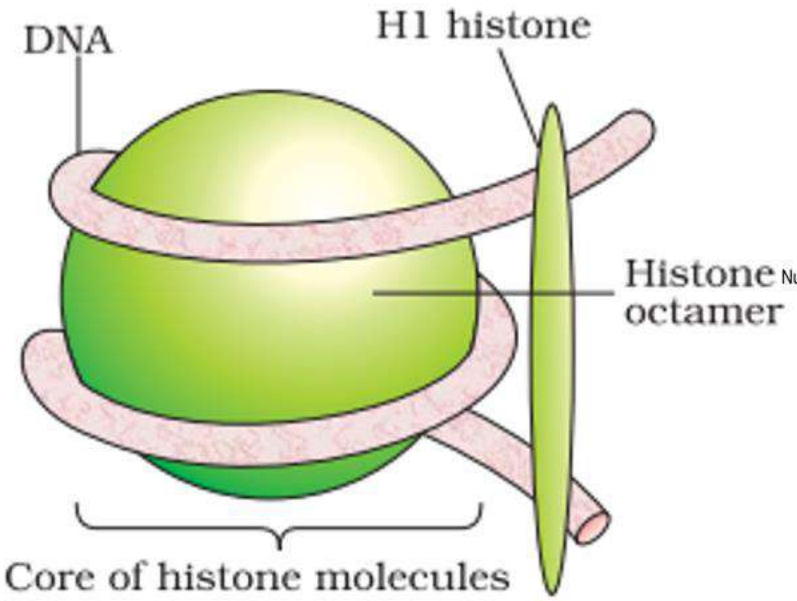
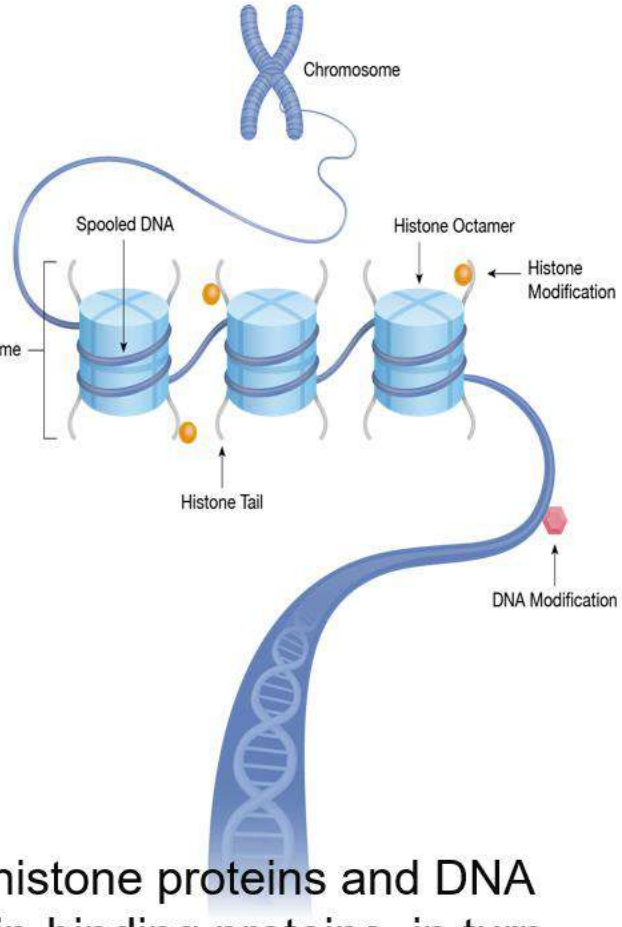
NON-MUTATIONAL EPIGENETIC REPROGRAMMING

(MUTATION LESS CANCER EVOLUTION
WITHOUT CHANGE IN DNA SEQUENCE)



STRUCTURE OF NUCLEOSOM

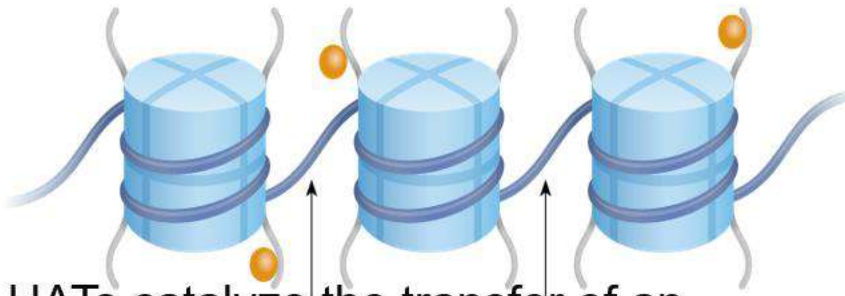




Epigenetic modifications to the histone proteins and DNA modulate the affinity of chromatin-binding proteins, in turn altering chromatin structure.

Acetylated Chromatin

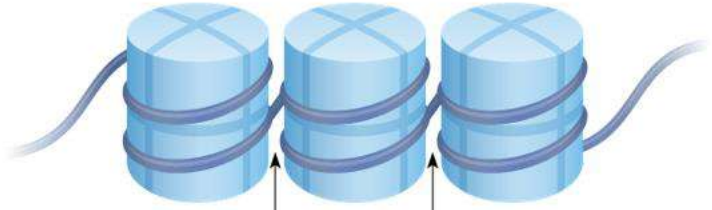
Open and transcriptionally active



HATs catalyze the transfer of an acetyl group to conserved lysine residues on the histone tail, promoting a relaxed (transcriptionally active) chromatin.

Deacetylated Chromatin

Compact and transcriptionally repressed



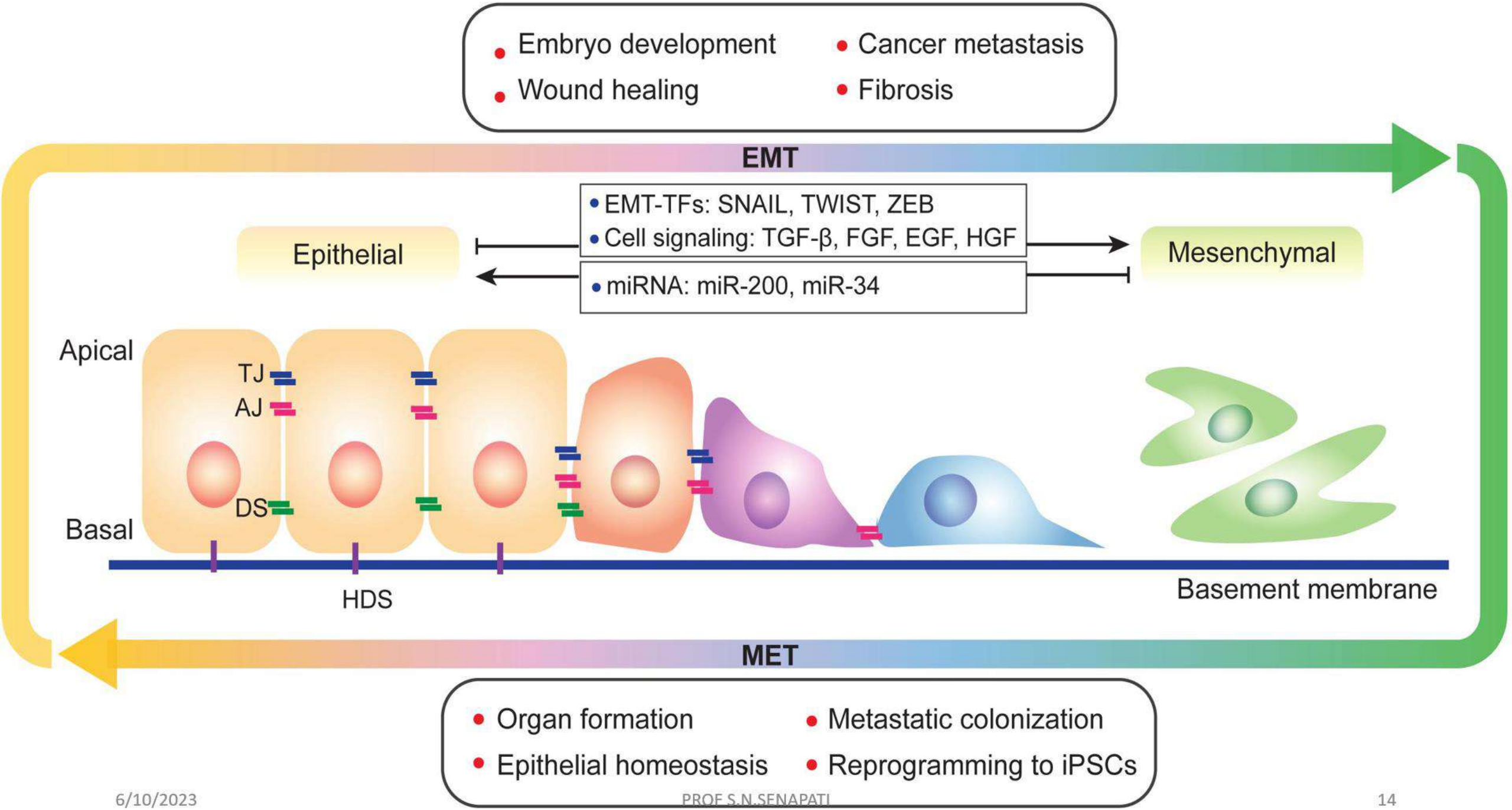
histone deacetylases (HDACs) catalyze the removal of acetyl groups from histones, leading to more tightly packaged (transcriptionally inactive) chromatin

ALTER OF CHROMATIN STRUCTURE

- **DNA METHYLATION**
  - **LOSS OF DNA METHYLATION**
  - **ADDN OF METHYL GROUP TO 5 CARBON OF CYTOSIN FOLLOWED BY GUANINE:- STABLE**
  - **HYPOXIA:-REDUCES ACTIVITY OF TET DEMETHYLASE,**
  - **DECREASES METHYLOME**

- **HISTONE MODIFICATION**
  - **HISTONE ASSIST IN DNA PACKAGING IN TO CHROMATIN**
  - **DNA WRAPPED WITH HISTONE TO FORM NUCLEOSOME**
  - **AMINOTERMINAL IS PRONE TO ACETYLATION,PHOSPHORYLATION,METHYLATION,ALTER CHROMATIN CONDENSATION,INTERFERING GENE EXPRESSION**
  - **METHYLATION BY HISTONE METHYLTRANSFERASE,LYSIN DEMETHYLASE**
  - **HISTONE ACETYLATION PATTERNS HAS DEMONSTRATED A HIGH CORRELATION BETWEEN HISTONE ACETYLATION AND ACTIVE TRANSCRIPTION, WHEREAS HISTONE METHYLATION CAN BE ASSOCIATED WITH THE ACTIVATION OR SILENCING**
  - EPITHELIAL TO MESENCHYMAL TRANSITION:-INDUCES HISTONE METHYL TRANSFERASE,UPREGULATION OF TH,SNAIL 1

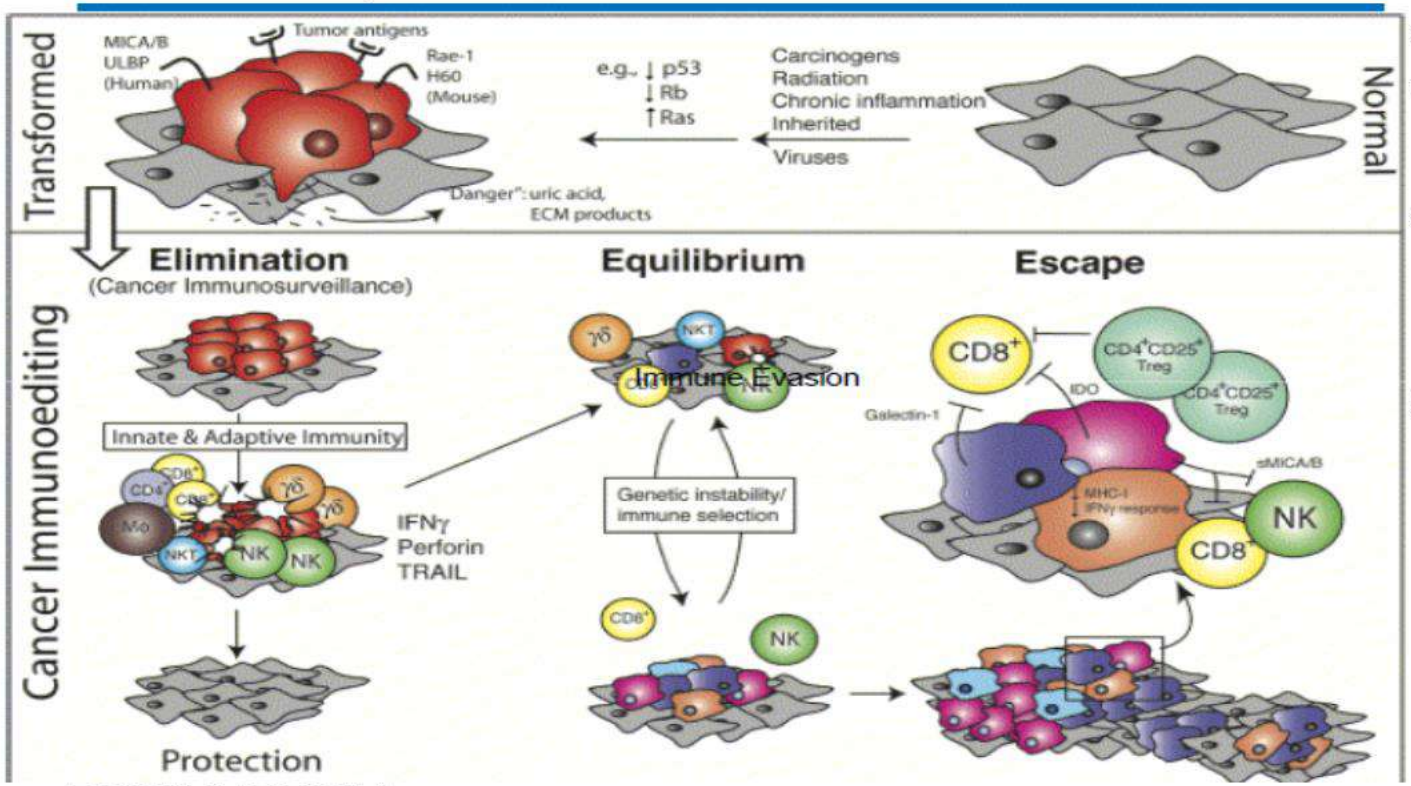
- **NON CODING RNA INTERACTION**
  - **ABARRENT MICRO RNA**

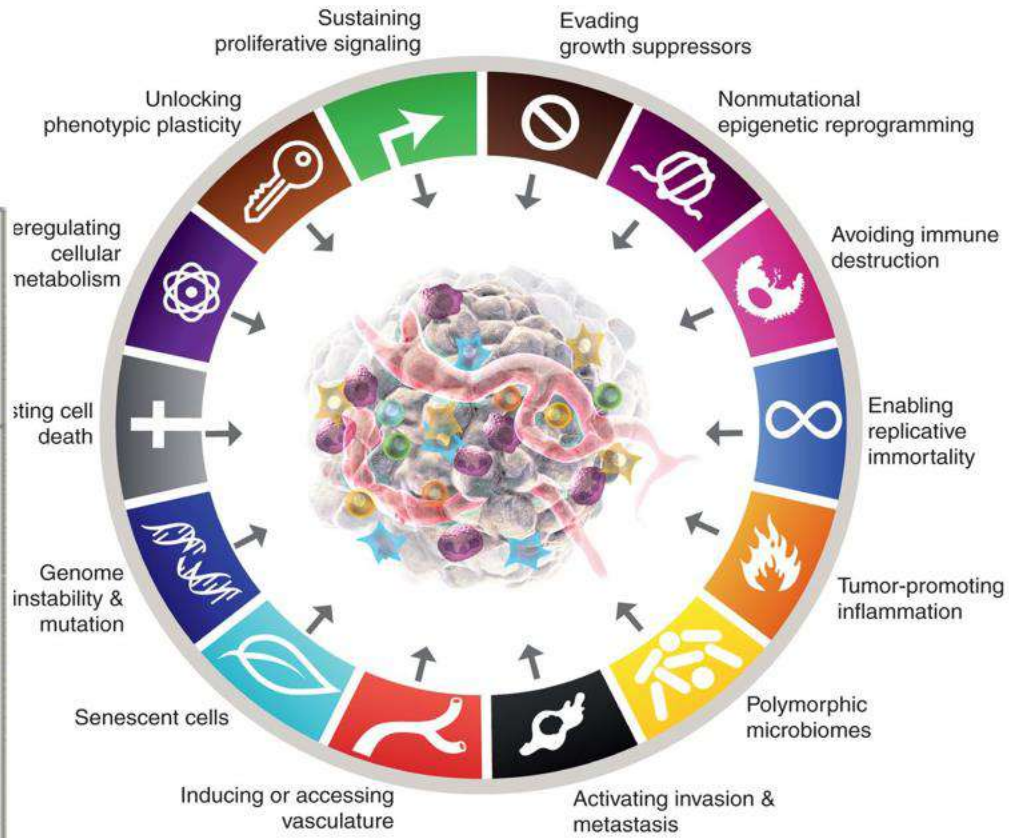

Embryo development
Wound healing
Cancer metastasis
Fibrosis
EMT
EMT-TFs: SNAIL, TWIST, ZEB
Cell signaling: TGF-β, FGF, EGF, HGF
miRNA: miR-200, miR-34
Epithelial
Mesenchymal
Apical
TJ
AJ
DS
Basal
HDS
Basement membrane
MET
Organ formation
Epithelial homeostasis
Metastatic colonization
Reprogramming to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

Wu et al, 2020

AVOIDING IMMUNE DESTRUCTION

CANCER IMMUNOEDITING IS A PROCESS IN WHICH IMMUNE SYSTEM INTERACTS WITH TUMOR CELLS. IT CONSISTS OF THREE PHASES: ELIMINATION, EQUILIBRIUM AND ESCAPE.



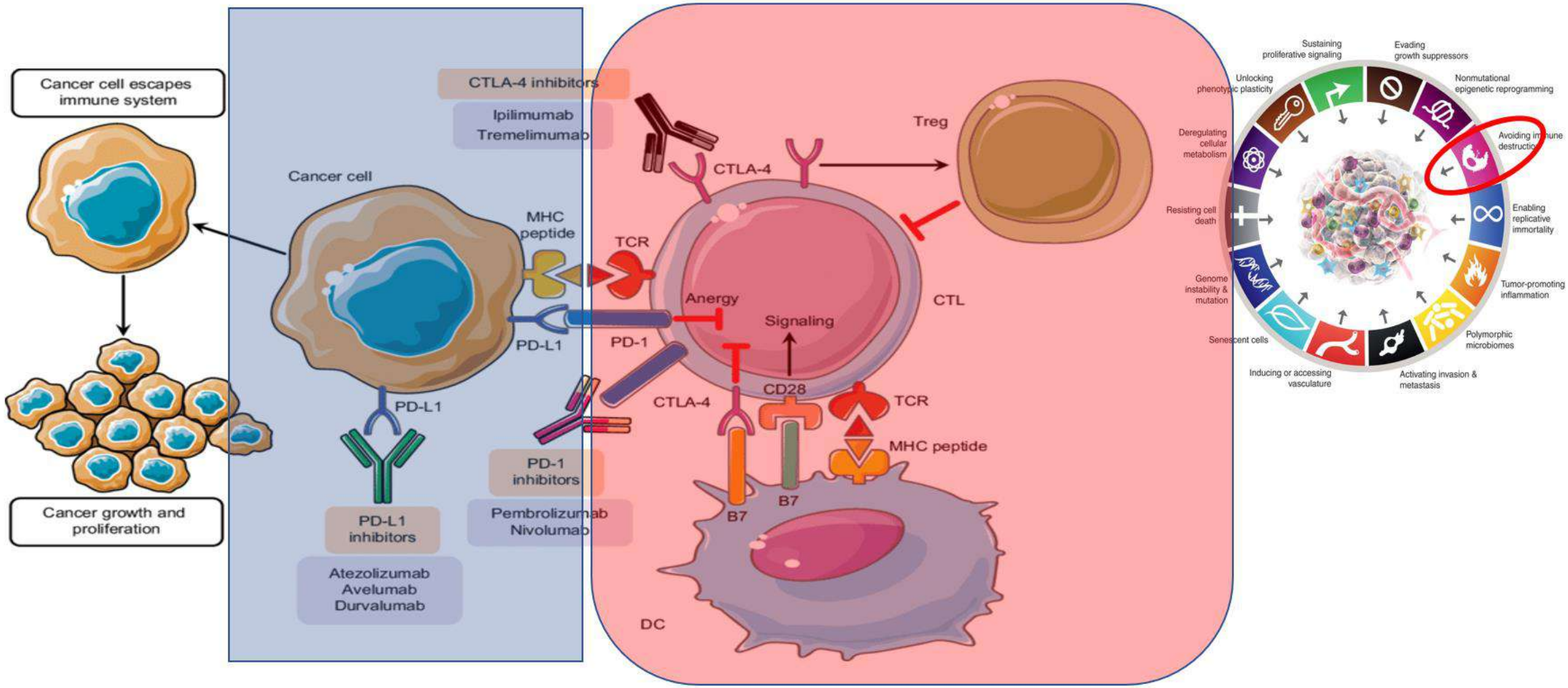


EQUILLIBRUM

IMMUNE SYSTEM DOES NOT RECOGNISE ALL TUMOR CELLS, AT THE SAME TIME THE TUMOR DOES NOT GROW.

IMMUNE EVASION

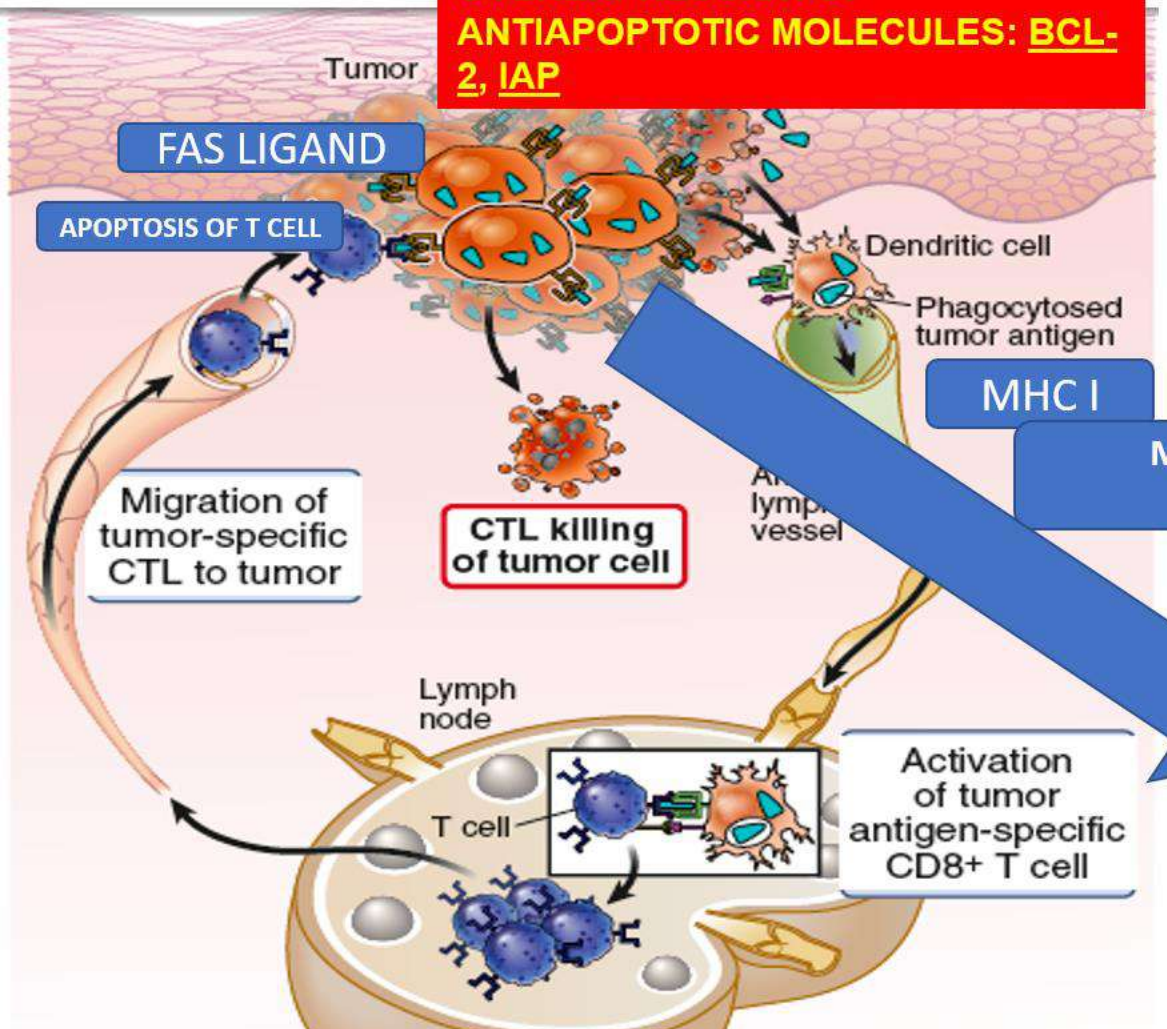
IMMUNE SURVEILLANCE

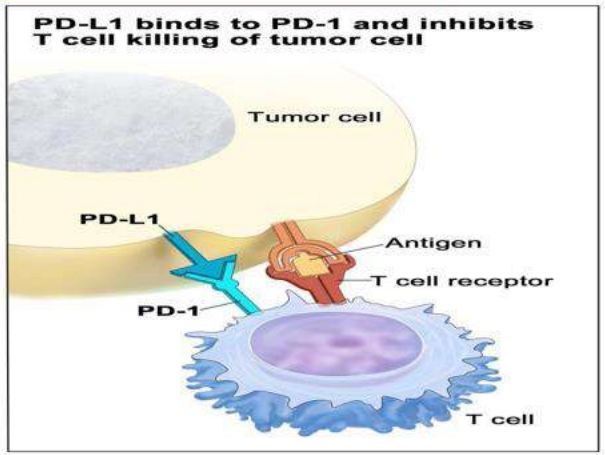


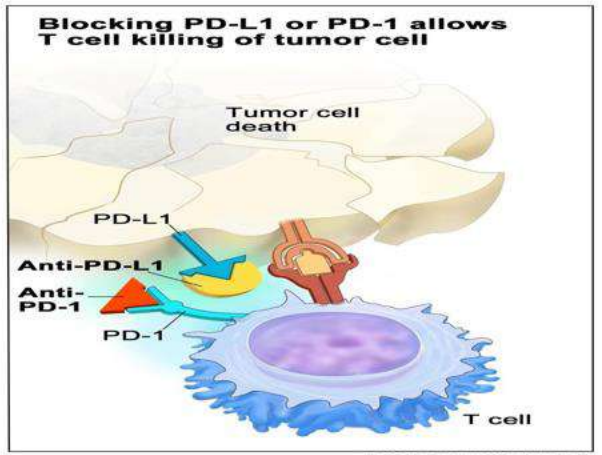
Zhang et al, Lancet Microbe 2022

TUMOR EVASION

OVERXPRESSION OF ANTIAPOPTOTIC MOLECULES: BCL-2, IAP







MUTATION OF MHCI GENE –LOWER EXPRESSION OF MHC
DEFECT IN ANTIGEN PRESENTATIONI

MICRO ENVIRONMENT

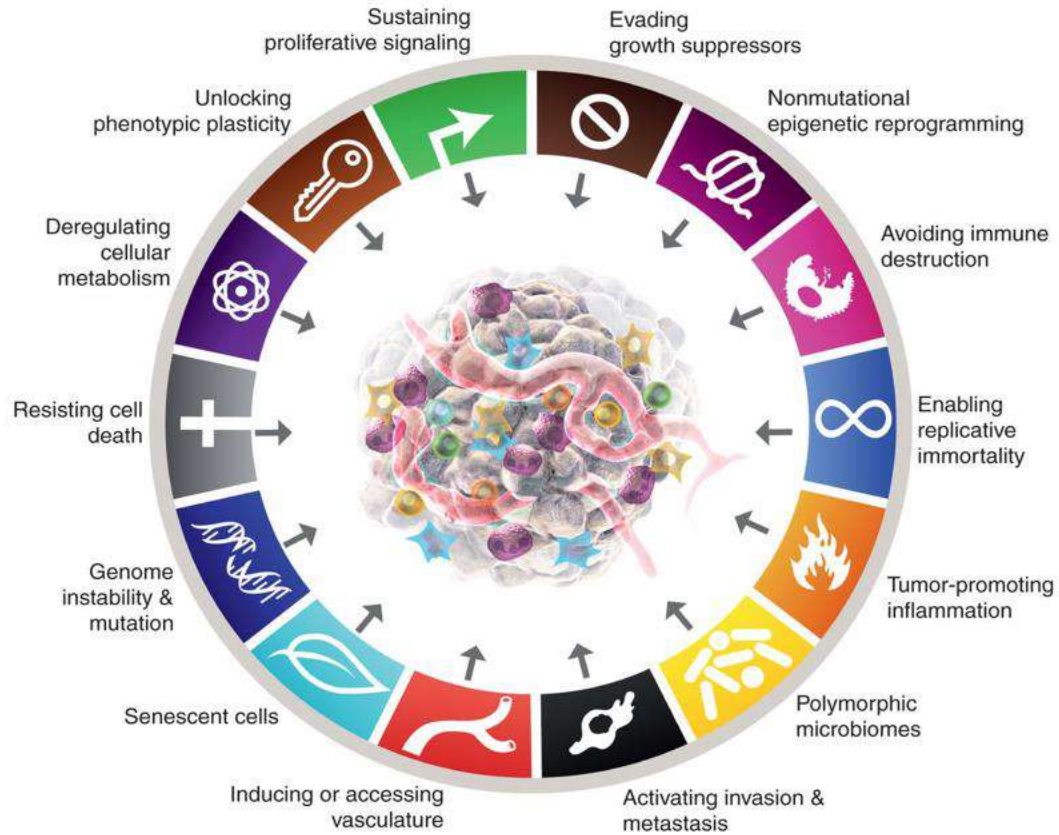
TGF-B :- CONVERSION OF CD4+ T CELL INTO SUPPRESSOR REGULATORY T CELL WHICH IS IMMUNOSUPPRESSIVE

SPECIAL CYTOKINES (SUCH AS COLONY-STIMULATING FACTOR) TO PRODUCE MYELOID-DERIVED SUPPRESSOR CELL.

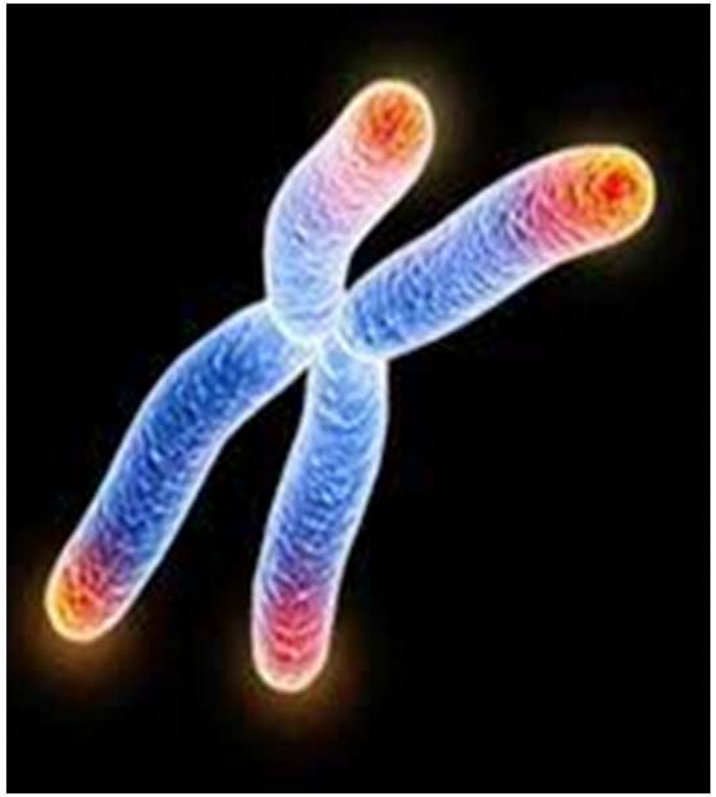
inhibition of apoptotic signal pathway molecules: APAF1, Caspase 8, Bcl-2-associated X protein (bax) and Bcl-2 homologous antagonist killer (bak).[*citation needed*]

ENABLING REPLICATIVE IMMORTALITY

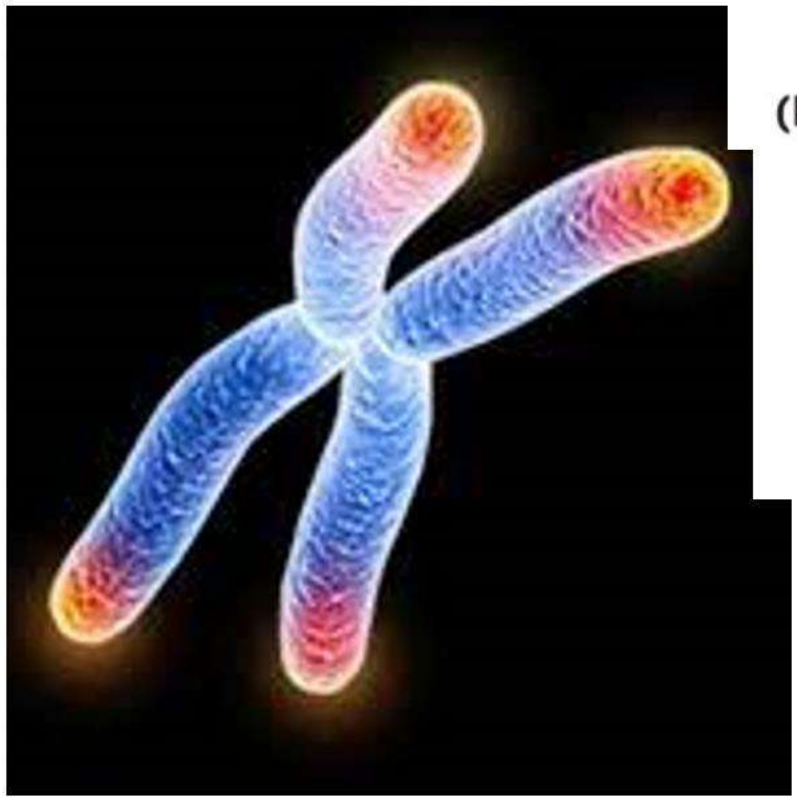
- NORMAL CELLS HAVE A FINITE REPLICATIVE ABILITY
- CANCER CELLS OVERCOME THIS BY:-
- OVEREXPRESSING TELOMERASE, AN ENZYME THAT MAINTAINS TELOMERE LENGTH, WHICH PROTECTS THE ENDS OF CHROMOSOMES AND ALLOWS THE CELL TO CONTINUE PROLIFERATING.
- THIS PROCESS IS ALSO AIDED IN PART BY THE LOSS OF TUMOR-SUPPRESSOR GENES, SUCH AS TP53.
- ADDITIONAL FUNCTIONS OF TELOMERASE THAT ARE INDEPENDENT OF TELOMERE MAINTENANCE AND MAY AID IN TUMOR GROWTH
  - ENHANCEMENT OF CELL PROLIFERATION AND/OR RESISTANCE TO APOPTOSIS
  - DNA DAMAGE REPAIR
  - RNA-DEPENDENT RNA POLYMERASE FUNCTION
  - ASSOCIATION WITH CHROMATIN



TELOMERE



- **TELOMERES, LOCATED AT THE ENDS OF EACH CHROMOSOME, CONSIST 5–10 KBP OF , TANDEM REPEAT, NONCODING DNA COMPLEXED WITH ASSOCIATED PROTEINS .**
- **IT CREATE A PROTECTIVE CAP THAT PREVENTS THE RECOGNITION DNA BREAK AND REPAIR BY DNA POLYMERASE**
- **TELOMERIC DNA IS LOST AT THE RATE OF APPROXIMATELY 100 BASE PAIRS (BP) PER TELOMERE PER CELL DIVISION**
- **IN CANCER CELL ACTIVATION OF TELOMERASE OR ALTERNATIVE LENGTHENING OF TELOMERES (ALT) TELOMERE SPECIFIC REVERSE TRANSCRIPTASE TELOMERASE, WHICH IS STRINGENTLY REPRESSED IN NORMAL SOMATIC CELLS, IS ACTIVATED, THEREBY RESTABILIZING THE TELOMERES, ALTHOUGH CANCER TELOMERES ON AVERAGE SEEM TO REMAIN VERY SHORT**
- **WHEREAS MOST CANCERS USE TELOMERASE TO MAINTAIN TELOMERE LENGTH, A SIGNIFICANT MINORITY OF CANCERS (TYPICALLY NON-CARCINOMAS) UTILIZE ALT, A TELOMERASE INDEPENDENT, HOMOLOGOUS RECOMBINATION BASED MECHANISM**



Telomere length is maintained by telomerase

(a) Telomerase is constitutively active in germline cells

(b) Telomerase is tightly repressed in normal somatic cells

5' TTAGGG TTAGGG TTAGGG TTAGGG TTAGGG TTAGGG 3'
5' TTAGGG TTAGGG TTAGGG TTAGGG TTAGGG 3'
5' TTAGGG TTAGGG TTAGGG TTAGGG 3'
5' TTAGGG TTAGGG TTAGGG 3'

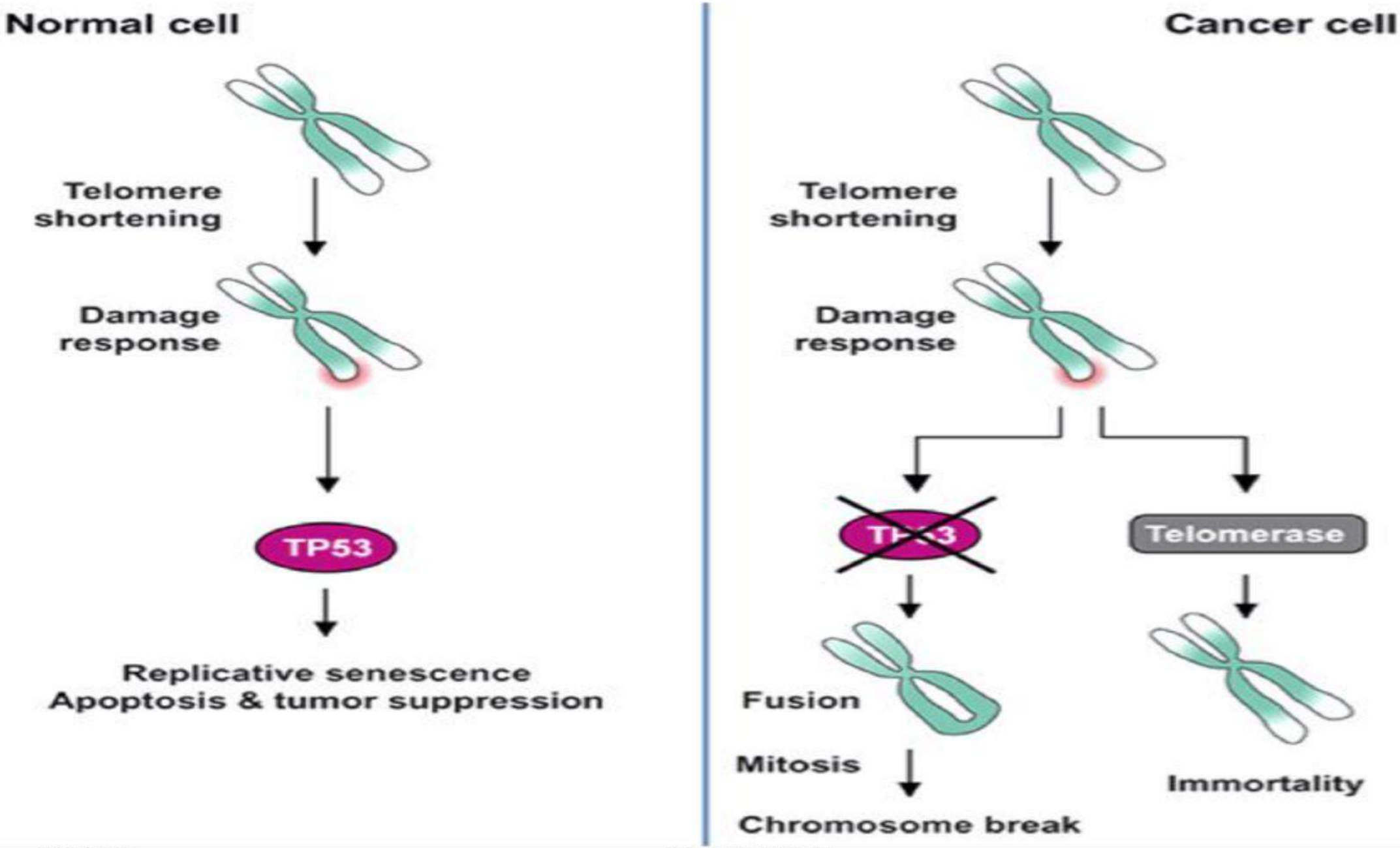
Normal somatic cells lose telomeres with cell division

Senescence or cell death

(c) Telomerase is reactivated in most cancers

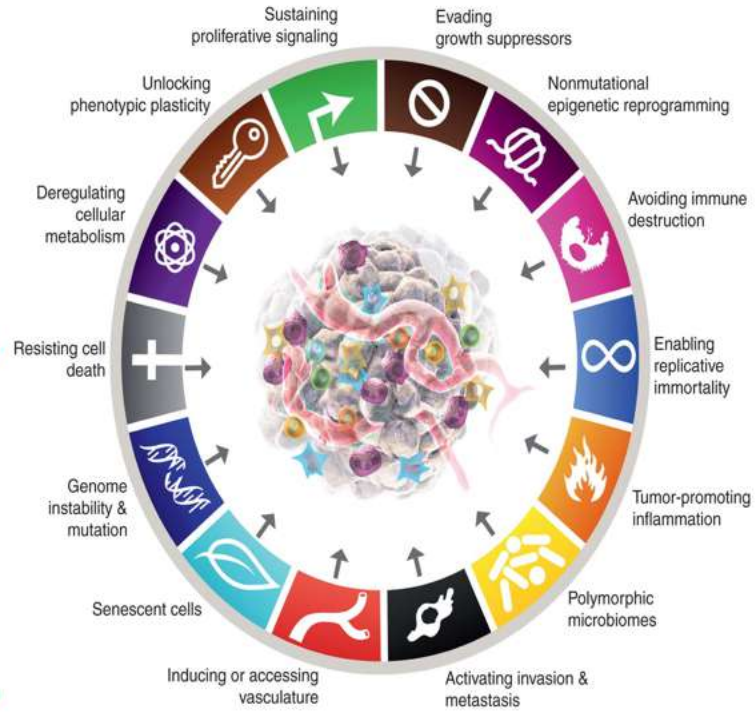
This elevated TA in cancer cells maintains their TL

5' TTAGGG TTAGGG 3'
5' TTAGGG TTAGGG 3'

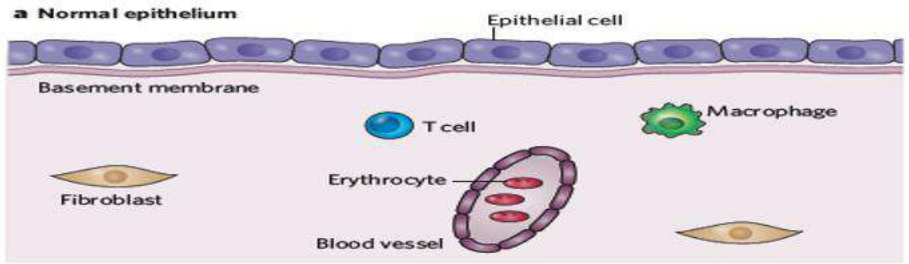

Normal cell
Telomere shortening
Damage response
TP53
Replicative senescence
Apoptosis & tumor suppression
Cancer cell
Telomere shortening
Damage response
Telomerase
Fusion
Mitosis
Chromosome break
Immortality

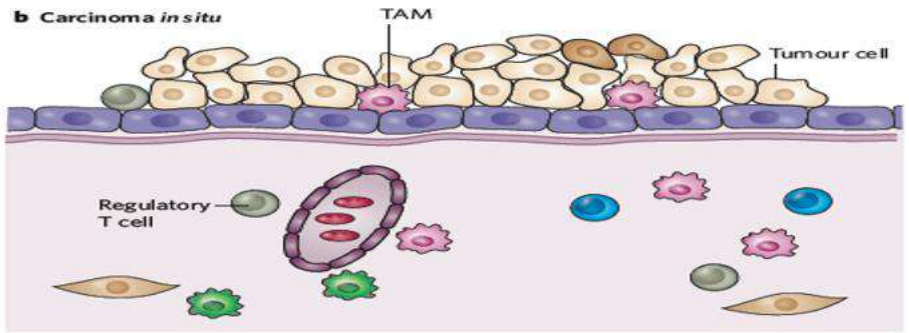
TUMOUR PROMOTING INFLAMMATION

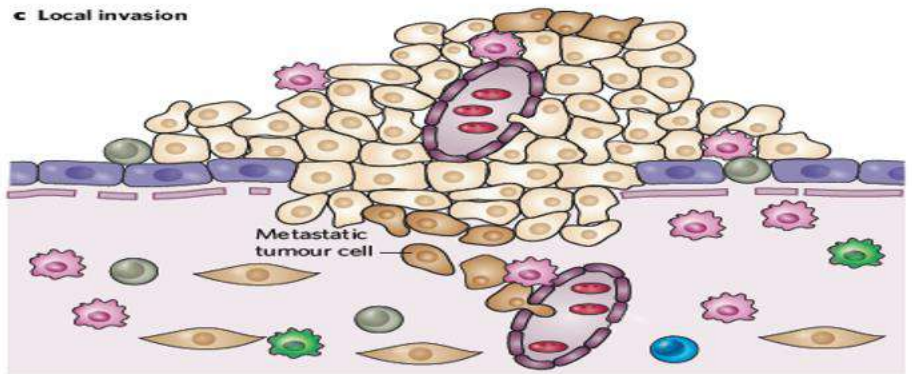
- THE TUMOR MICROENVIRONMENT IS OFTEN INFILTRATED BY INNATE AND ADAPTIVE IMMUNE SYSTEM CELLS THAT ENABLE TUMORS TO MIMIC INFLAMMATORY CONDITIONS SEEN IN NORMAL TISSUES.
- TUMOR-ASSOCIATED INFLAMMATION MIGHT AID IN TUMOR GROWTH. BY SUPPLYING THE TUMOR MICROENVIRONMENT WITH
  - GROWTH FACTORS
  - PRO-ANGIOGENIC FACTORS
  - EXTRACELLULAR MATRIX (ECM)–MODIFYING ENZYMES THAT PROMOTE ANGIOGENESIS, INVASION, AND METASTASIS
  - INDUCTIVE SIGNALS THAT ACTIVATE EPITHELIAL-MESENCHYMAL TRANSITION (EMT
- INFLAMMATION IS OFTEN SEEN IN EARLY STAGES OF NEOPLASTIC DISEASE. EARLY INFLAMMATION CAN RELEASE CHEMICALS INTO THE TUMOR MICROENVIRONMENT AND MAY LEAD TO GENETIC MUTATIONS THAT ENABLE AND ACCELERATE THE FORMATION OF A TUMOR.

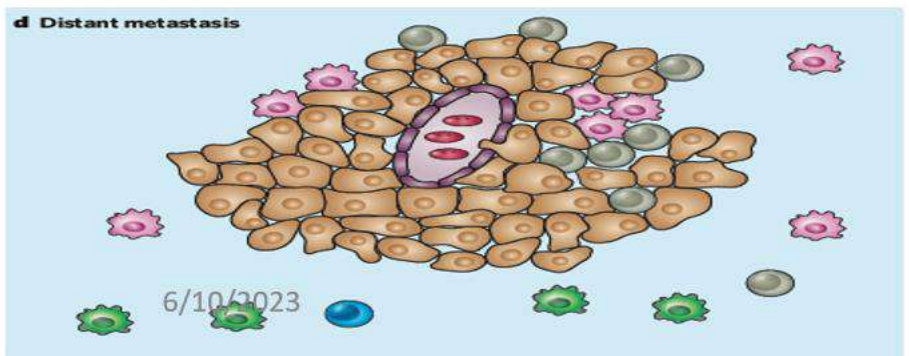


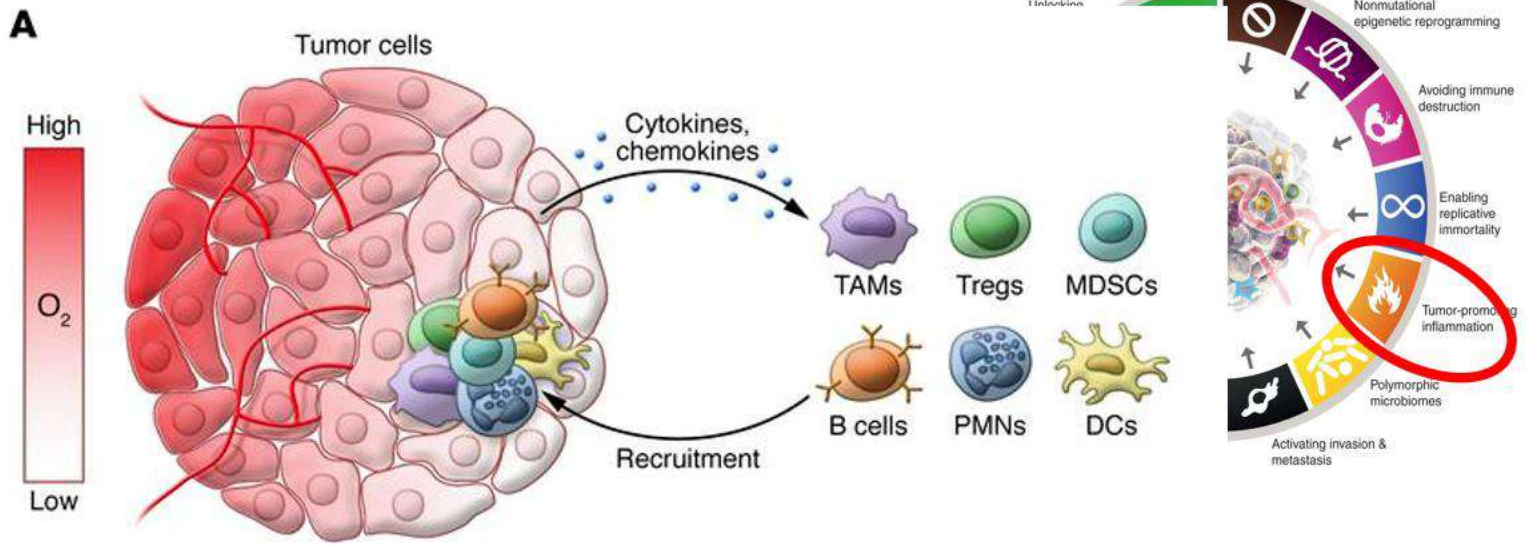
Tumour promoting Inflammation

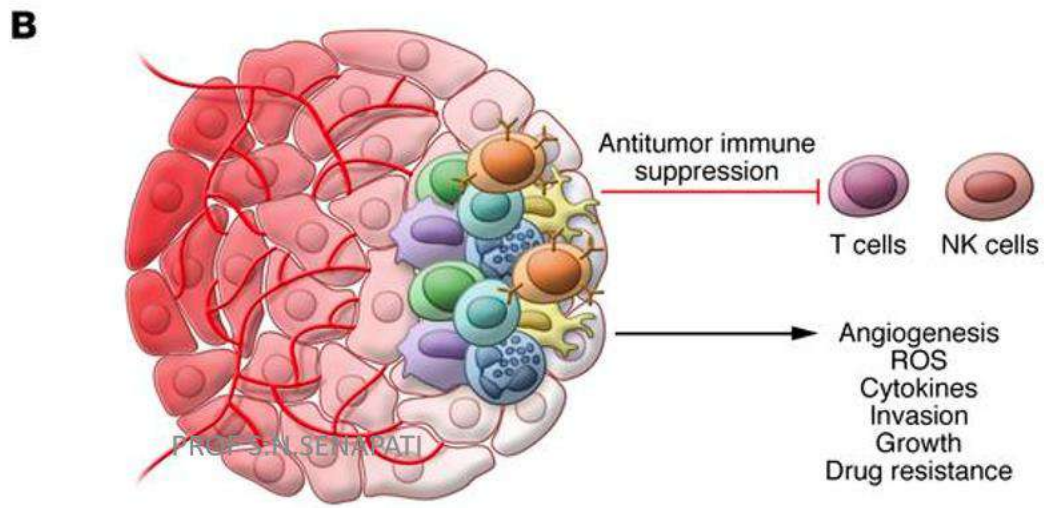






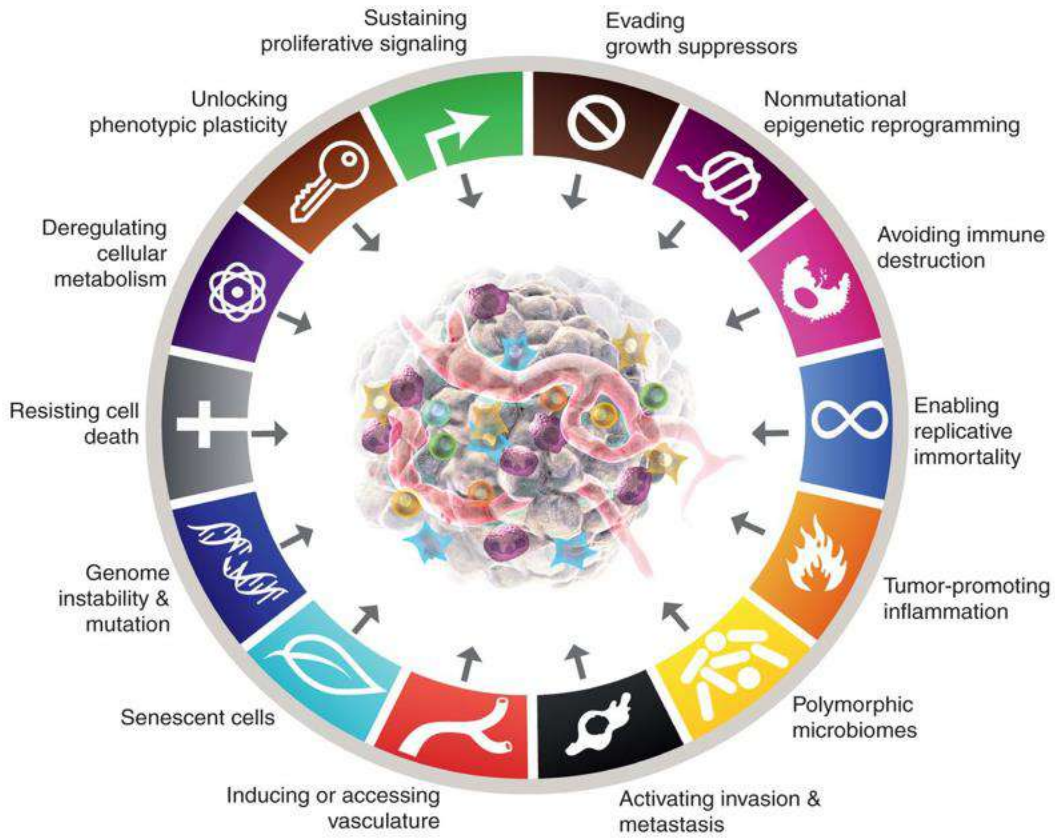




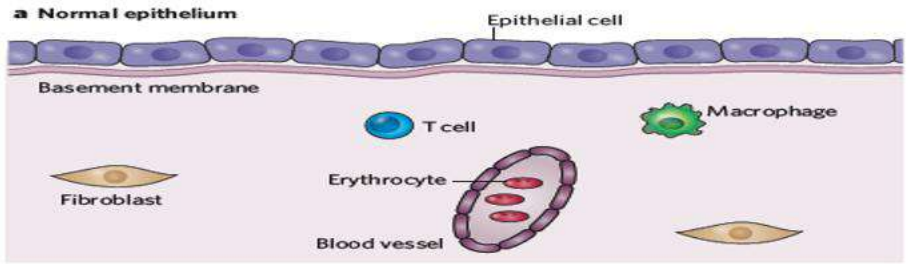


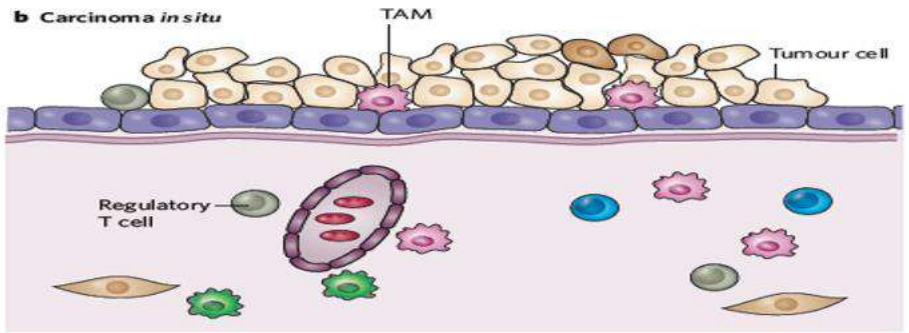
et al, J Clin Invest. 2016
Mantovani et al, 2008

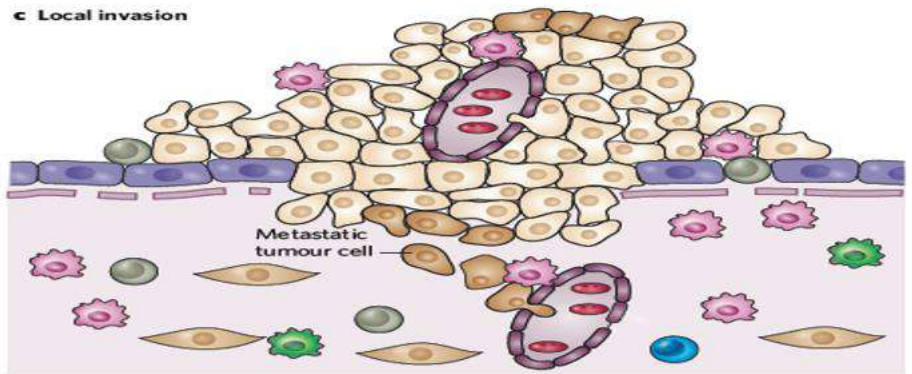
POLYMORPHIC MICROBIOME

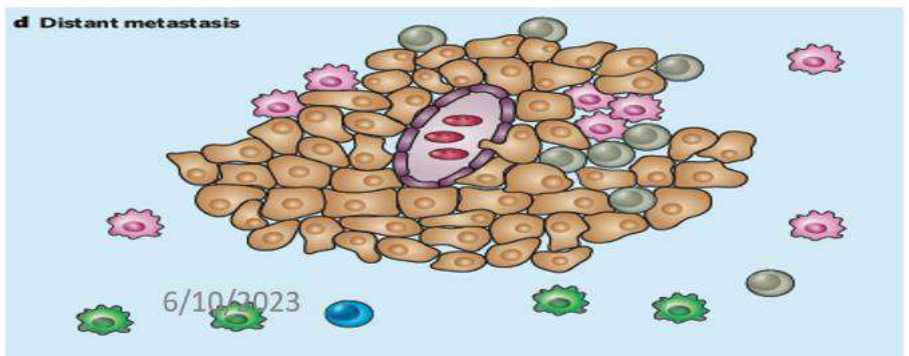


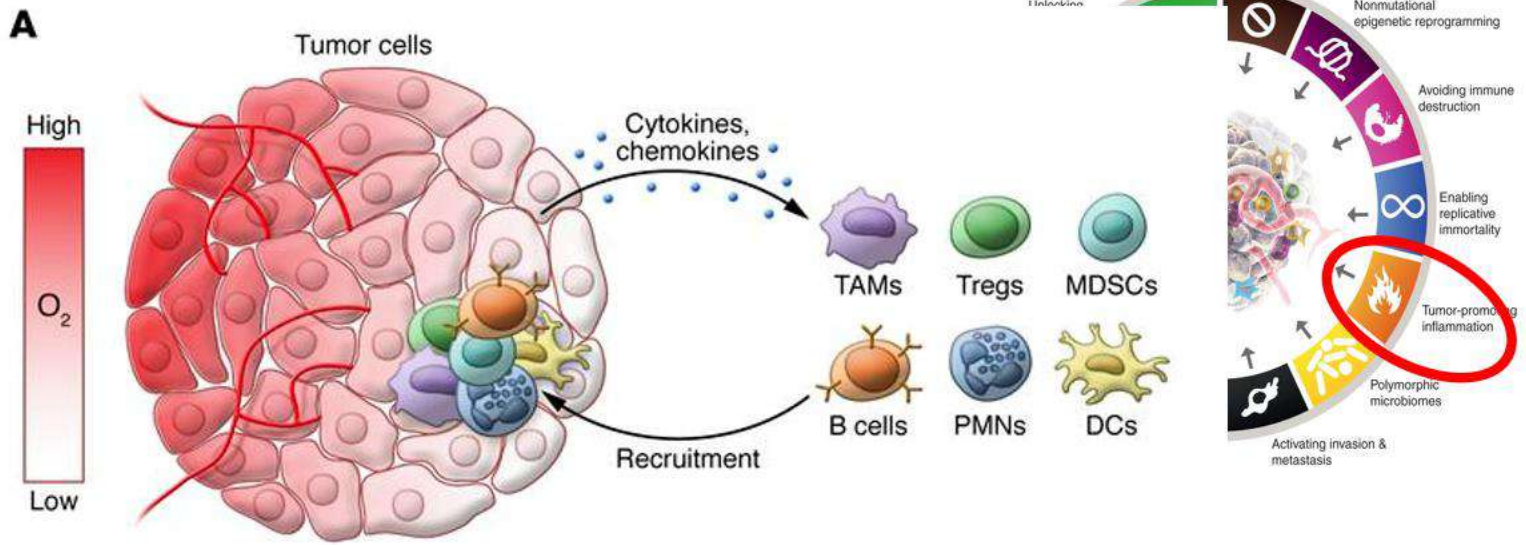
Tumour promoting Inflammation

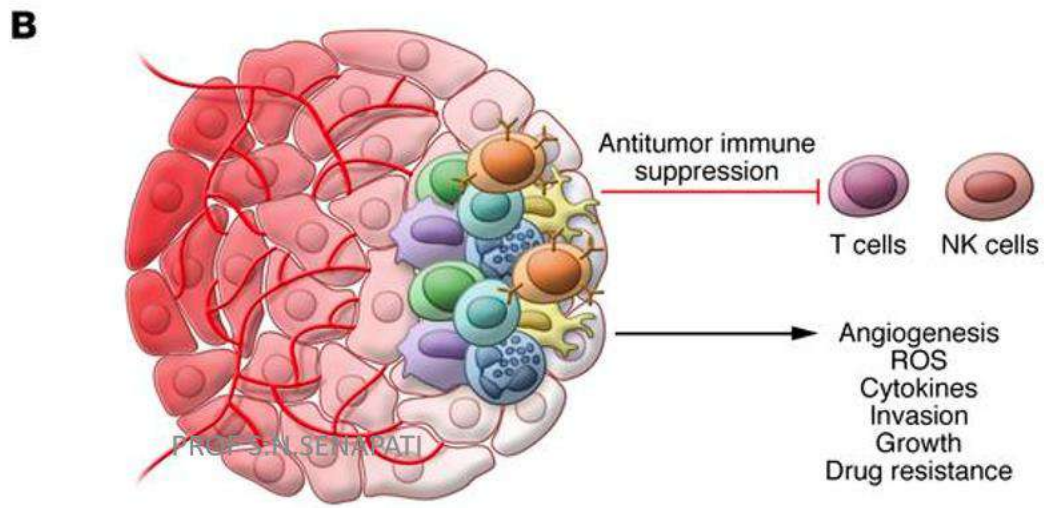






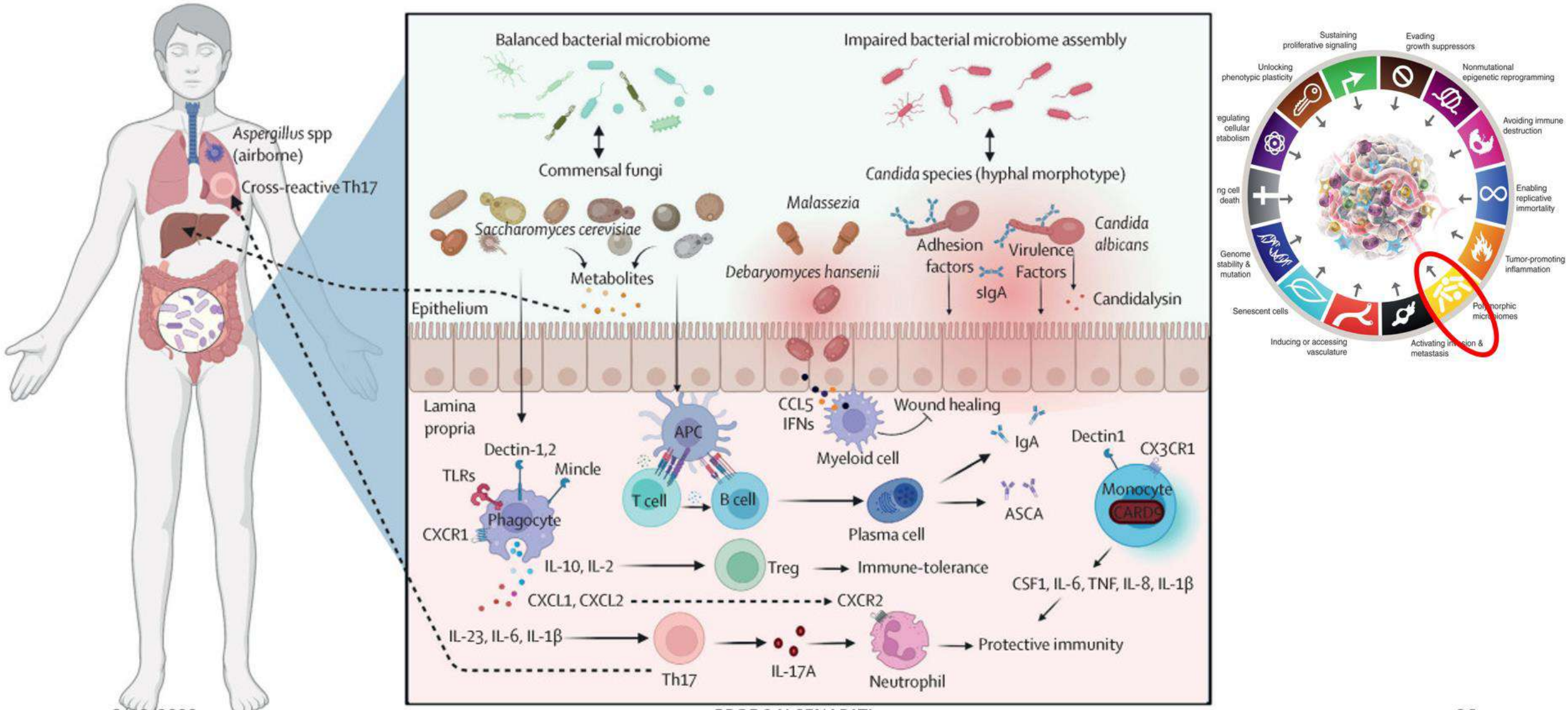






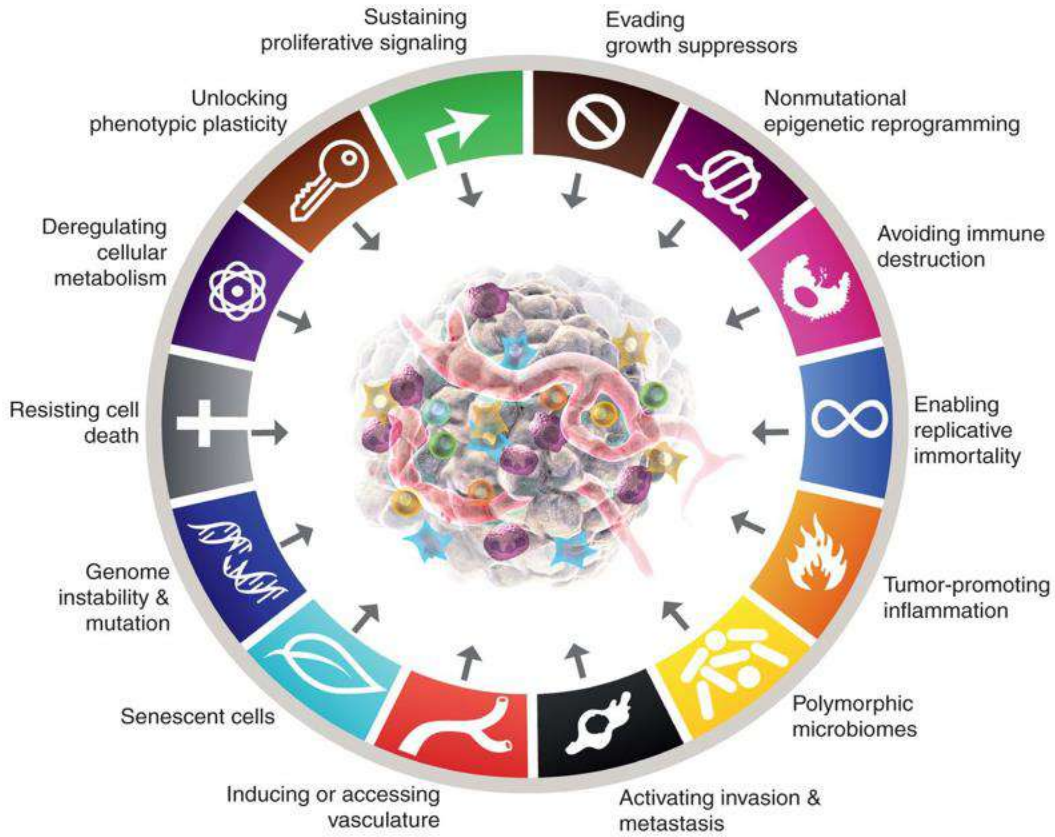
et al, J Clin Invest. 2016
Mantovani et al, 2008

Polymorphic microbiome

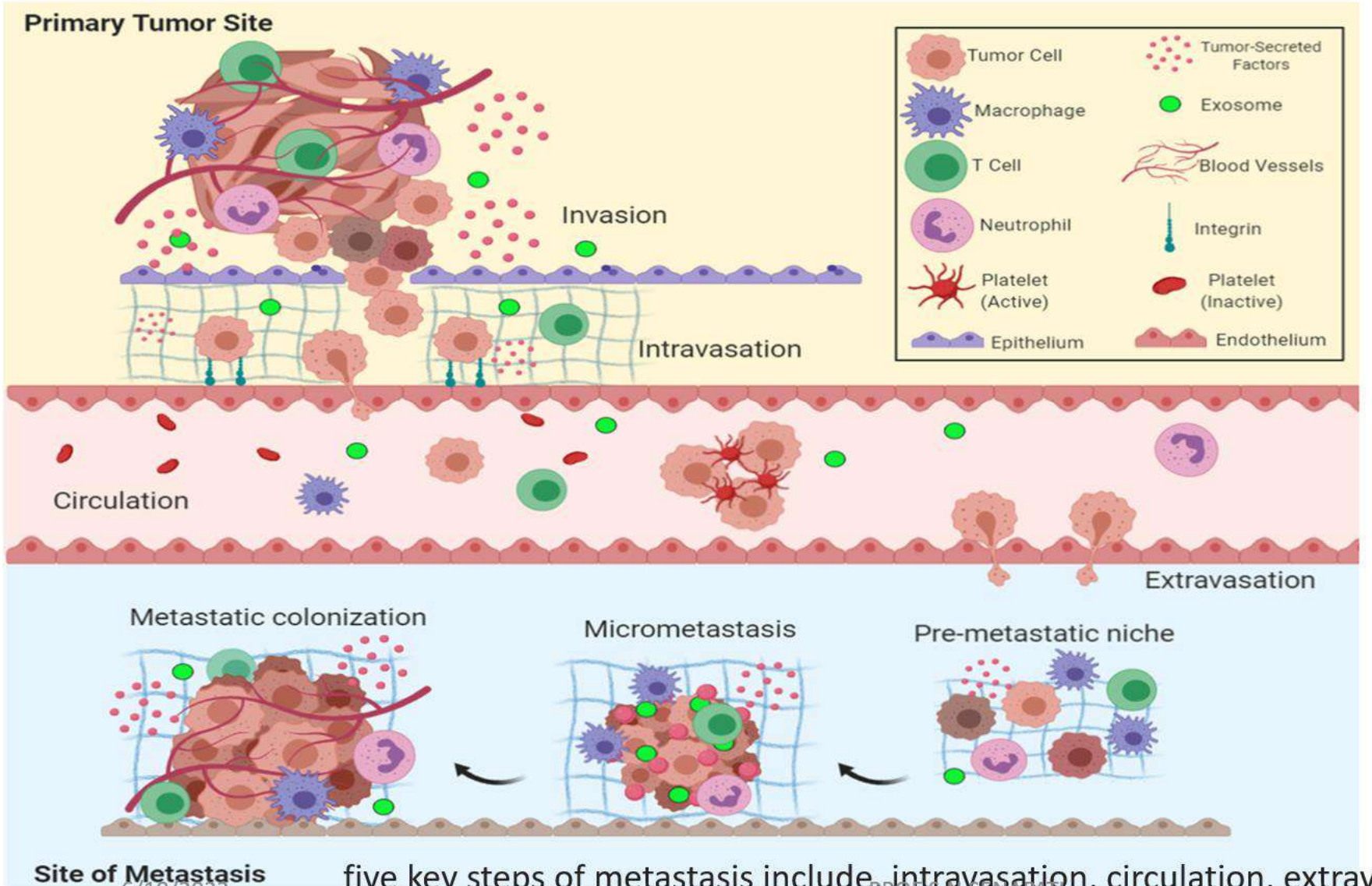


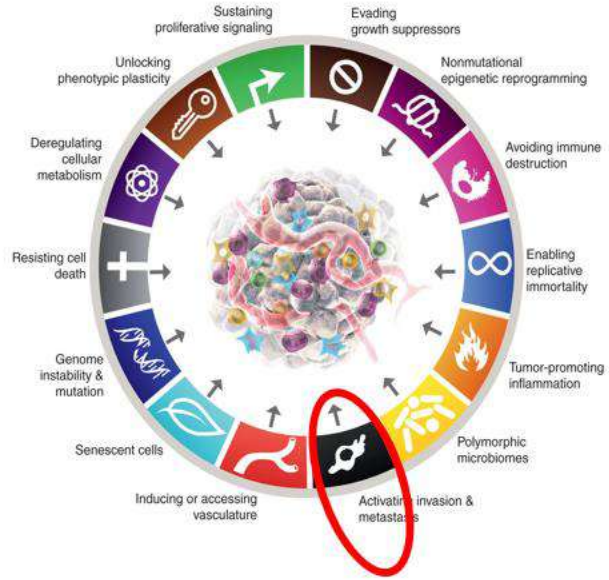
Hanahan D et al Cancer Disc 2022
Zhang et al, Lancet Microbe 2022

ACTIVATING INVASION AND METASTASIS



Activating invasion and metastasis



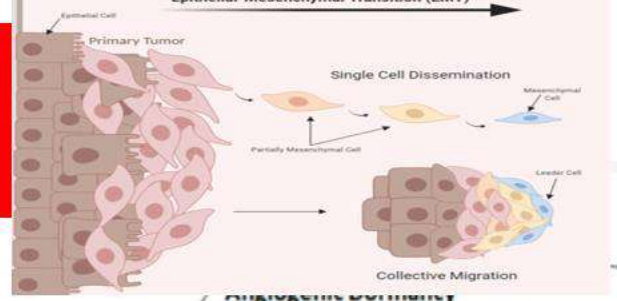


five key steps of metastasis include, intravasation, circulation, extravasation, and colonization

Duffy et al, 2007
Neophytou et al, J. Mol. Sci. 2019
https://www.ncbi.nlm.nih.gov/books/NBK164700/

exosomes that transfer invasion-promoting factors, such as microRNAs (miRNAs)drives metastatic properties

HYPOXIA-INDUCIBLE FACTORS (HIF) PERMIT CANCER CELLS TO ADAPT TO THEIR CELLULAR ENVIRONMENT BY REGULATING ANGIOGENESIS, EMT, INVASION, METASTASIS, AND ENERGY METABOLISM



Primary tumor

EMT

Local invasion

Intravasation

Circulation

Extravasation

Blood Vessel

Micrometastases

Macrometastases

MET

Angiostatin↑, TSP-1↑, VEGF-A↓

Hypoxic Dormancy
LIFR↑, STAT3↑, SOCS↑

Immunologic Dormancy
IFN-γ↑, *IL-12*↑

CSC Dormancy
FBXW7↑, Cyclin E↓, c-Myc ↓, BMP-7↑, p38MAPK↑, GDF-10↑

EMT-induced Dormancy
PRRX1↑,TGF-β2↑, miR-642-3p↓, p38↑

Stress-induced Dormancy
MSK1↑, [ERK/p38]↓, MKK4↑, Nanog↑, ATG7↓, N2RF1↑, p38↑, CDK4↑

DORMANCY
RAS–MEK–ERK/MAPK AND PI3K-AKT SIGNALING
BMP7 ACTIVATES THE METASTATIC SUPPRESSOR GENE N-MYC DOWNSTREAM-REGULATED GENE 1 (*NDGR1*), LEADING TO AN INCREASE IN P38 MAPK ACTIVATION, CELL CYCLE INHIBITOR P21 EXPRESSION, AND CELL CYCLE ARREST

THE RATIO OF EXTRACELLULAR SIGNAL-REGULATED KINASE (ERK1/2) TO P38 MAPK REGULATES THE CELL CYCLE. HIGH LEVELS OF ERK1/2 ACTIVITY FAVOR PROLIFERATION, WHEREAS HIGH LEVELS OF P38 FAVOR DORMANCY.

INTEGRIN
ONCOGENIC GROWTH FACTOR SIGNALLING
E-CADHERIN

CLUSTERED CELLS SURVIVE TUMOR CELL+NEUTROPHIL(SUPPRESS LEUCOCYTE ACTIVATION)+PLATELET THAT PROTECTS BEING DETECTED BY IMMUNE CELL)

REGIONS WITH LOW HEMODYNAMIC FLOW ARE THE REGIONS WHERE MOST CTCS STABILIZE

IL-1B,IL-5,IL-6,IL-8

Epithelial cells

Platelets

Cancer cells

Neutrophils

Macrophages

Extracellular Matrix

Basement Membrane

ESCAPE FROM DORMANCY

Angiogenesis
Angiostatin↓, VEGF-A↑, POSTN↑, TSP-1↓

Cell Adhesion
COL-1↑, FN↑, POSTN↑, AnnexinII↑, AXL↓, GAS6↓, α5β1 integrin↑, uPAR↑, ERK↑

Hypoxia-mediated escape
LIFR↓, LOXL2↑

Inflammation-mediated escape
ERK↑, IL-8↑, MCP-1↑

LUNG METASTASIS
Cell Adhesion
POSTN↑(Wnt1, Wnt3A), TGF-β2↓, VCAM-1, Akt↑

Hypoxia-mediated escape
LOXL2↑, LOX↑

Inflammation-mediated escape
TBK1↑ (GSK-3B, ZEB1)

CSC Dormancy Inhibition
COCO↑, BMP-7↓

Stress-induced Dormancy Inhibition
CDK4↑, p27↓, [ERK/p38]↑,

BONE METASTASIS
Cell Adhesion
MLCK↑, CXCL12↑,CXCR4↑, CXCL5↑, TGF-B2↓, E-Selectin↑, VCAM-1↑

Hypoxia-mediated escape
LIFR↓, STAT3↓

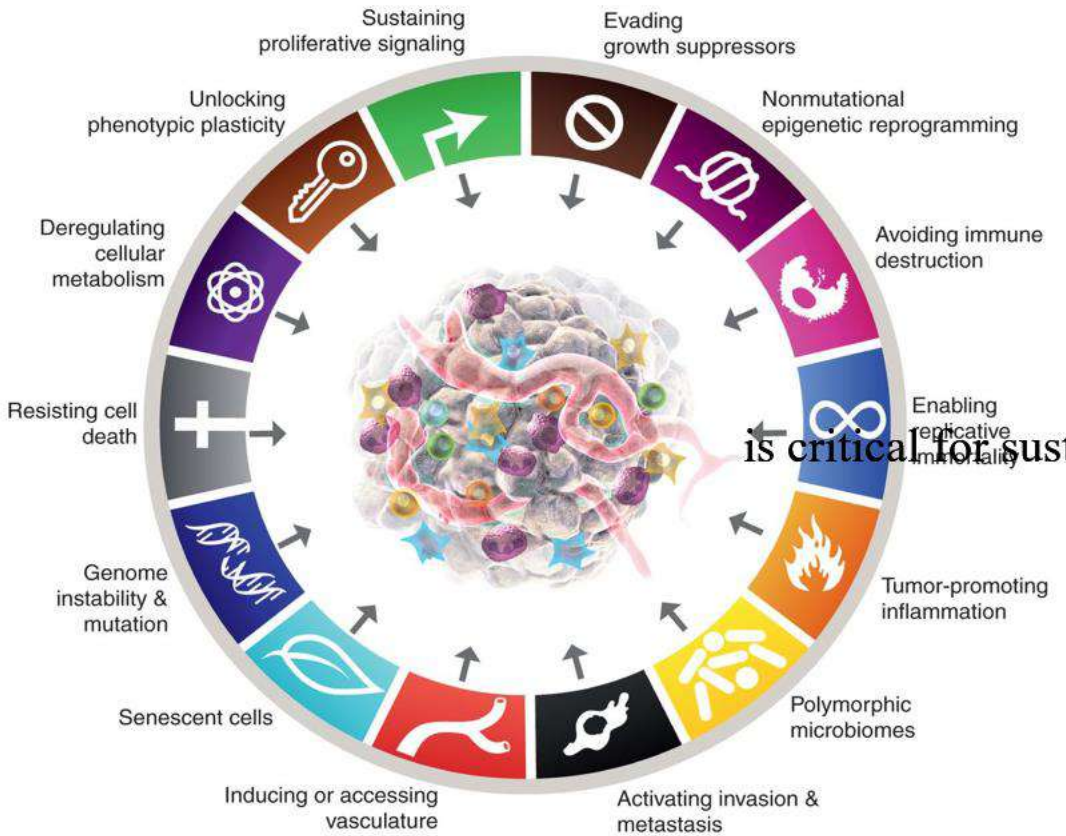
Stress-induced Dormancy Inhibition
MSK1↓, GATA3↓, FOXA1↓

Metabolism-mediated escape
PTHRP↑, TNF-α↑, RANKL↑, IL-6↑, IL-11↑

BRAIN METASTASIS
Angiogenesis
MMP-9↑, VEGF-A↑

Cell Adhesion
CYR61↓, PRAME↑

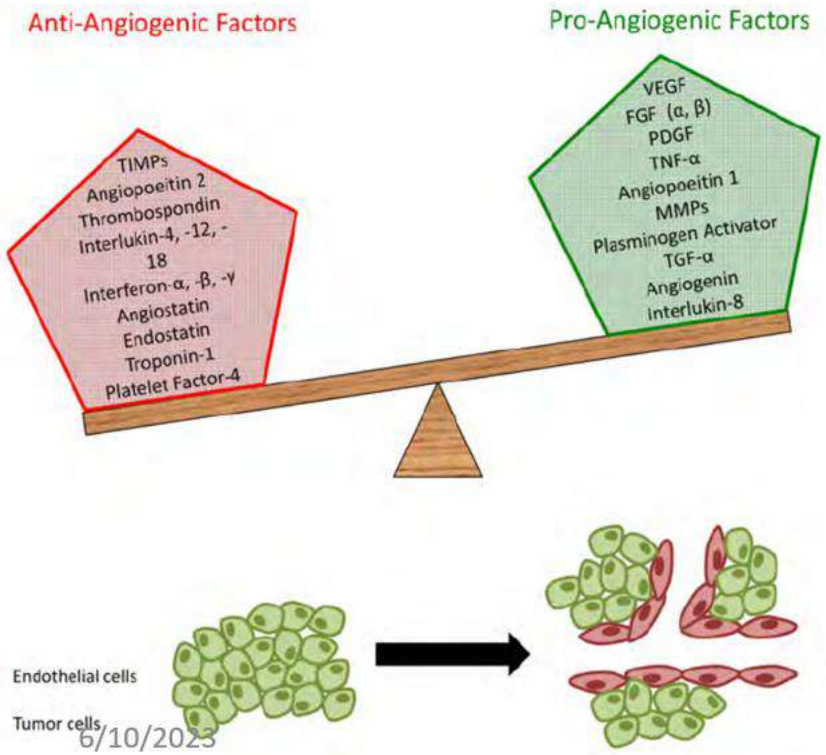
INDUCING OR ACCESSING VASCULATURE

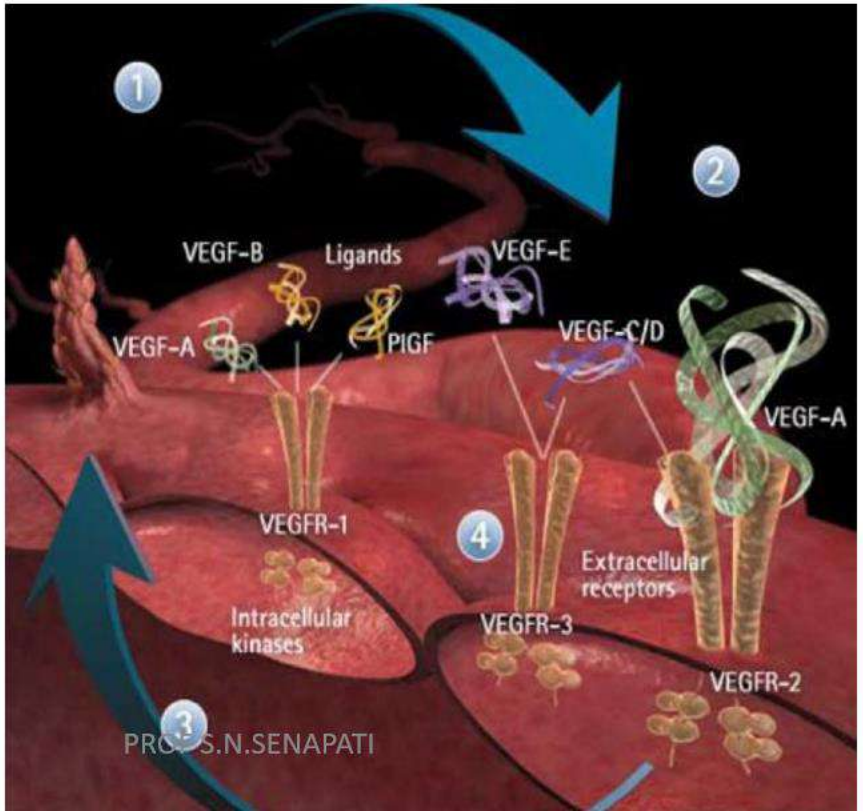


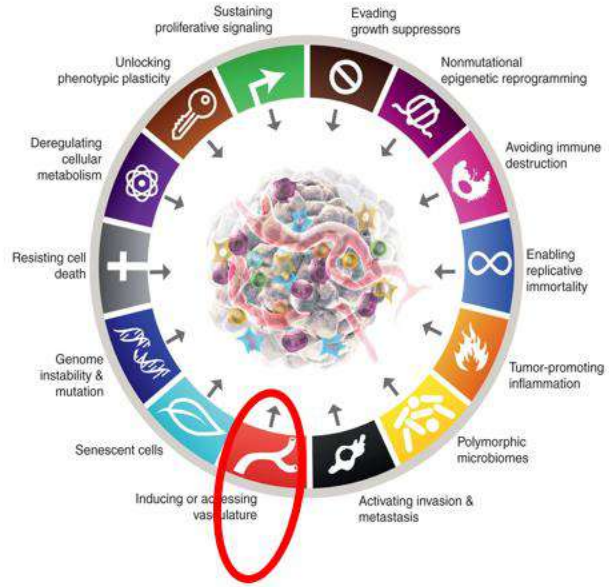
is critical for sustained

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.

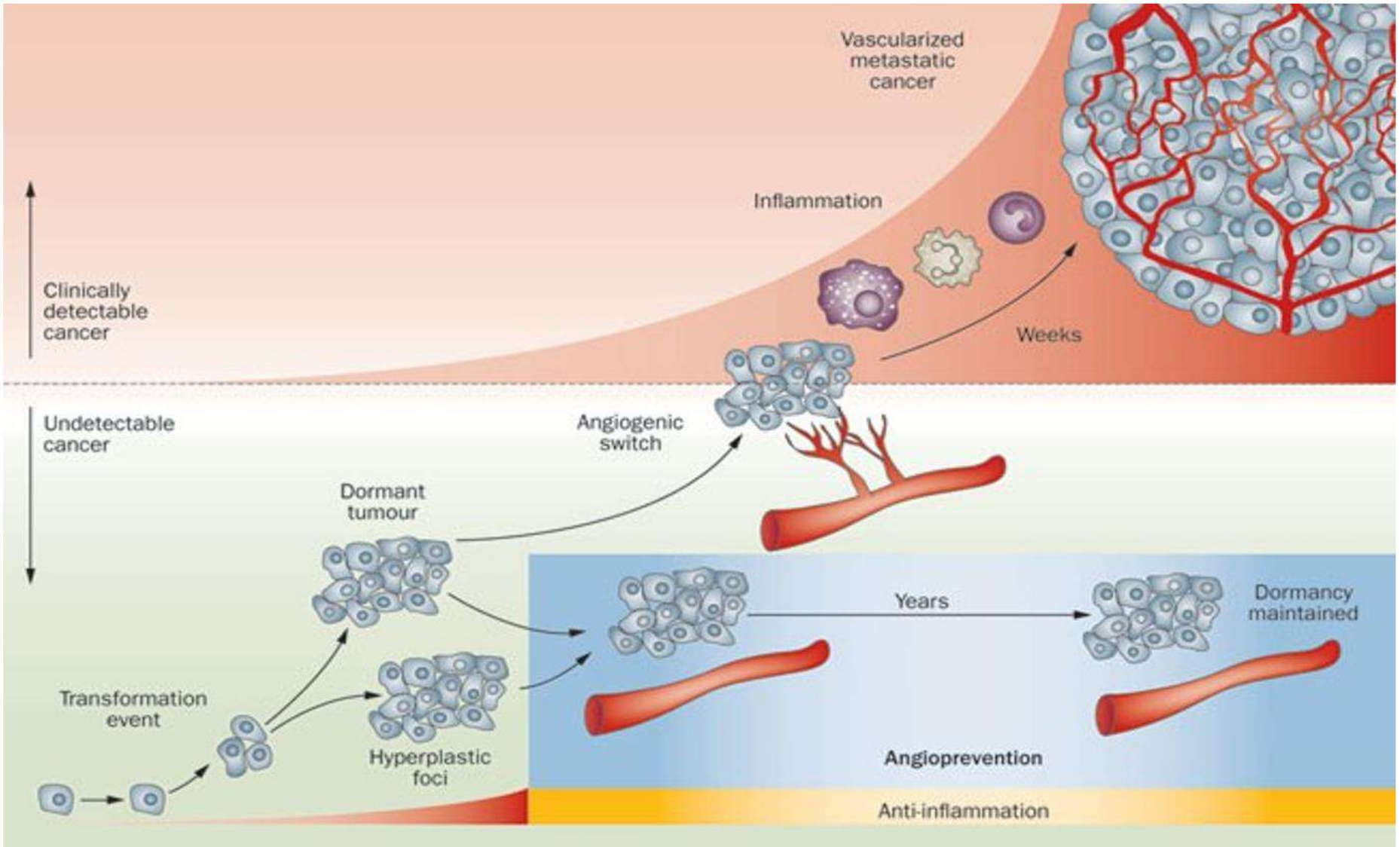


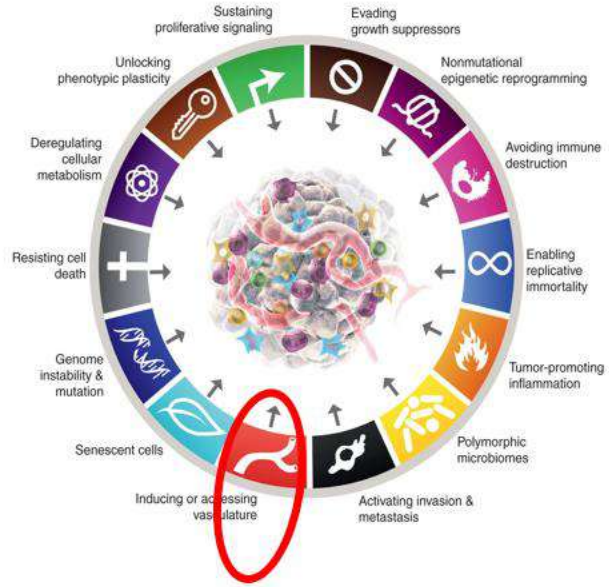




Mabeta et al, 2022

Angiogenic switch





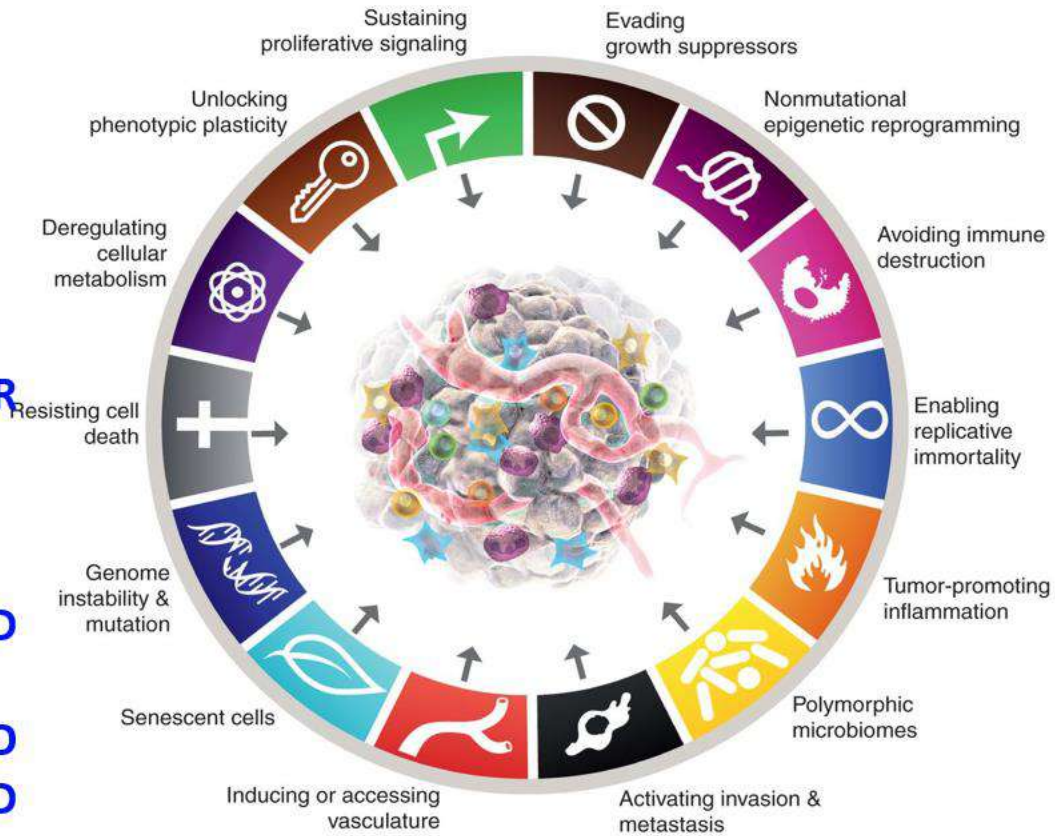
- Anti-angiogenic agents can be used not only for the treatment of cancer, but also for the prevention of cancer recurrence or metastasis.

Niu et al, 2020

SENESCENT CELLS

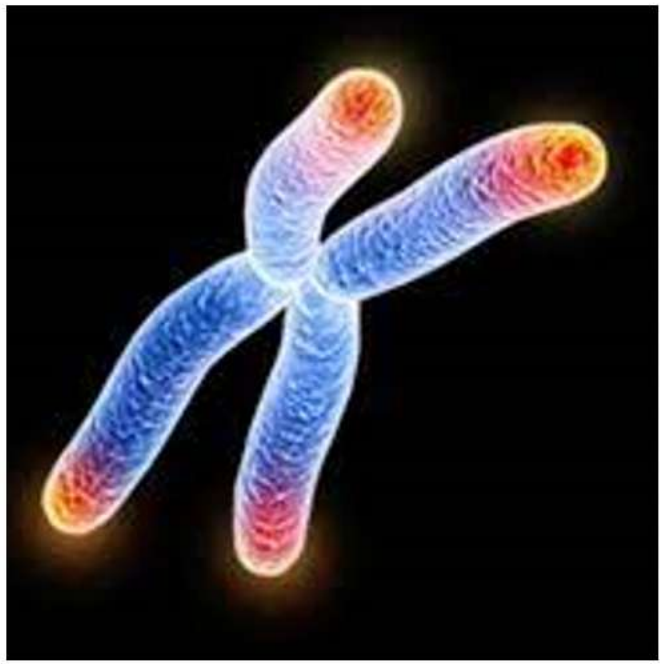
SENESCENT CELLS ARE CHARACTERIZED BY :

1) **OCCURS IN PROLIFERATIVE CELLS**
2) **CELL CYCLE ARREST,FAILS TO RE ENTER THE CELL CYCLE UNDER MITOTIC STIMULATION**
3) **RESISTANCE TO APOPTOTIC CELL DEATH**
4) **ENHANCED SECRETORY PHENOTYPE**
5) **OCCURS DUE TO TELOMERE SHORTENING,DNA DAMAGE AND INAPPROPRIATE EXPRESSION OF ONCOGENE**
6) **PARADOXICAL ROLE CAN DEVELOP ONCOGENESIS DUE TO SASP WHICH PRODUCES IMMUNOSUPPRESSION AND PROGRESSION AND RELAPSE OF THE DISEASE.**



TELOMERE SHORTENING

TELOMERIC REPEAT BINDING FACTOR 2 & POT 1 LOST



DNA DAMAGE

PROTEINE KINASE ATM,ATR

PHOSPHORYLATION OF p53 &MDM2

RELEASE OF p53 FROM MDM2

ACTIVATE CDKN1A GENE

RELEASES p21

INHIBIT CDK4/CYCLIN D

E2F+ HYPOPHOSPHORYLATED RB RECRUIT HISTONE DEACETYLASE AND METHYLE TRANSFERASE

E2F DESTROYED DESTROYED

INAPPROPRIATE EXPRESSION OF ONCOGENE

ACTIVATION OF MITOCHONDRIAL ROS

ACTIVATION OF ONCOGENE RAS,BRAF & INACTIVATION OF PTEN,NF1,VHL,RB

NORMAL PROLLIFERATING CELL

IRREVERSIBLE CELL CYCLE ARREST

CELLULAR SENESCENCE PARADOXICAL ROLE

MALIGNANT CELL

PROLLIFERATION

NORMAL PROLLIFERATING CELL

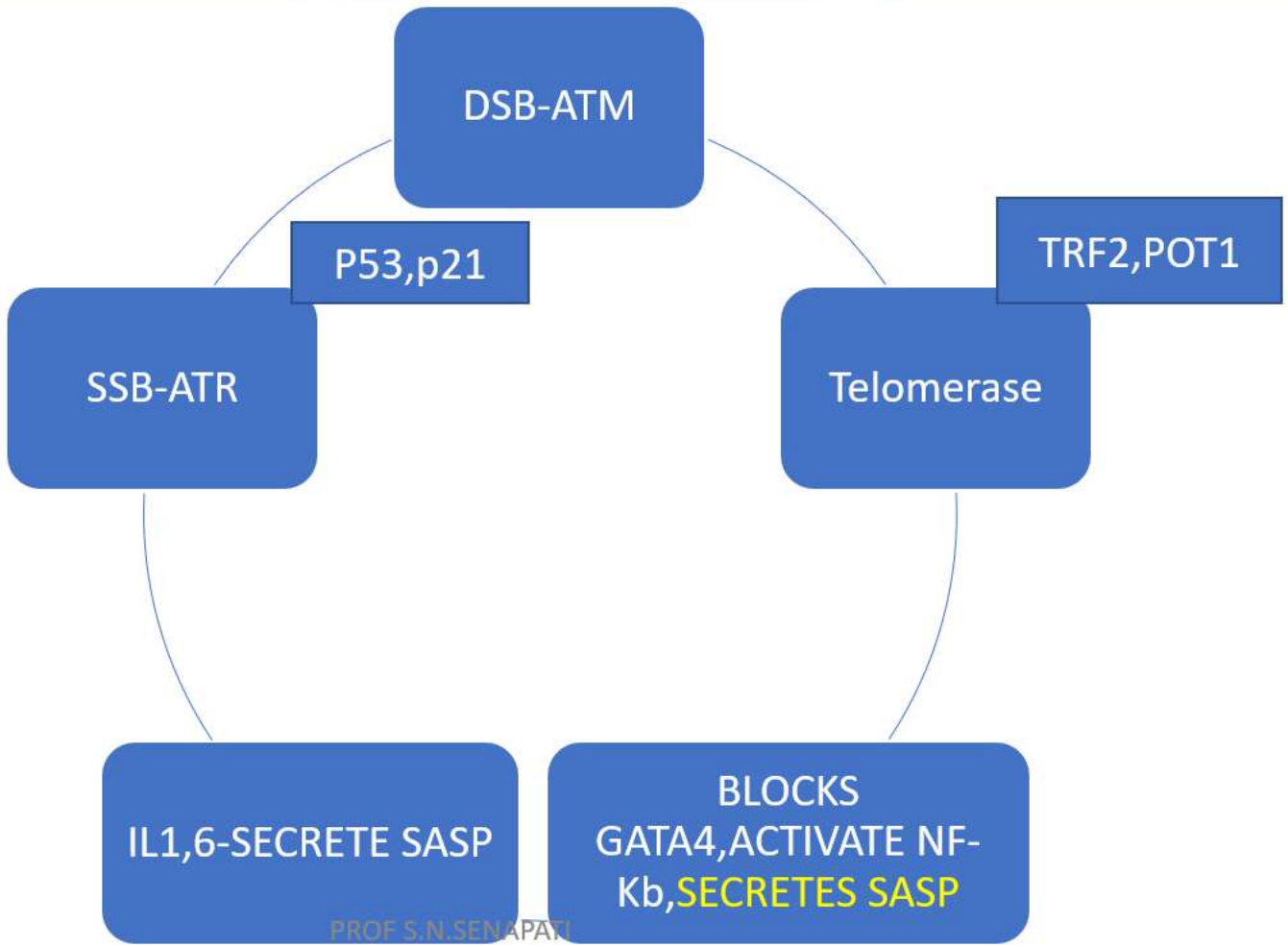
IRREVERSIBLE CELL CYCLE ARREST

AGEING

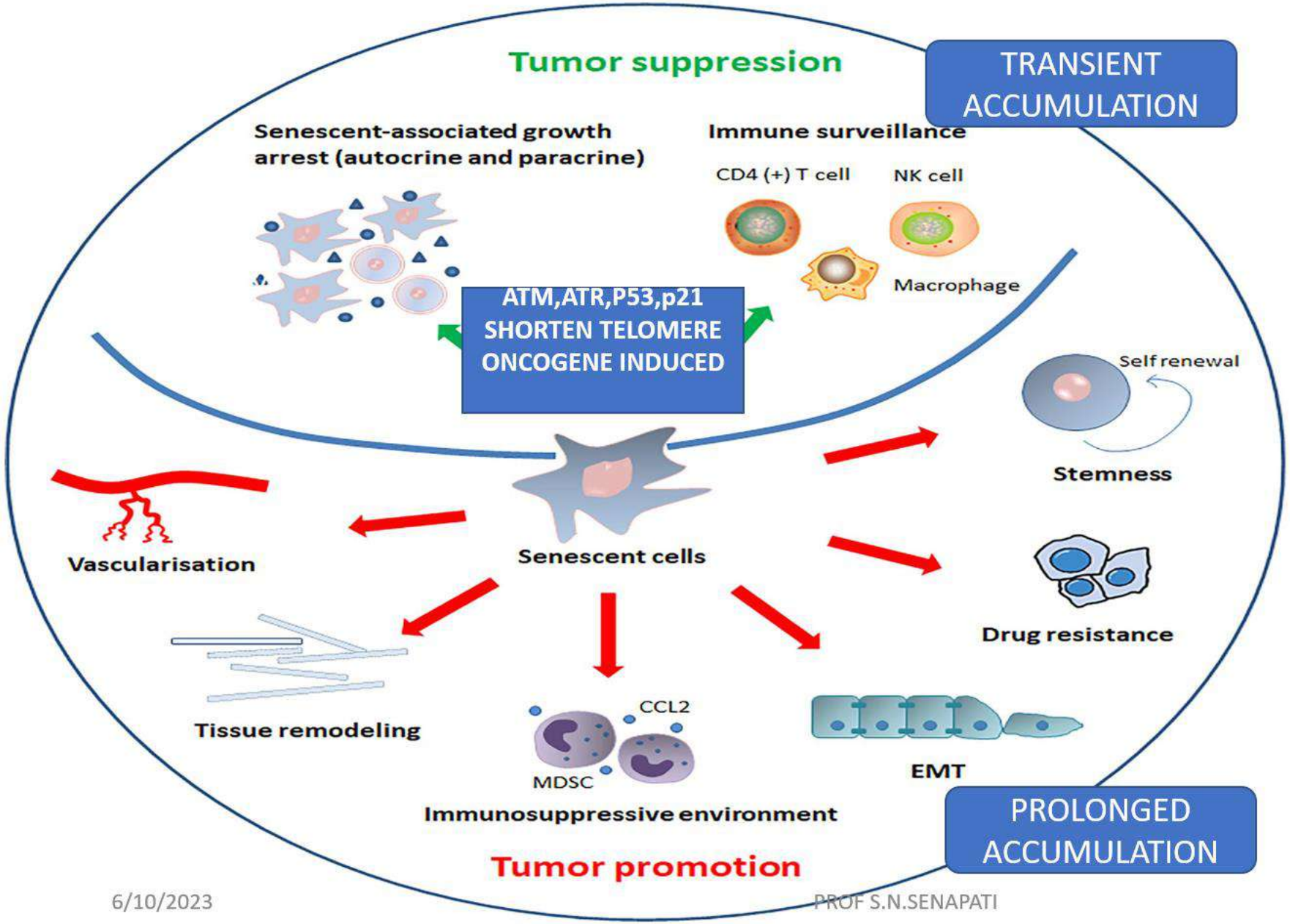
CANCER PREVENTION

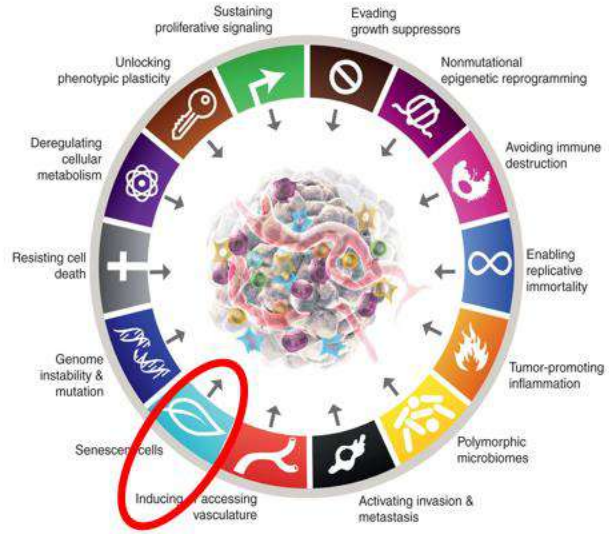
IMMUNE MEDIATED TUMOR CLEARANCE

THERAPY INDUCED SENESCENCE



Senescent cells





SENESCENT CELL ACCUMULATE

SENESCENT FIBROBLAST

SASP DEPENDANT MANNER

PROMOTE PRE AND MALIGNANT EPITHELIAL CELL TO PROLLIFERATE

FORM BLEBS ON SURFACE CONTAIN EphA2 BINDS TO EPHRINA-CELLULAR PROLLIFERATION

GENOMIC INSTABILITY AND MUTATION

CANCER CELL:-INCREASED RATE OF MUTATION TO SURVIVE

INCREASED RATE OF MUTATION:-

- Increased sensitivity to mutagenic agents
- Breakdown in DNA repair mechanisms mediated by TP53 or (BRCA1)
- A combination of these factors

DEFECTIVE DNA-MAINTENANCE MACHINERY, OR "CARETAKER" GENES.

These genes are responsible for

- Detecting DNA damage and activating repair machinery
- Directly repairing damaged DNA
- Inactivating or intercepting mutagenic molecules

By inactivating or suppressing caretaker genes, tumor cells can increase the rate of mutations and, subsequently, tumorigenesis.

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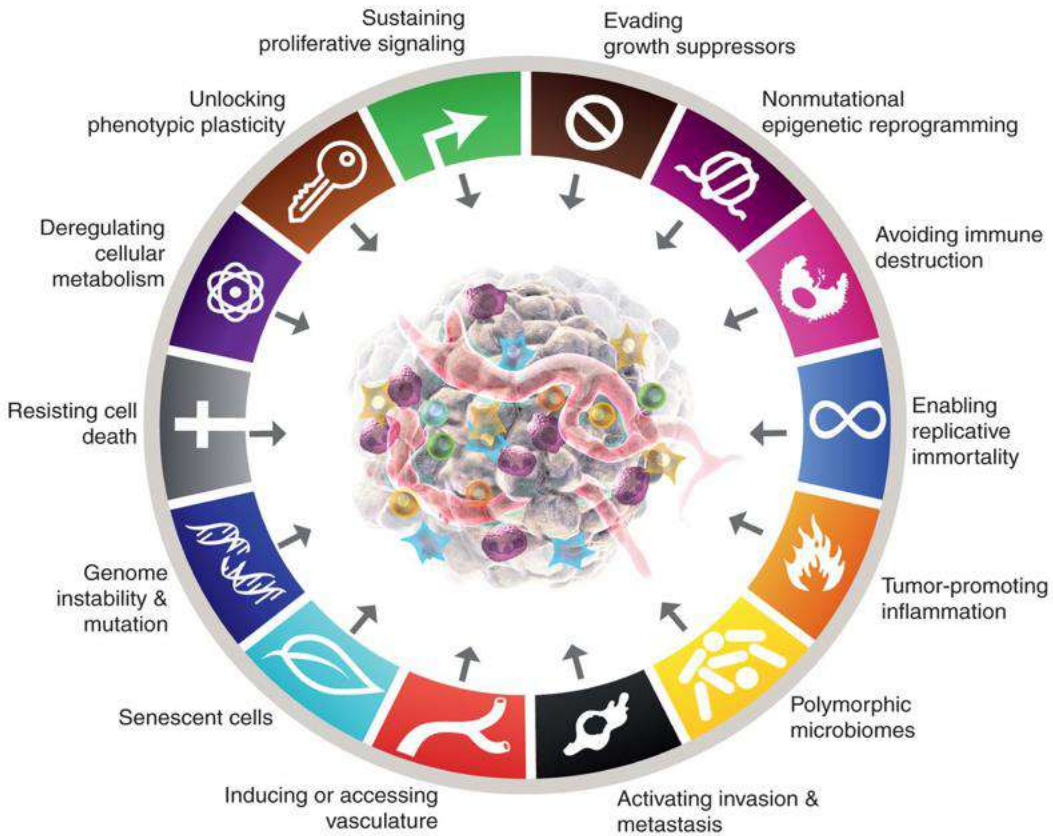
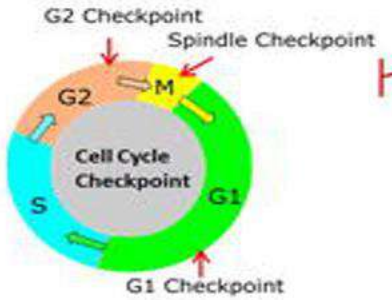


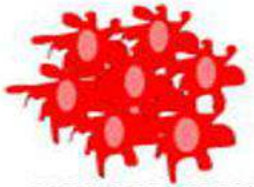
Genomic instability and mutations

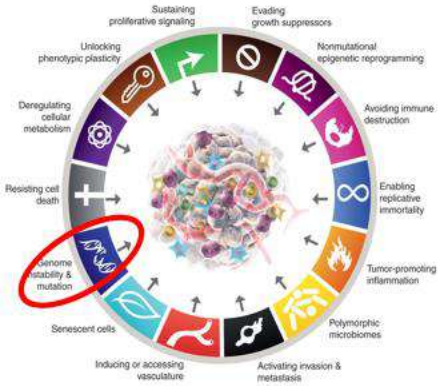
1
2

Ploidy Change
Copy Number Variation
Inversions
Insertions
Deletions
Translocation
DNA tertiary structure change
Point Mutation

GENOME INSTABILITY







6/10/2023 PROF S.N.SENAPATI

Charames et al, Nature 2003

Click to add notes

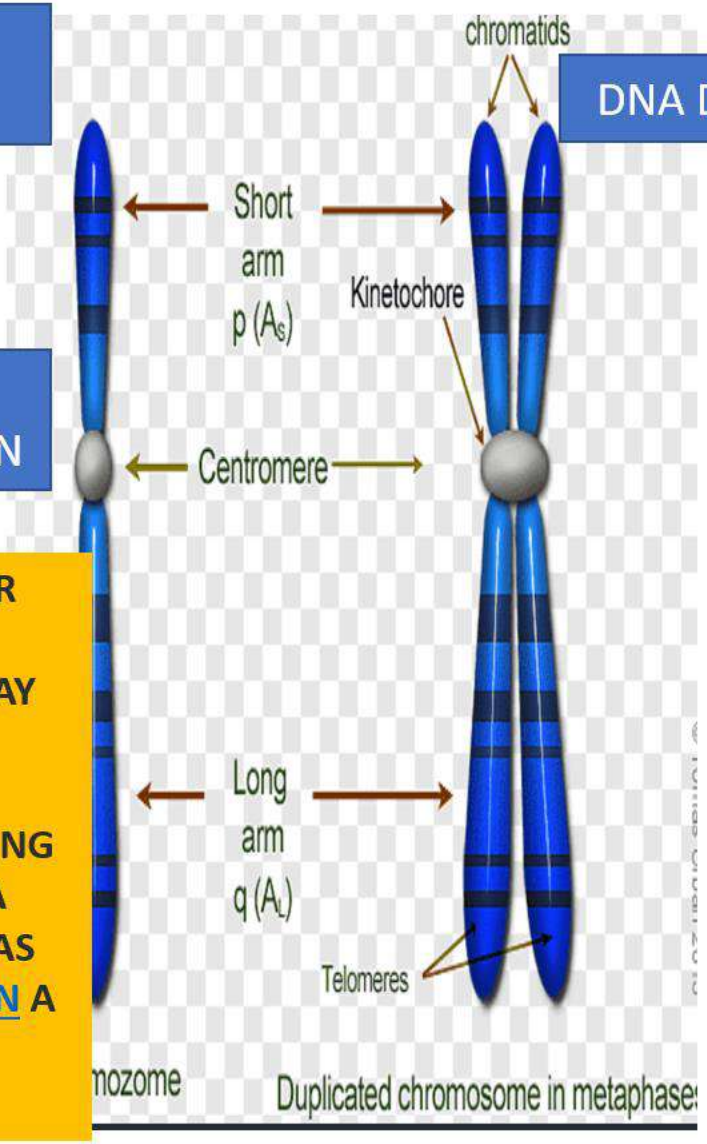
GENETIC INSTABILITY

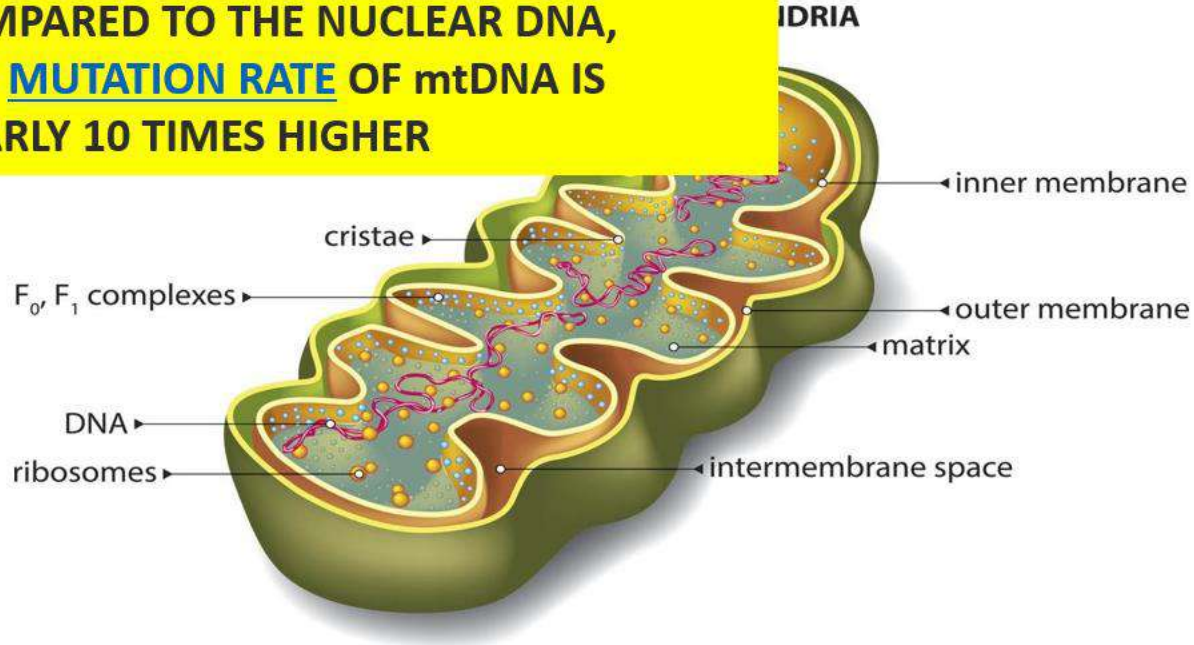
COMPARED TO THE NUCLEAR DNA, THE MUTATION RATE OF mtDNA IS NEARLY 10 TIMES HIGHER

TELOMERE DAMAGE

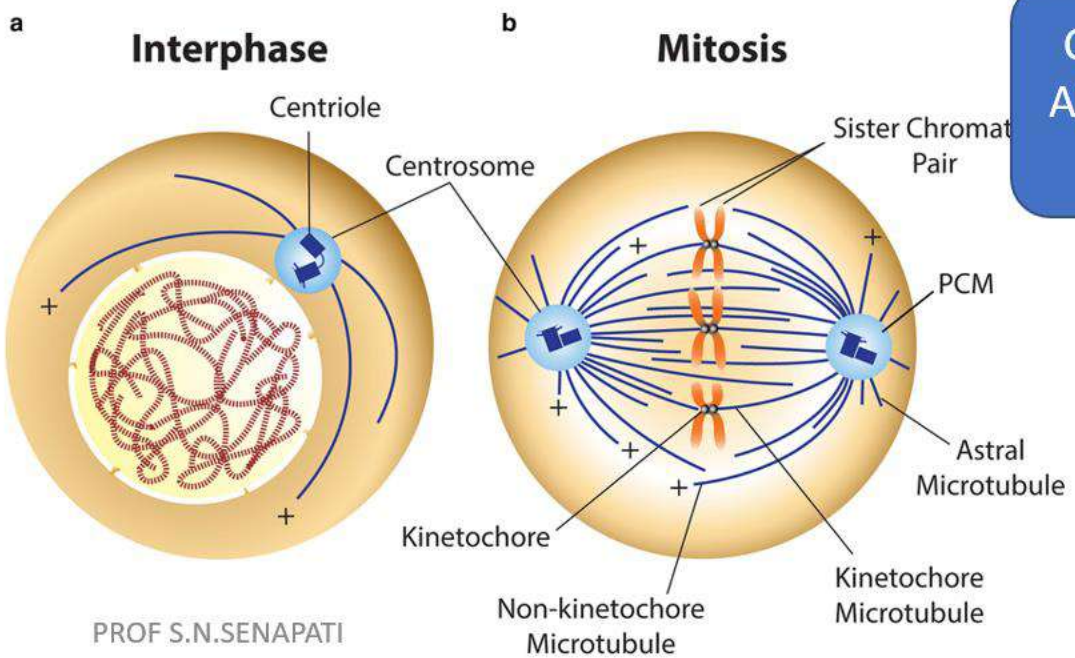
DNA DAMAGE

EPIGENETIC MODIFICATION



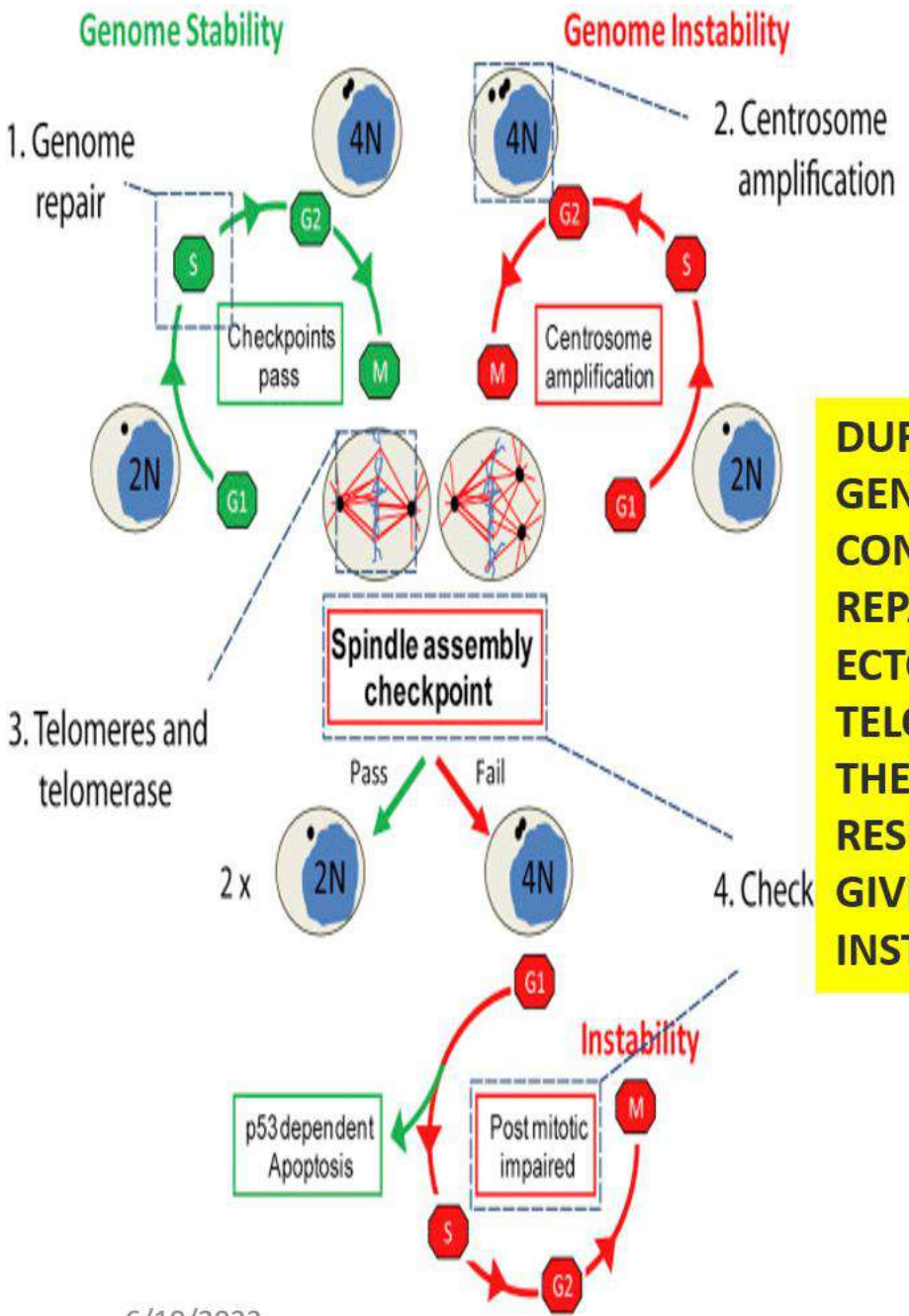


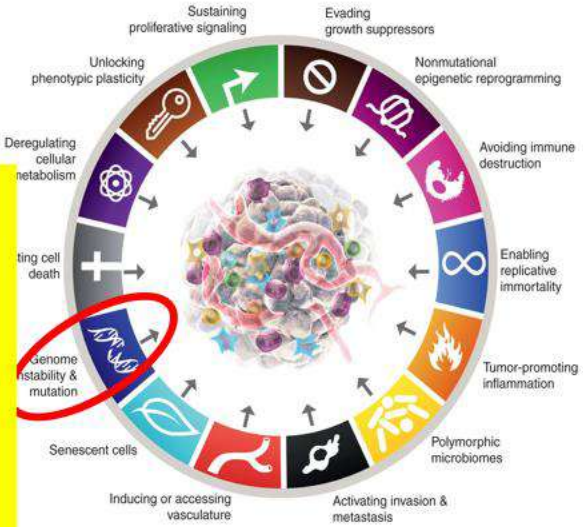
EPIGENETICS REFER TO ALL HERITABLE CHANGES THAT MAY MODIFY GENE EXPRESSION WITHOUT CHANGING THE PRIMARY DNA SEQUENCE, SUCH AS DNA METHYLATION A ND CHROMATIN REMODELLING



CENTROSOME AMPLIFICATION > 2

Genomic instability

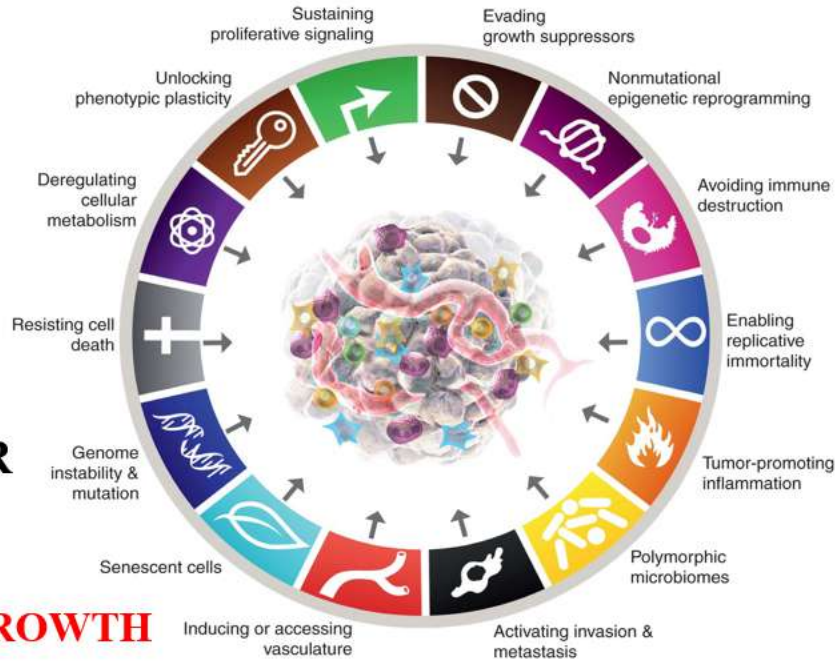




DURING S PHASE, THE CENTROSOME AND GENOMIC MATERIAL ARE REPLICATED CONCURRENTLY, AND REPLICATION ERRORS ARE REPAIRED PRIOR TO MITOTIC ENTRY (1). ECTOPIC AMPLIFICATION OF CENTROSOMES (2), TELOMERASE DYSFUNCTION (3) AND FAILURE OF THE SPINDLE ASSEMBLY CHECKPOINT (4) MAY RESULT IN ABORTED MITOSIS. MITOTIC FAILURE GIVES RISE TO A SINGLE TETRAPLOID CELL (4 N) INSTEAD OF TWO DIPLOID CELLS (2 N).

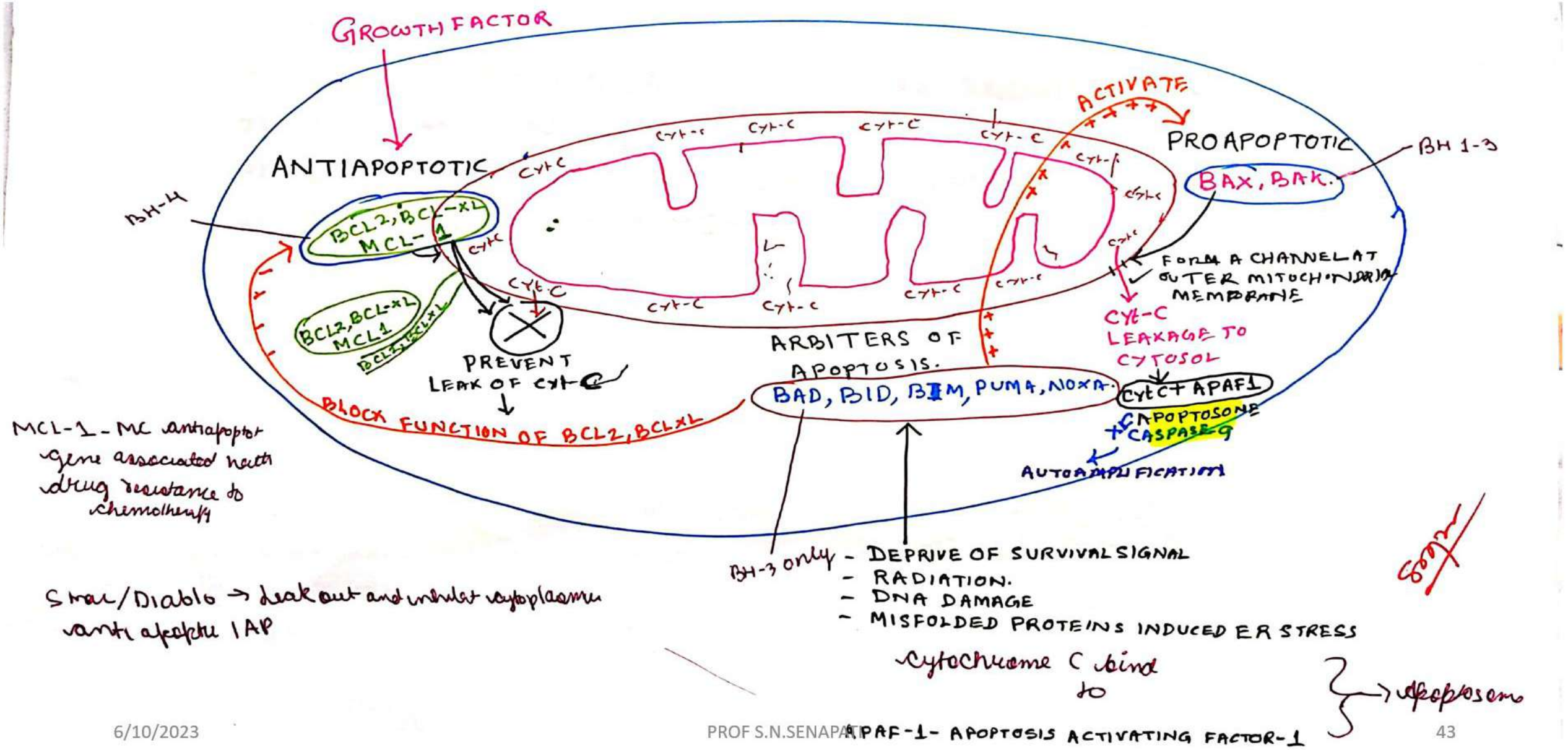
Schmitt et al, Nature 2022

RESISTING CELL DEATH



- **NORMAL CELLS :- APOPTOSIS IF DNA DAMAGE**
- **CANCER CELL:-AVOID APOPTOSIS**
- **APOPTOSIS OCCURS THROUGH 2 PATHWAYS: THE INTRINSIC OR MITOCHONDRIAL PATHWAY AND THE EXTRINSIC DEATH-RECEPTOR PATHWAY**
- **THE INTRINSIC PATHWAY IMPORTANT IN CANCER,- AS DNA DAMAGE AND GROWTH FACTOR DEPRIVATION, AS WELL AS TREATMENT WITH CHEMO- AND IMMUNOTHERAPEUTICS ACTIVATE THE INTRINSIC PATHWAY.**
- **INTRINSIC PATHWAY IS TIGHTLY REGULATED BY A GROUP OF RELATED PROTEINS CALLED THE BCL-2 FAMILY.**
- **CANCERS ARE ABLE TO RESIST THE APOPTOTIC PATHWAY THROUGH DYSREGULATION OF BCL-2 FAMILY MEMBERS. CANCER CELLS ARE THOUGHT TO ACHIEVE THIS THROUGH 2 MAIN MECHANISMS: A DOWN-REGULATION OF PRO-APOPTOTIC PROTEINS, OR AN INCREASE IN BCL-2 EXPRESSION.**

INTRINSIC PATHWAY OF APOPTOSIS

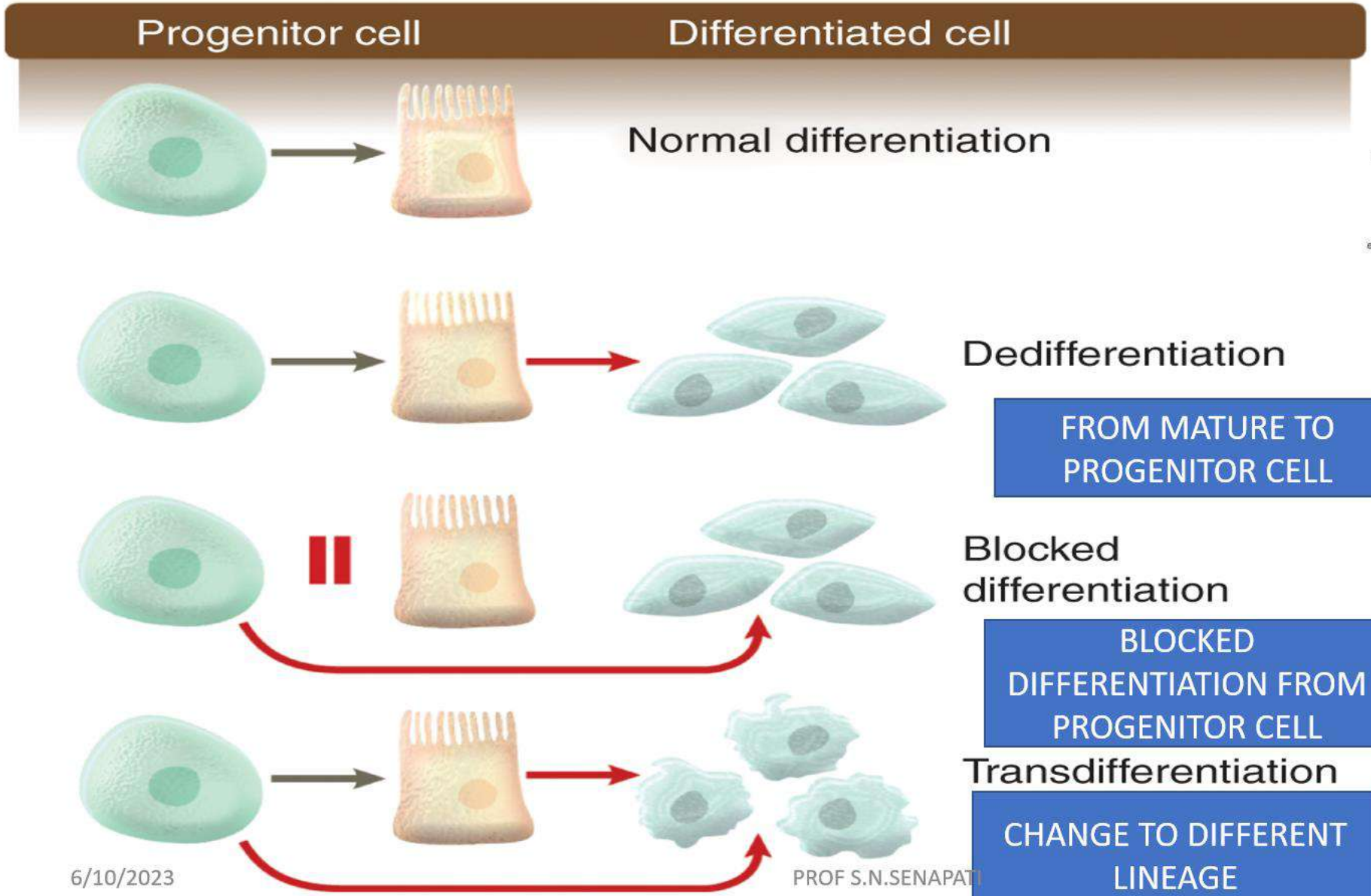


MCL-1 - MC antiapoptor gene associated with drug resistance to chemotherapy

Smac/Diablo → leak out and inhibit cytoplasmic anti apoptic IAP

Cytochrome C bind to APAF-1- APOPTOSIS ACTIVATING FACTOR-1 → apoptosome

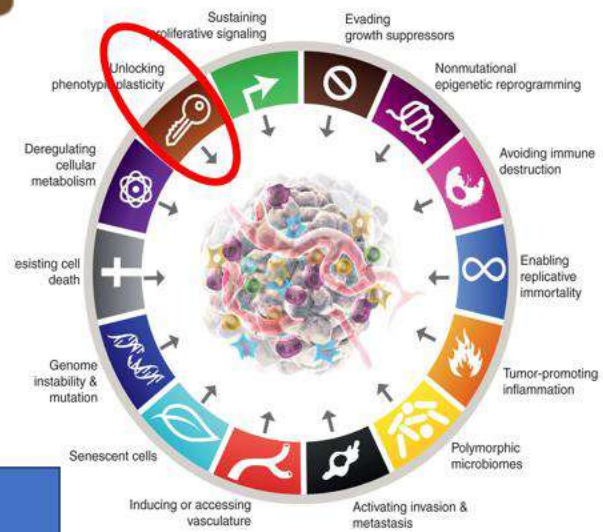
Unlocking phenotypic plasticity



FROM MATURE TO PROGENITOR CELL

BLOCKED DIFFERENTIATION FROM PROGENITOR CELL

CHANGE TO DIFFERENT LINEAGE



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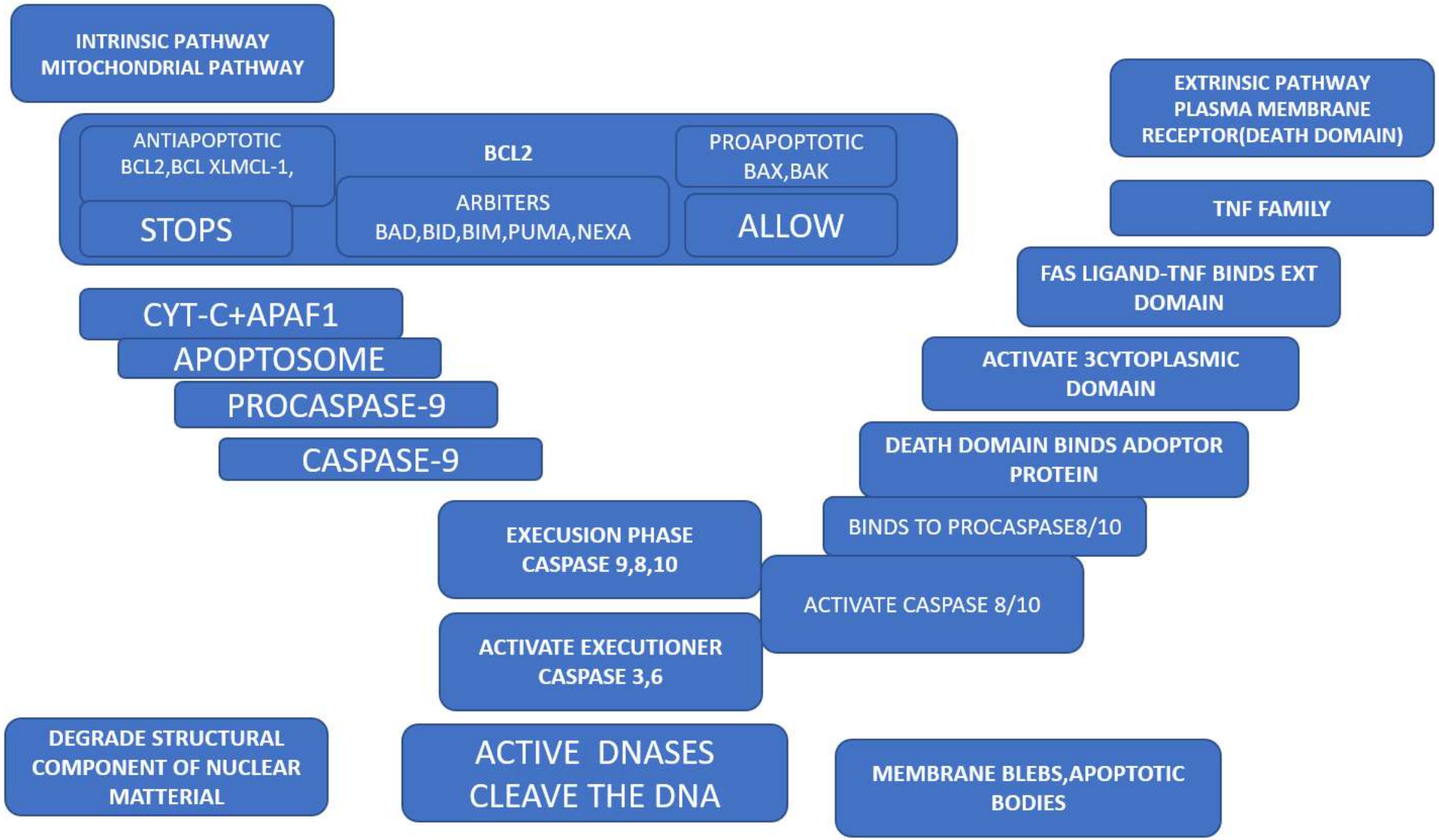
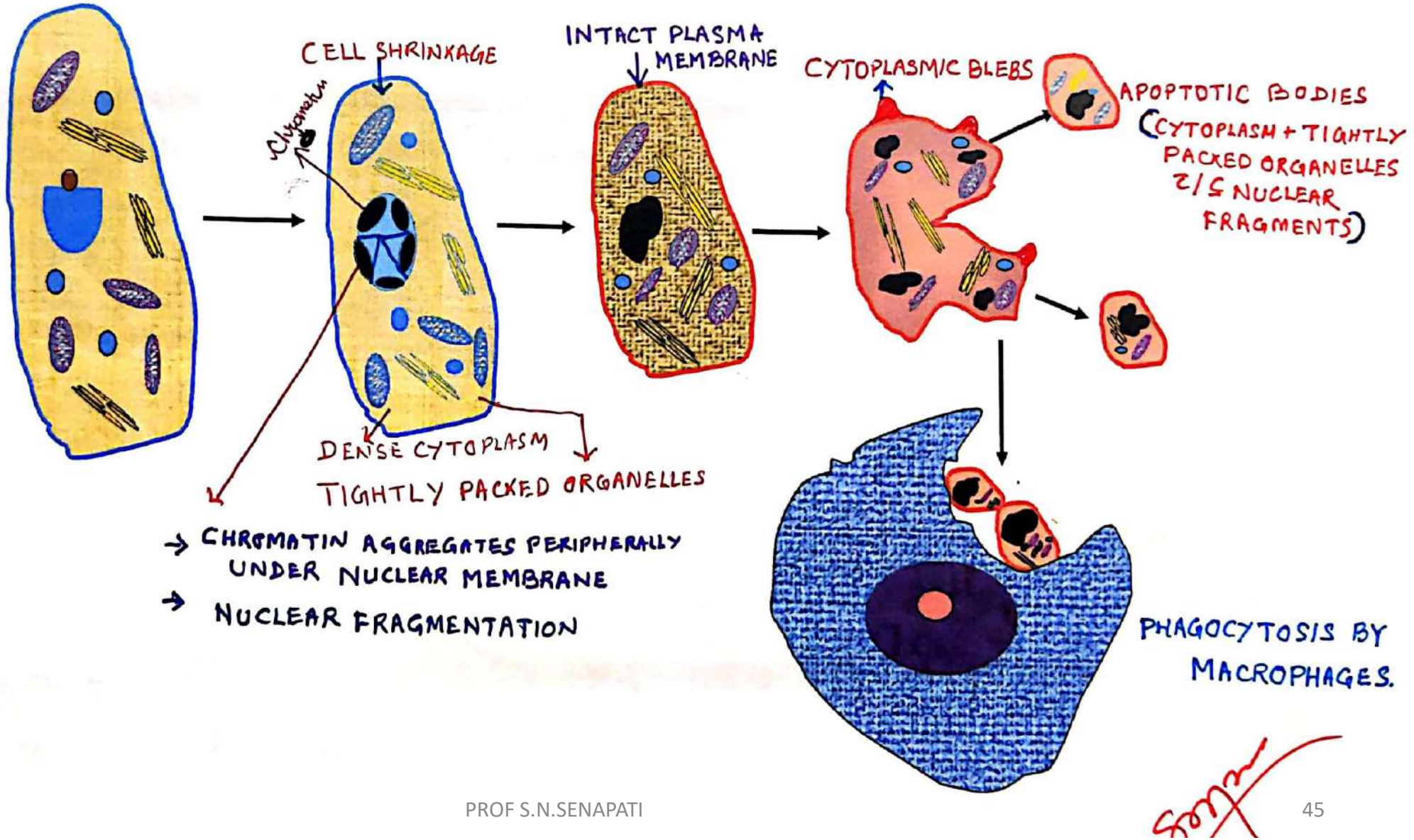
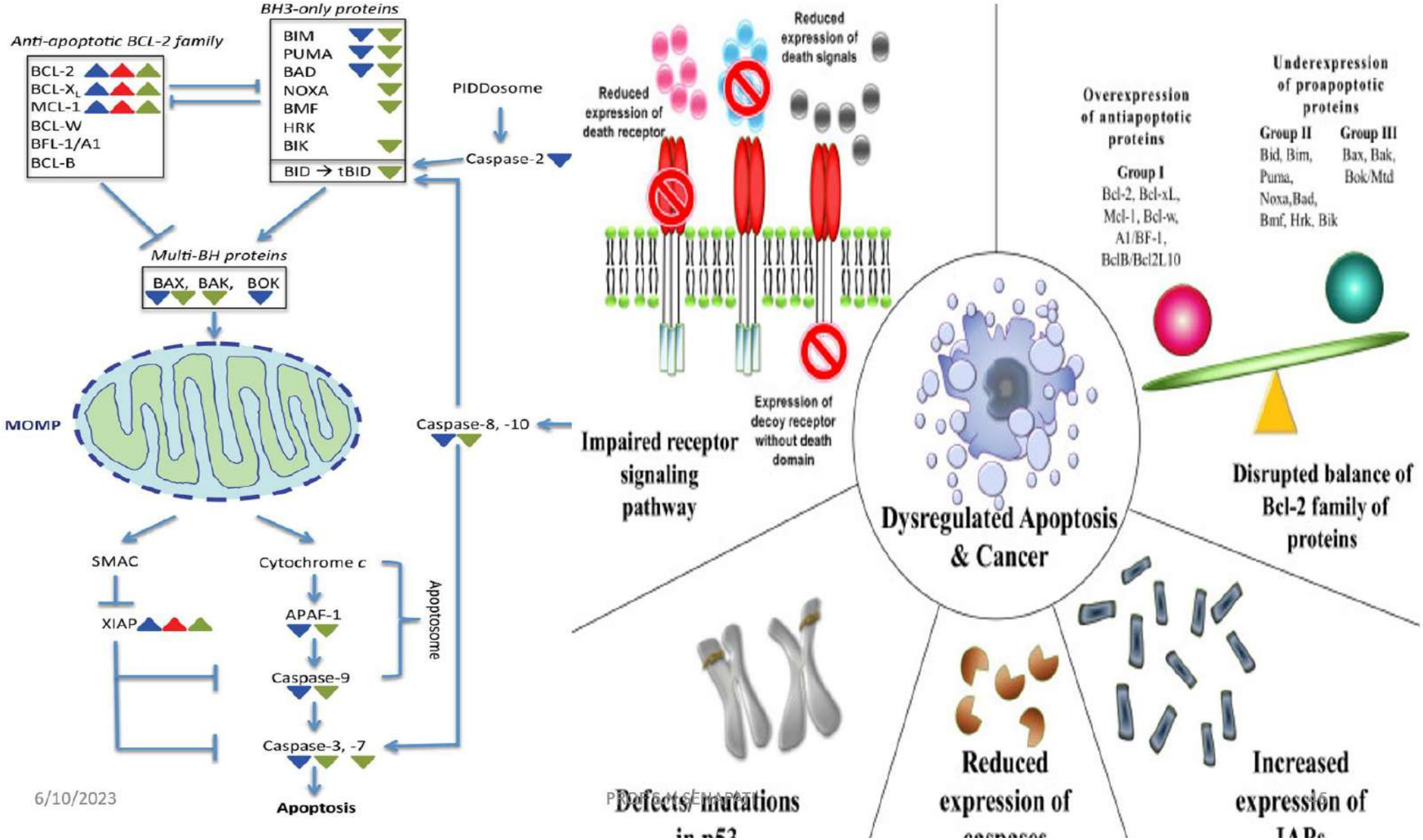
APOPTOSIS


INTRINSIC PATHWAY
MITOCHONDRIAL PATHWAY
ANTIAPOPTOTIC
BCL2,BCL XLMCL-1,
STOPS
BCL2
ARBITERS
BAD,BID,BIM,PUMA,NEXA
PROAPOPTOTIC
BAX,BAK
ALLOW
CYT-C+APAF1
APOPTOSOME
PROCASPASE-9
CASPASE-9
EXECUSION PHASE
CASPASE 9,8,10
ACTIVATE EXECUTIONER
CASPASE 3,6
DEGRADE STRUCTURAL
COMPONENT OF NUCLEAR
MATTERIAL
ACTIVE DNASES
CLEAVE THE DNA
MEMBRANE BLEBS,APOPTOTIC
BODIES
EXTRINSIC PATHWAY
PLASMA MEMBRANE
RECEPTOR(DEATH DOMAIN)
TNF FAMILY
FAS LIGAND-TNF BINDS EXT
DOMAIN
ACTIVATE 3CYTOPLASMIC
DOMAIN
DEATH DOMAIN BINDS ADOPTOR
PROTEIN
BINDS TO PROCASPASE8/10
ACTIVATE CASPASE 8/10

MORPHOLOGY OF APOPTOSIS




Anti-apoptotic BCL-2 family
BCL-2
BCL-XL
MCL-1
BCL-W
BFL-1/A1
BCL-B
BH3-only proteins
BIM
PUMA
BAD
NOXA
BMF
HRK
BIK
BID → tBID
Multi-BH proteins
BAX, BAK, BOK
MOMP
SMAC
XIAP
Cytochrome c
APAF-1
Caspase-9
Apoptosome
Caspase-3, -7
Apoptosis
PIDDosome
Caspase-2
Caspase-8, -10
Reduced expression of death receptor
Reduced expression of death signals
Expression of decoy receptor without death domain
Impaired receptor signaling pathway
Dysregulated Apoptosis & Cancer
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
Disrupted balance of Bcl-2 family of proteins
Defects/ mutations in p53
Reduced expression of caspases
Increased expression of IAPs

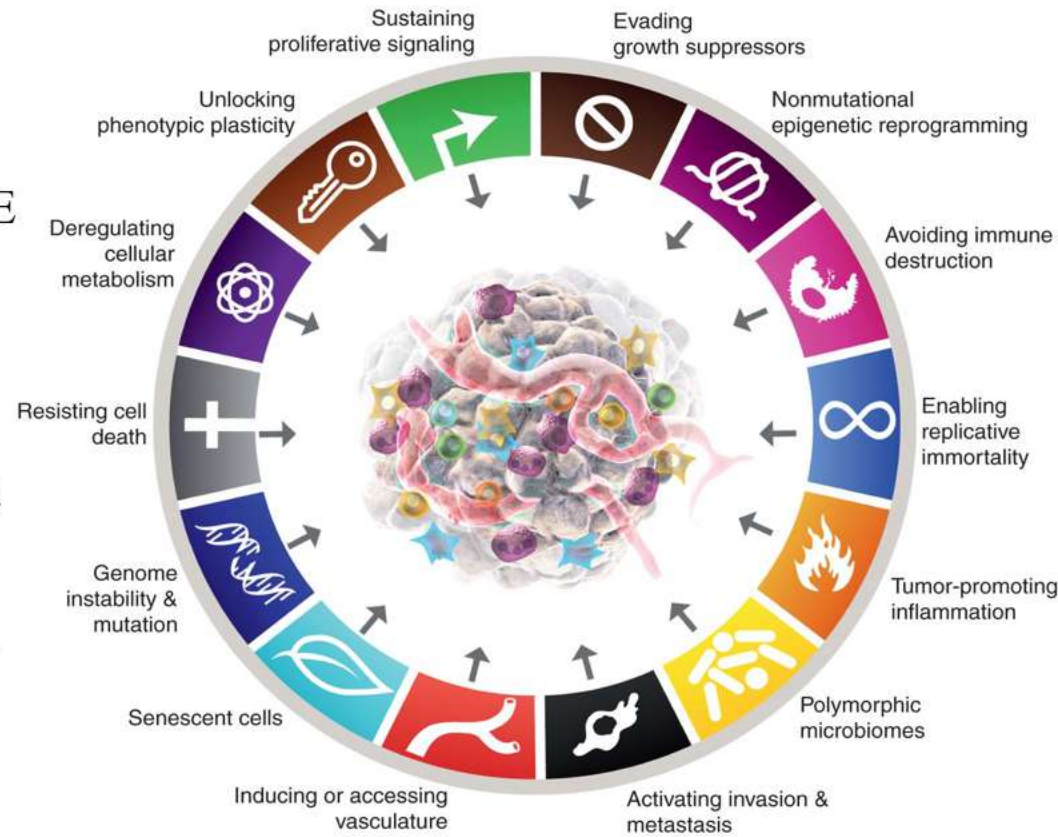
Deregulating cellular metabolism

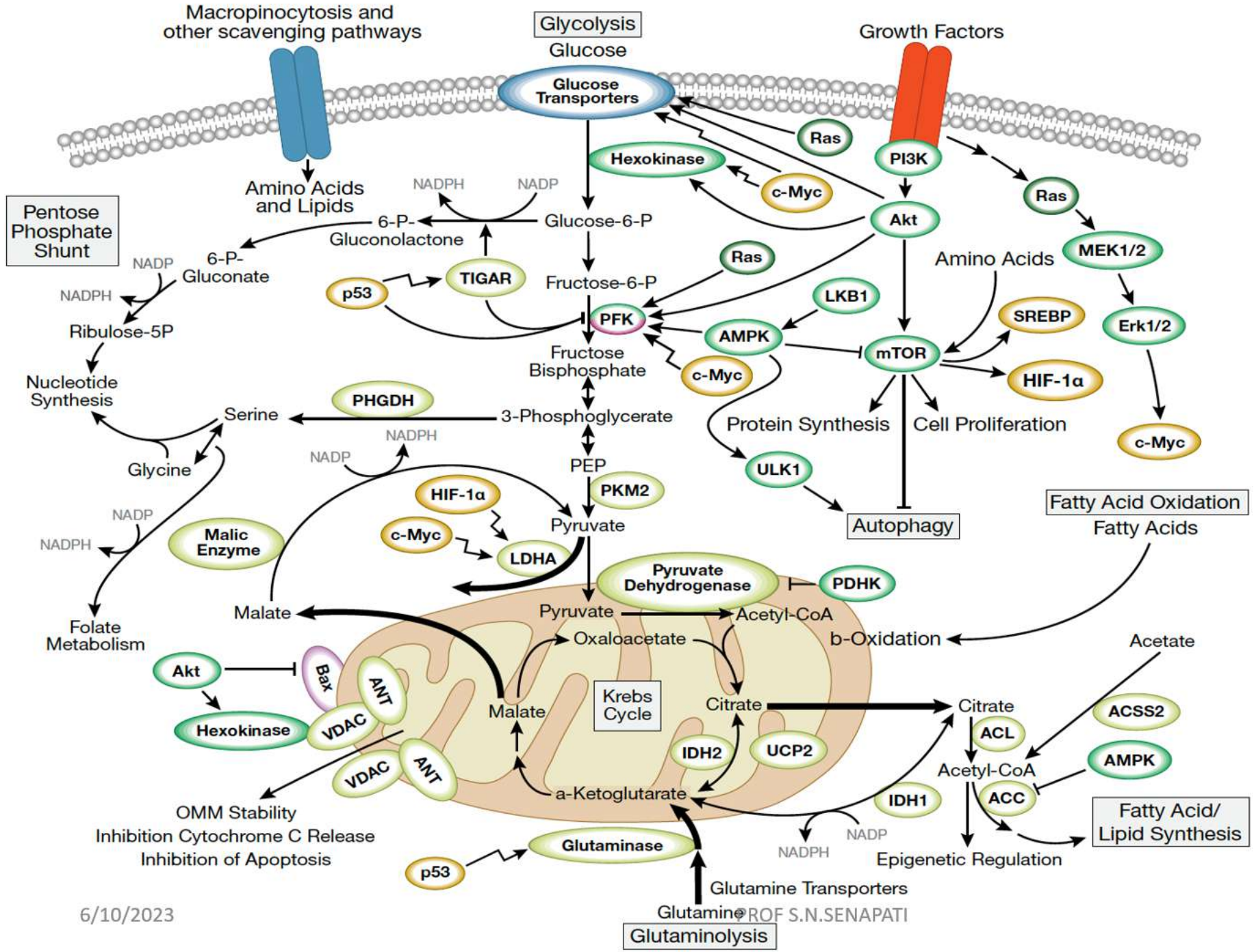
TO SUSTAIN UNCONTROLLED PROLIFERATION, CANCER CELLS MAKE ADJUSTMENTS TO THEIR ENERGY PRODUCTION BY

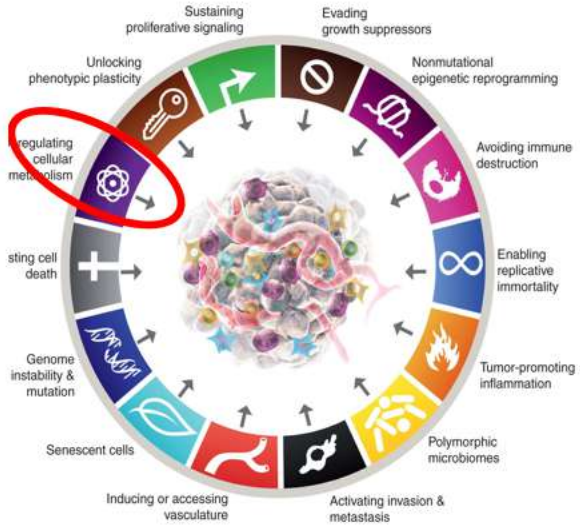
•REPROGRAMMING THEIR GLUCOSE METABOLISM

•UPREGULATING GLUCOSE TRANSPORTERS SUCH AS GLUCOSE TRANSPORTER 1 (GLUT1)

•DEPENDING ON ALTERNATE METABOLIC PATHWAYS ALTHOUGH LIMITING ENERGY PRODUCTION TO THE GLYCOLYSIS PHASE DECREASES THE AMOUNT OF ADENOSINE TRIPHOSPHATE (ATP) PRODUCED, IT ALSO ALLOWS CANCER CELLS TO DIVERT GLYCOLIC INTERMEDIATES TO VARIOUS PATHWAYS, INCLUDING THOSE REQUIRED TO ASSEMBLE NEW CELLS.







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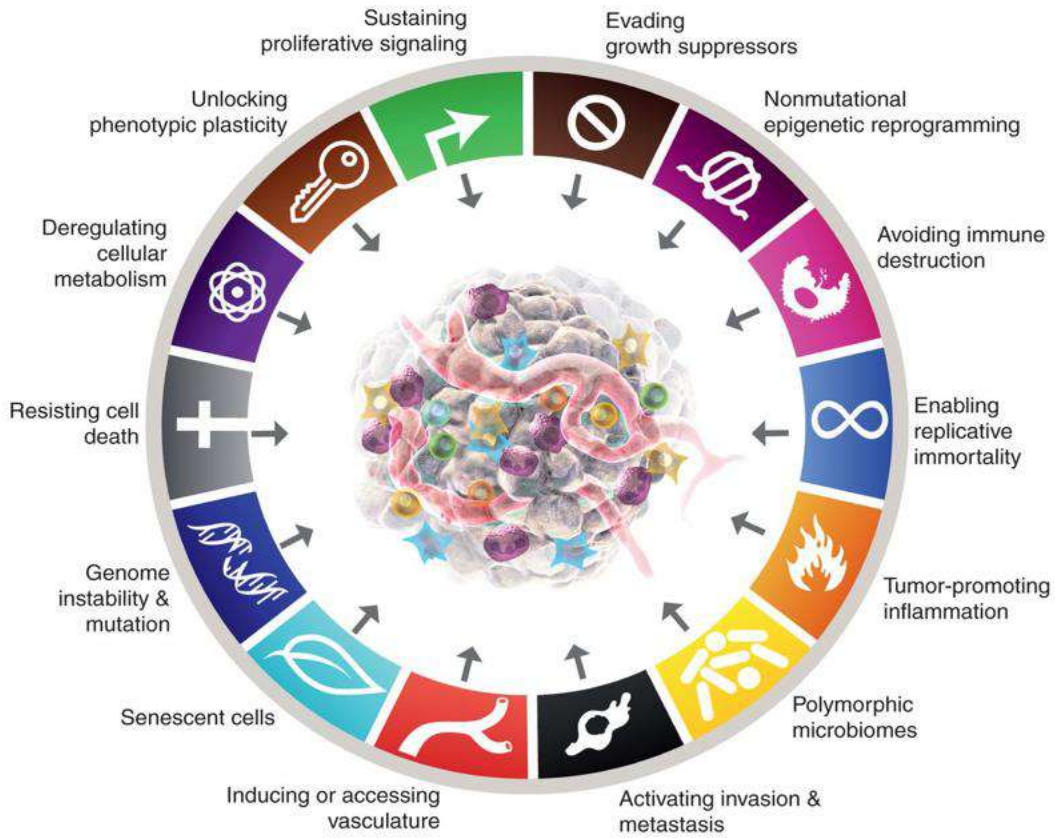
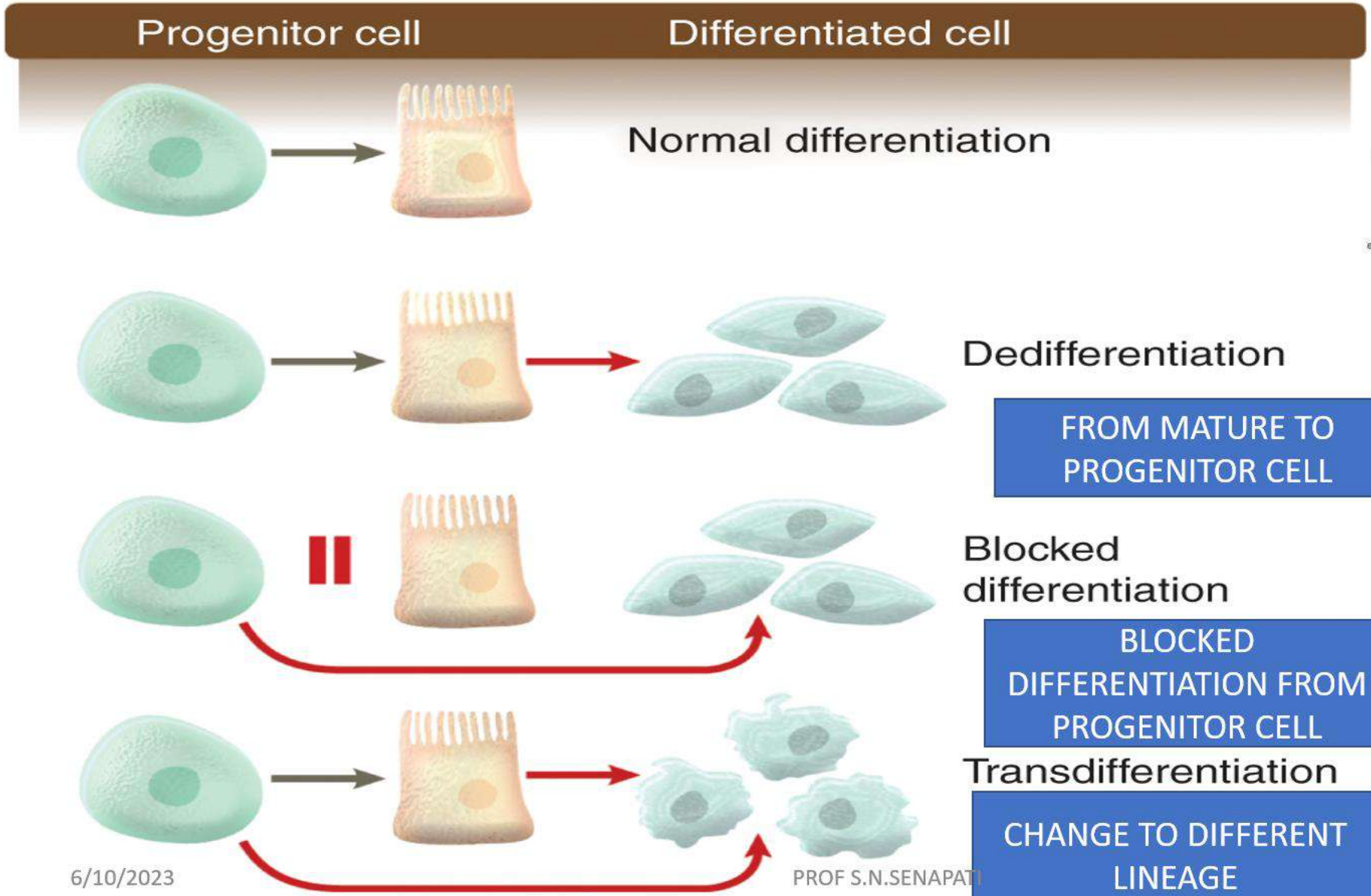
UNLOCKING PHENOTYPIC PLASTICITY



Unlocking phenotypic plasticity



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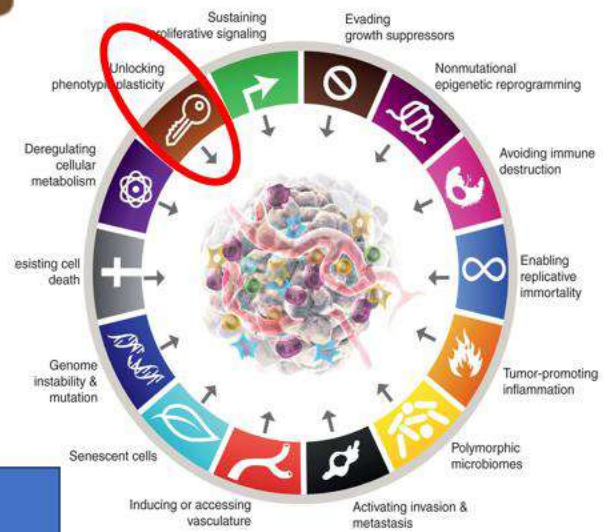

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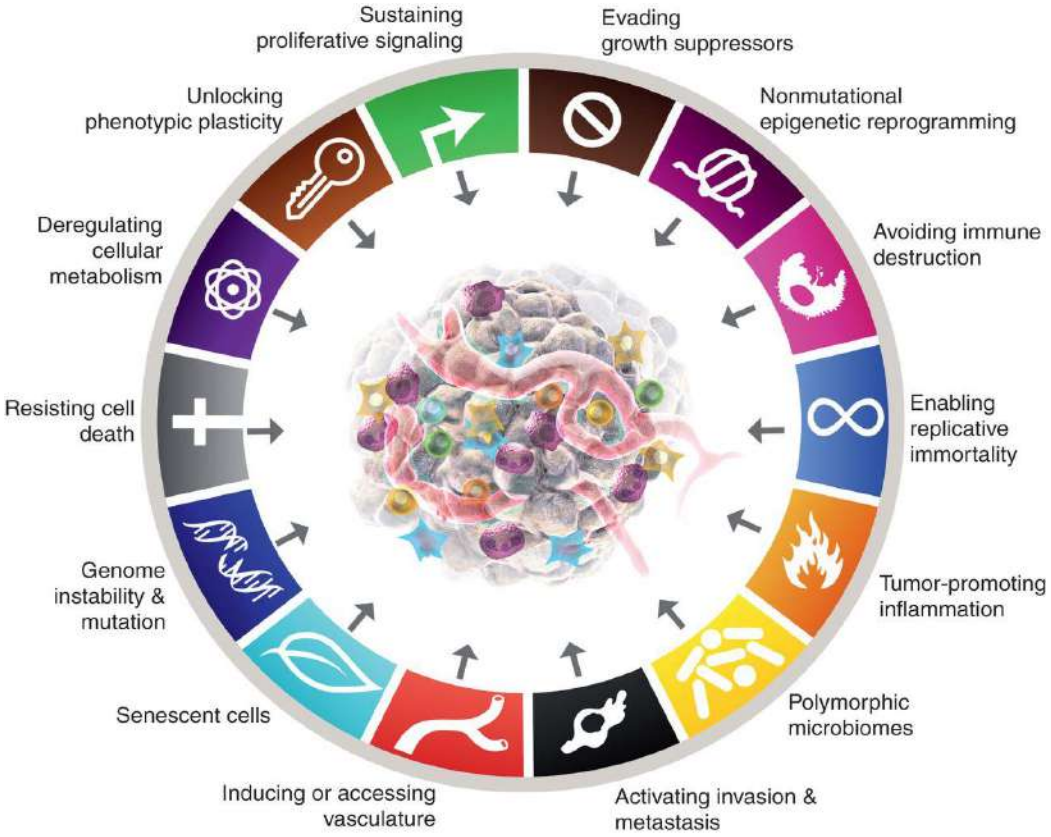
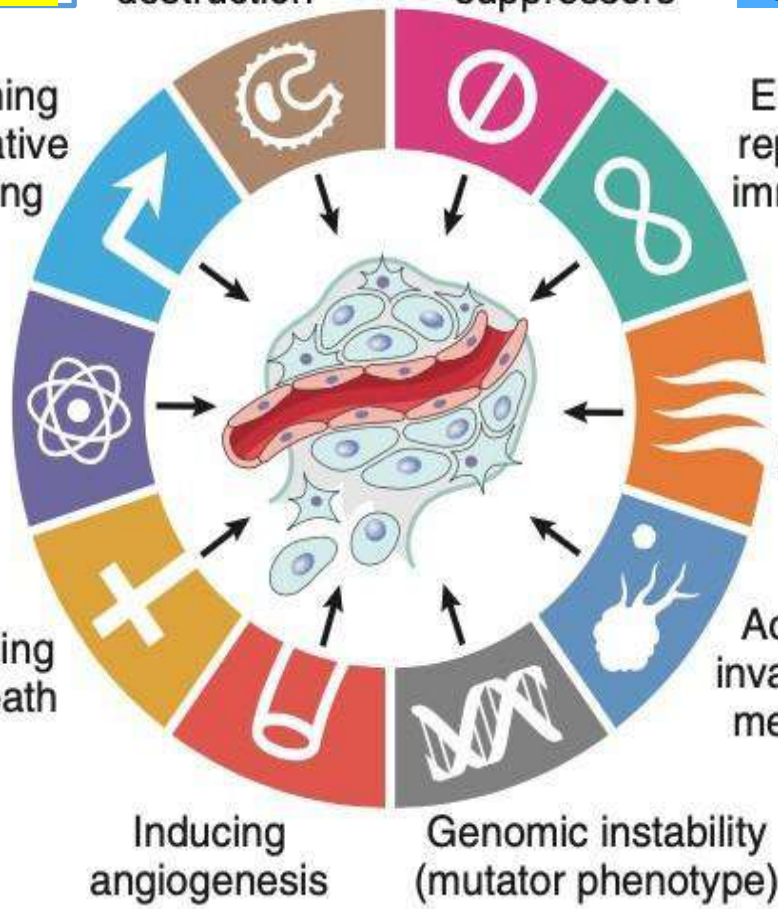
Summary


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

Cancer cells show extensive alterations in protein expression levels[1]



PDL1, TGF-b, Cytokines

SUPPRESSED RB, TP53, TGF-b, TIMP1, IGF

TYROSINE KINASE, RAS, RAF, MTOR, MAP KINASE, PI3 KINASE

INCREASED TELOMERASE ACTIVITY, C-MYC, MAX, LRP6N

IL6

PD1, IL8, IL6, Cytokines

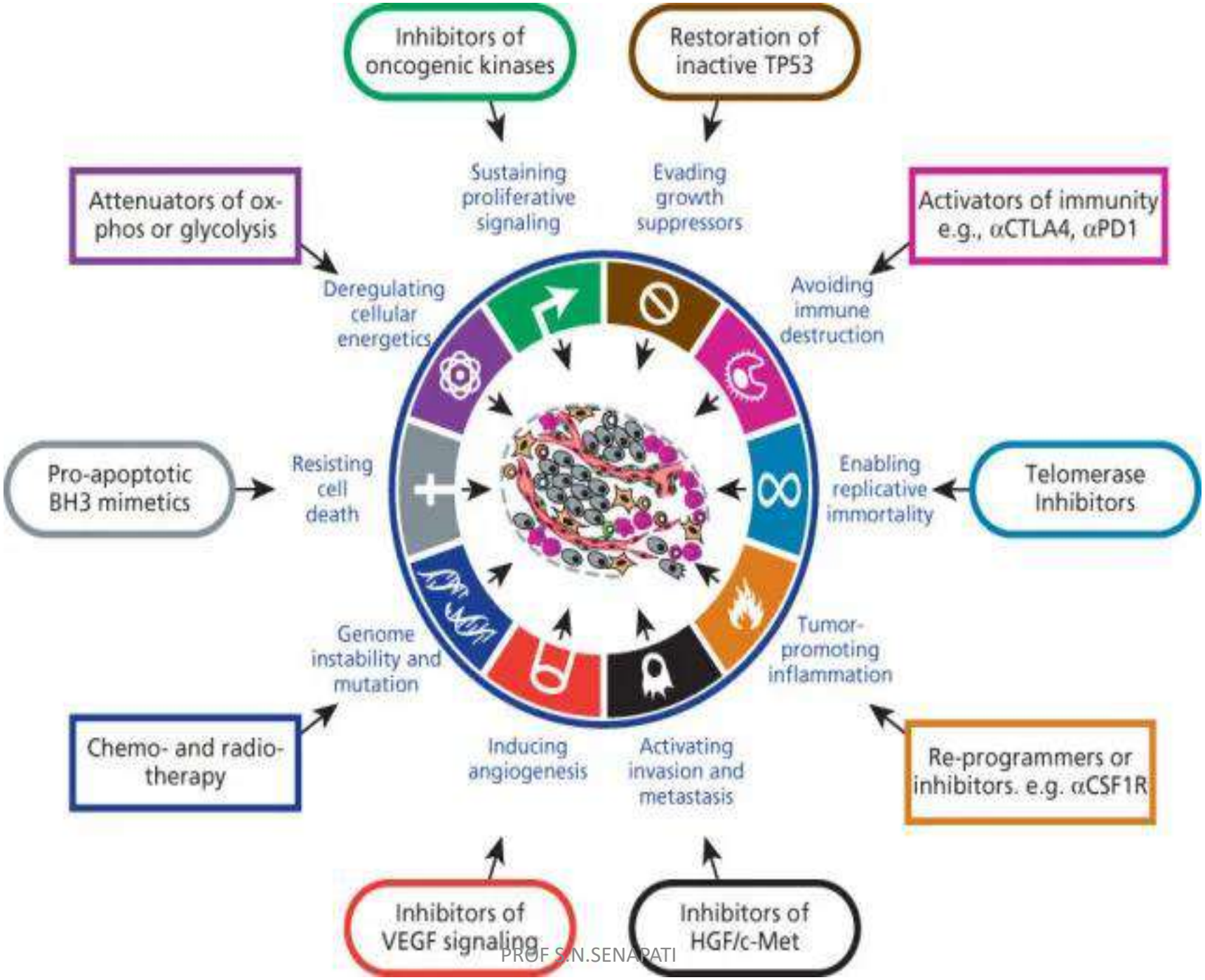
INCREASE ANTI-APOPTOTIC SIGNALS, DECREASE PRO-APOPTOTIC SIGNALS

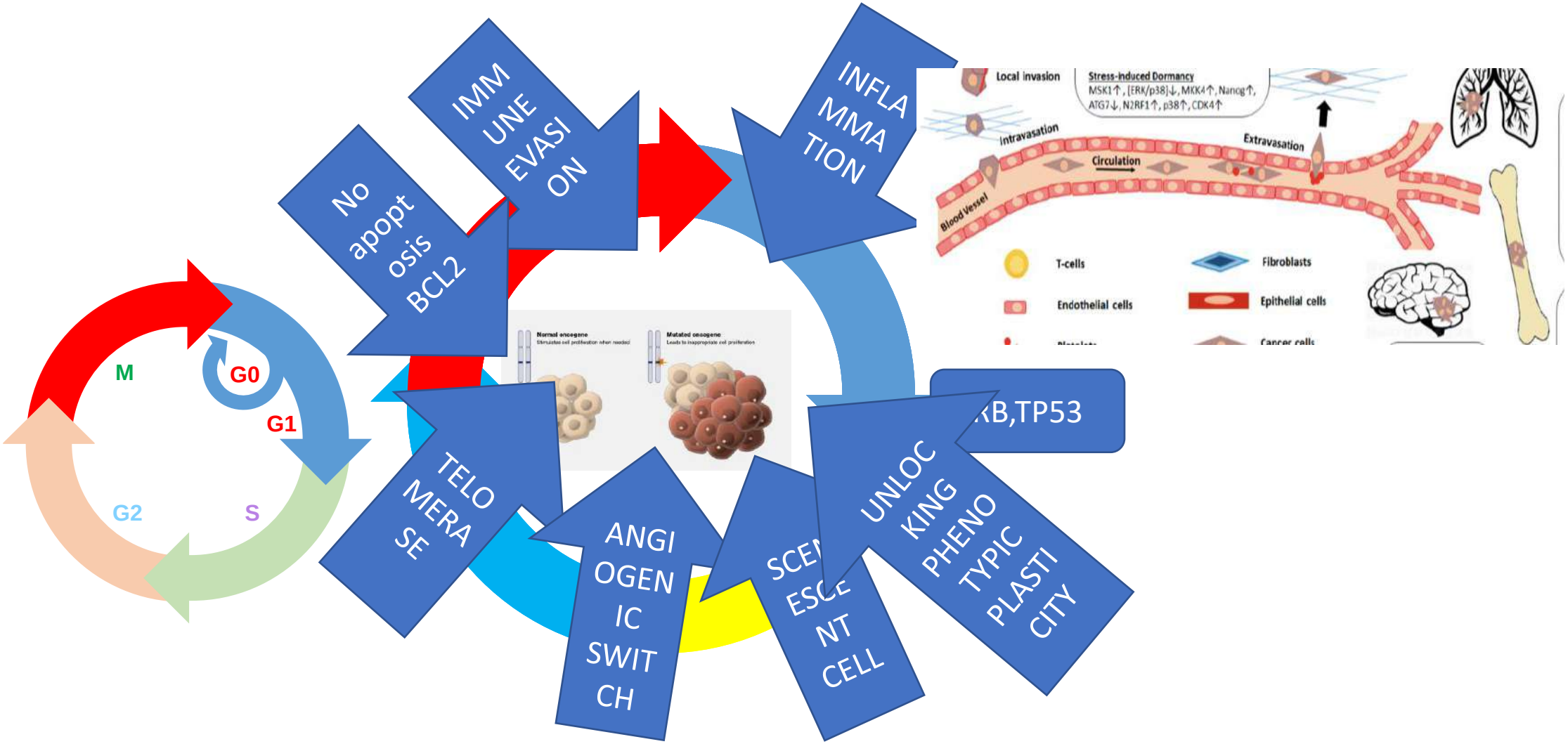
HGF, MMP9 E-cadherin, TIMP1, LCN2

VEGR,ANG2, MMP9, CYTOKINES, THROMBOSPONDIN

Histone proteins

How can we target cancer?




No apoptosis BCL2
IMMUNE EVASION
INFLAMMATION
M
G0
G1
G2
S
TELOMERASE
ANGIOGENIC SWITCH
UNLOCKING PHENOTYPIC PLASTICITY
Local invasion
Stress-induced Dormancy
Intravasation
Circulation
Extravasation
Blood Vessel
T-cells
Fibroblasts
Endothelial cells
Epithelial cells

THANK YOU