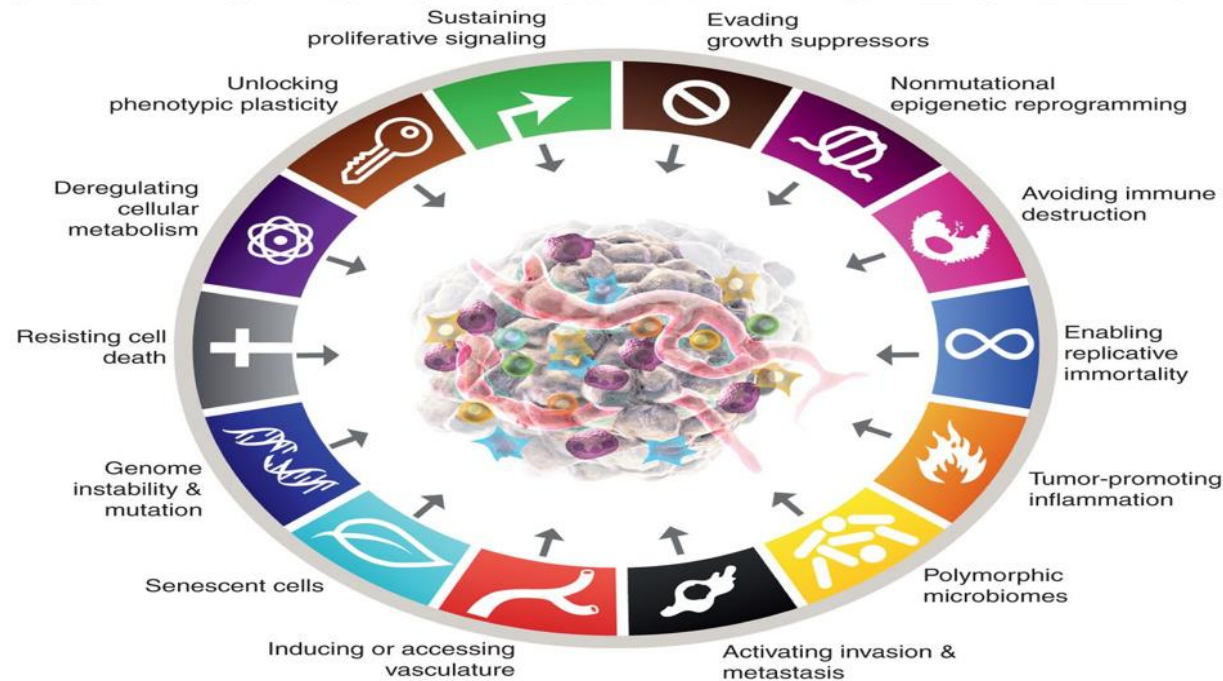


AN INTRODUCTION TO CANCER CELL BIOLOGY AND GENETICS



Dr. SURENDRA NATH SENAPATI

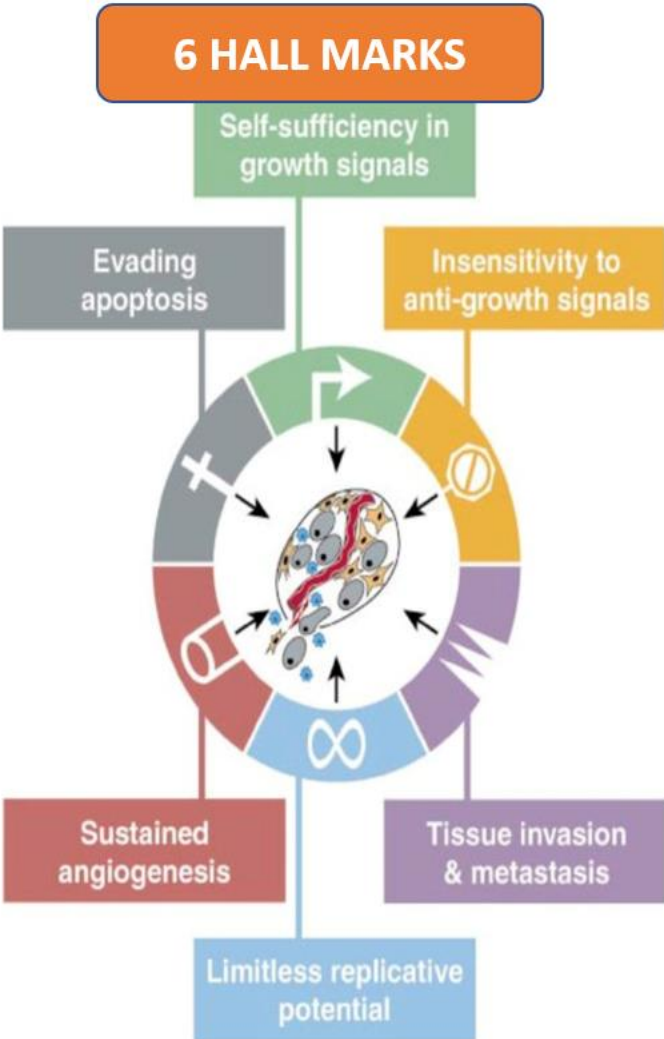
PROFESSOR, DEPARTMENT OF RADIATION ONCOLOGY,

AH POST GRADUATE INSTITUTE OF CANCER,

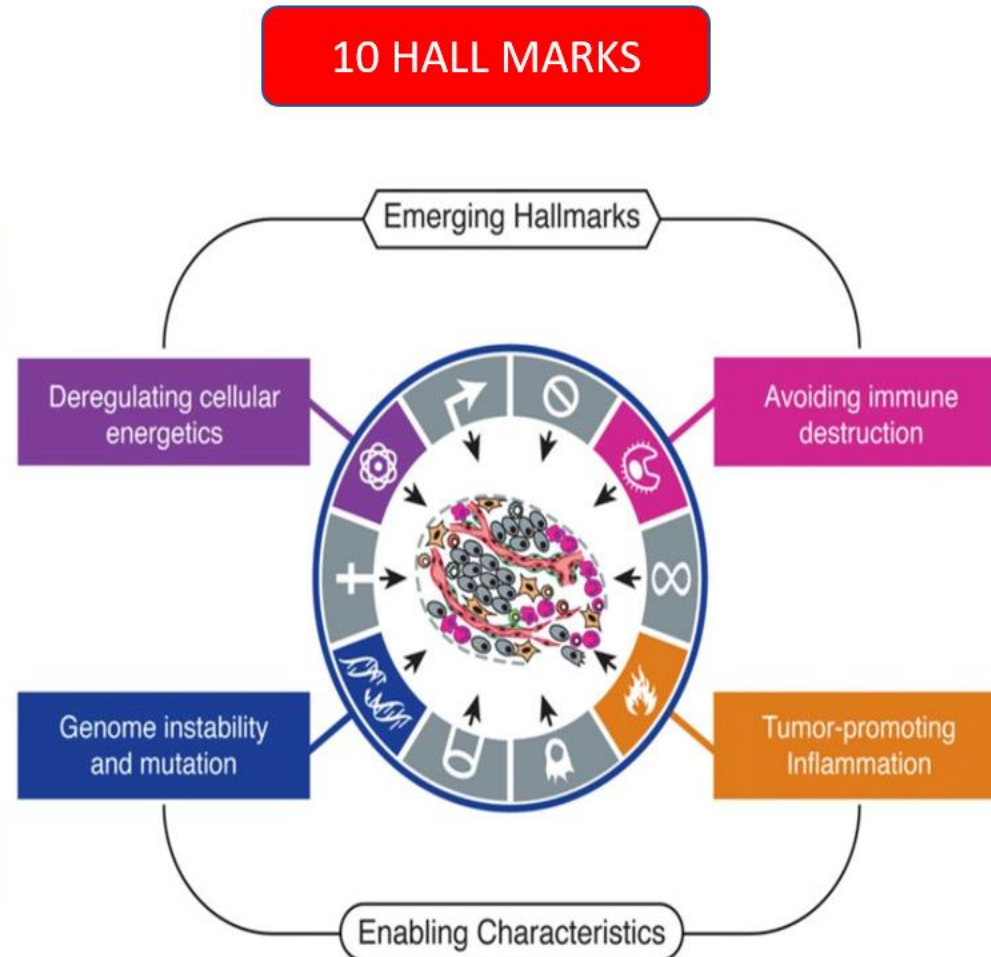
CUTTACK, ODISHA PROF S.N.SENAPATI

Evolution of Hallmarks of Cancer

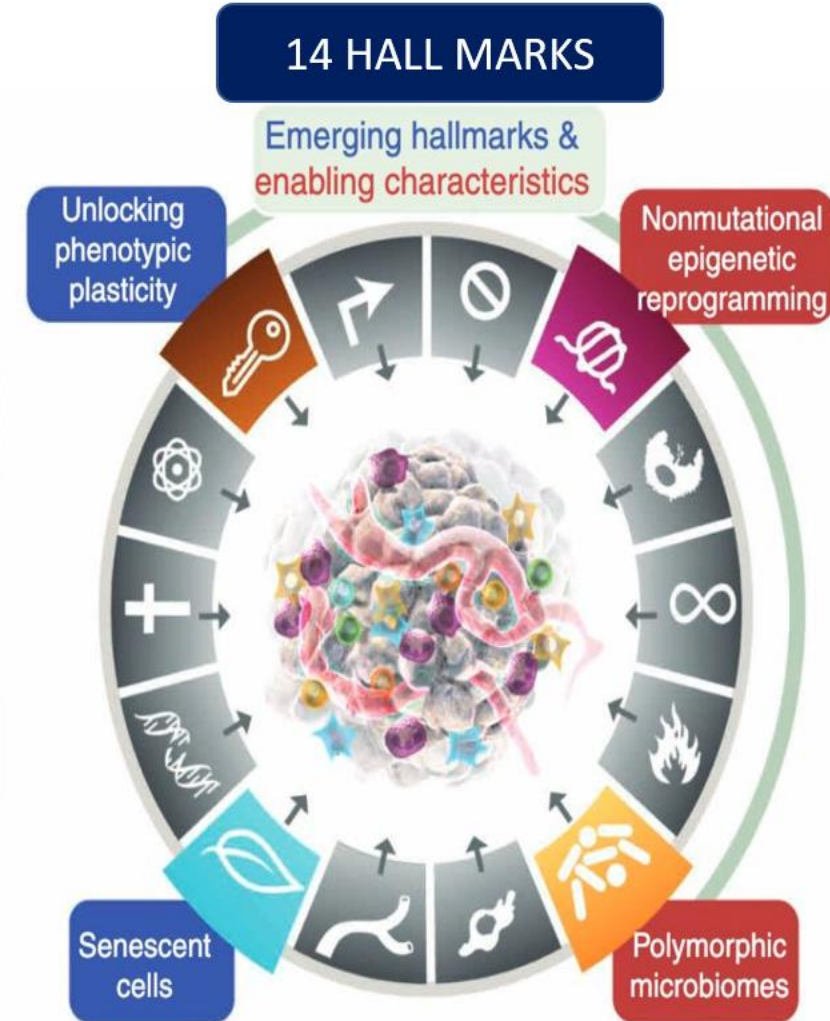
6 HALL MARKS



10 HALL MARKS



14 HALL MARKS



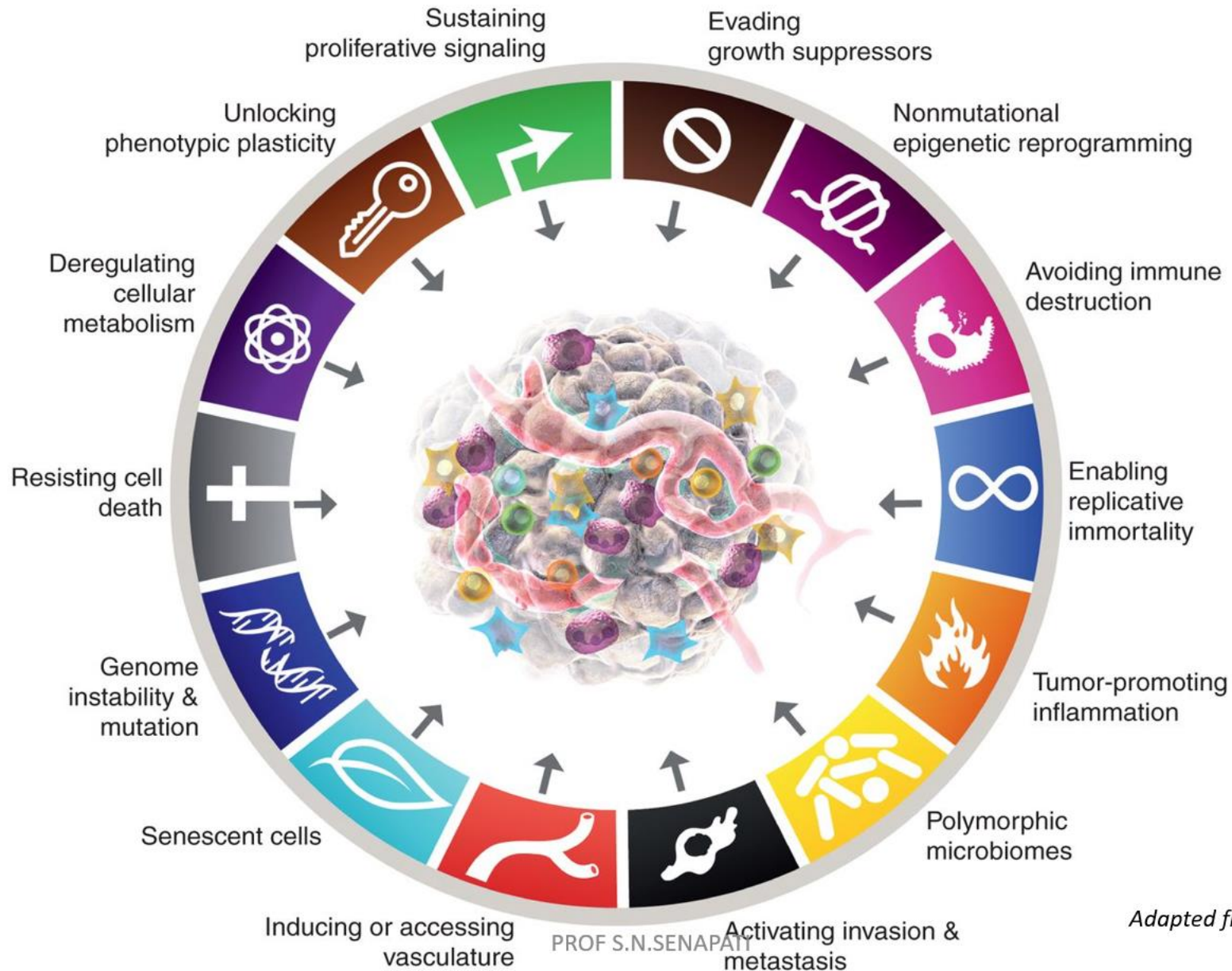
Hanahan and Weinberg. Cell (2000).

Hanahan and Weinberg. Cell (2011).

Hanahan. Cancer Disc (2022).

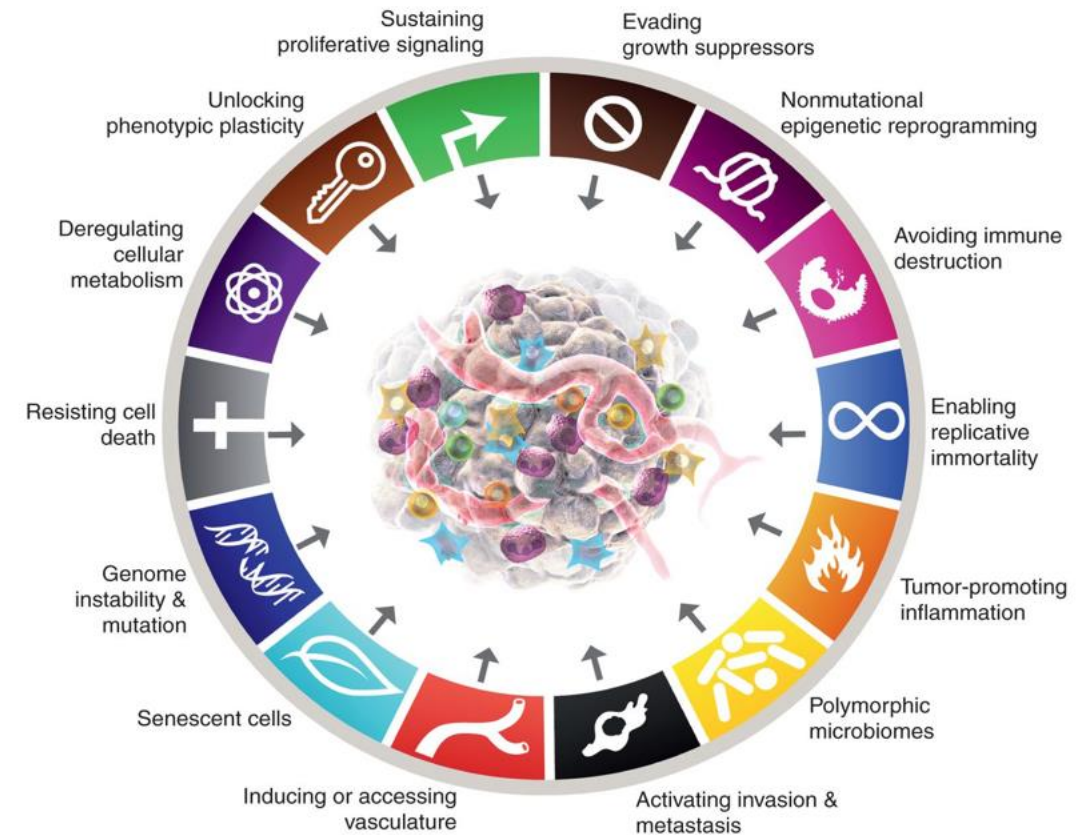
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A more complicated picture



Adapted from Hanahan D et al Cancer Disc 2022

SUSTAINING PROLIFERATIVE SIGNALING



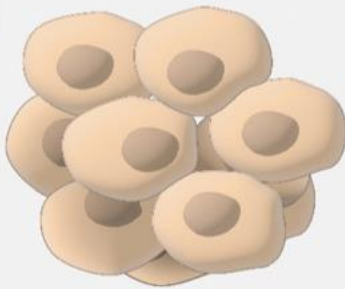
Sustaining proliferative signaling

- 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.



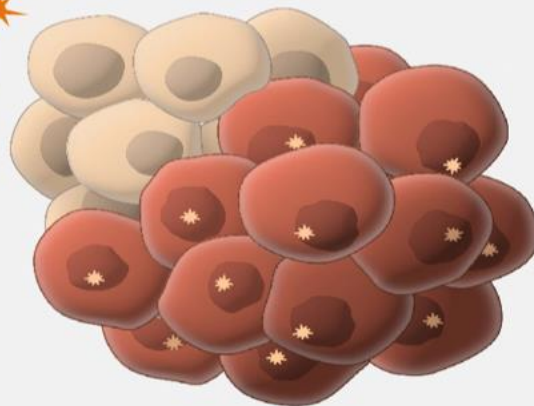
Normal oncogene

Stimulates cell proliferation when needed

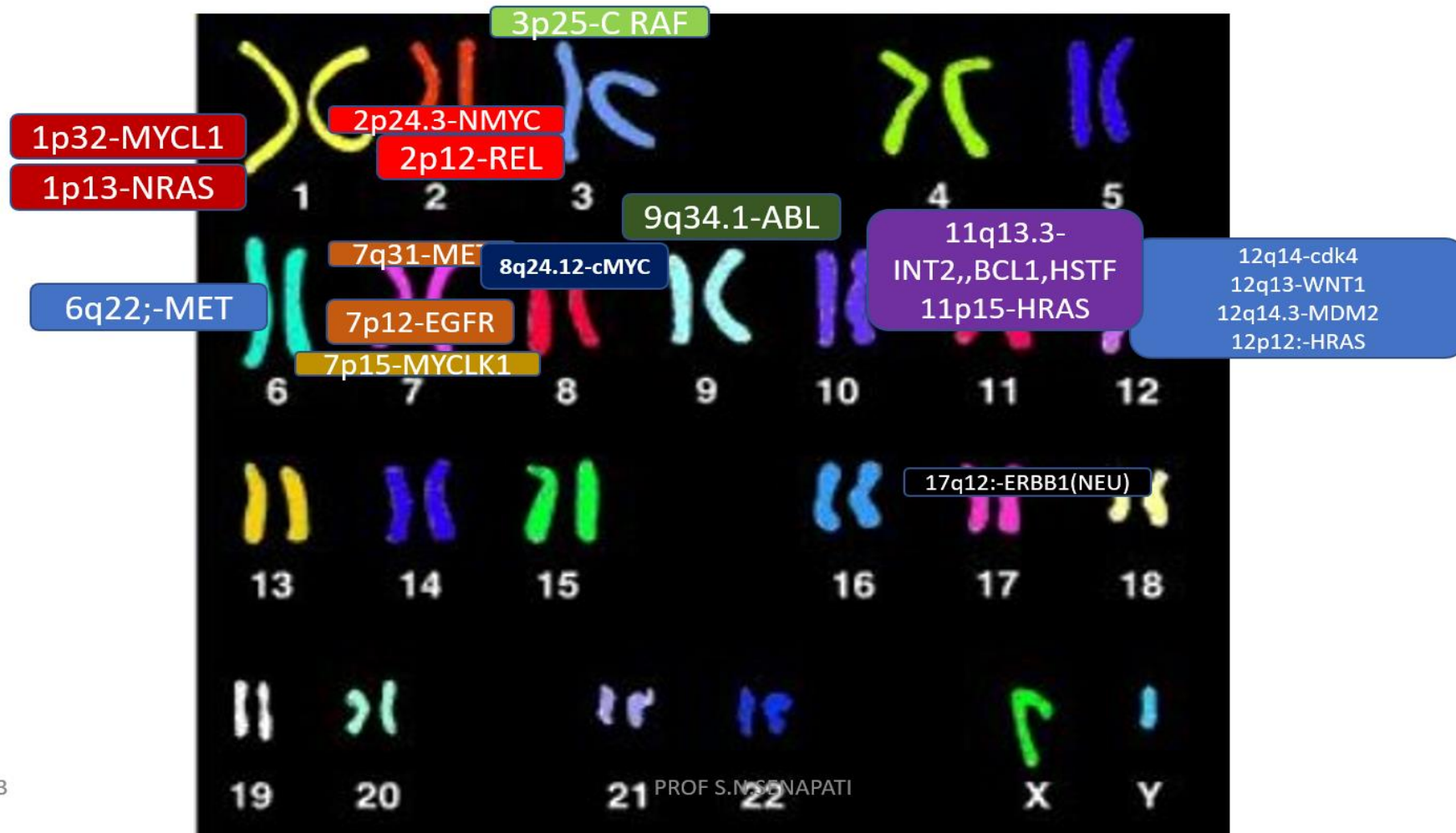


Mutated oncogene

Leads to inappropriate cell proliferation



CHROMOSOME AND ONCOGENES



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Oncogenes

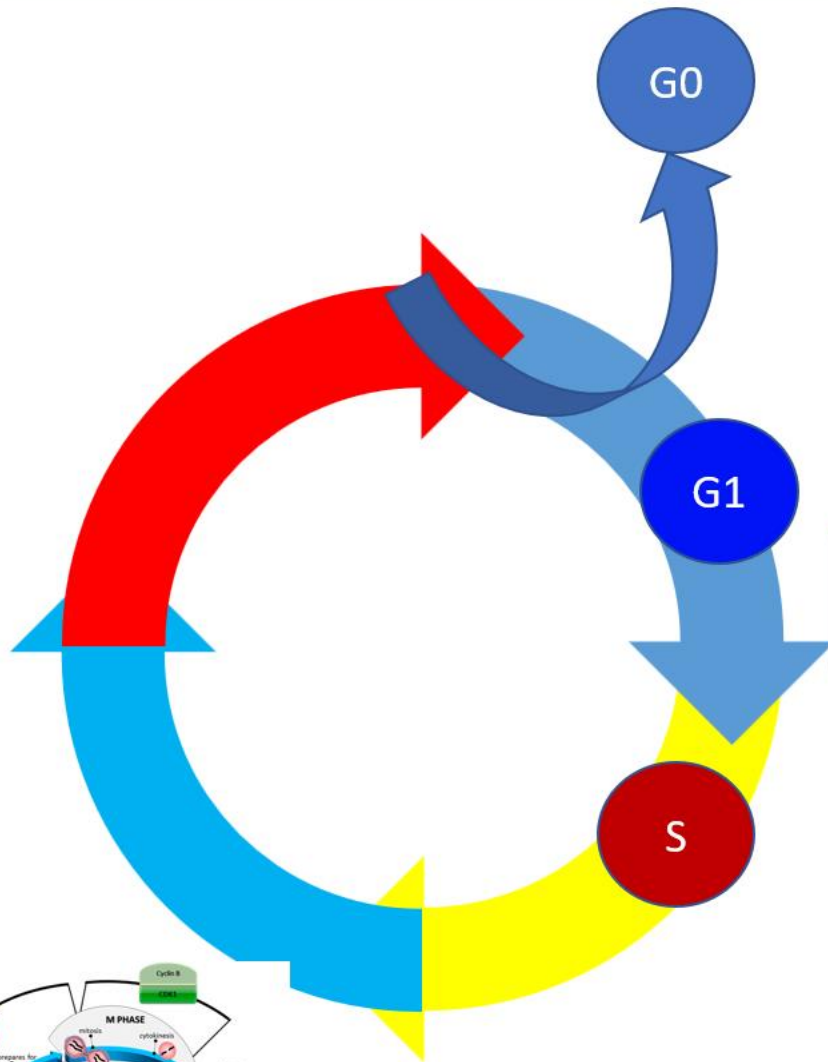
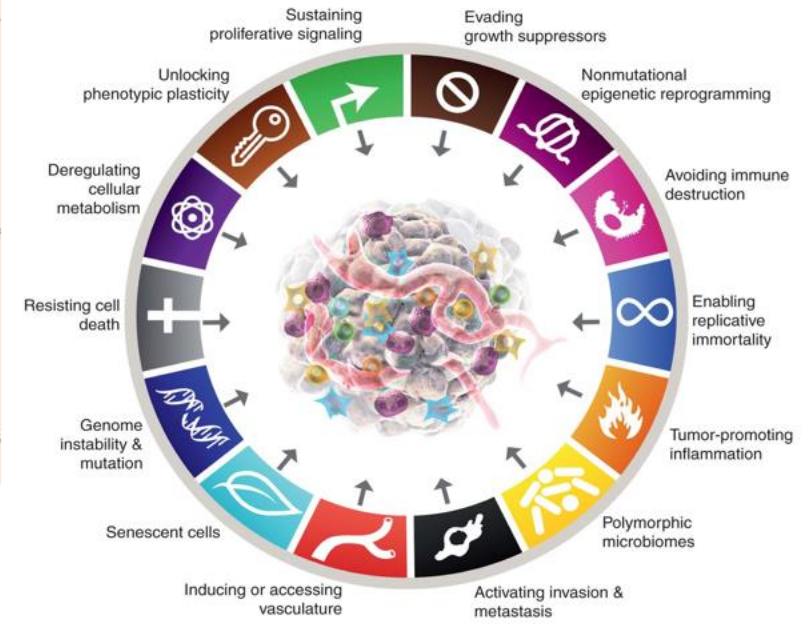
Cellular oncogene	Location	Protein function	Type of cancer
<i>ABL</i>	9q34.1	Protein tyrosine kinase	Chronic myeloid leukemia
<i>BCL1</i>	11q13.3	G ₁ /S-specific cyclin D1	Breast cancer, squamous cell carcinoma of the head and neck, bladder cancer
<i>CDK4</i>	12q14	Cyclin-dependent kinase	Sarcomas
<i>EGFR/ERBB1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

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

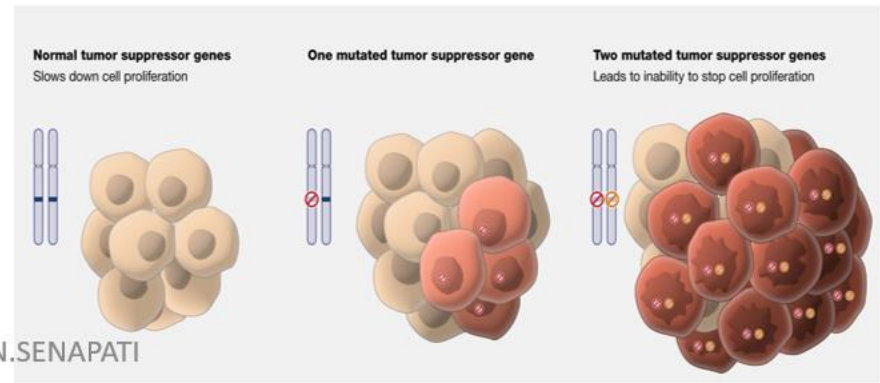
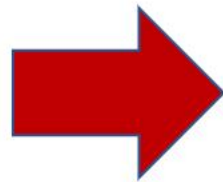


EVADING GROWTH SUPPRESSORS

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	Li-Fraumeni syndrome, carcinomas of oral cavity
APC	5 q 21	Cytoplasm	Unknown	Carcinomas of colon, stomach and pancreas	Familial adenomatous polyposis coli, carcinoma of colon
WT 1	11 p 13	Nucleus	Transcriptional factor	Nephroblastoma	Wilms' tumor
DCC	18 q 21	Cell 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

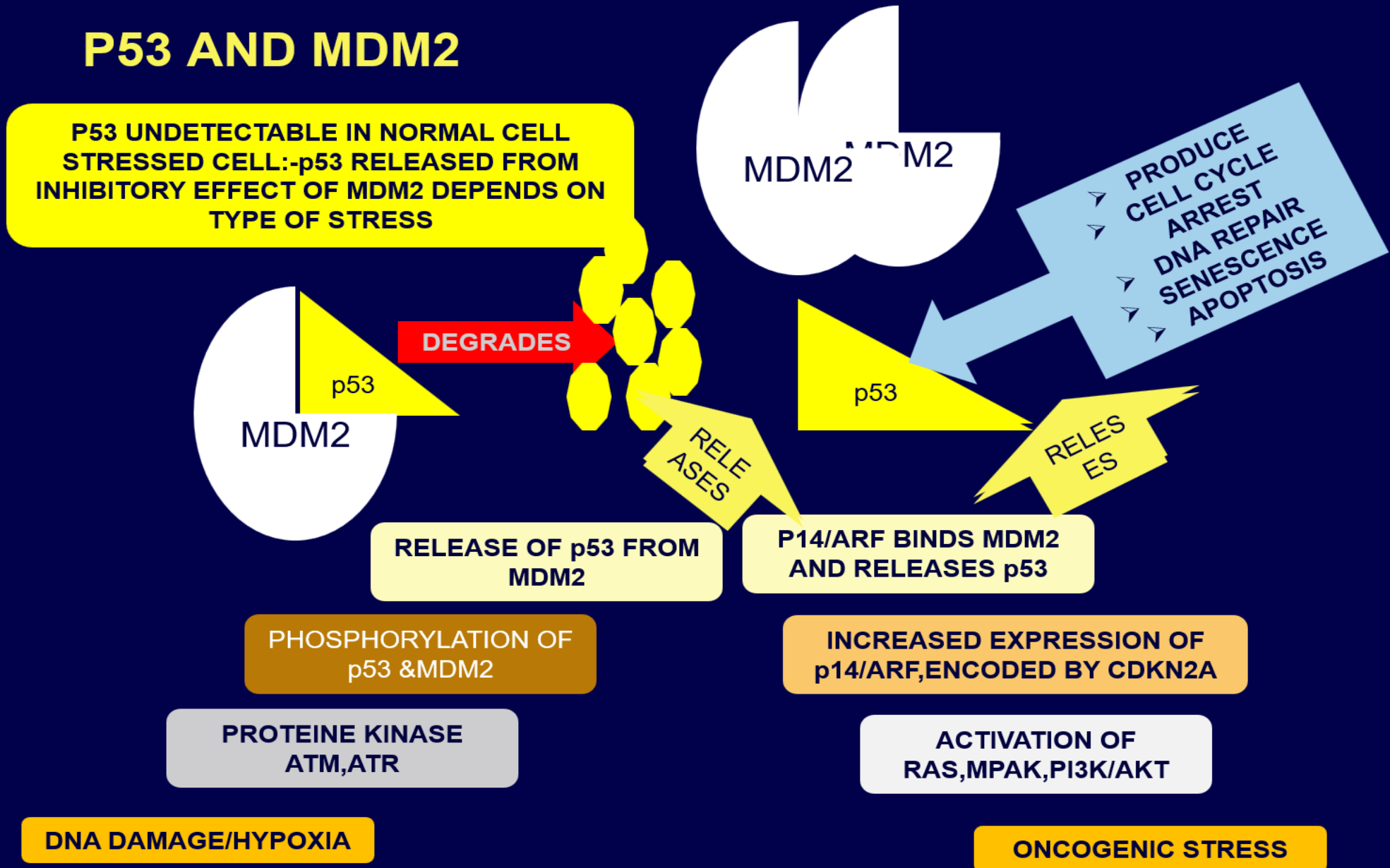


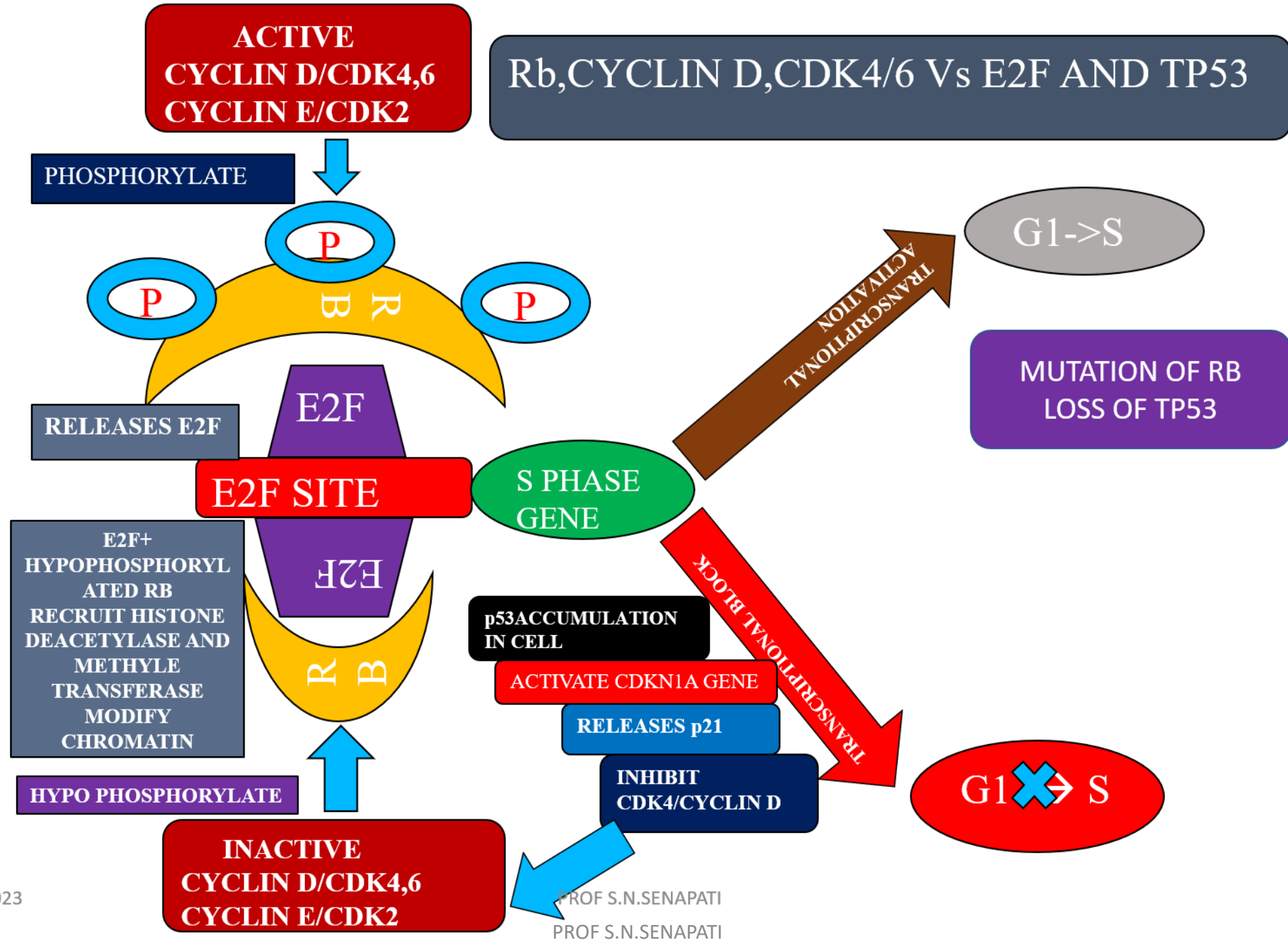
MUTATION OF RB
LOSS OF TP53



P53 AND MDM2

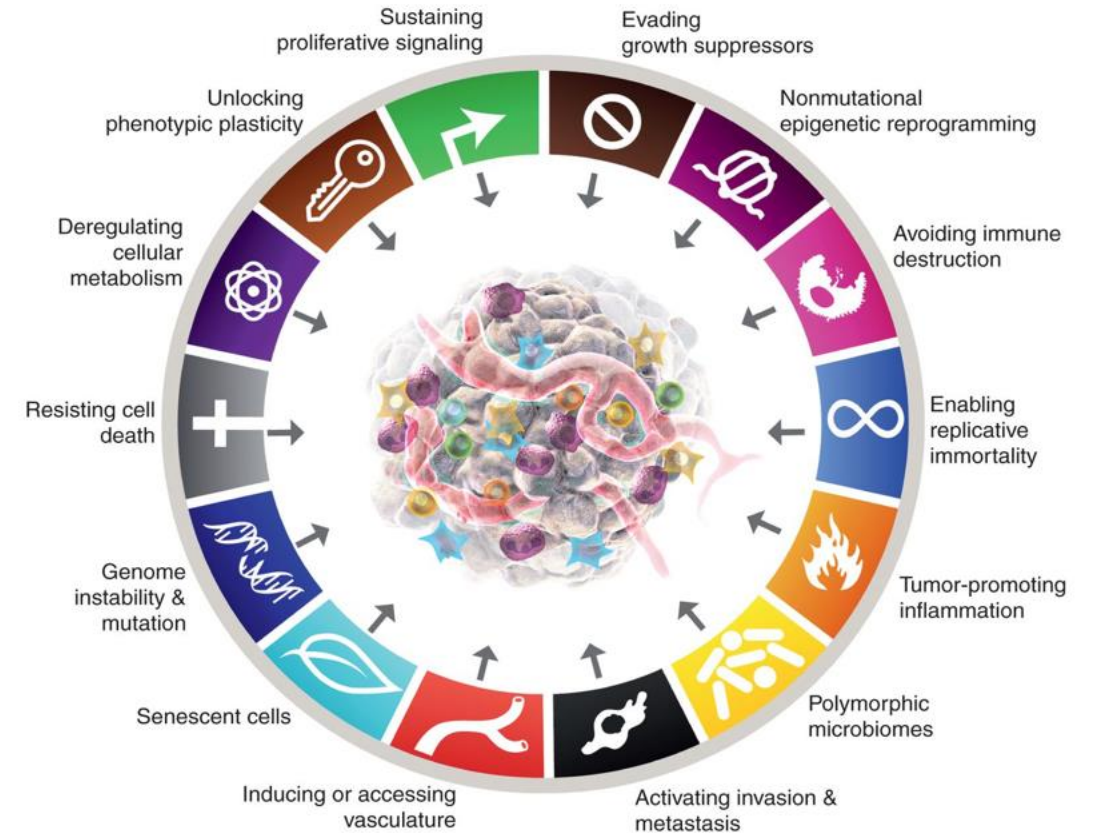
P53 UNDETECTABLE IN NORMAL CELL
STRESSED CELL:-p53 RELEASED FROM
INHIBITORY EFFECT OF MDM2 DEPENDS ON
TYPE OF STRESS



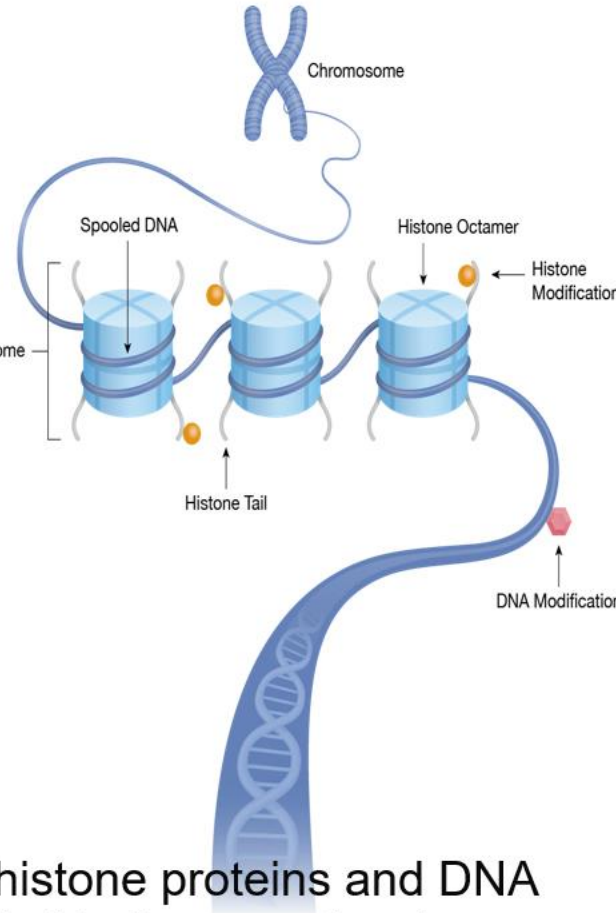
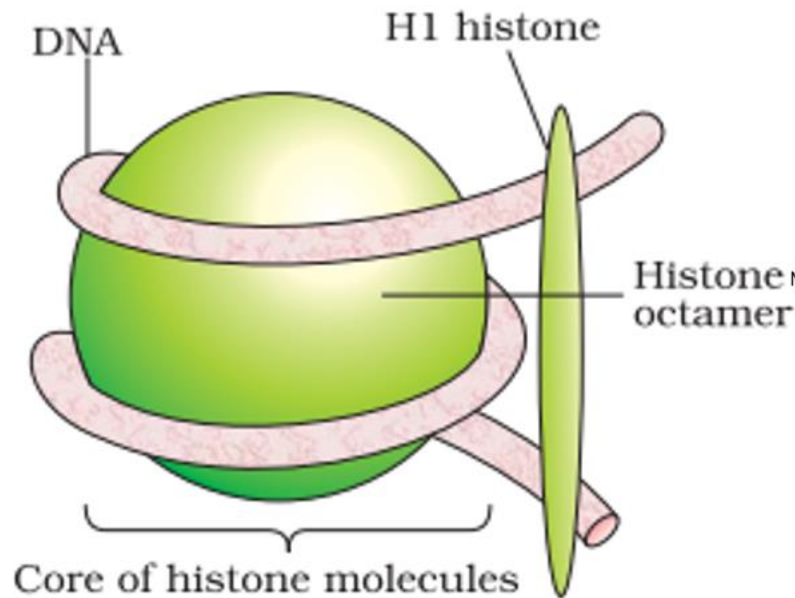


NON-MUTATIONAL EPIGENETIC REPROGRAMMING

(MUTATION LESS CANCER
EVOLUTION
WITHOUT CHANGE IN DNA
SEQUENCE)

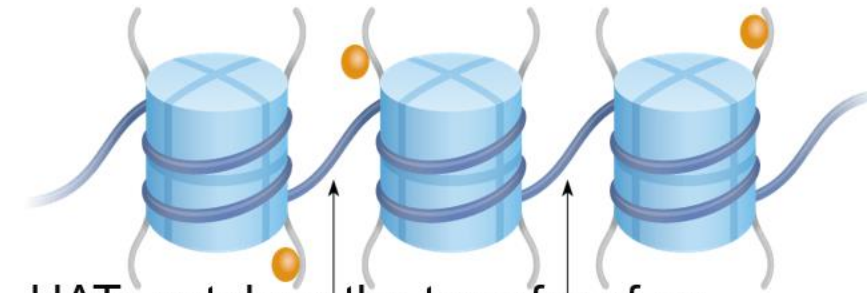


STRUCTURE OF NUCLEOSOM



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

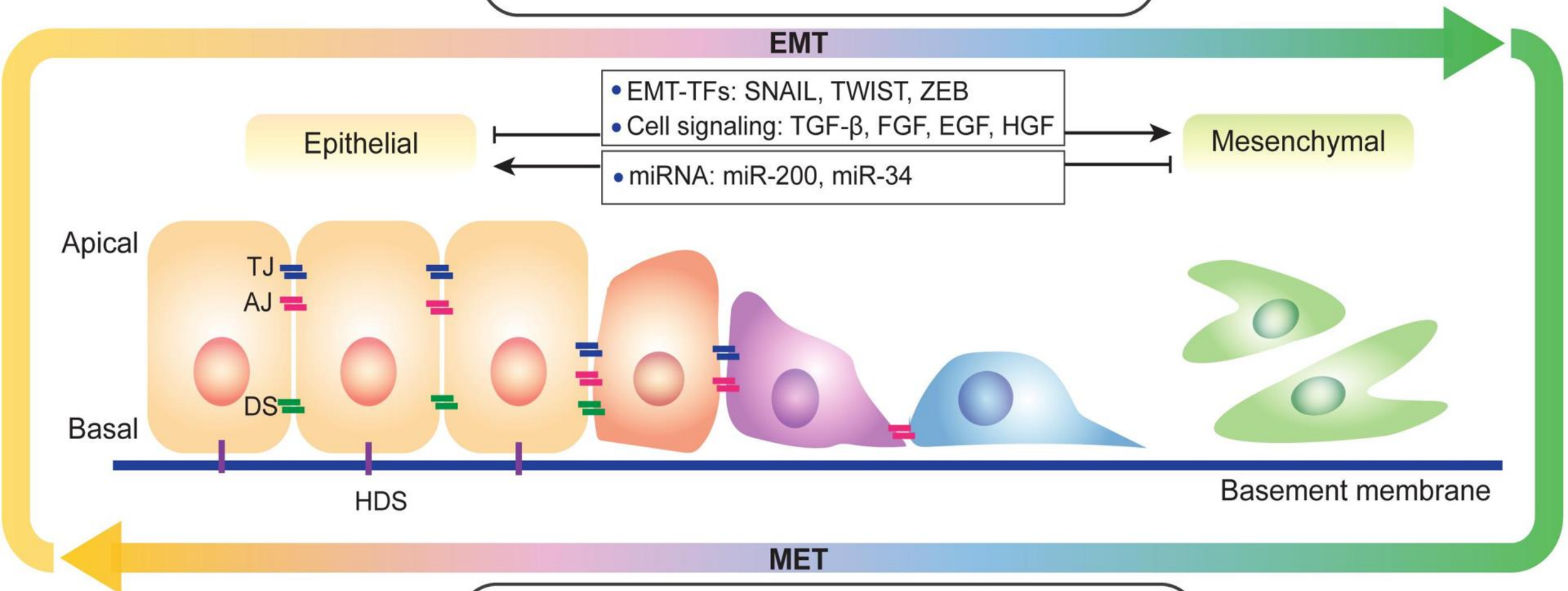


histone deacetylases (HDACs) catalyze the removal of acetyl groups from histones, leading to more tightly packaged (transcriptionally inactive) chromatin

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**

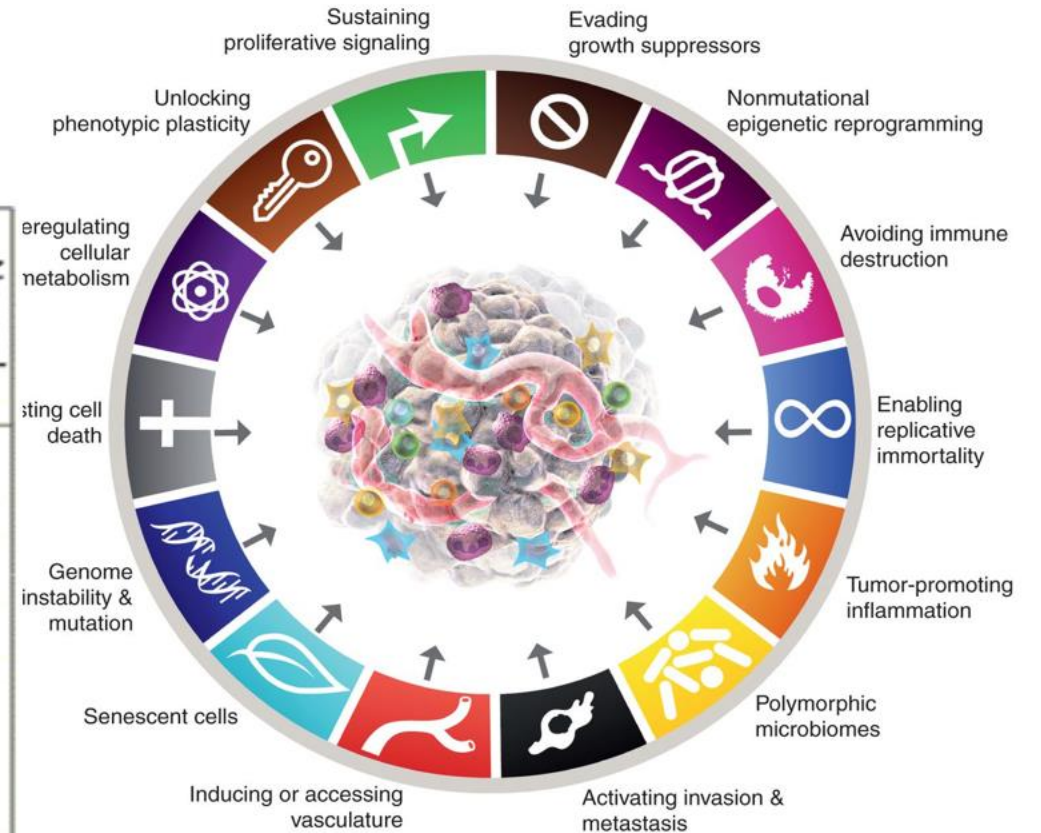
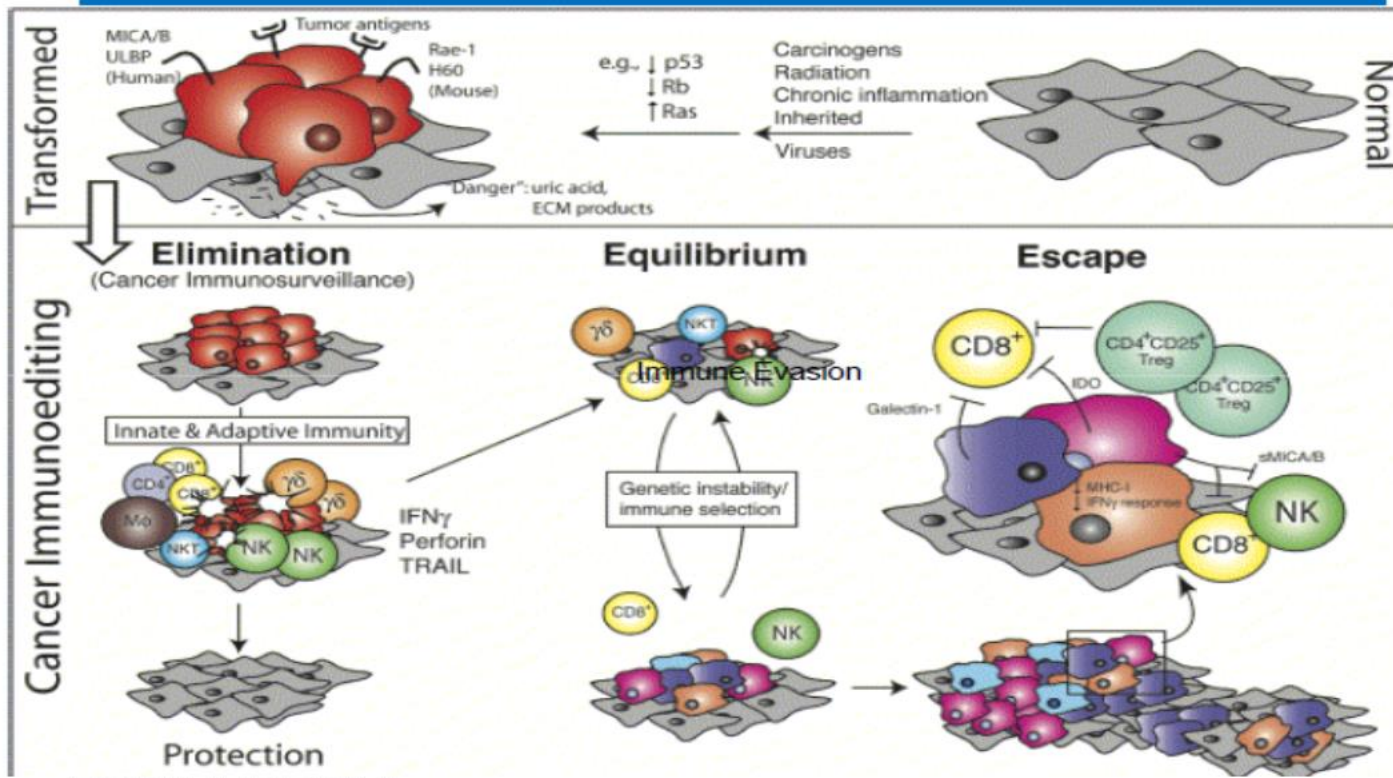
- Embryo development
- Wound healing
- Cancer metastasis
- Fibrosis



- Organ formation
- Epithelial homeostasis
- Metastatic colonization
- Reprogramming to iPSCs

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.

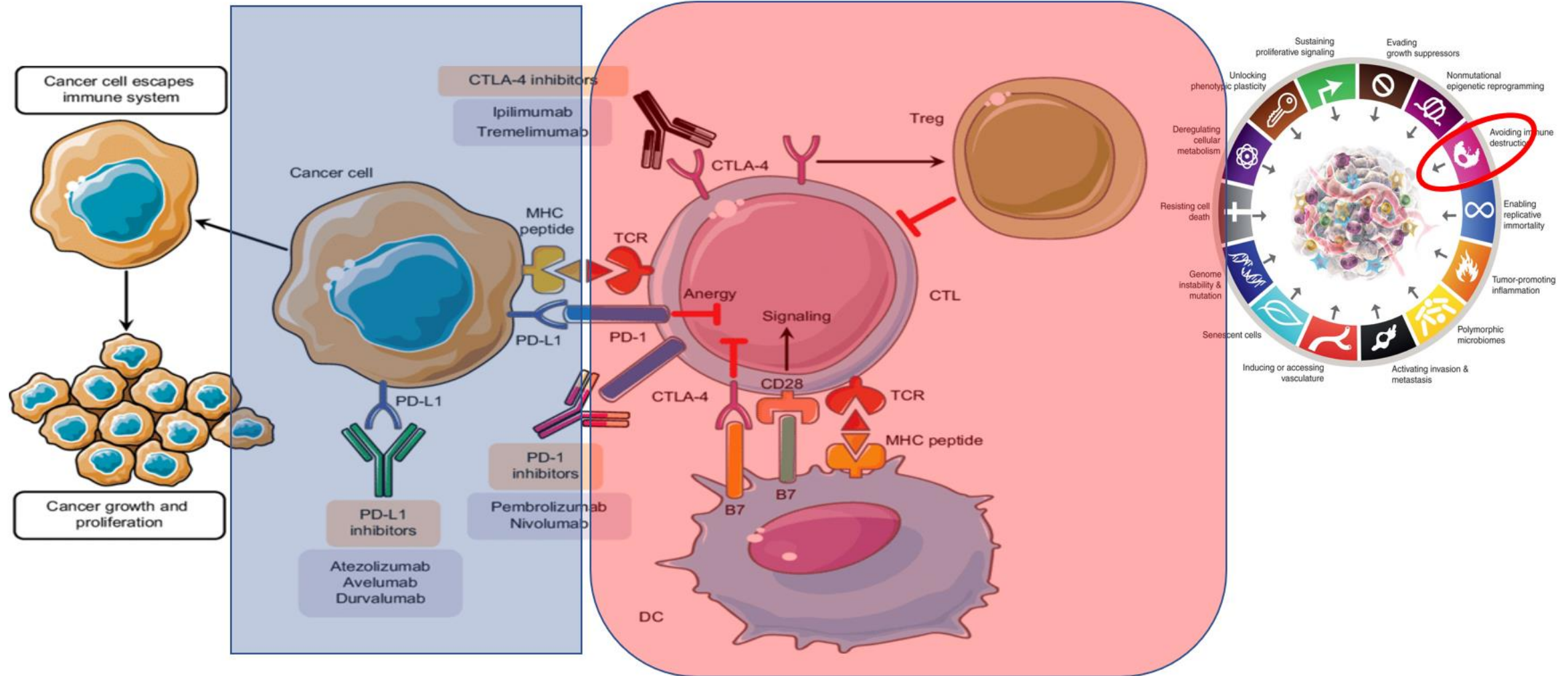


EQUILLIBRIUM

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

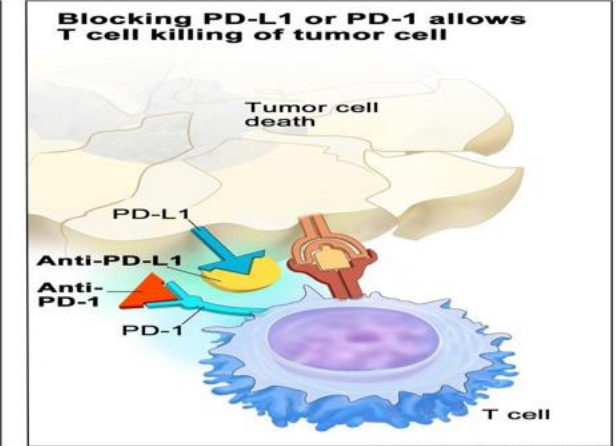
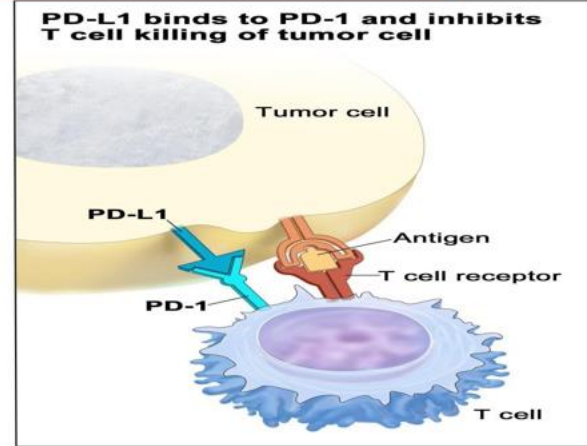
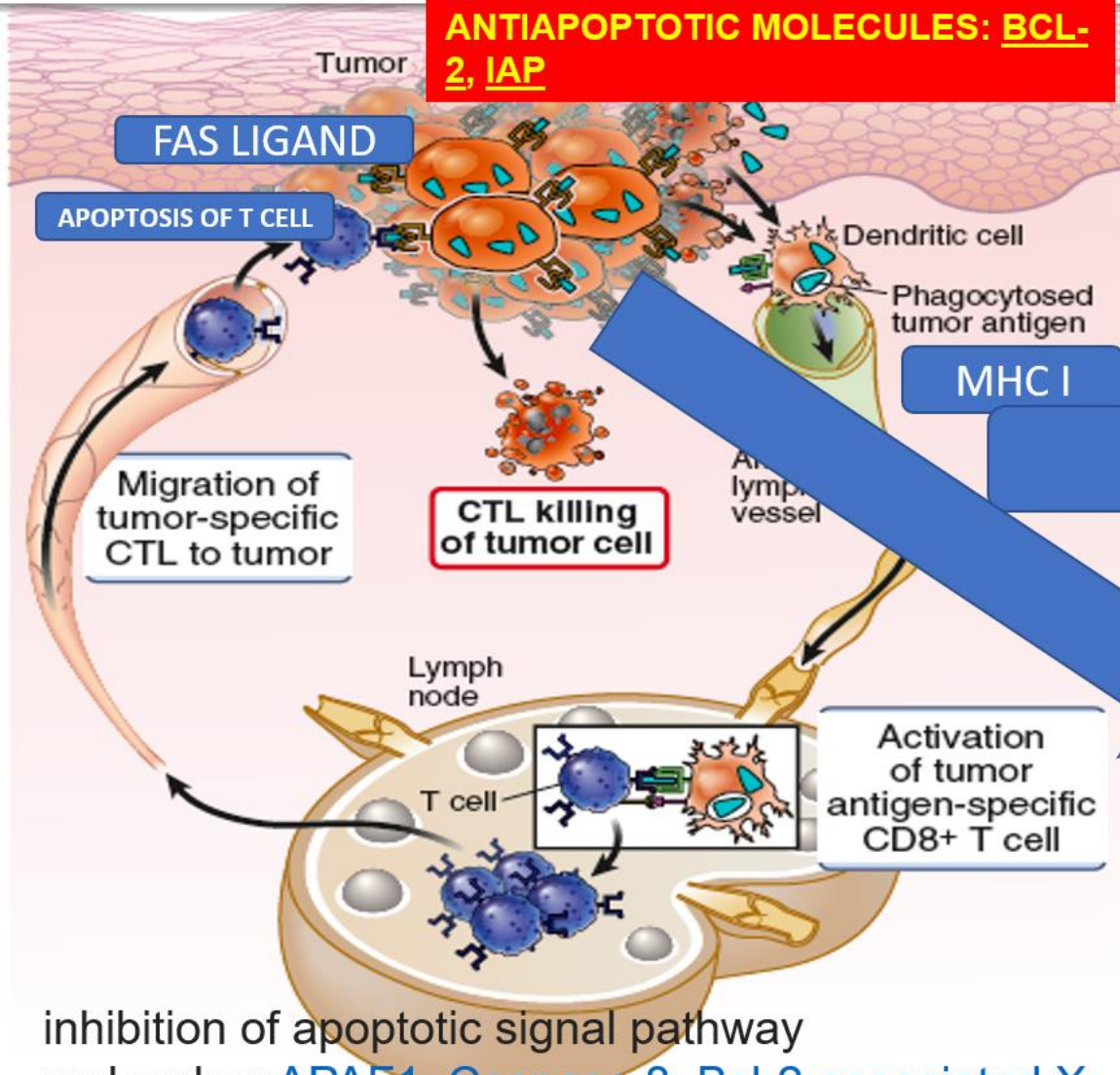
IMMUNE EVASION

IMMUNE SURVEILLANCE



TUMOR EVASION

OVEREXPRESSION OF ANTIAPOPTOTIC MOLECULES: BCL-2, IAP



**MUTATION OF MHC I GENE –LOWER EXPRESSION OF MHC
DEFECT IN ANTIGEN PRESENTATION!**

MICRO ENVIRONMENT

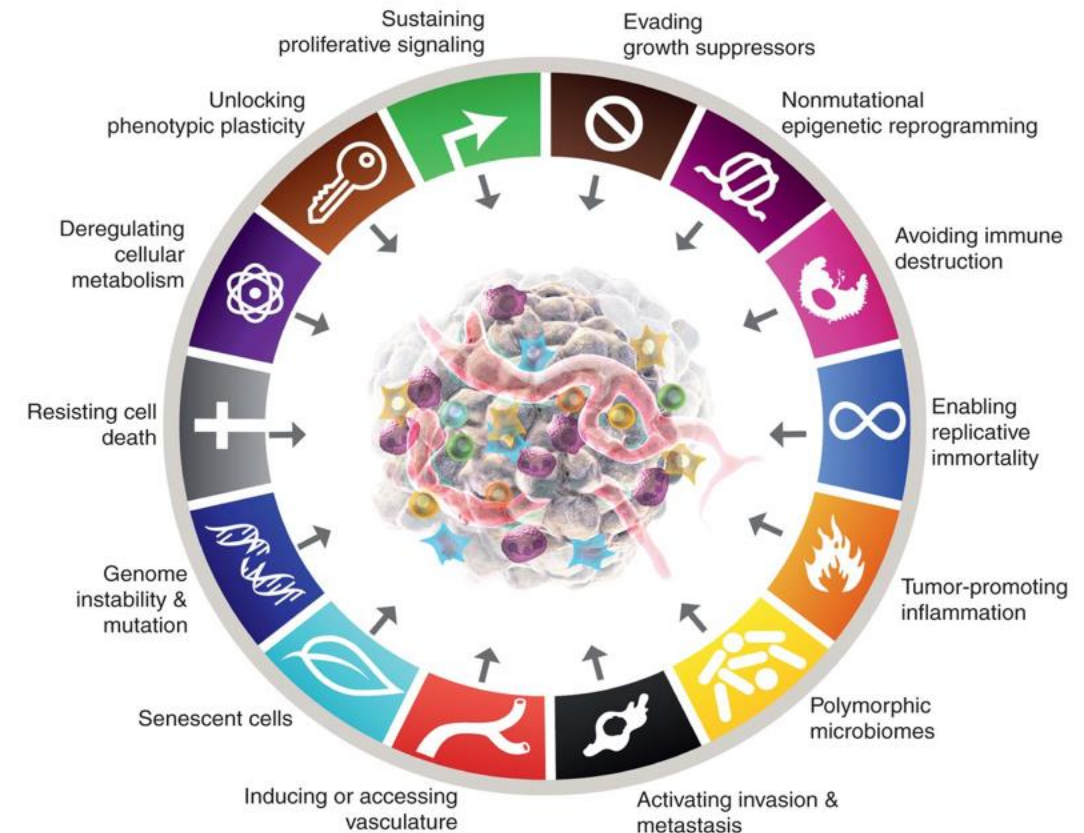
TGF- β :- CONVERSION OF CD4+ T CELL INTO SUPPRESSOR REGULATORY T CELL WHICH IS IMMUNOSUPPRESSIVE

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

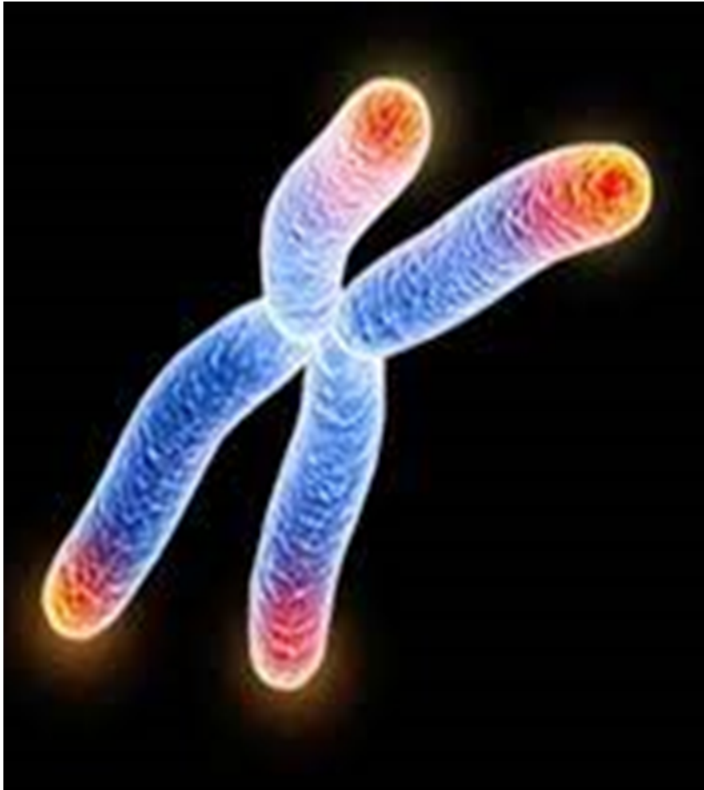
inhibition of apoptotic signal pathway
molecules: APAF1, Caspase 8, Bcl-2-associated X protein (bax) and Bcl-2 homologous antagonist killer (bak). [citation needed]

ENABLING REPLICATIVE IMMORTALITY

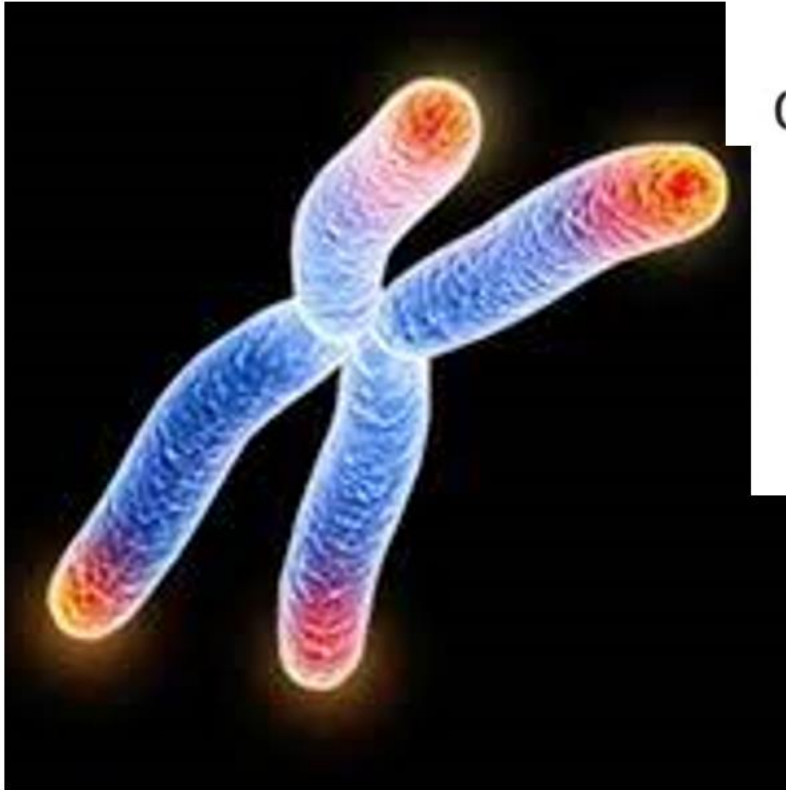
- NORMAL CELLS HAVE A FINITE REPLICATIVE ABILITY
- CANCER CELLS OVERCOME THIS BY:-
- OVEREXPRESSING TELOMERASE, AN ENZYME THAT MAINTAINS TELOMERE LENGTH, WHICH PROTECTS THE ENDS OF CHROMOSOMES AND ALLOWS THE CELL TO CONTINUE PROLIFERATING.
- THIS PROCESS IS ALSO AIDED IN PART BY THE LOSS OF TUMOR-SUPPRESSOR 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



Senescence or cell death

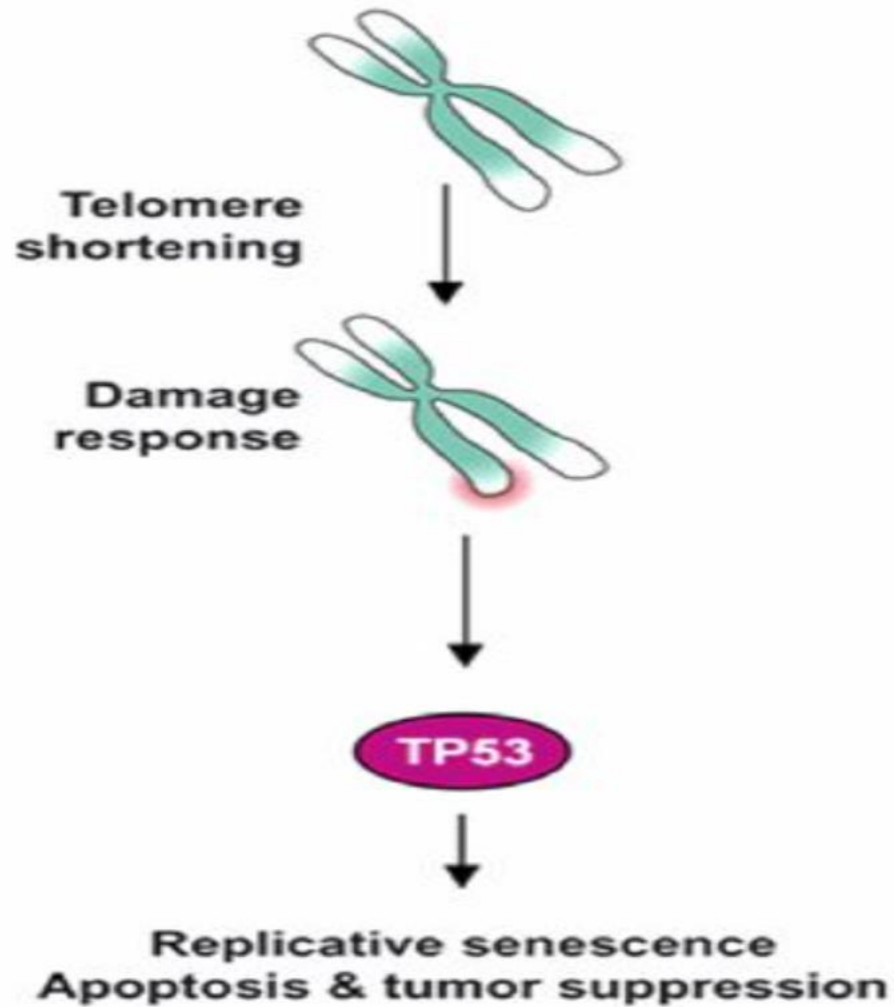
Normal somatic cells lose telomeres with cell division

(c) Telomerase is reactivated in most cancers

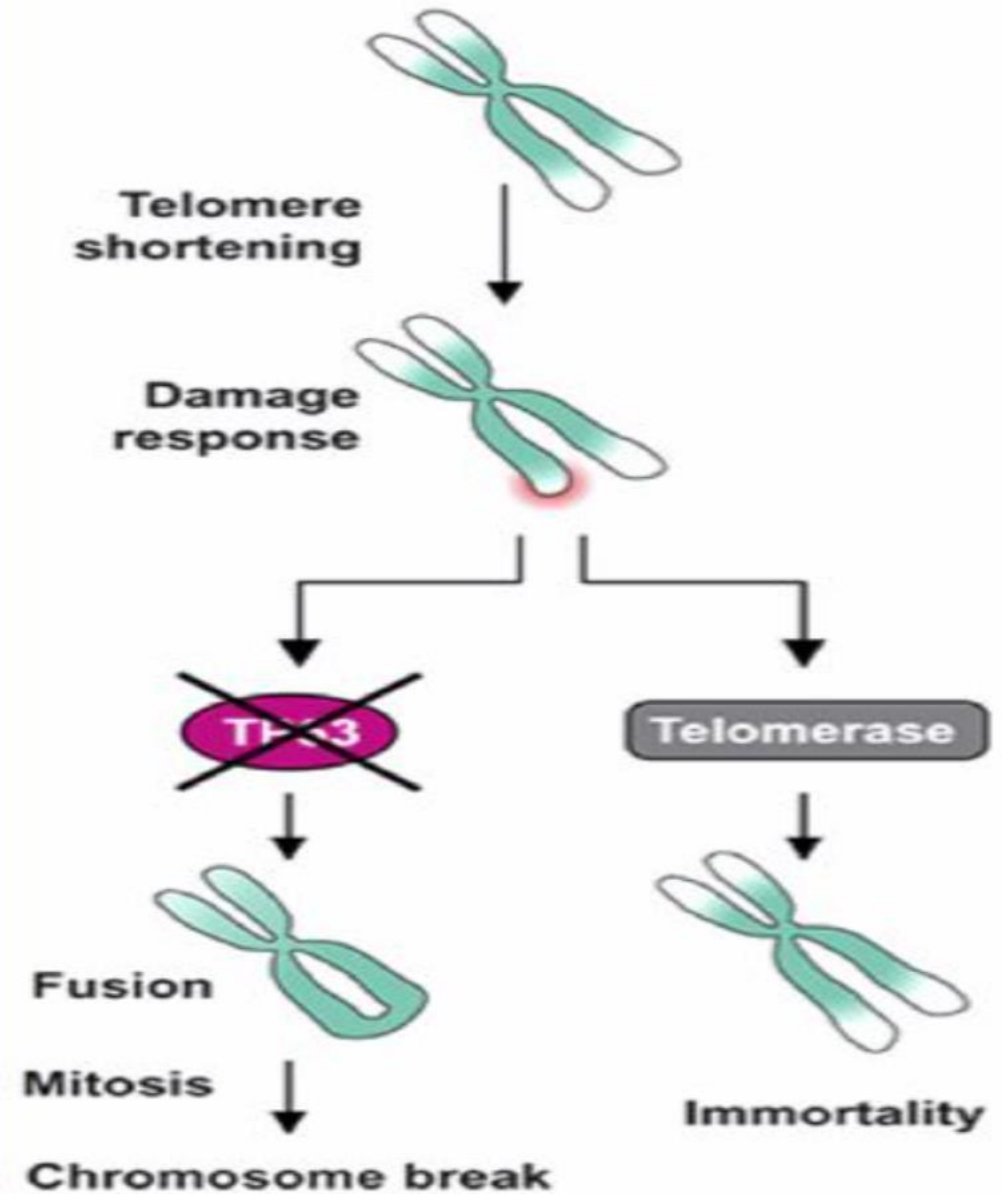
This elevated TA in cancer cells maintains their TL



Normal cell

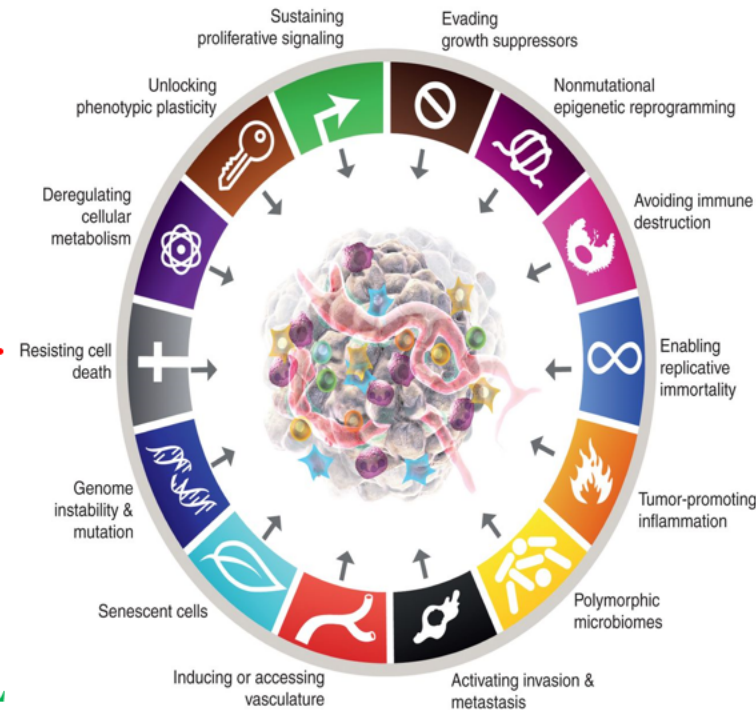


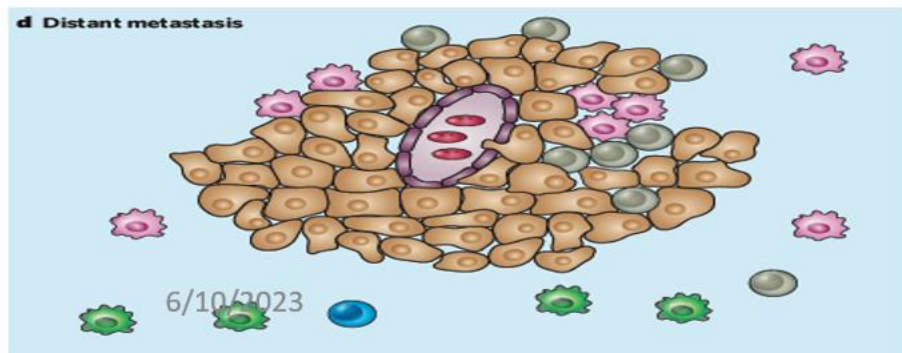
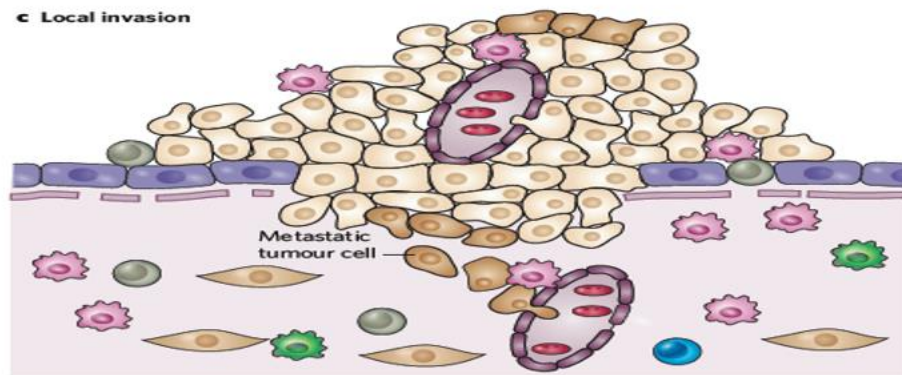
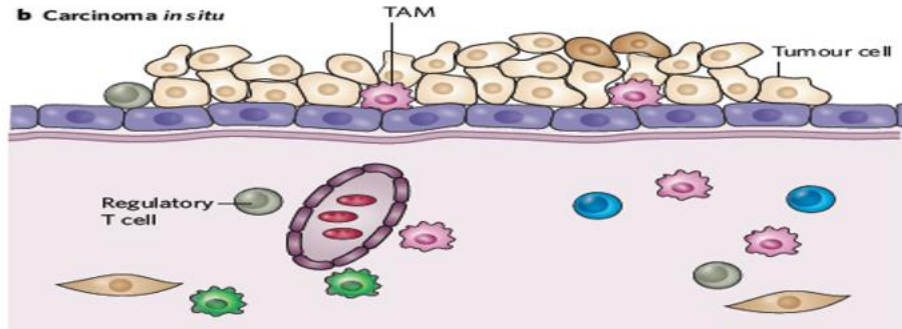
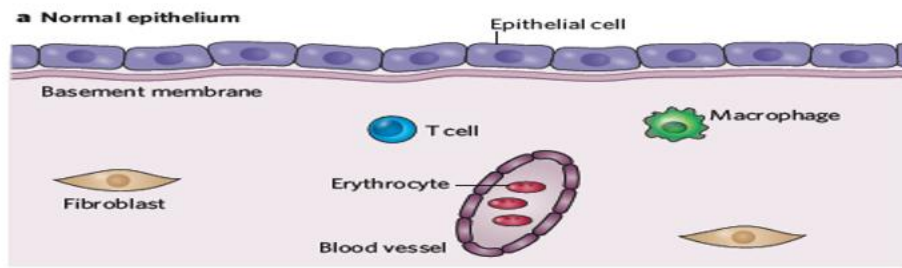
Cancer cell



TUMOUR PROMOTING INFLAMMATION

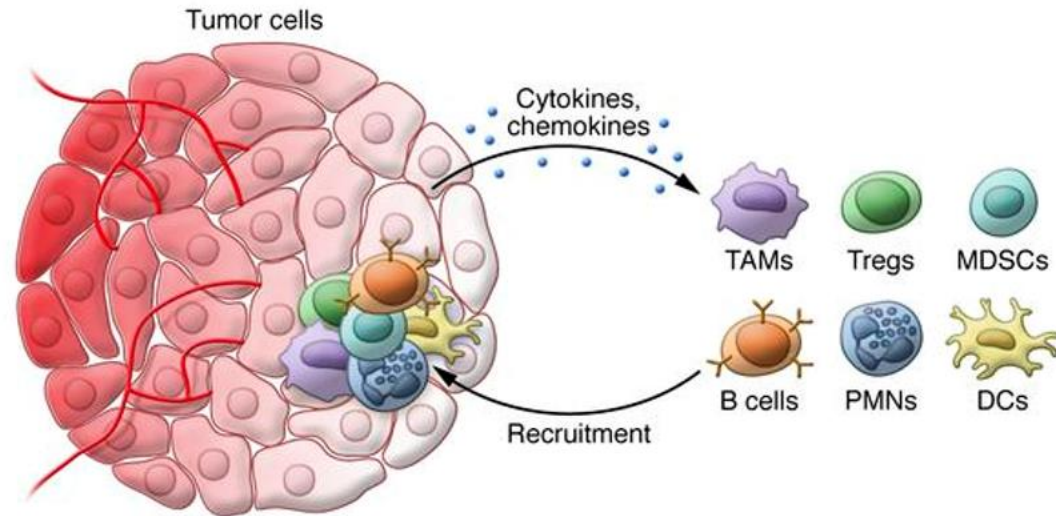
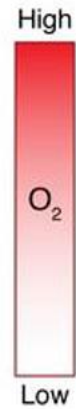
- **THE TUMOR MICROENVIRONMENT IS OFTEN INFILTRATED BY INNATE AND ADAPTIVE IMMUNE SYSTEM CELLS THAT ENABLE TUMORS TO MIMIC INFLAMMATORY CONDITIONS SEEN IN NORMAL TISSUES.**
- **TUMOR-ASSOCIATED INFLAMMATION MIGHT AID IN TUMOR GROWTH. BY SUPPLYING THE TUMOR MICROENVIRONMENT WITH**
 - **GROWTH FACTORS**
 - **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.**



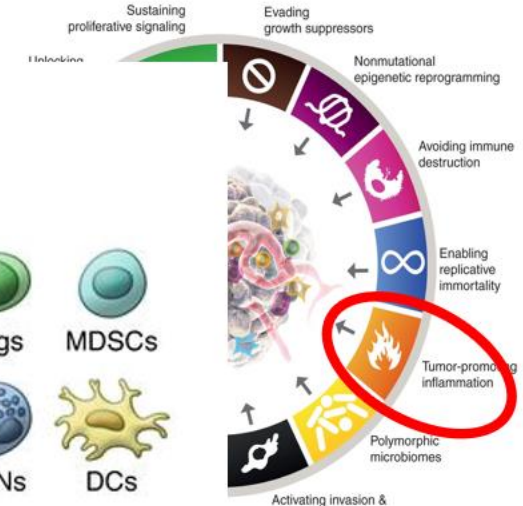
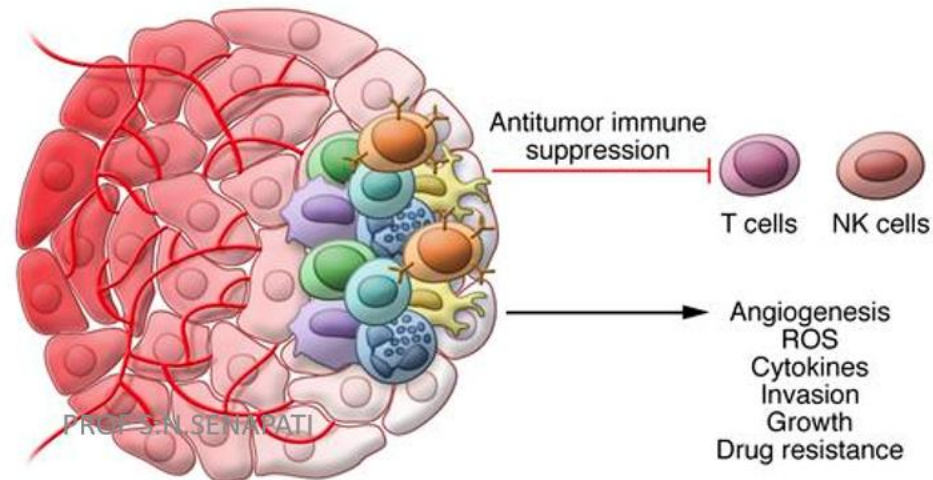


Tumour promoting Inflammation

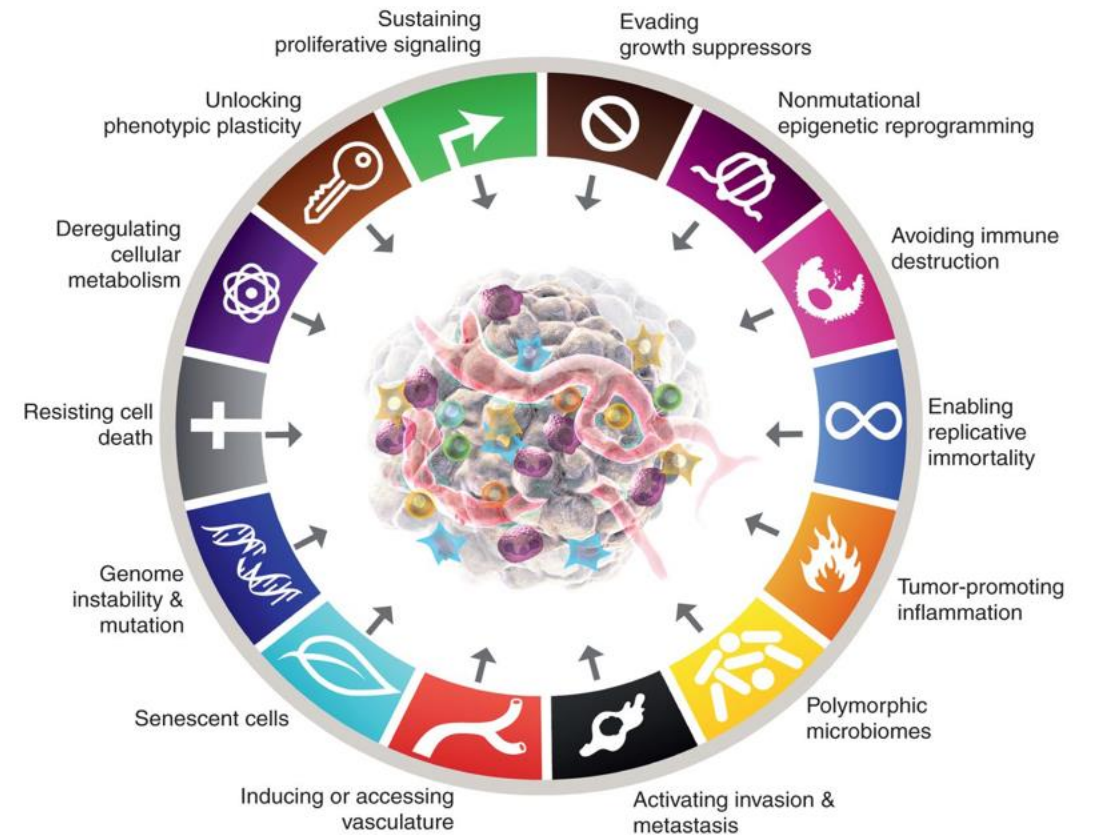
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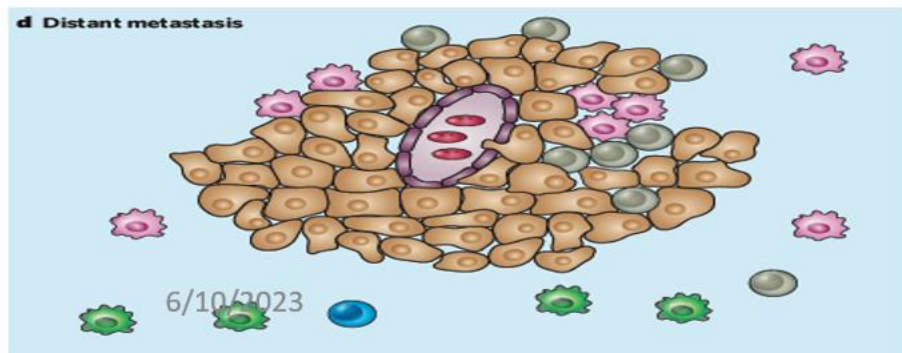
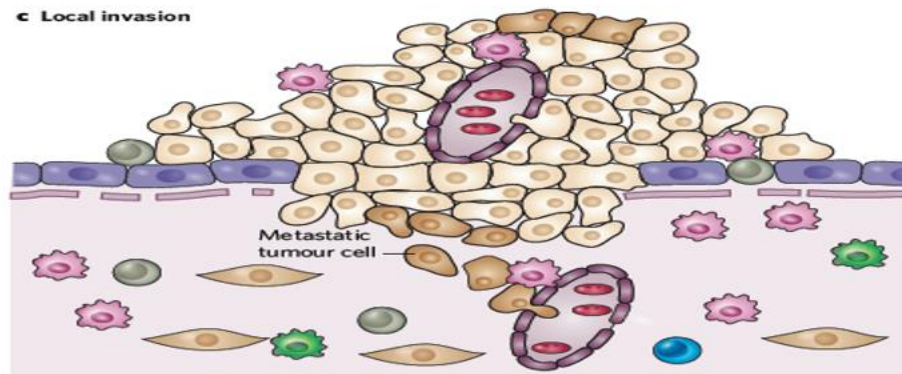
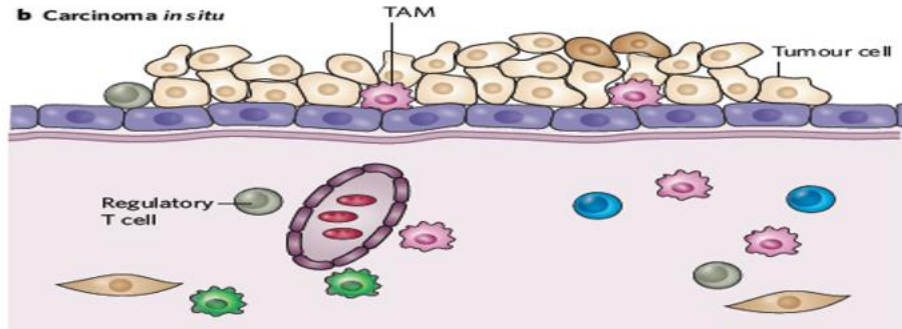
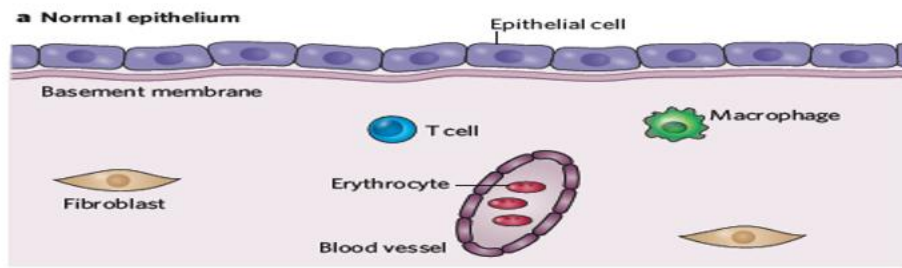


B



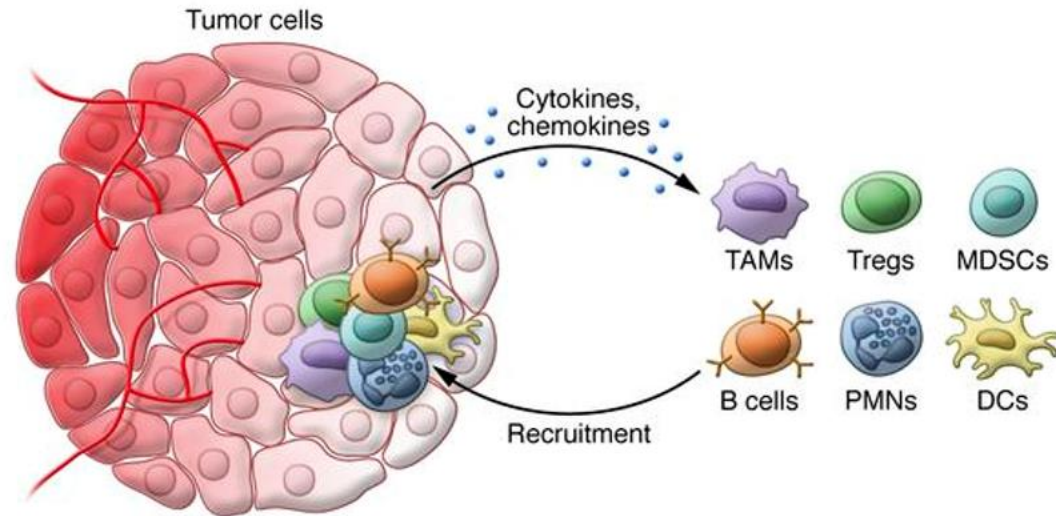
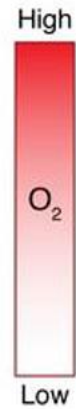
POLYMORPHIC MICROBIOME



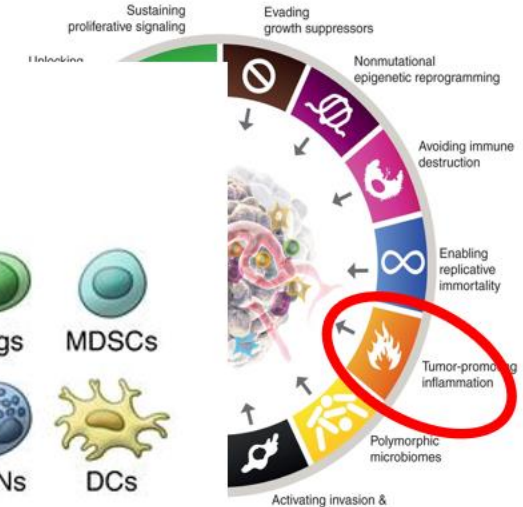
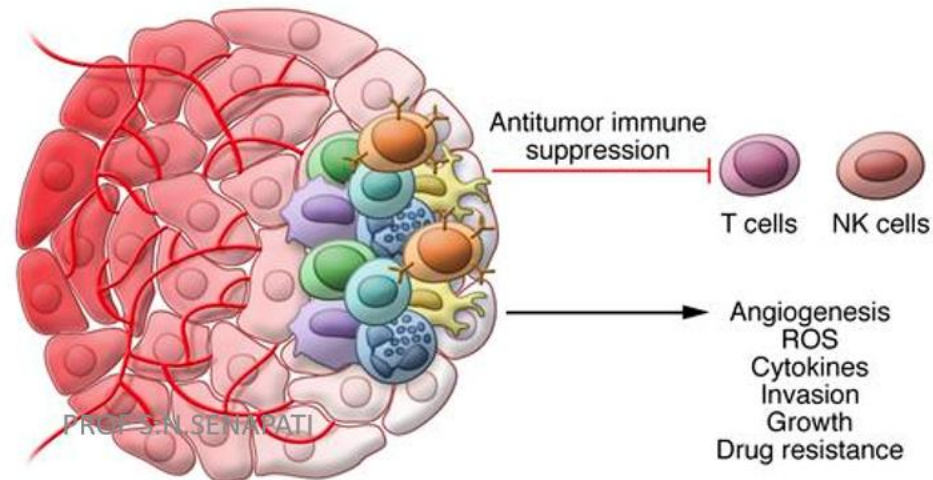


Tumour promoting Inflammation

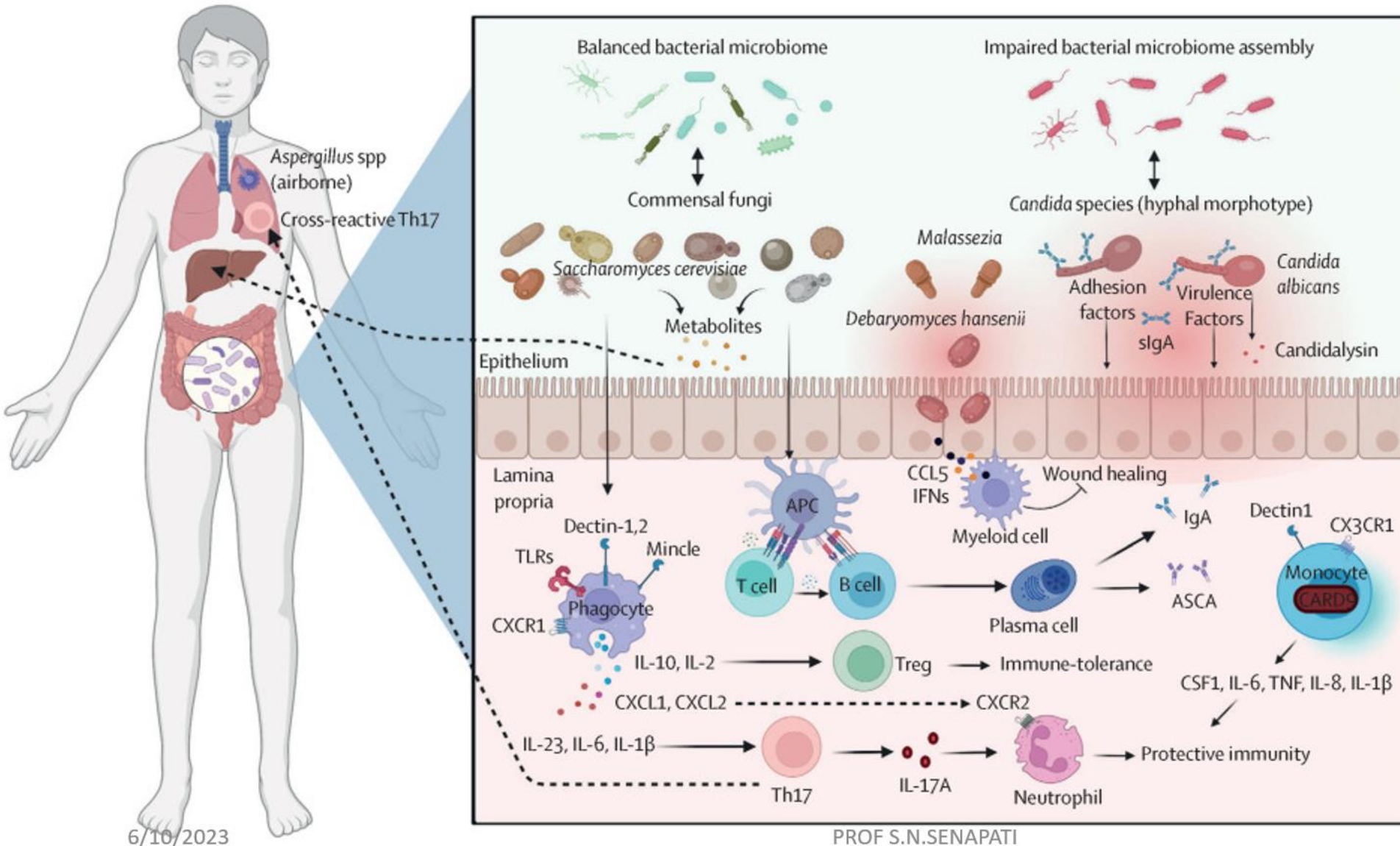
A



B



Polymorphic microbiome

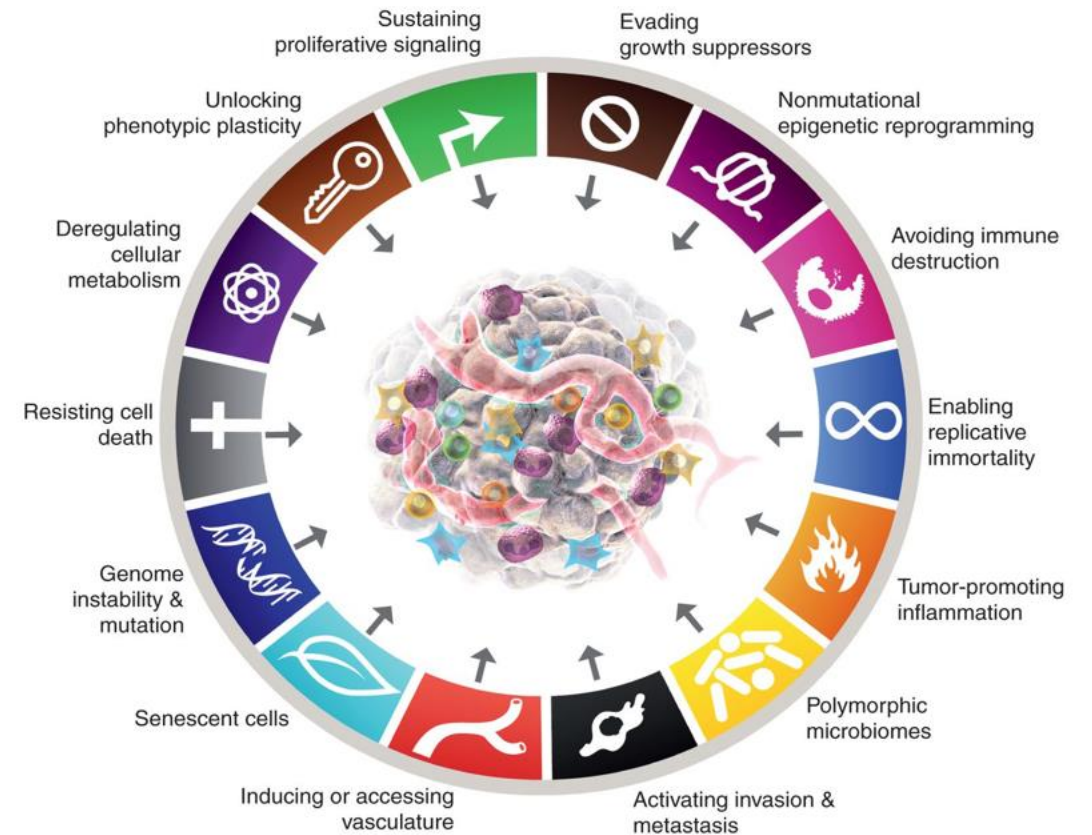


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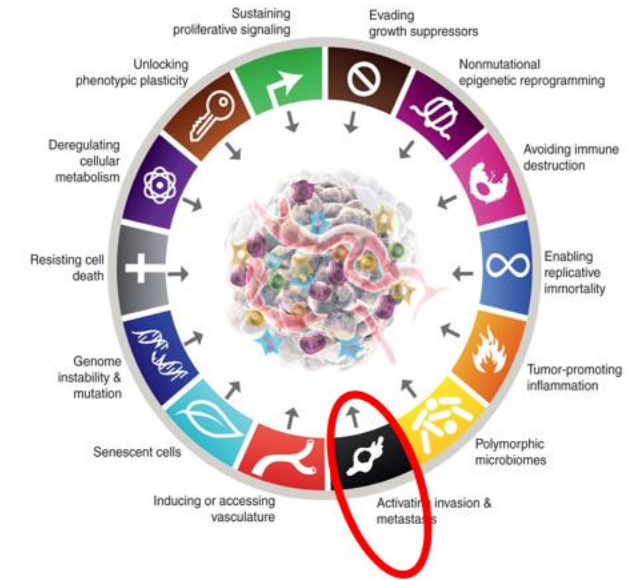
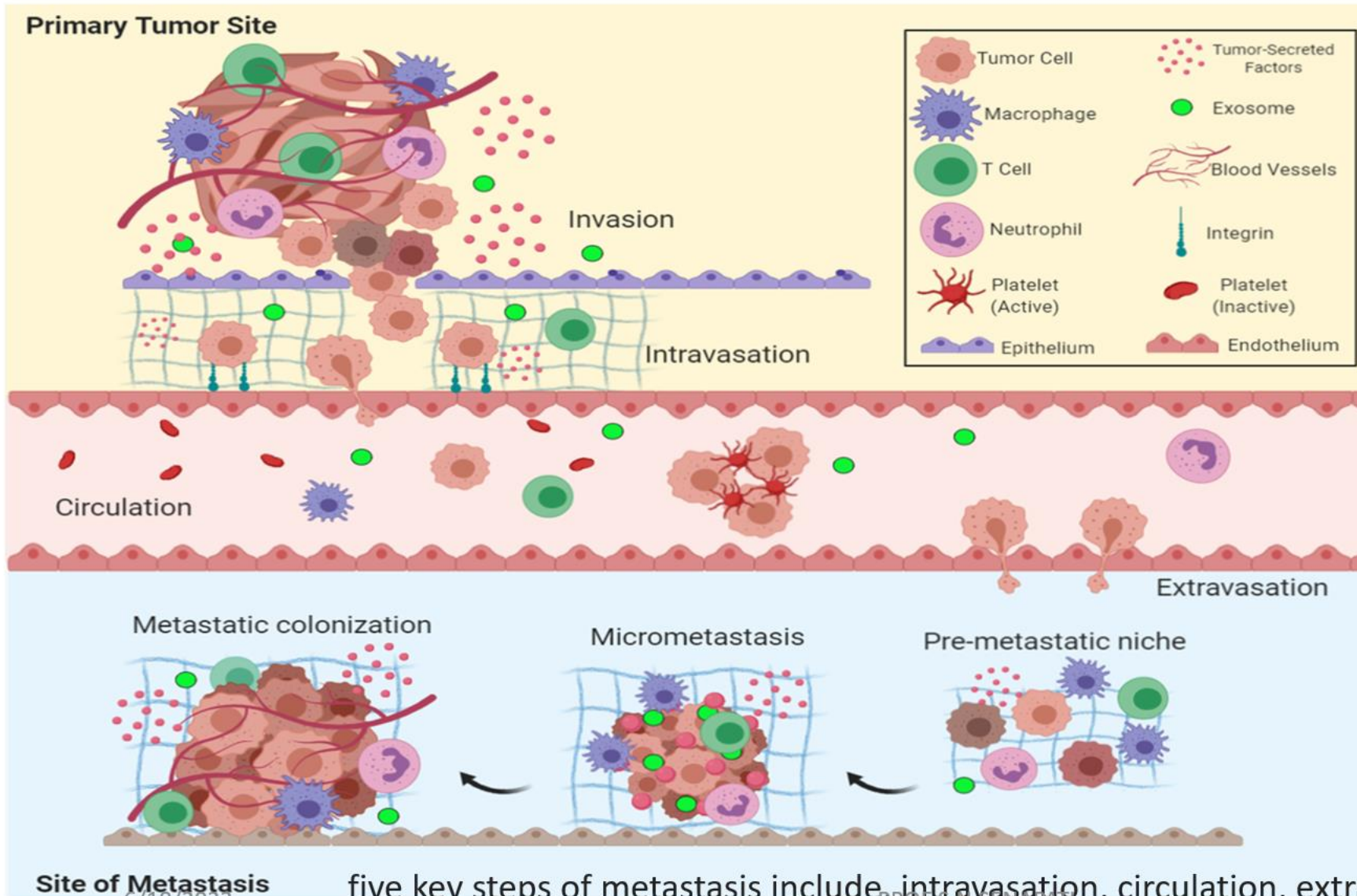
PROF S.N.SENAPATI

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

ACTIVATING INVASION AND METASTASIS



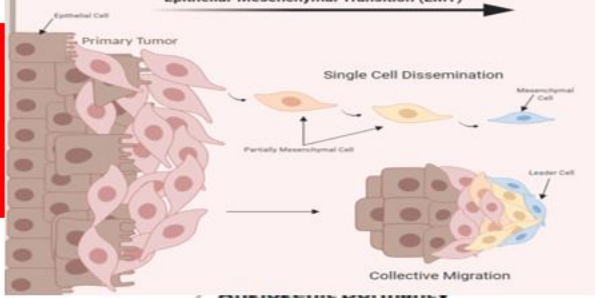
Activating invasion and metastasis



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

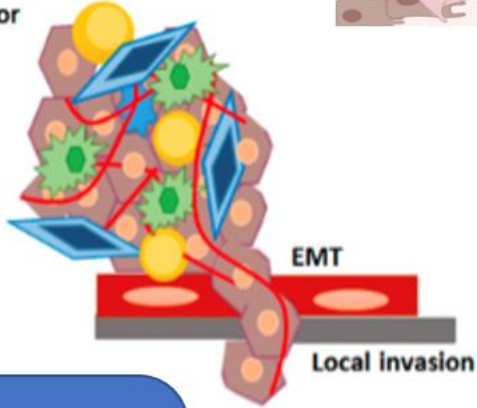
Duffy et al, 2007
 Neophytou et al, J. Mol. Sci. 2019
<https://www.ncbi.nlm.nih.gov/books/NBK164700/>

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

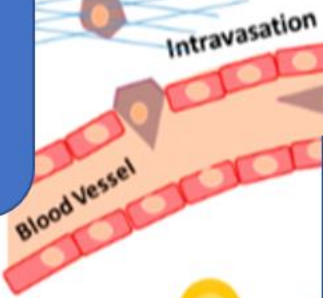


exosomes that transfer invasion-promoting factors, such as microRNAs (miRNAs) drives metastatic properties

Primary tumor



INTEGRIN
ONCOGENIC GROWTH
FACTOR SIGNALLING
E-CADHERIN



Angiogenic Dormancy
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↑

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

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



Platelets



Neutrophils



Extracellular Matrix



Epithelial cells



Cancer cells



Macrophages



Basement Membrane

Micrometastases



Macrometastases



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

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

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-β2↓, 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

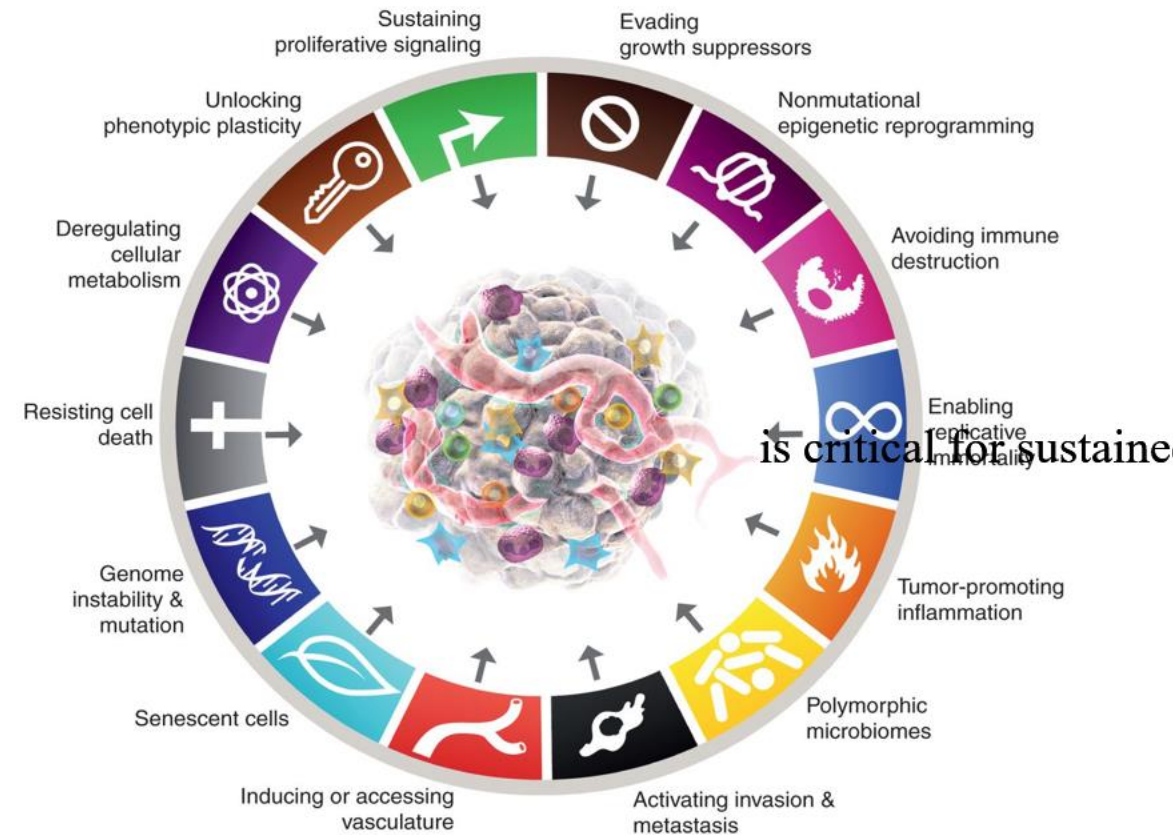
Angiogenesis

MMP-9↑, VEGF-A↑

Cell Adhesion

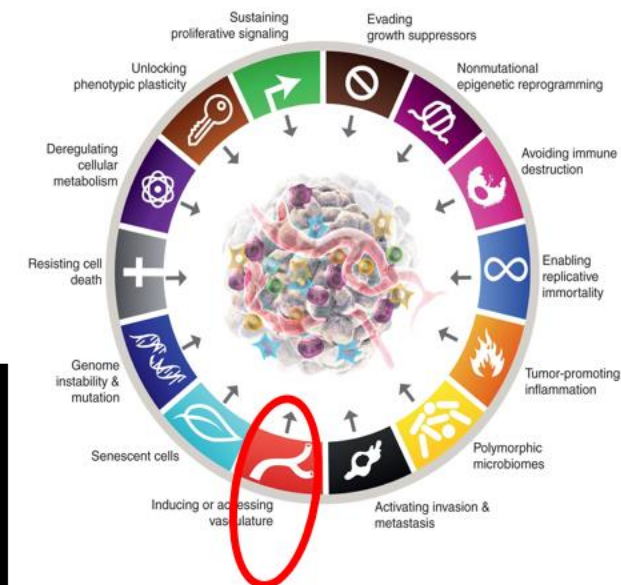
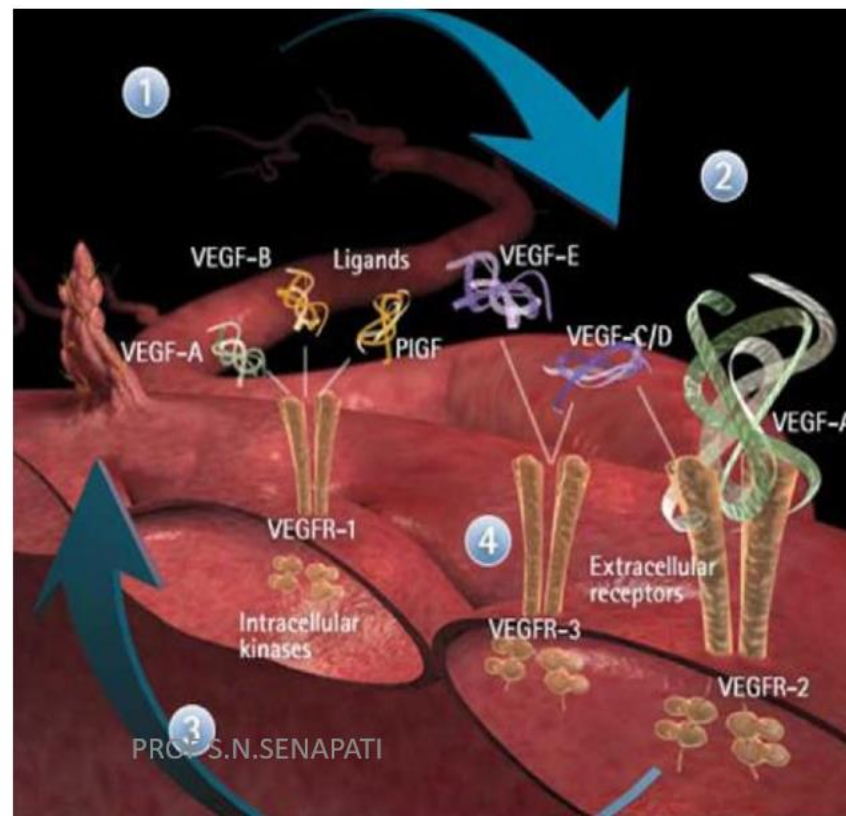
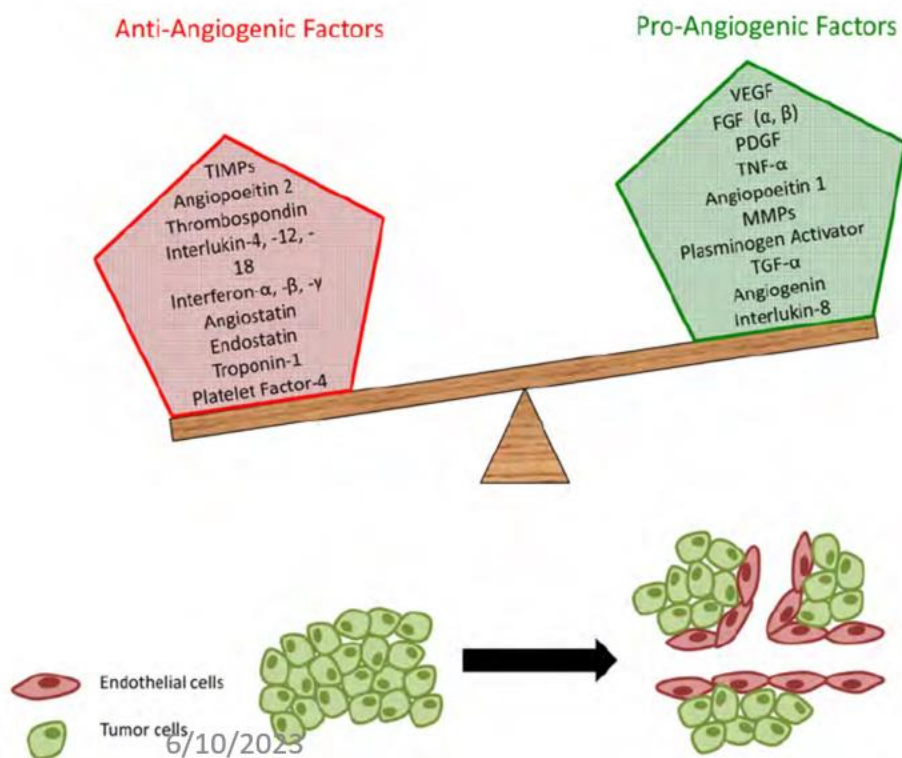
CYR61↓, PRAME↑

INDUCING OR ACCESSING VASCULATURE

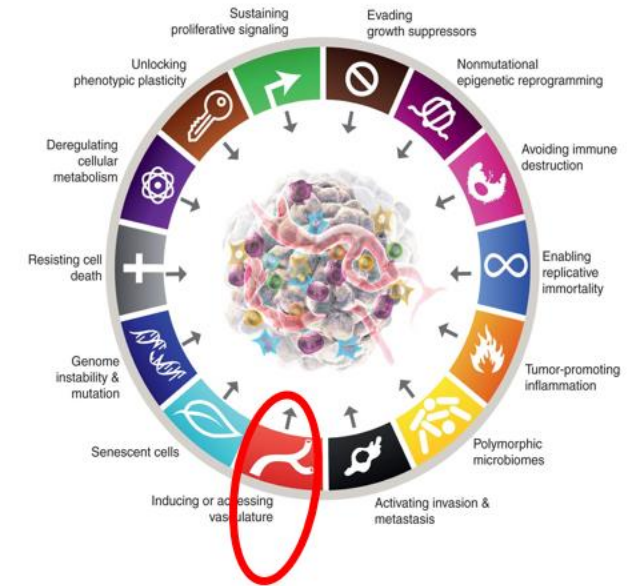
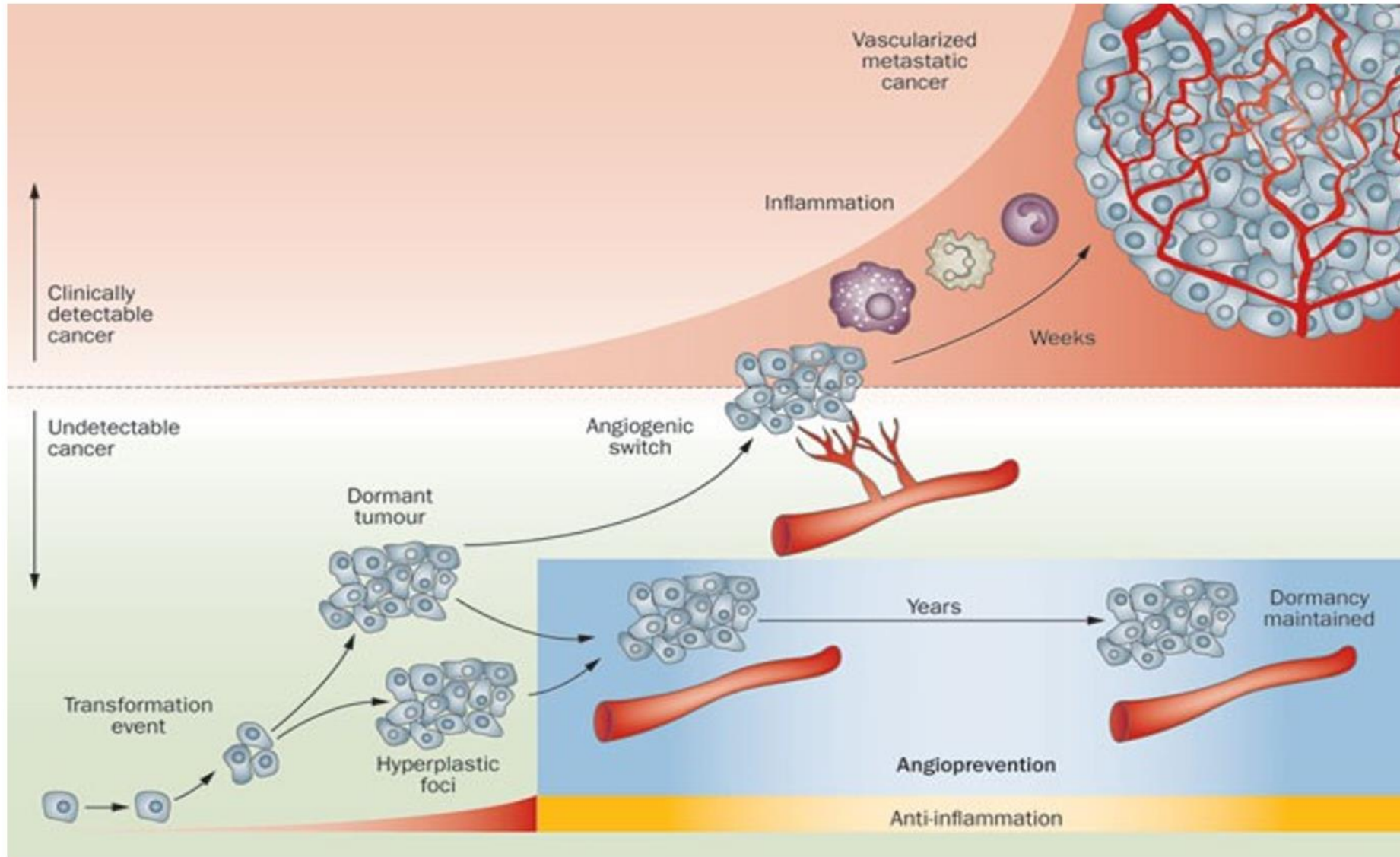


Inducing or accessing vasculature

- **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.**



Angiogenic switch

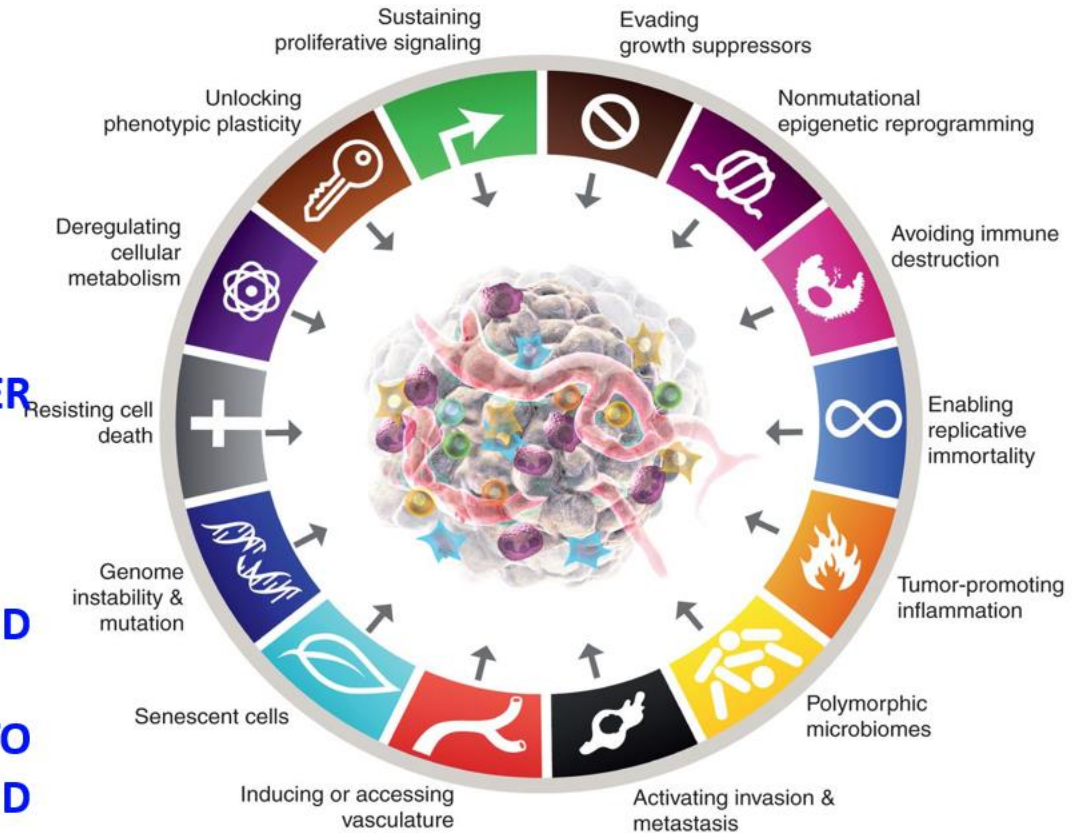


- Anti-angiogenic agents can be used not only for the treatment of cancer, but also for the **prevention of cancer recurrence or metastasis**.

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

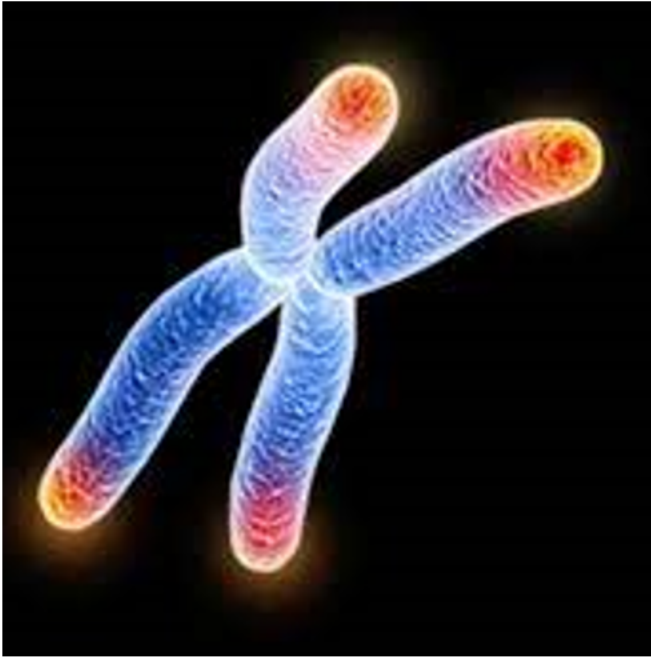
E2F+
HYPOPHOSPHORYLATED RB
RECRUIT HISTONE
DEACETYLASE AND
METHYLE TRANSFERASE

E2F DESTROYED
DESTROYED

INAPPROPRIATE EXPRESSION
OF ONCOGENE

ACTIVATION OF
MITOCHONDRIAL ROS

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



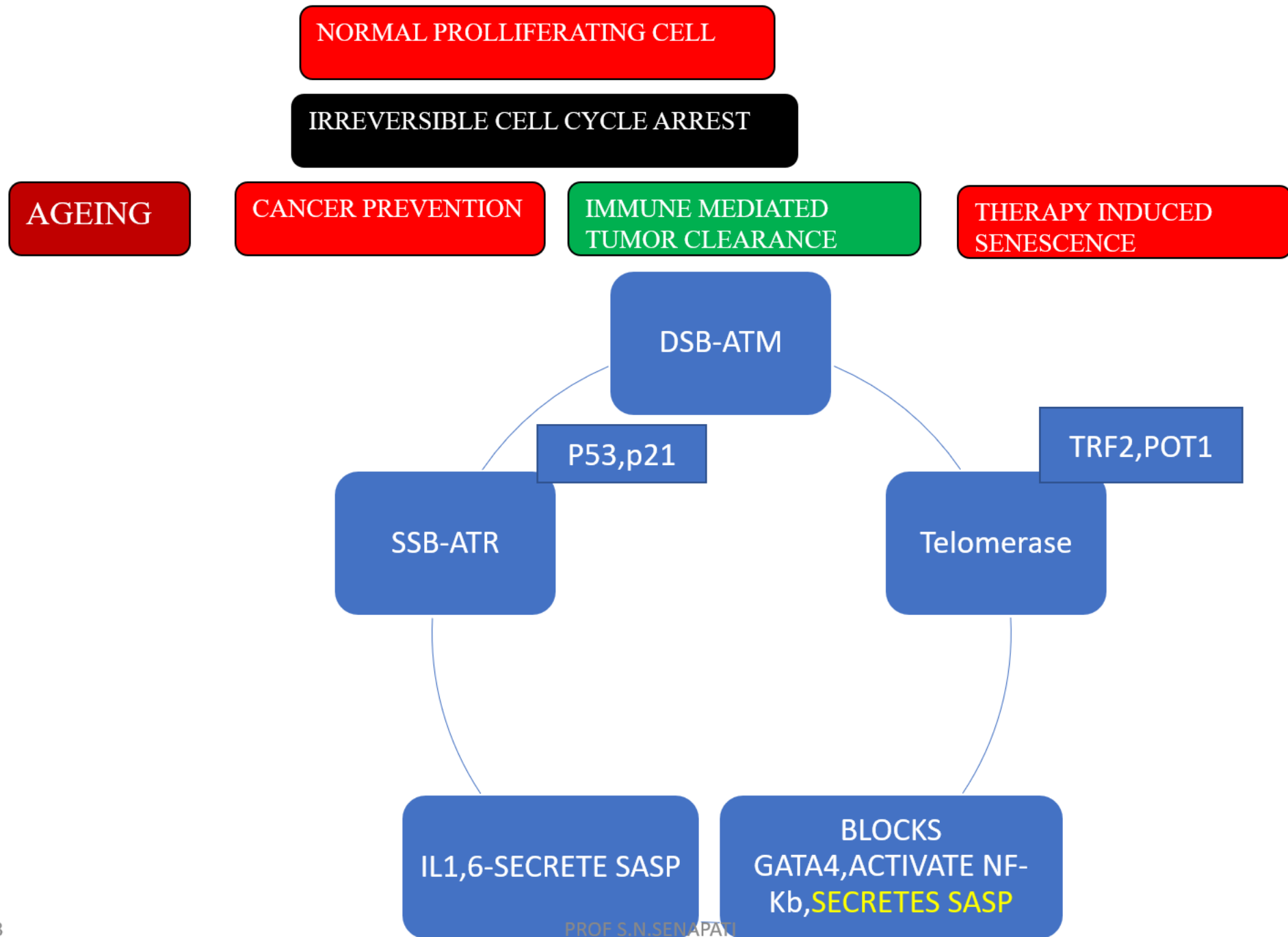
NORMAL PROLIFERATING CELL

MALIGNANT CELL

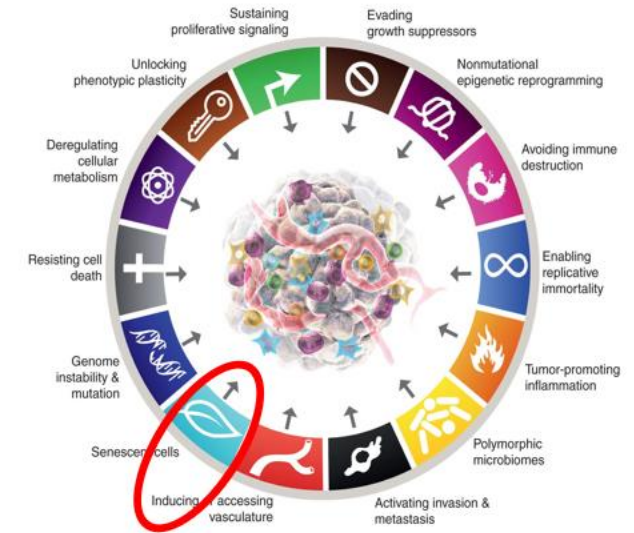
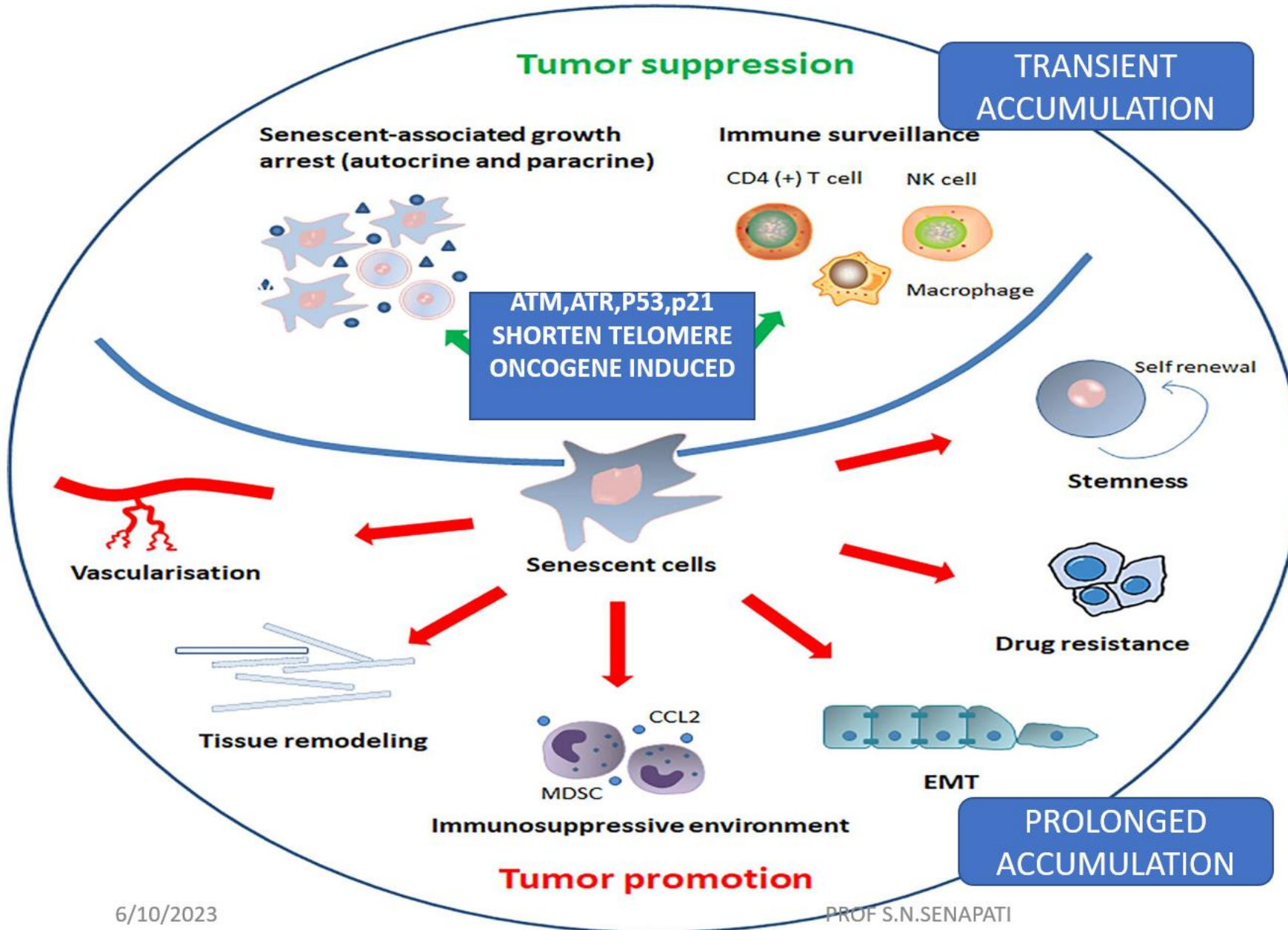
PROLIFERATION

IRREVERSIBLE
CELL CYCLE ARREST

CELLULAR SENESCENCE,PARADOXICAL ROLE



Senescent cells



SENESCENT CELL ACCUMULATE

SENESCENT FIBROBLAST

SASP DEPENDANT MANNER

PROMOTE PRE AND
MALIGNANT EPITHELIAL CELL
TO PROLIFERATE

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

GENOMIC INSTABILITY AND MUTATION

CANCER CELL:-INCREASED RATE OF MUTATION TO SURVIVE

INCREASED RATE OF MUTATION:-

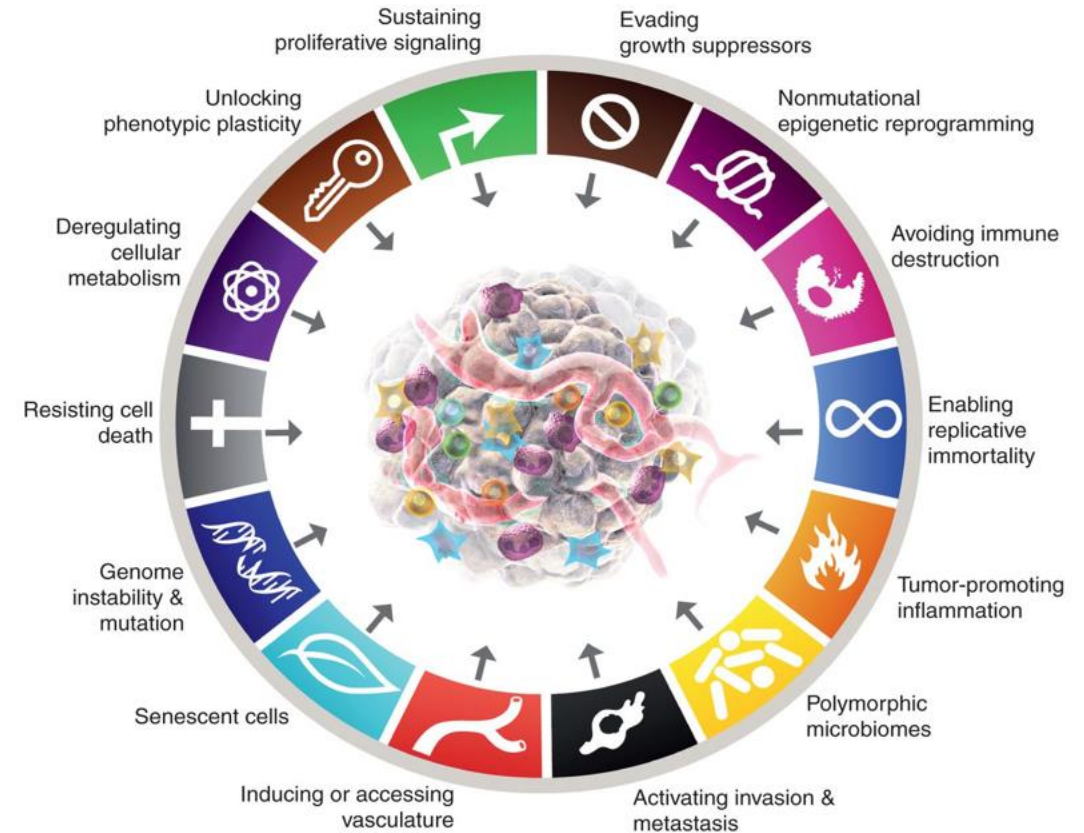
- Increased sensitivity to mutagenic agents
- Breakdown in DNA repair mechanisms mediated by TP53 or (BRCA1)
- A combination of these factors

DEFECTIVE DNA-MAINTENANCE MACHINERY, OR “CARETAKER” GENES.

These genes are responsible for

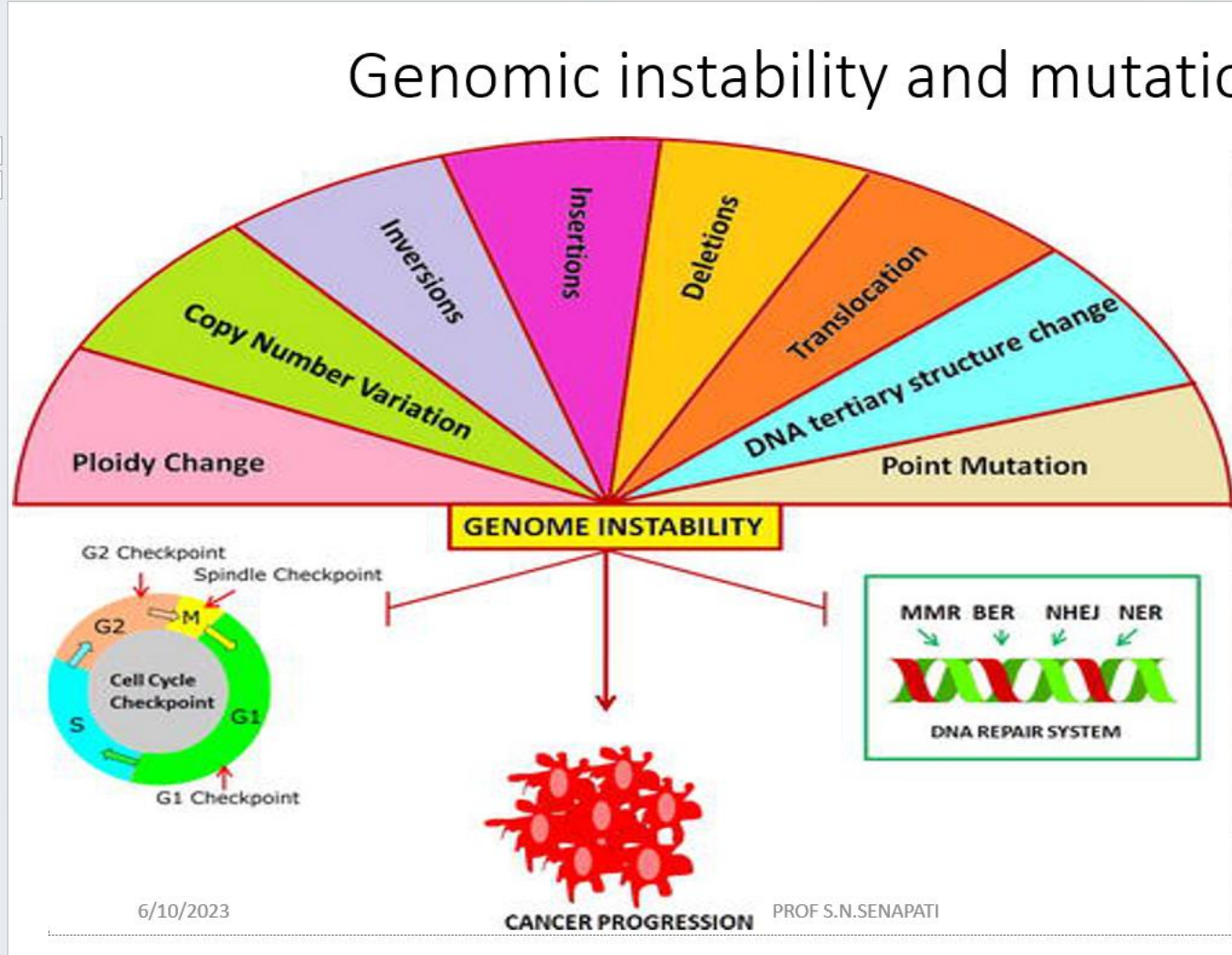
- Detecting DNA damage and activating repair machinery
- Directly repairing damaged DNA
- Inactivating or intercepting mutagenic molecules

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



- 36 Senescent cells
- 37 GENOMIC INSTABILITY AND MUTATION
- 38 Genomic instability and mutations
- 39 GENETIC INSTABILITY
- 40 Genomic instability
- 41 RESISTING CELL DEATH

1
2



Charames et al Nature 2003

Click to add notes

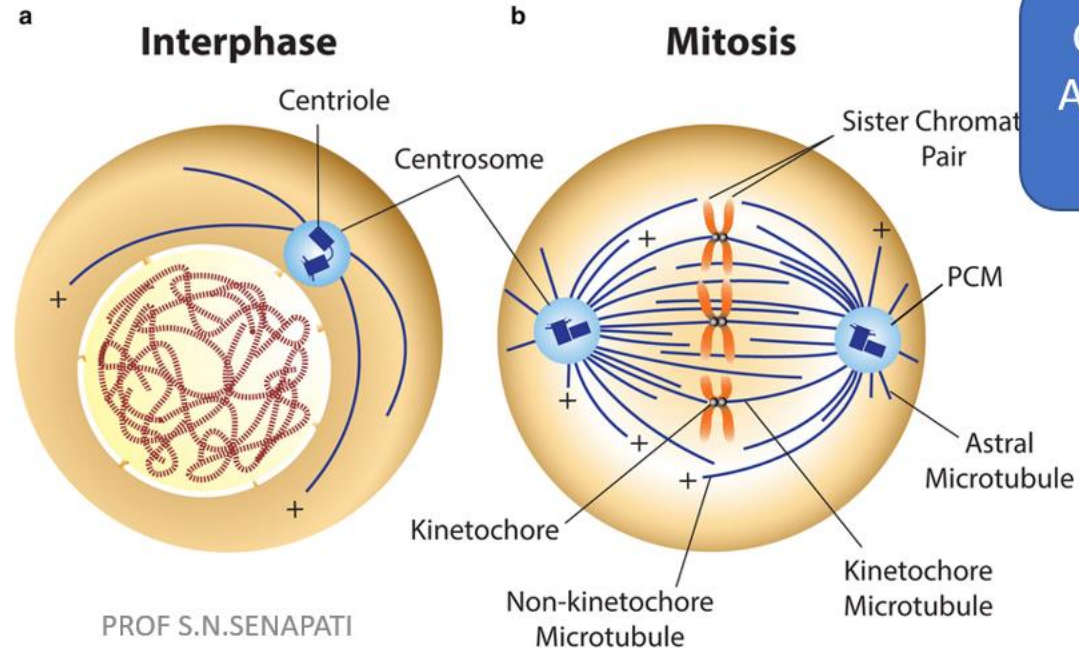
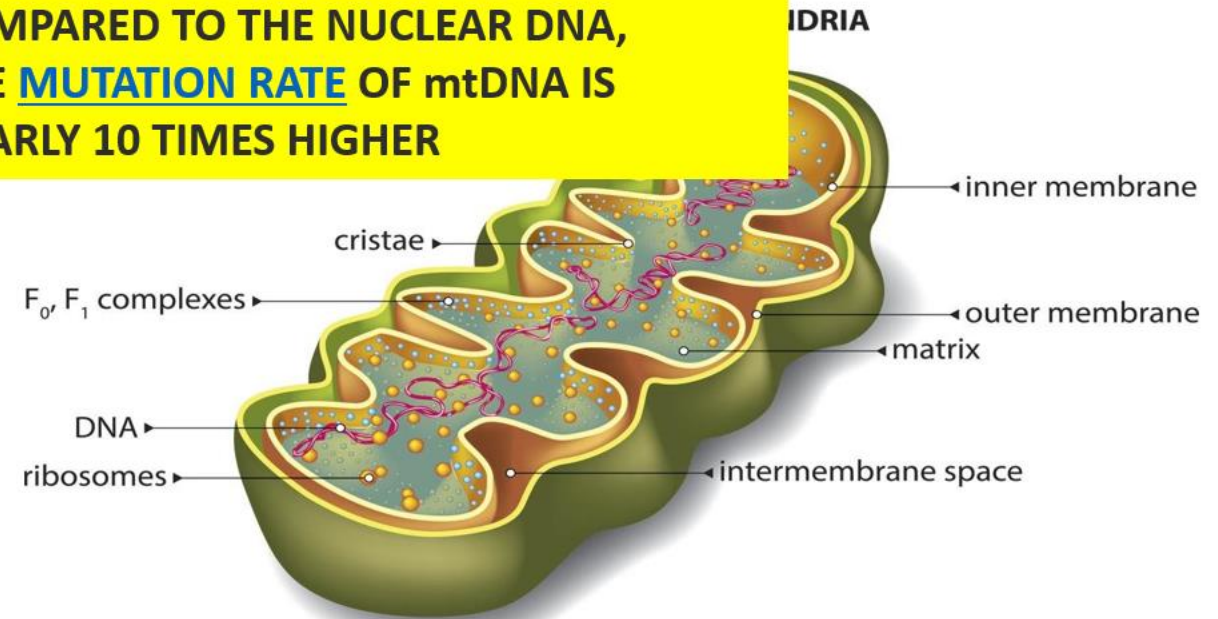
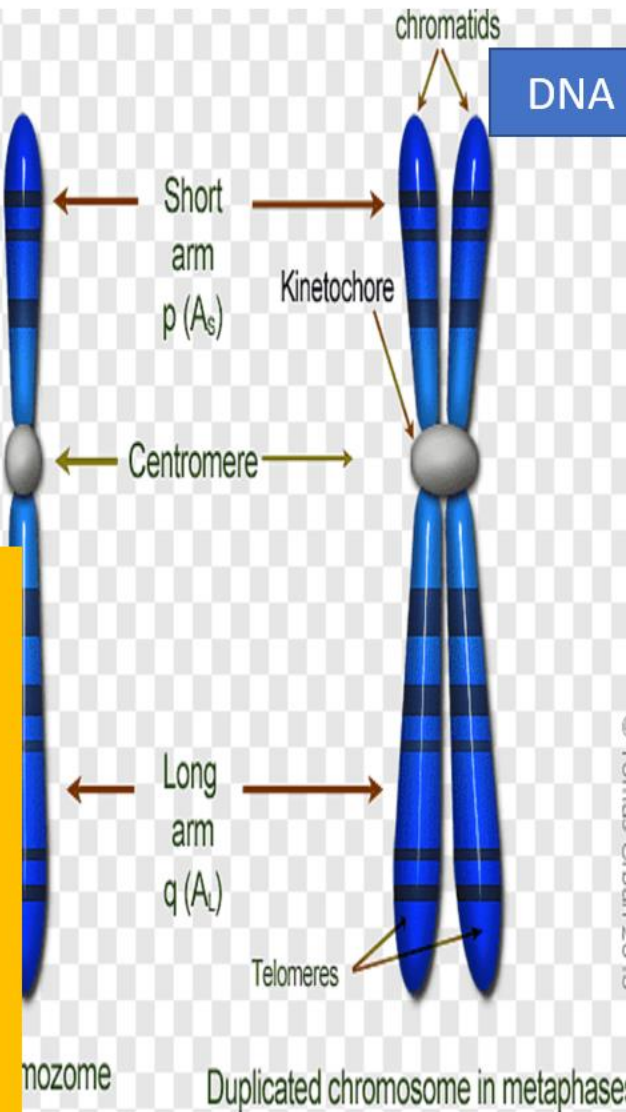
GENETIC INSTABILITY

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

TELOMERE
DAMAGE

EPIGENETIC
MODIFICATION

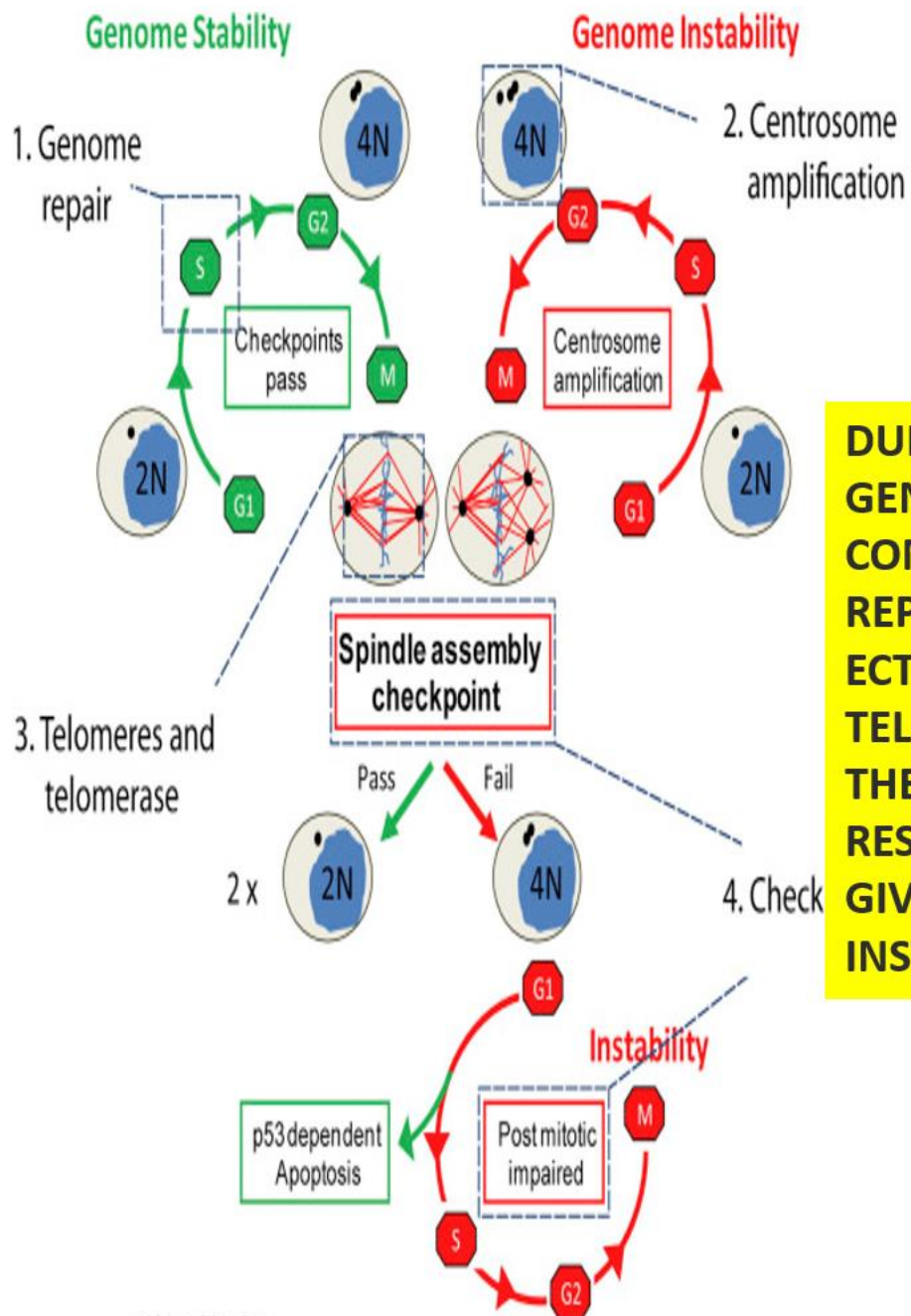
DNA DAMAGE



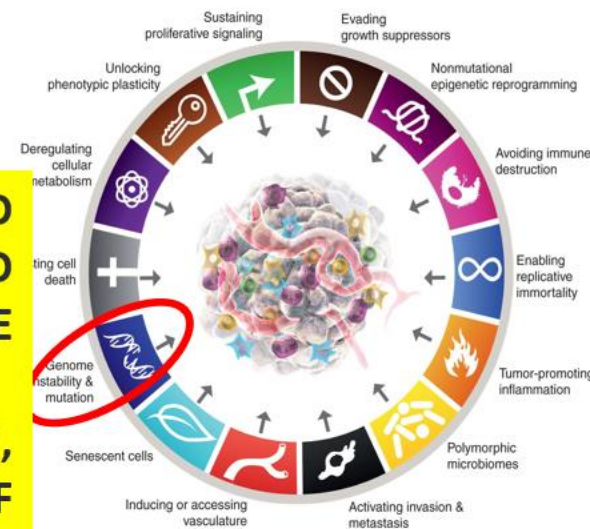
CENTROSOME
AMPLIFICATION
> 2

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

Genomic instability

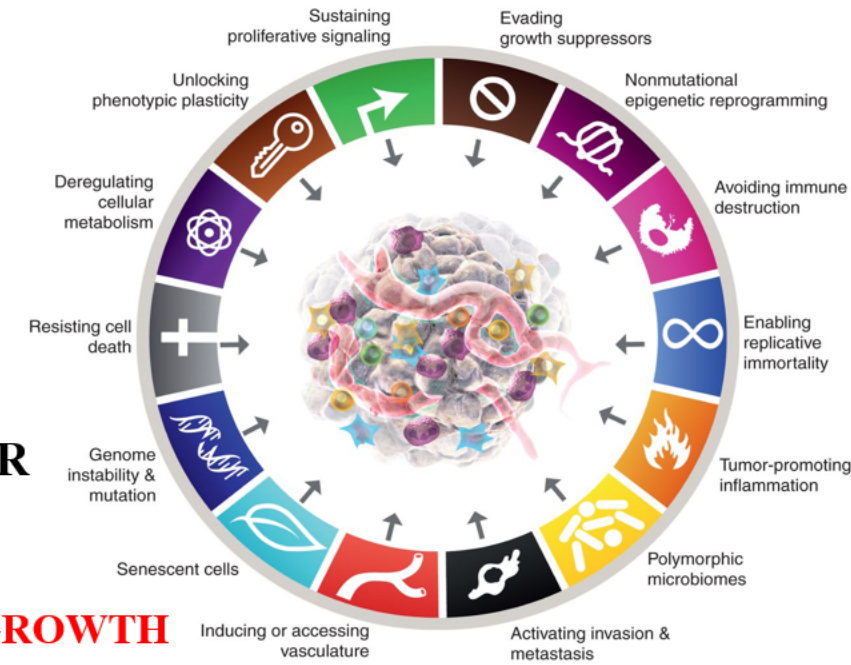


DURING S PHASE, THE CENTROSOME AND GENOMIC MATERIAL ARE REPLICATED CONCURRENTLY, AND REPLICATION ERRORS ARE REPAIRED PRIOR TO MITOTIC ENTRY (1). ECTOPIC AMPLIFICATION OF CENTROSOMES (2), TELOMERASE DYSFUNCTION (3) AND FAILURE OF THE SPINDLE ASSEMBLY CHECKPOINT (4) MAY RESULT IN ABORTED MITOSIS. MITOTIC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

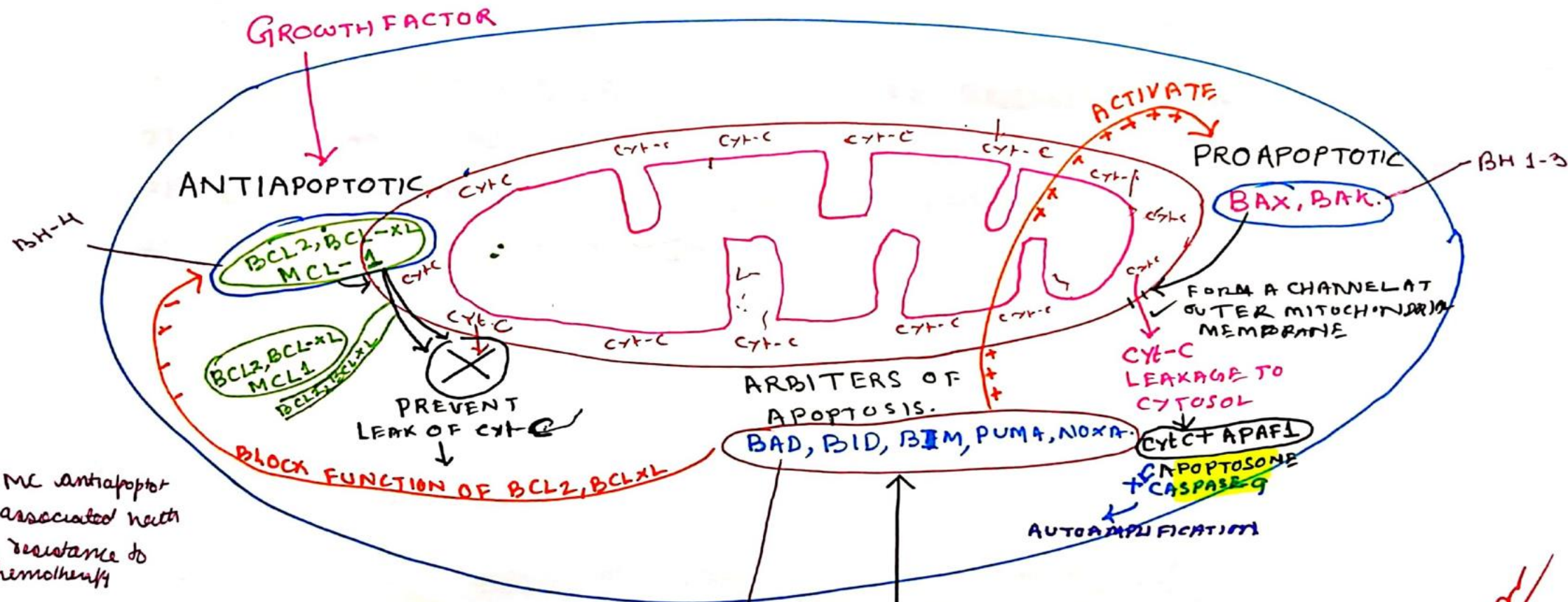


RESISTING CELL DEATH

- **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 antiapoptotic gene associated with drug resistance to chemotherapy

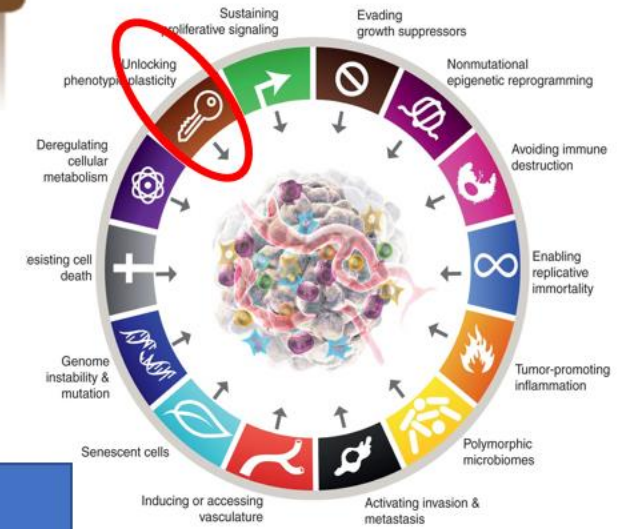
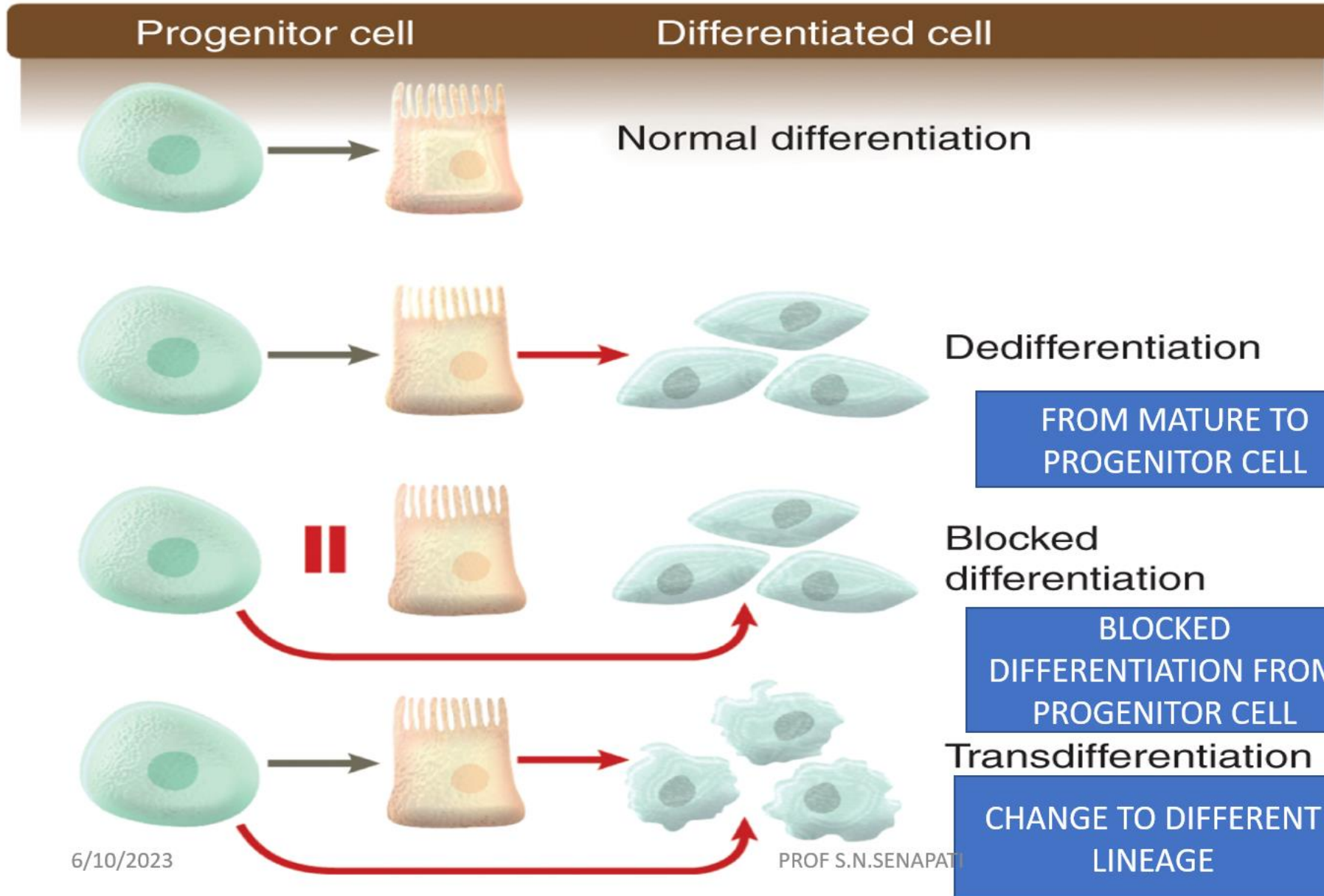
Smac/Diablo → leak out and inhibit cytoplasmic anti-apoptotic IAP

- BH-3 only**
- DEPRIVE OF SURVIVAL SIGNAL
 - RADIATION
 - DNA DAMAGE
 - MISFOLDED PROTEINS INDUCED ER STRESS

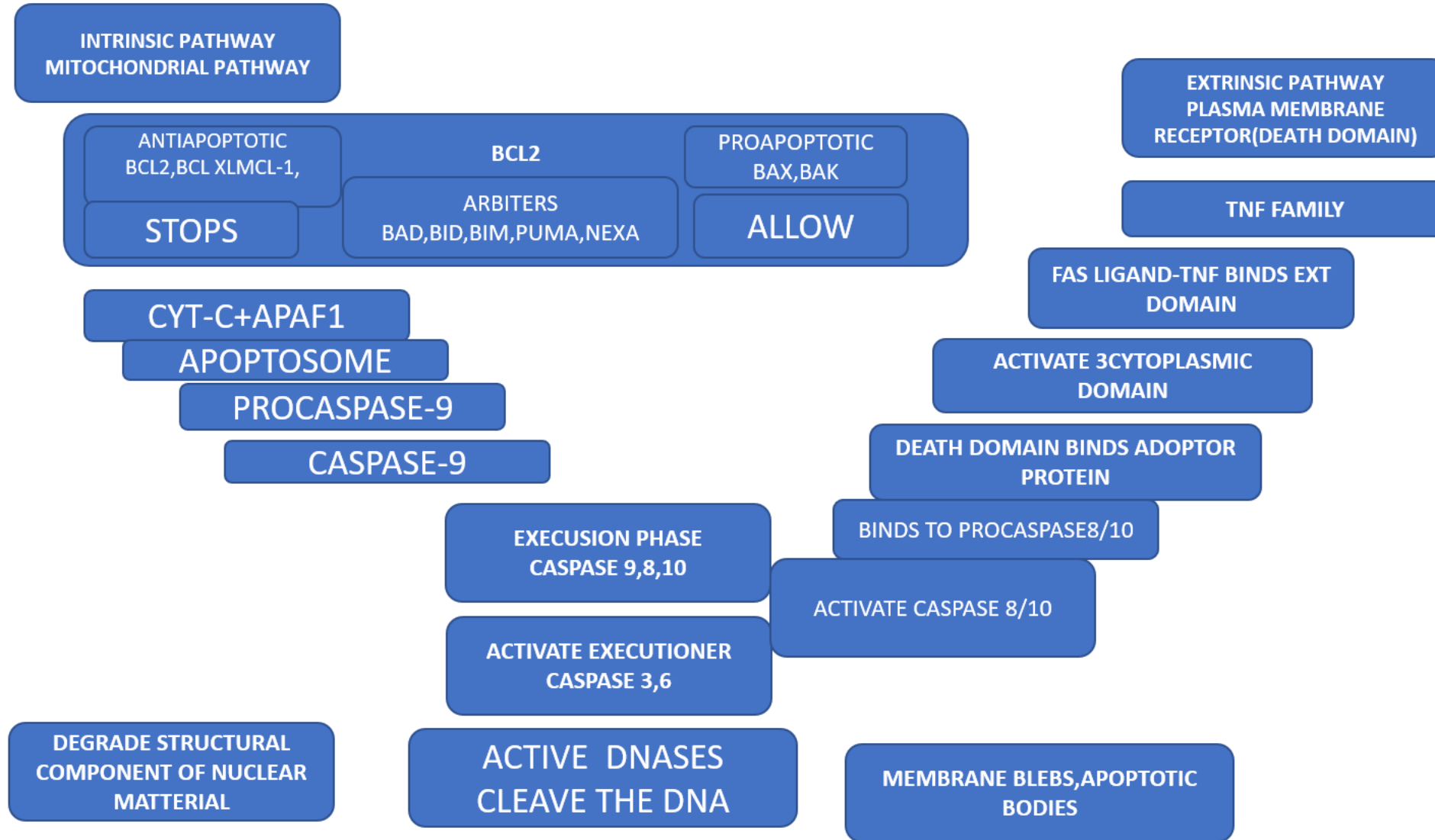
Cytochrome C bind to

} → apoptosome

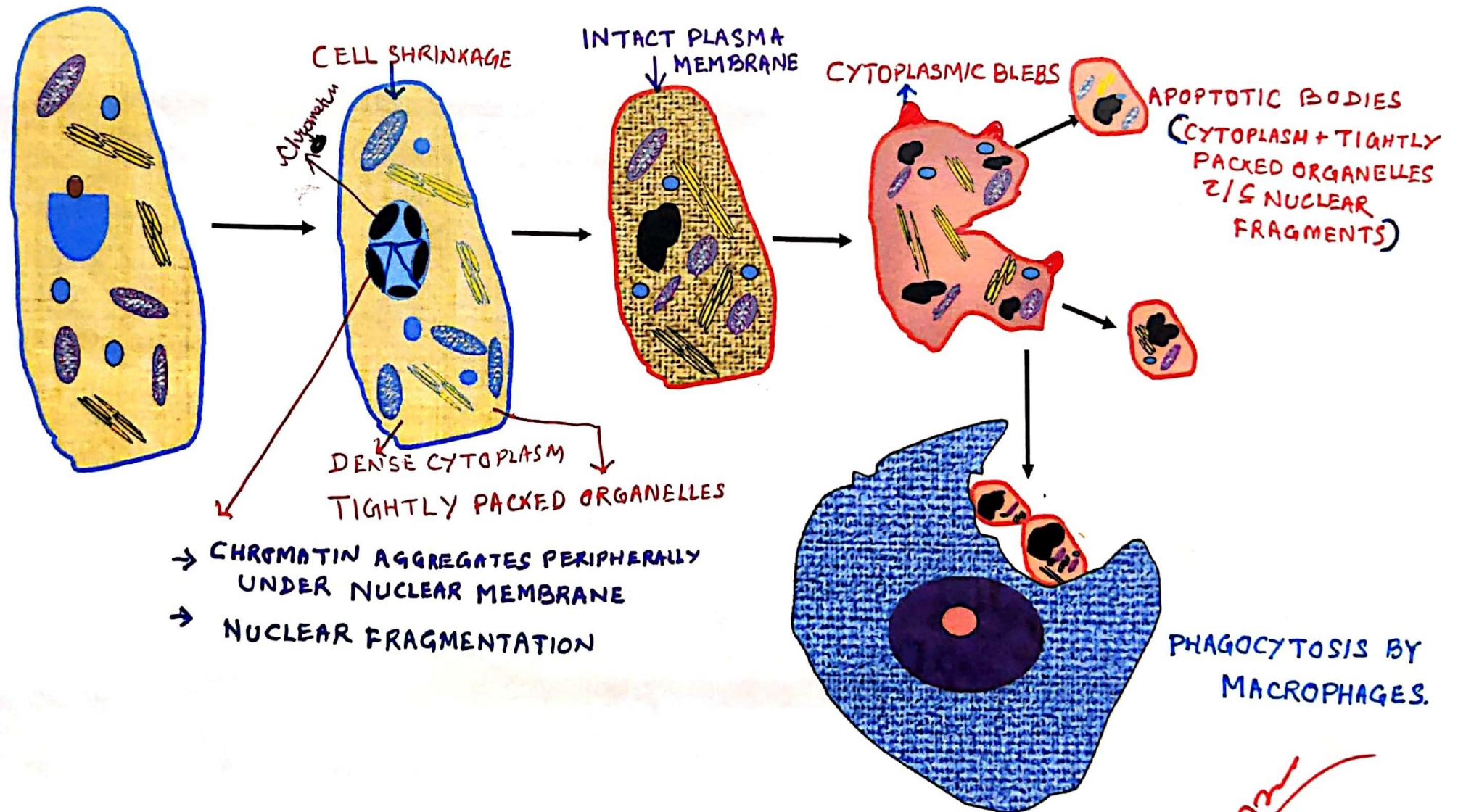
Unlocking phenotypic plasticity

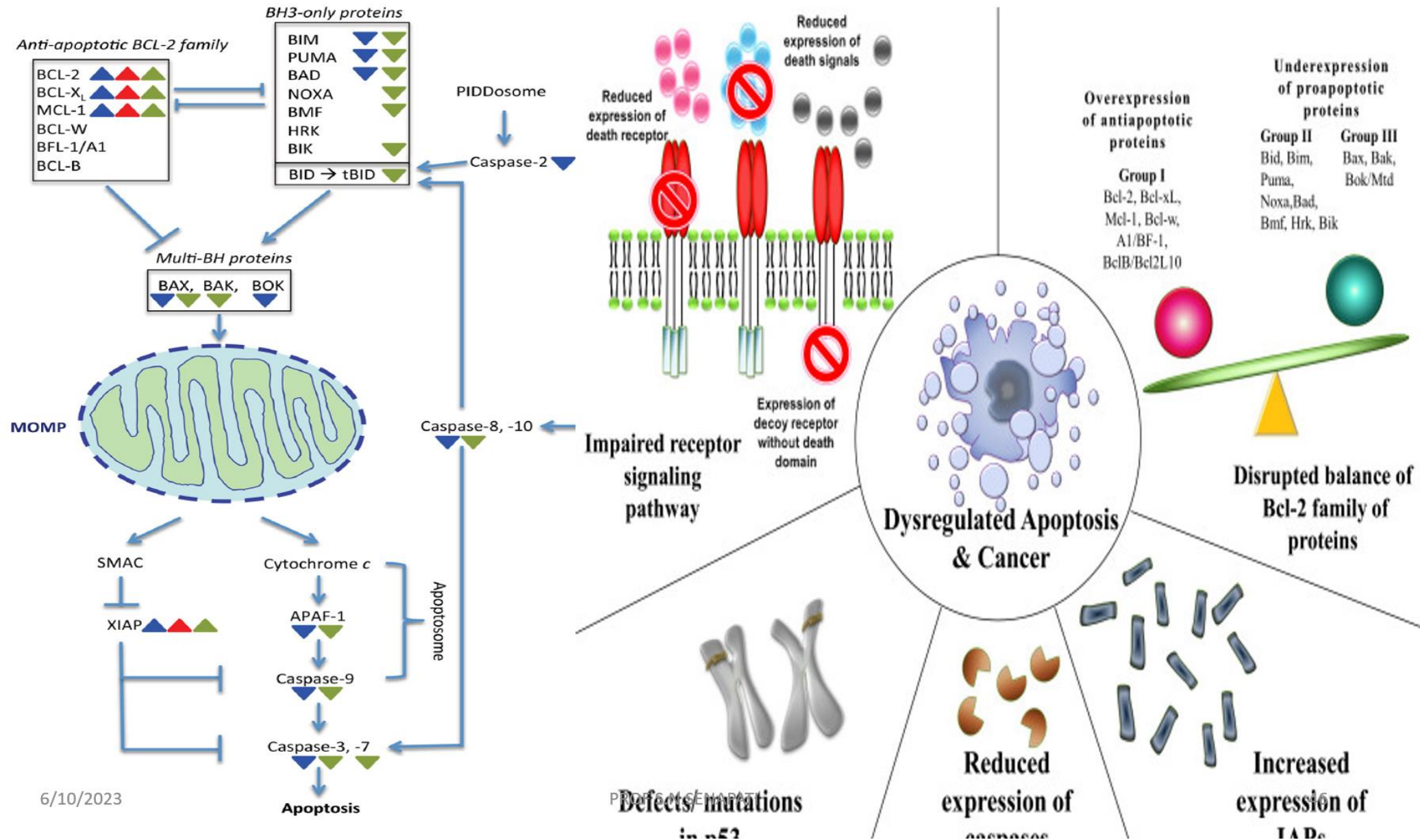


APOPTOSIS



MORPHOLOGY OF APOPTOSIS



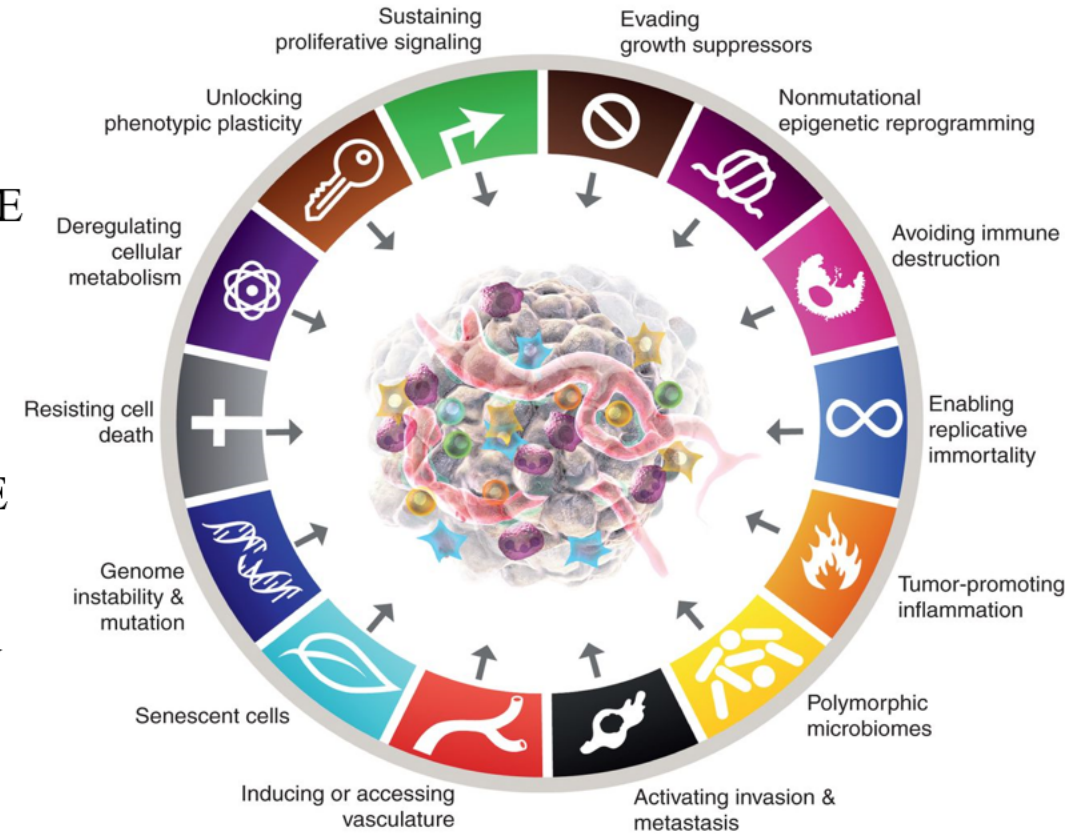


6/10/2023

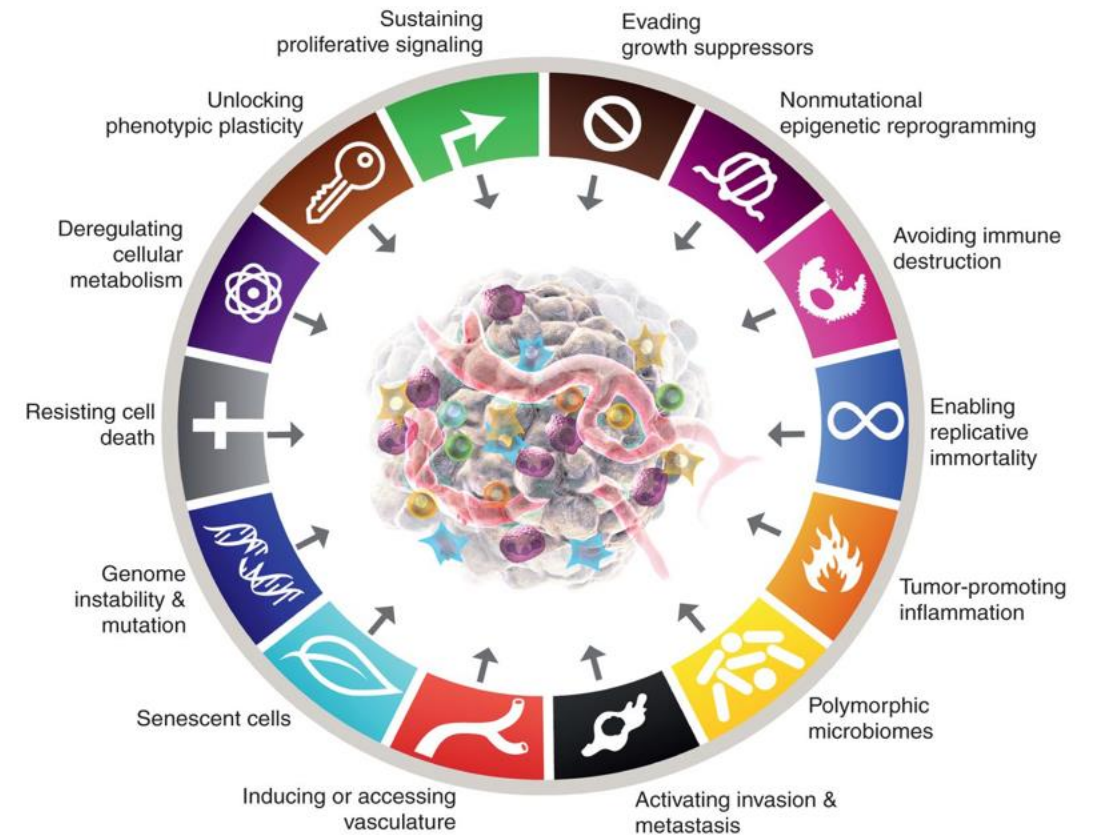
Deregulating cellular metabolism

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

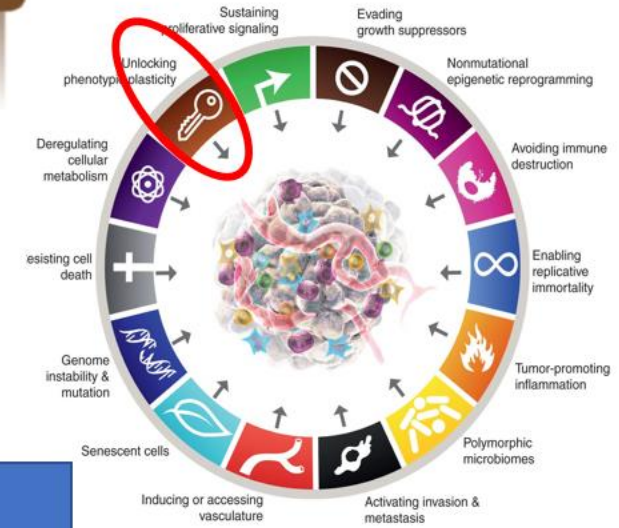
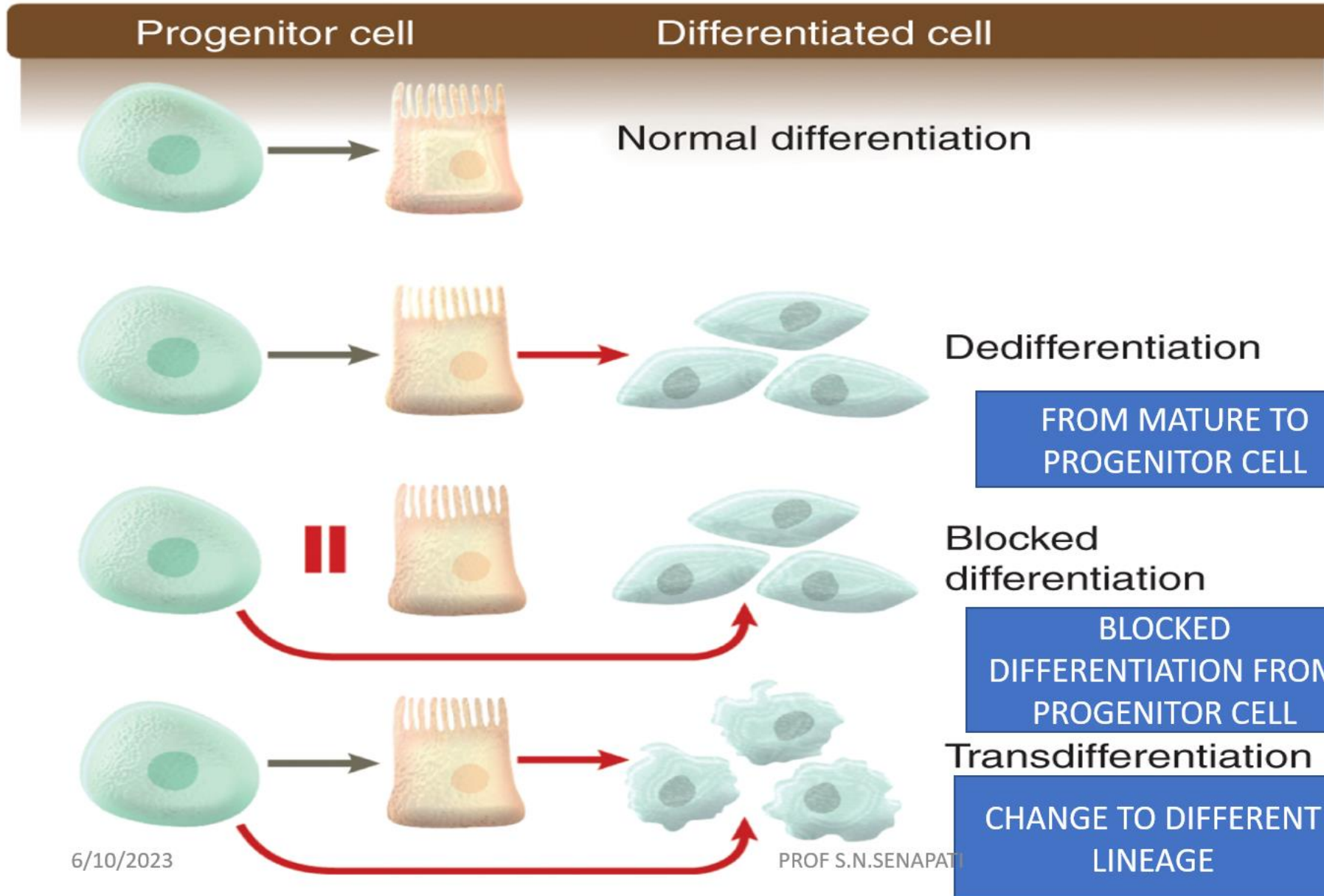
- REPROGRAMMING THEIR GLUCOSE METABOLISM
- UPREGULATING GLUCOSE TRANSPORTERS SUCH AS GLUCOSE TRANSPORTER 1 (GLUT1)
- DEPENDING ON ALTERNATE METABOLIC PATHWAYS ALTHOUGH LIMITING ENERGY PRODUCTION TO THE GLYCOLYSIS PHASE DECREASES THE AMOUNT OF ADENOSINE TRIPHOSPHATE (ATP) PRODUCED, IT ALSO ALLOWS CANCER CELLS TO DIVERT GLYCOLIC INTERMEDIATES TO VARIOUS PATHWAYS, INCLUDING THOSE REQUIRED TO ASSEMBLE NEW CELLS.



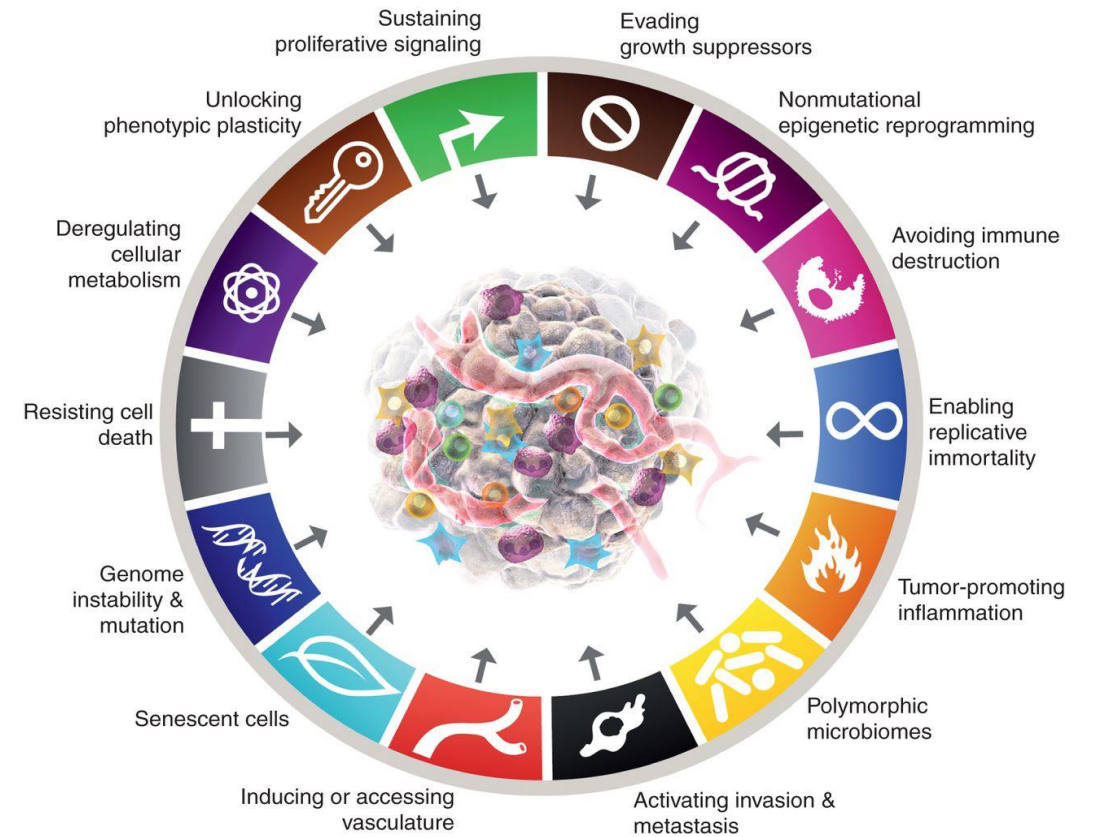
UNLOCKING PHENOTYPIC PLASTICITY



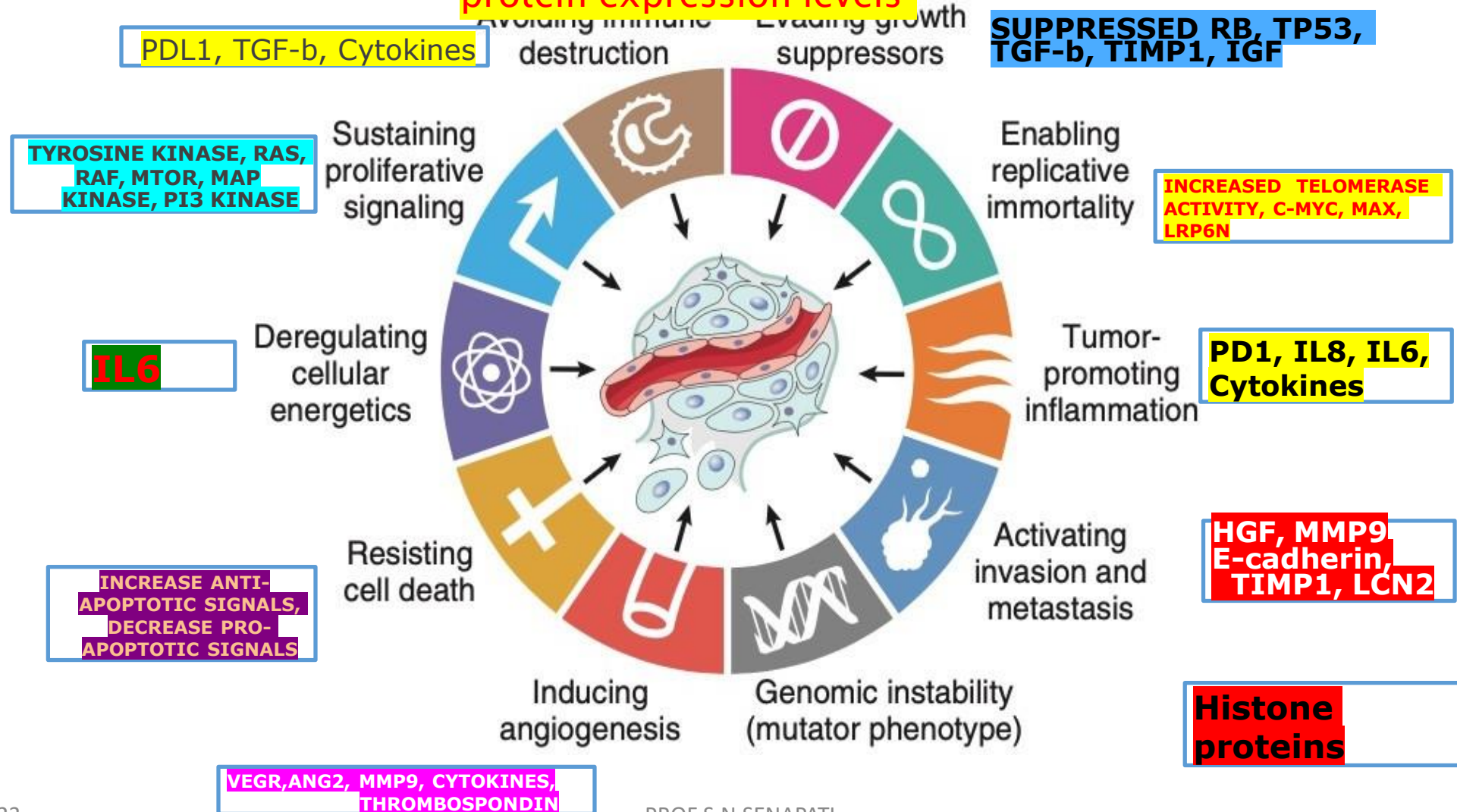
Unlocking phenotypic plasticity



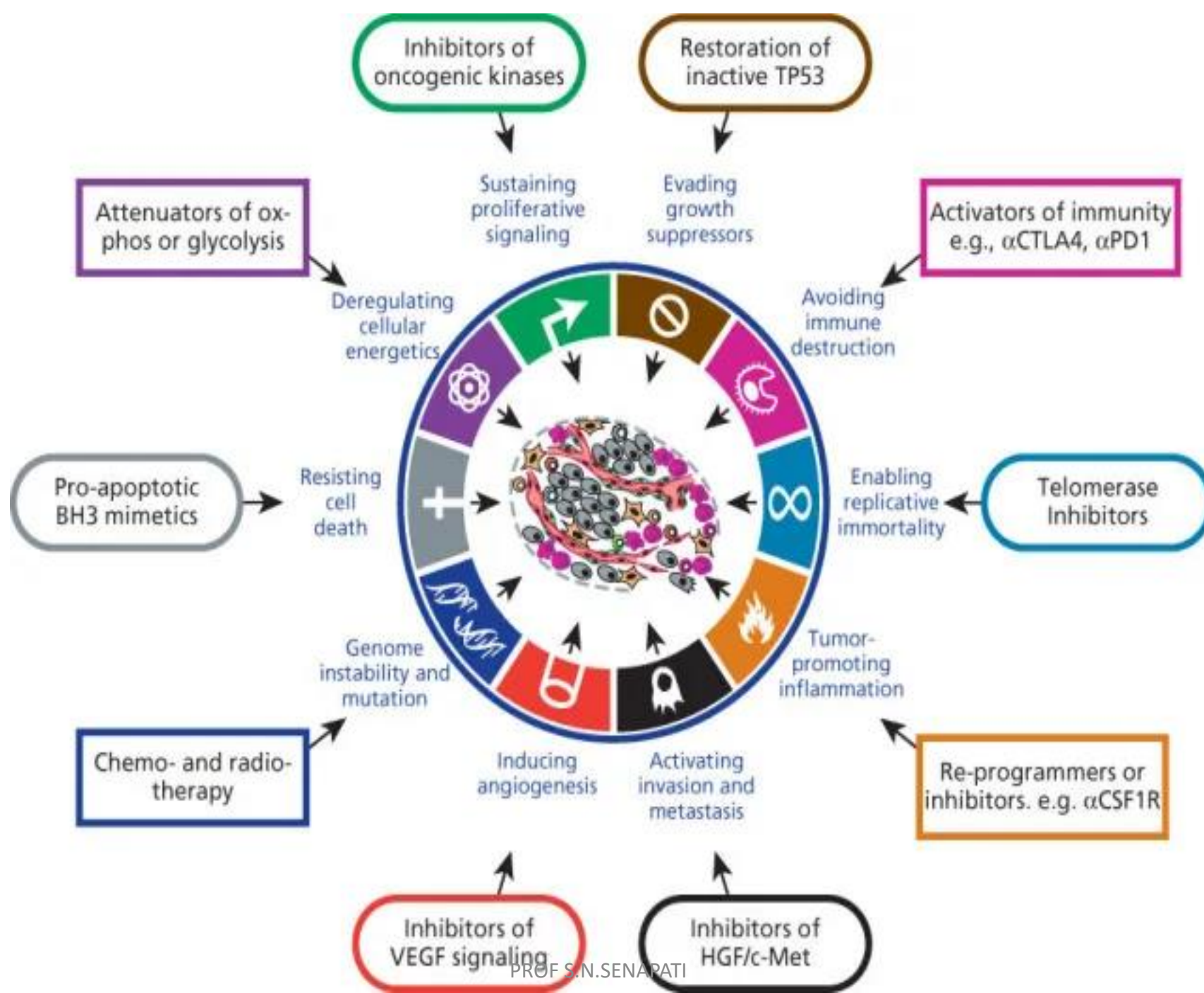
Summary

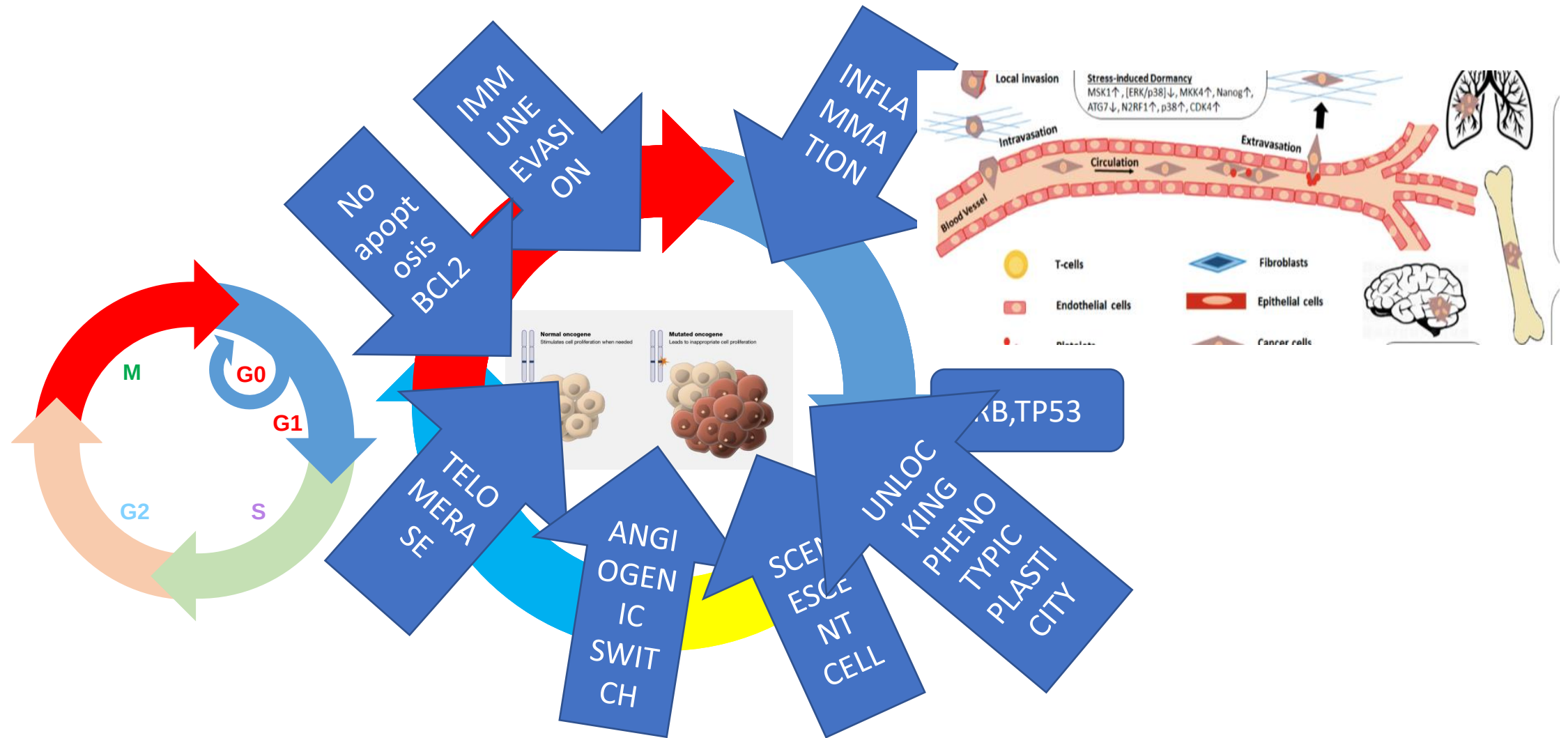


Cancer cells show extensive alterations in protein expression levels¹



How can we target cancer?





THANK YOU