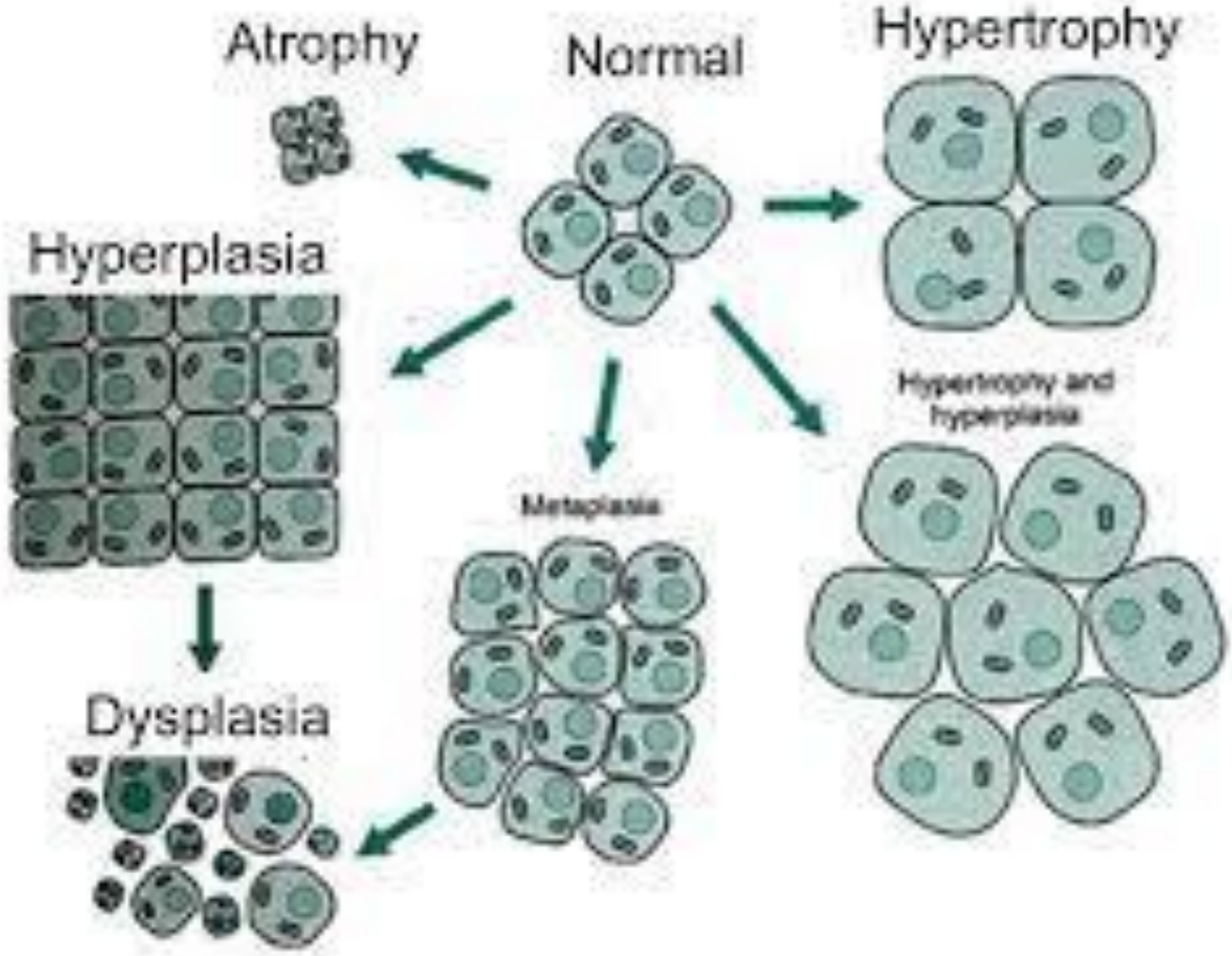
CANCER BIOLOGY
22ZOOME32

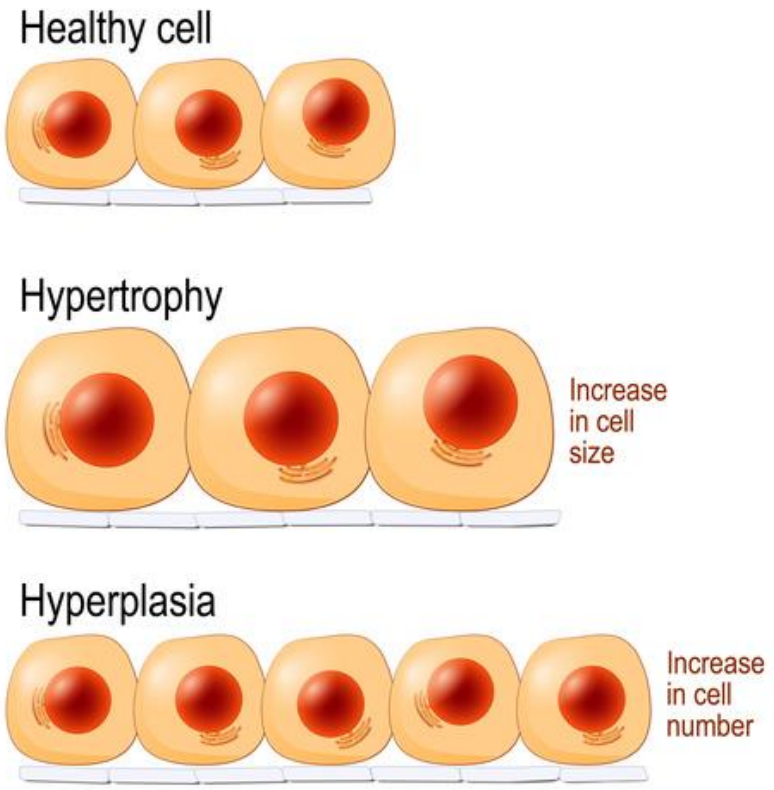
Types of abnormal growth

- Hyperplasia
- Hypertrophy
- Metaplasia
- Dysplasia
- Hyperplasia, metaplasia, and dysplasia - reversible because they are results of a stimulus.
- Neoplasia is irreversible because it is autonomous


Atrophy
Normal
Hypertrophy
Hyperplasia
Hypertrophy and hyperplasia
Metaplasia
Dysplasia

Hyperplasia & Hypertrophy

- **Hypertrophy:**
- Enlargement of cell size
- **Hyperplasia:**
- an increase in the number of normal cells in a tissue



Metaplasia

- Metaplasia refers to the replacement of a mature, differentiated cell type by another mature, differentiated cell type that does not typically occur in the tissue in which it is found.
- Metaplasia typically occurs as a response to chronic irritation of cells, which can be environmental (e.g., smoking and alcohol) or pathological (e.g., acid reflux).
- Metaplasia itself is a benign, non-cancerous condition; however, if left untreated, the cells undergoing metaplasia can be
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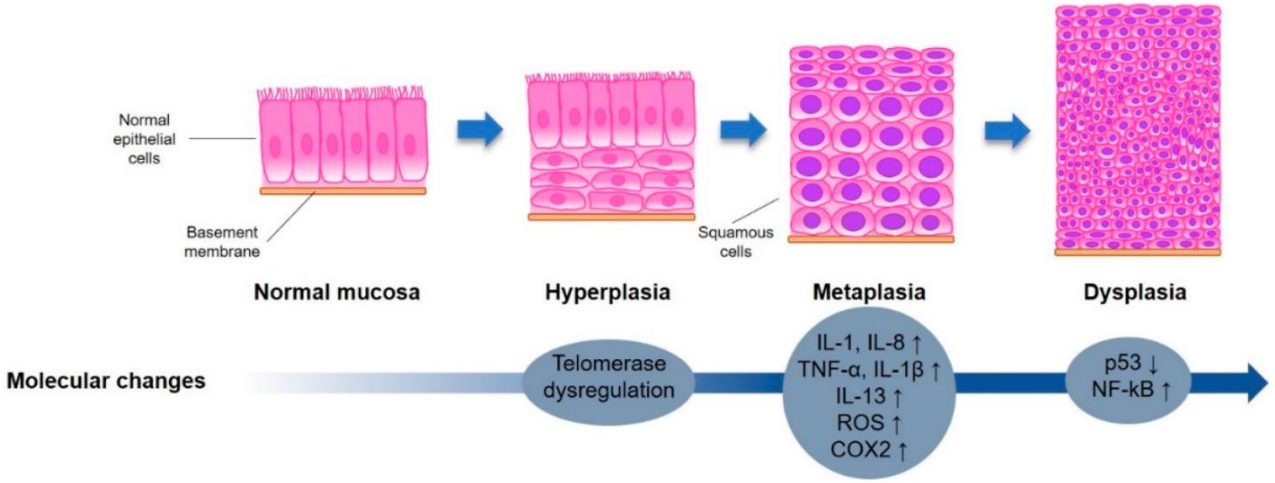
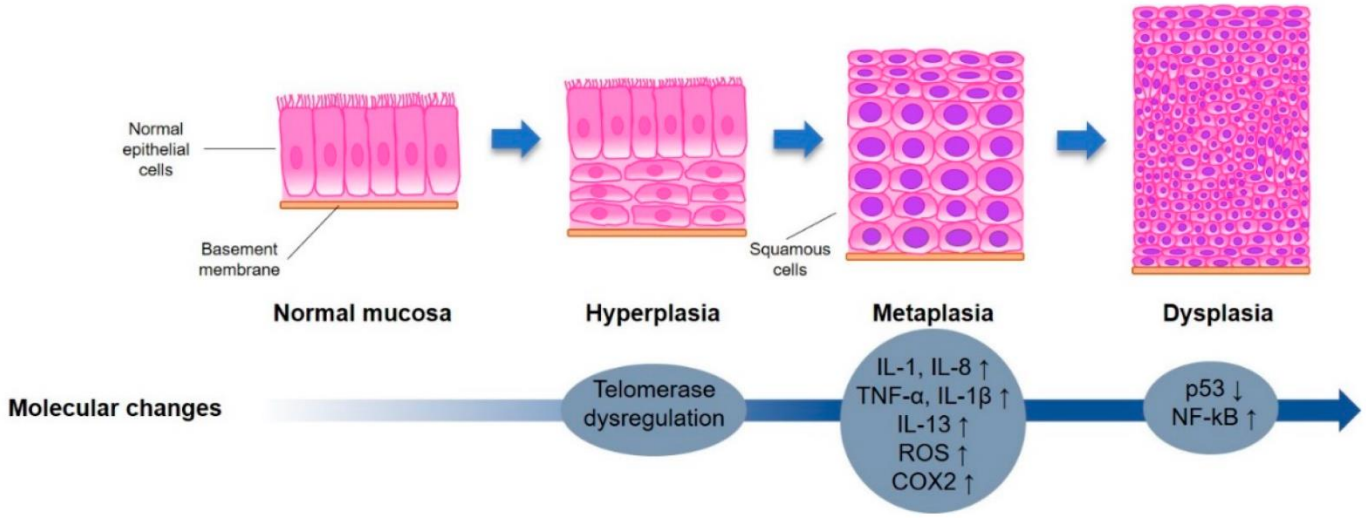


Dysplasia

- A pre-cancerous state characterized by increased cell proliferation with highly abnormal and variable appearance to the cells.
- Cell to cell interactions are diminished, and the architecture of the tissue is less organized.
- Dysplasia is potentially reversible, and it doesn't always progress to cancer, but it indicates a pre-cancerous state with a high probabability of progressing to cancer.



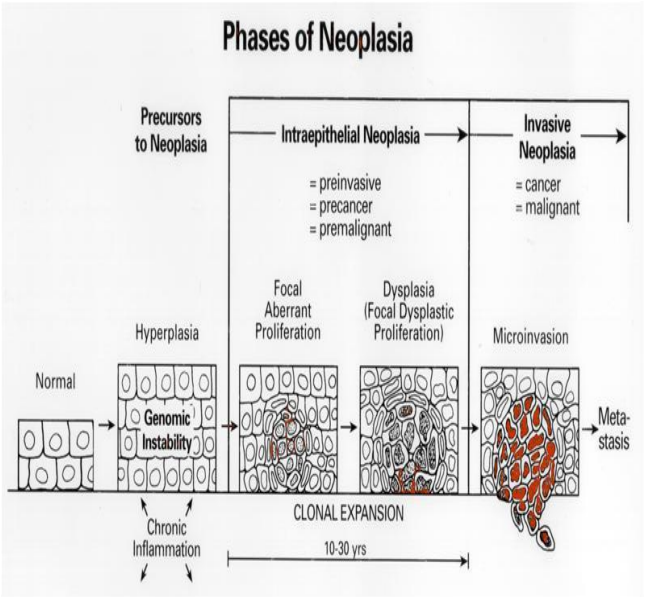
METAPLASIA
VERSUS
DYSPLASIA

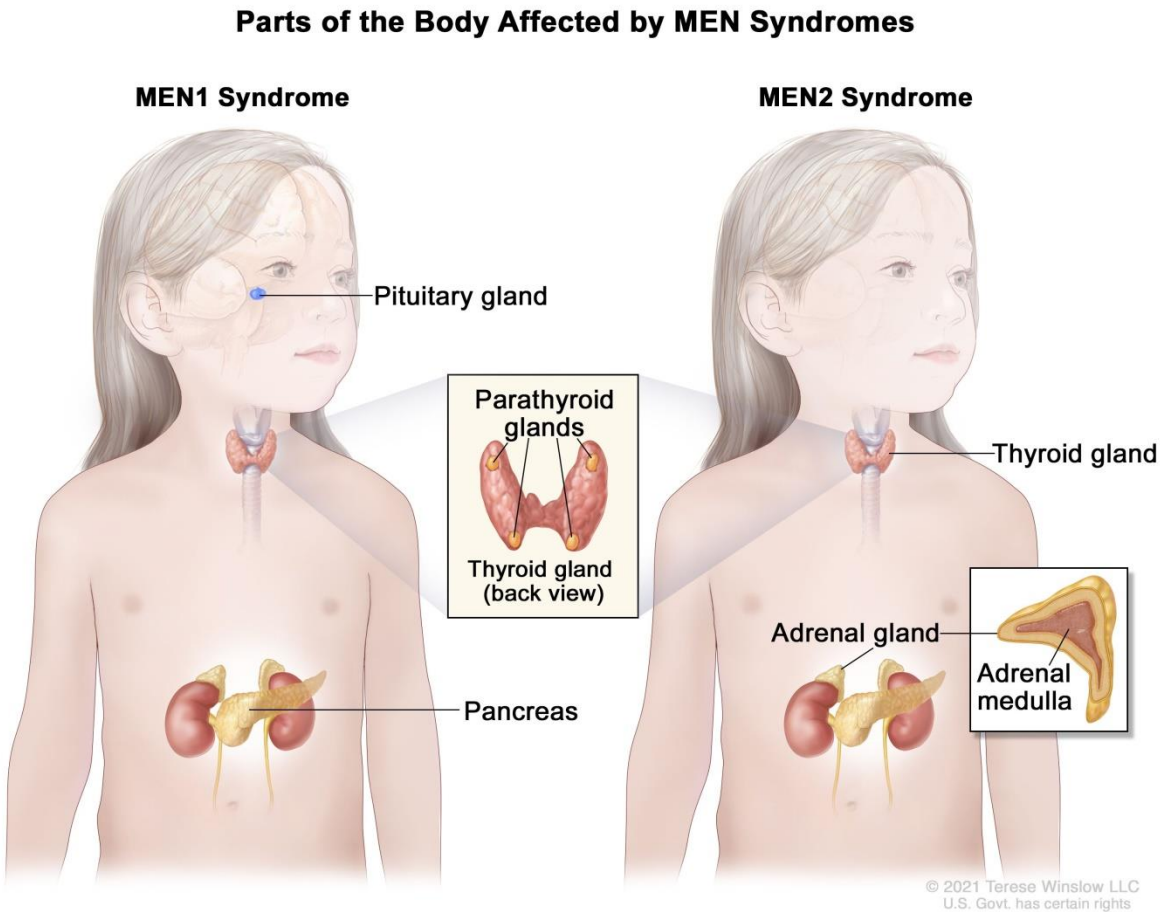
METAPLASIA	DYSPLASIA
Conversion of a mature, differentiated cell into another form of a mature cell type, often following injury or insult	Development of abnormal types of cells within a tissue, which may signify a stage preceding the development of cancer
Conversion in cell type	Change in the phenotype of cells or a tissue
Occurs in various types of tissues	Mainly occurs in the epithelium
An adaptive process that occurs due to an external stimulus	Occurs due to the alteration of genetic material
A reversible process	An irreversible process
Does not lead to the formation of cancers	May cause cancers

Neoplasia

neo = new, plasia = tissue or cells

- Abnormal growth and proliferation of abnormal cells or abnormal amounts of cells due to a benign or malignant process





HYPERPLASIA VERSUS NEOPLASIA

HYPERPLASIA	NEOPLASIA
The enlargement of an organ or tissue caused by an increase in the reproduction rate of its cells, often as the initial stage in the development of cancer	The presence of formation of new, abnormal growth of tissue, which is not under physiologic control
The abnormal multiplication of cells that look normal	The uncontrolled cell proliferation with the loss of control of physiologic processes
Occurs either due to physiological or pathological conditions	Occurs due to genetic conditions
Stops when the stimulus is removed in hyperplasia	Contains continuous cell growth
Mainly benign	Mainly malignant
Examples: Fibroma, gingival enlargement	Examples: Osteoma, squamous cell carcinoma

METASTASIS

- Metastasis is the movement or spreading of cancer cells from one organ or tissue to another and proliferate at the new site.
- Cancer cells usually spread through the bloodstream or the lymph system.
- The tumor mass can also spread locally, compress other structures, and damage surrounding tissues.

Types of Cancer

Benign

Do not invade or metastasize
Slow growing
Low mitotic rate
Clearly demarcated from surrounding tissue – encapsulated or pseudo capsule
Nuclear morphology often normal
Mitotic figures normal
Clonal chromosome abnormalities –not aneuploid

Malignant

Invade and metastasize
Not demarcated clearly
Surface often ulcerated and necrotic
Cut surface heterogenous
Often high mitotic rate
Rapid growth
Nuclei pleomorphic, hyperchromatic
Abnormal mitoses
Usually aneuploid

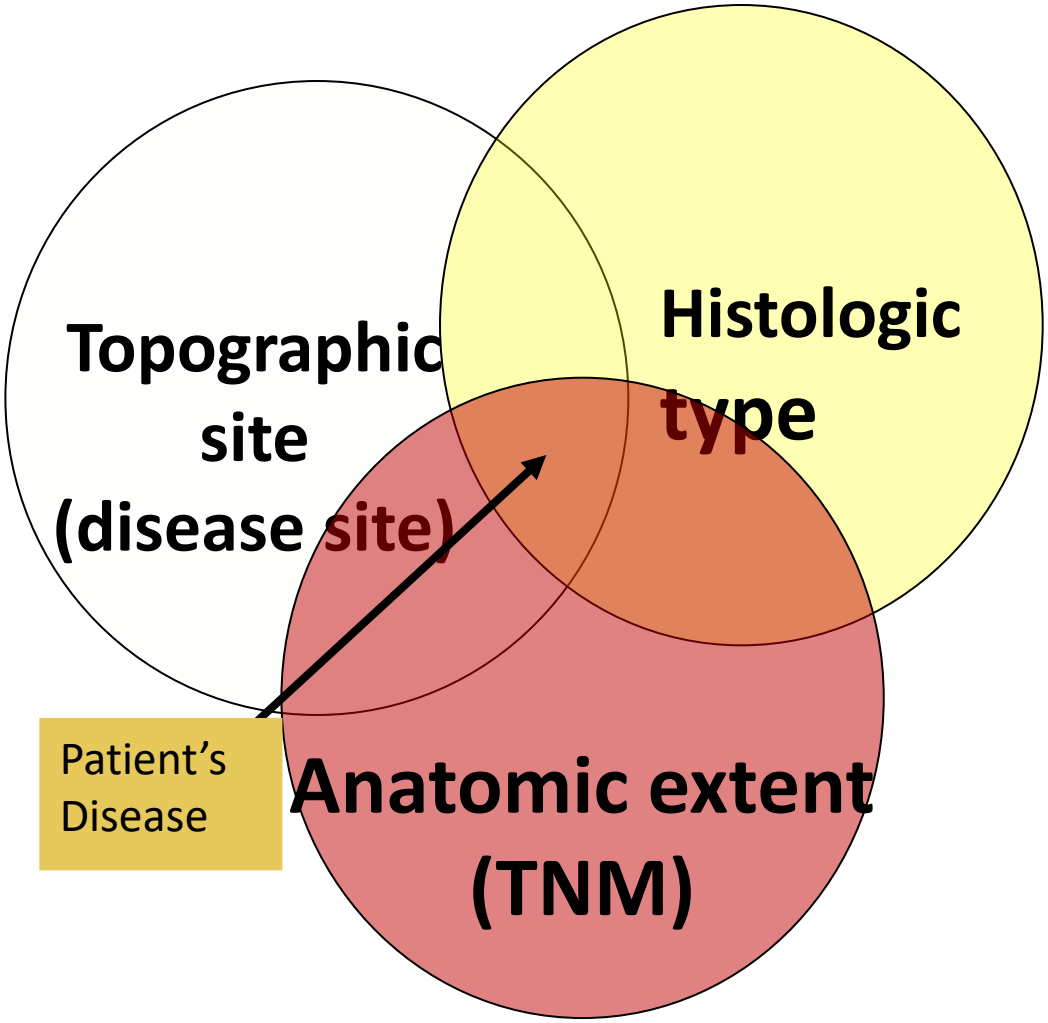
Tumor characteristics

- Invade and destroy the surrounding tissue.
- The cells are genetically unstable
- Loss of normal cell architecture results in cells that are atypical of their origin.
- Lose the ability to perform their usual functions.
- Metastasize, and consequently, recurrences are common after removal or destruction of the primary tumor.

The three axes of cancer classification

- Topographic site
- Histology
- Anatomic extent

  (Staging)



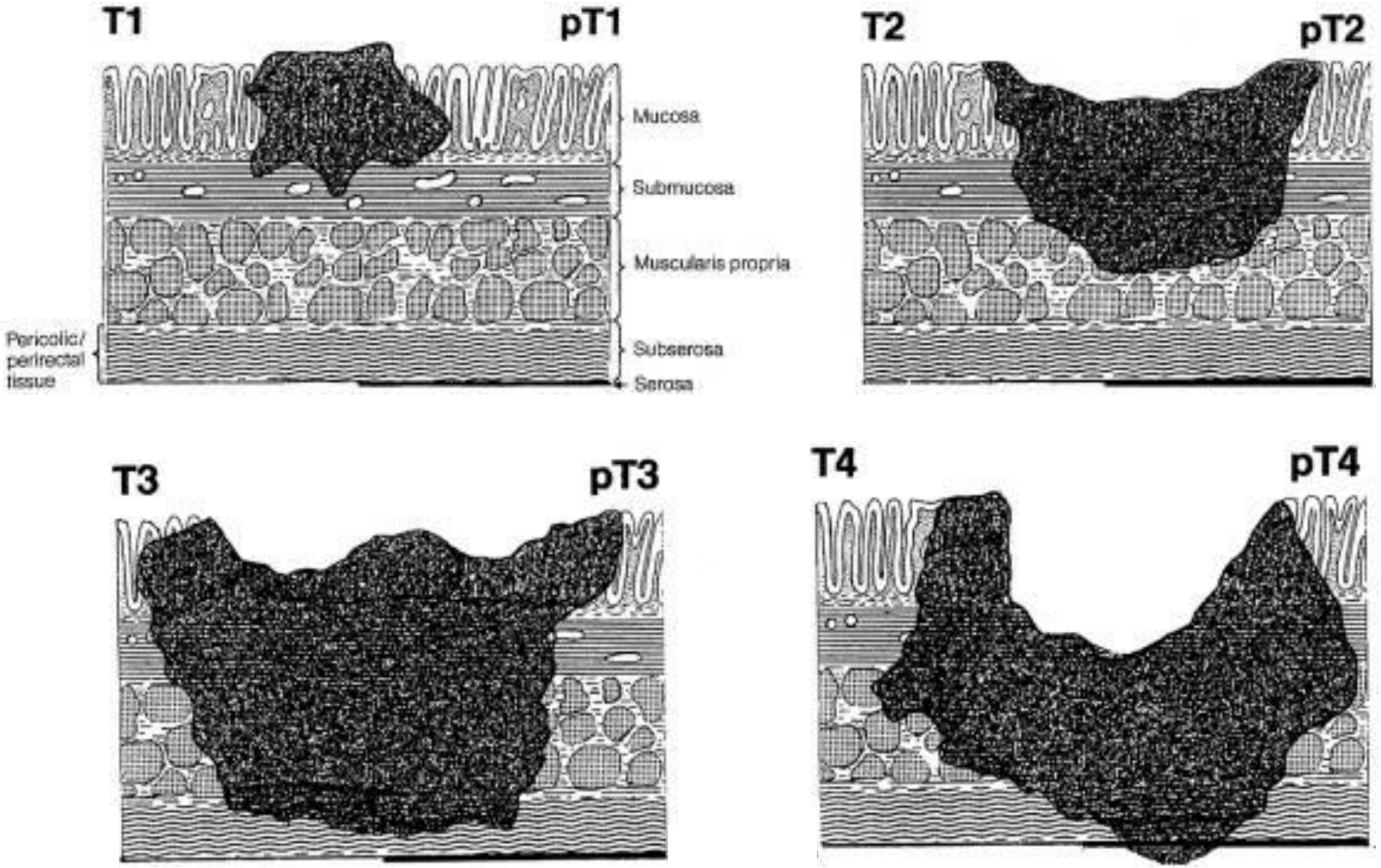
- To aid the clinician in planning treatment
- To give some indication of prognosis
- To assist in evaluating the results of treatment
- To facilitate the exchange of information between treatment centers
- To contribute to continuing investigations of human malignancies

Anatomic Staging

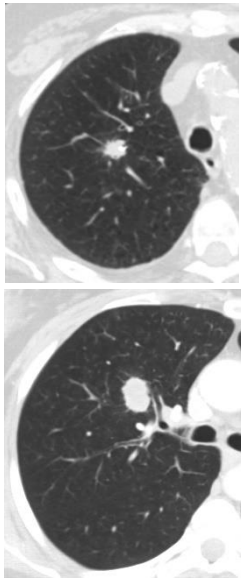
- Based on three components

T	**The extent of the primary tumor**
N	**The absence or presence and extent of regional lymph node metastasis**
M	**The absence or presence of distant metastasis**

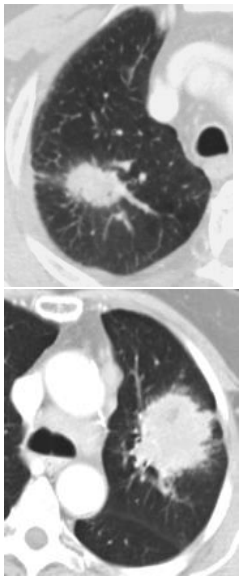
Tumor (T): Colorectal Cancer



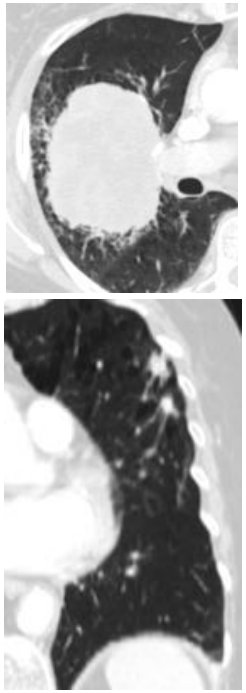
Tumor (T): Lung Cancer

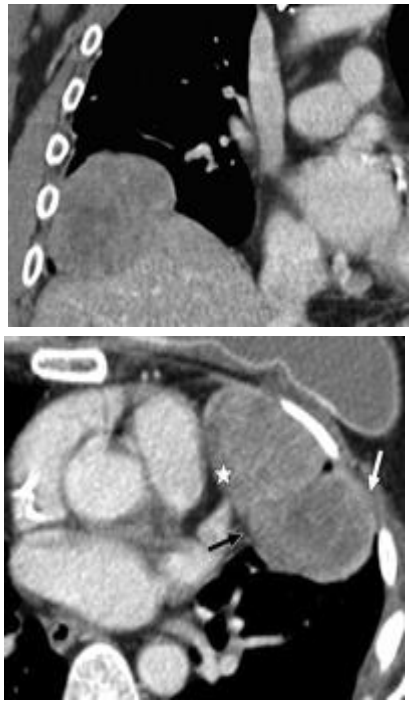


T1

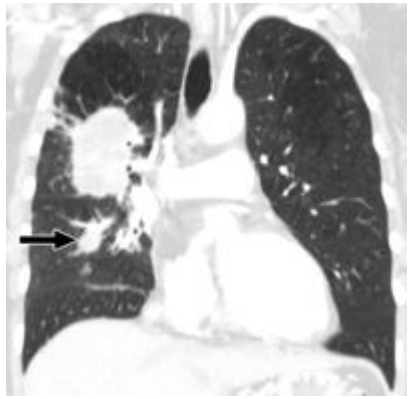


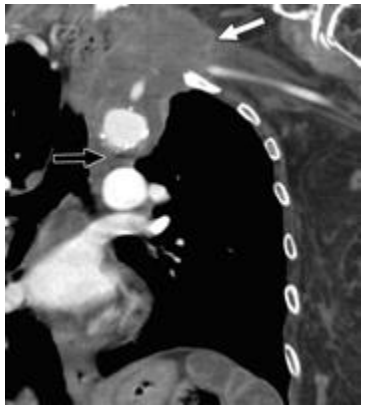
T2



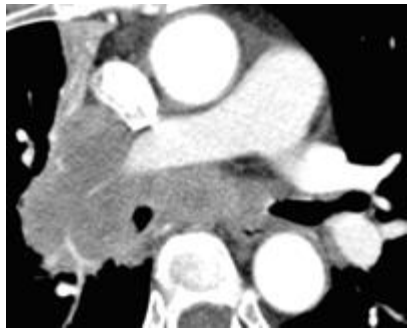


T3





T4



Clinical, Pathologic, Collaborative Staging

- **Clinical (cT, cN, cM)**
  - Before initiation of primary treatment
  - Important in deciding primary treatment
- **Pathologic (pT, pN, pM)**
  - From resected tissues
- **Collaborative (CS)**
  - Clinical, pathologic staging & non anatomic (site-specific) factors

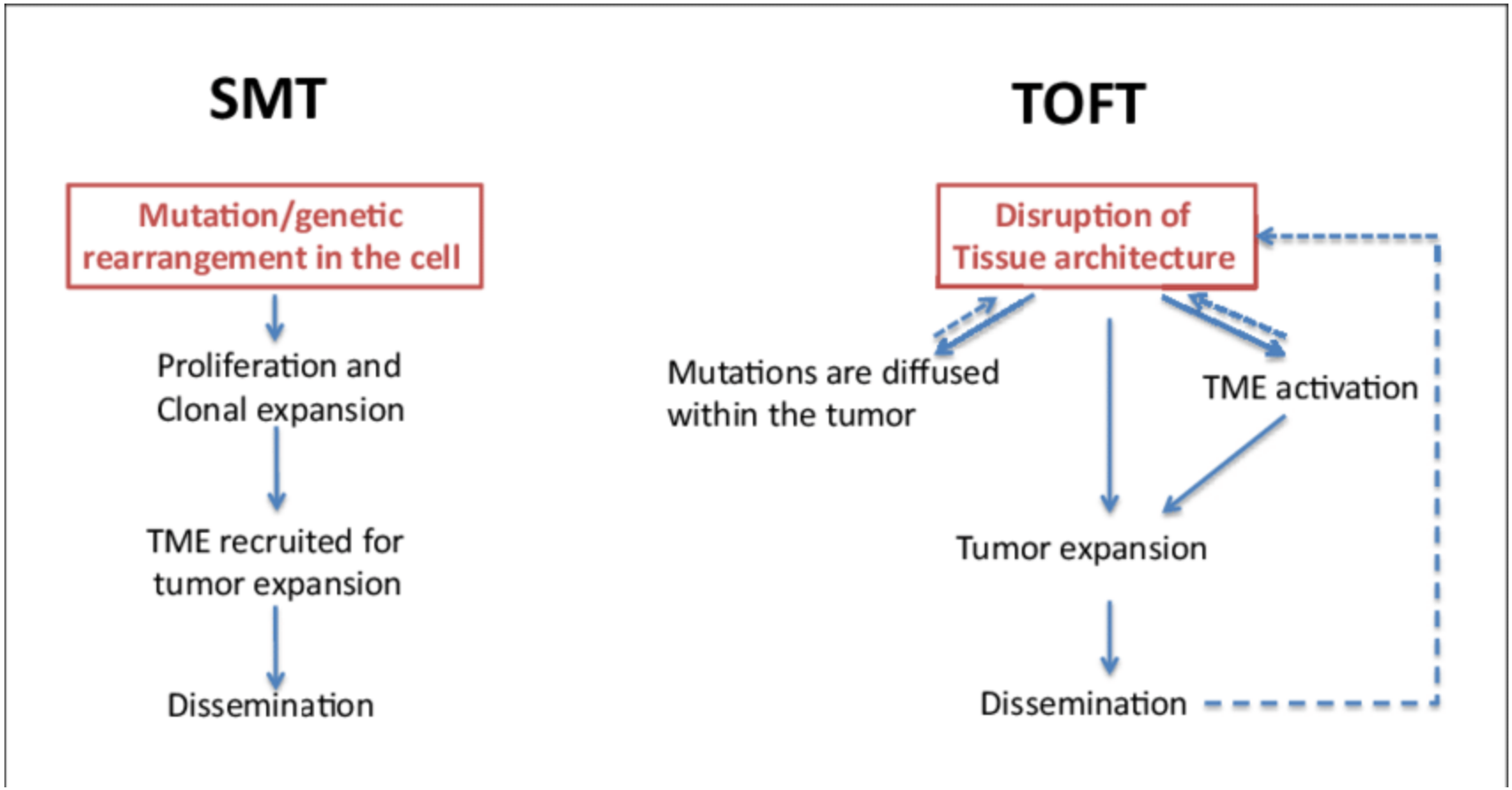
Limitations of Staging

- **Not used in hematologic malignancies**
  - Ann Arbor Staging System
- Not used in pediatric cancer

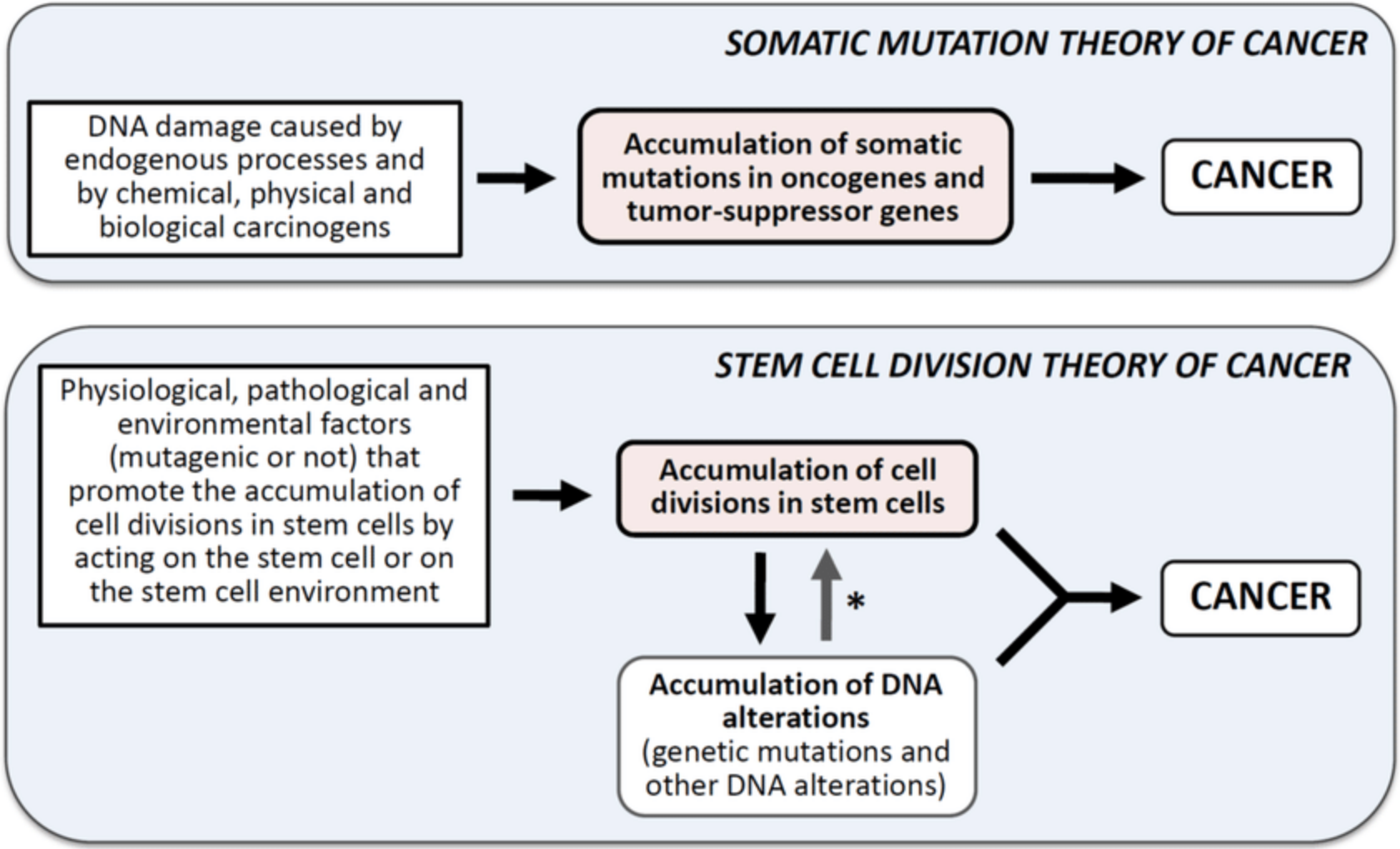
- Not useful in rare diseases
  - Not enough cases to stratify T, N, M (Merkel Cell Cancer)
  - Lumping different histopathologic subtypes (Soft tissue sarcoma: multiple histologies)
- Dominated by anatomic pathology and histology (size, nodes, histopathology, grade)
  - Gradually incorporating other prognostic variables

Suffix	m	Presence of multiple primary T	pT(m)NM
Prefix	y	Post initial treatment (staging after preop treatment)	ycTNM or ypTNM
	r	Recurrent tumor after a disease free interval	rTNM
	a	Autopsy	aTNM

Theories of tumour formation

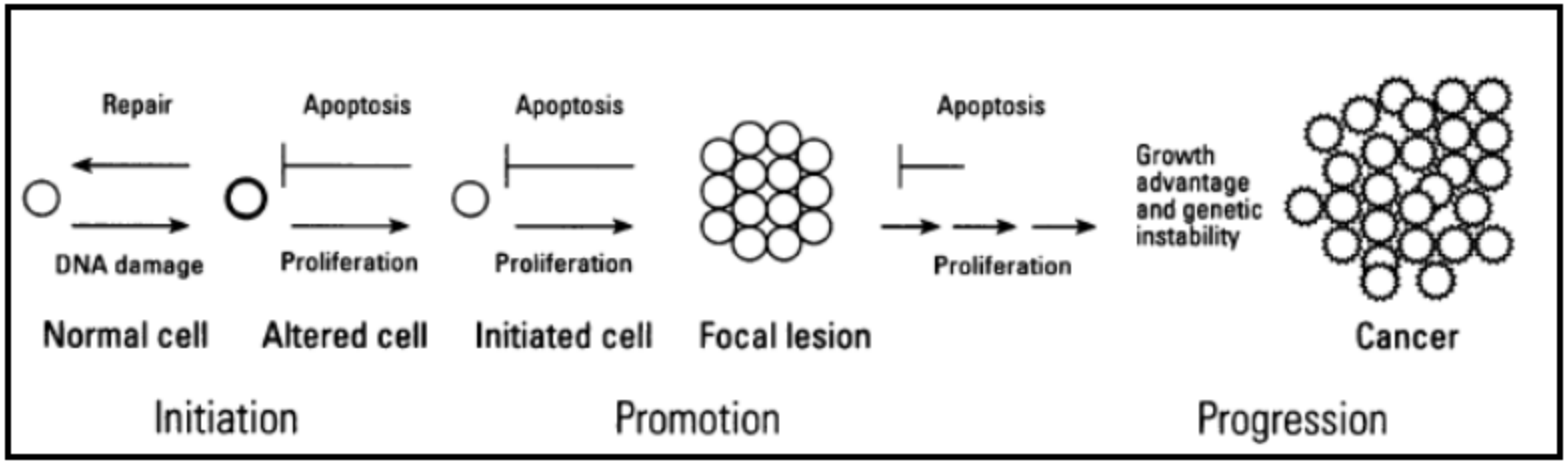


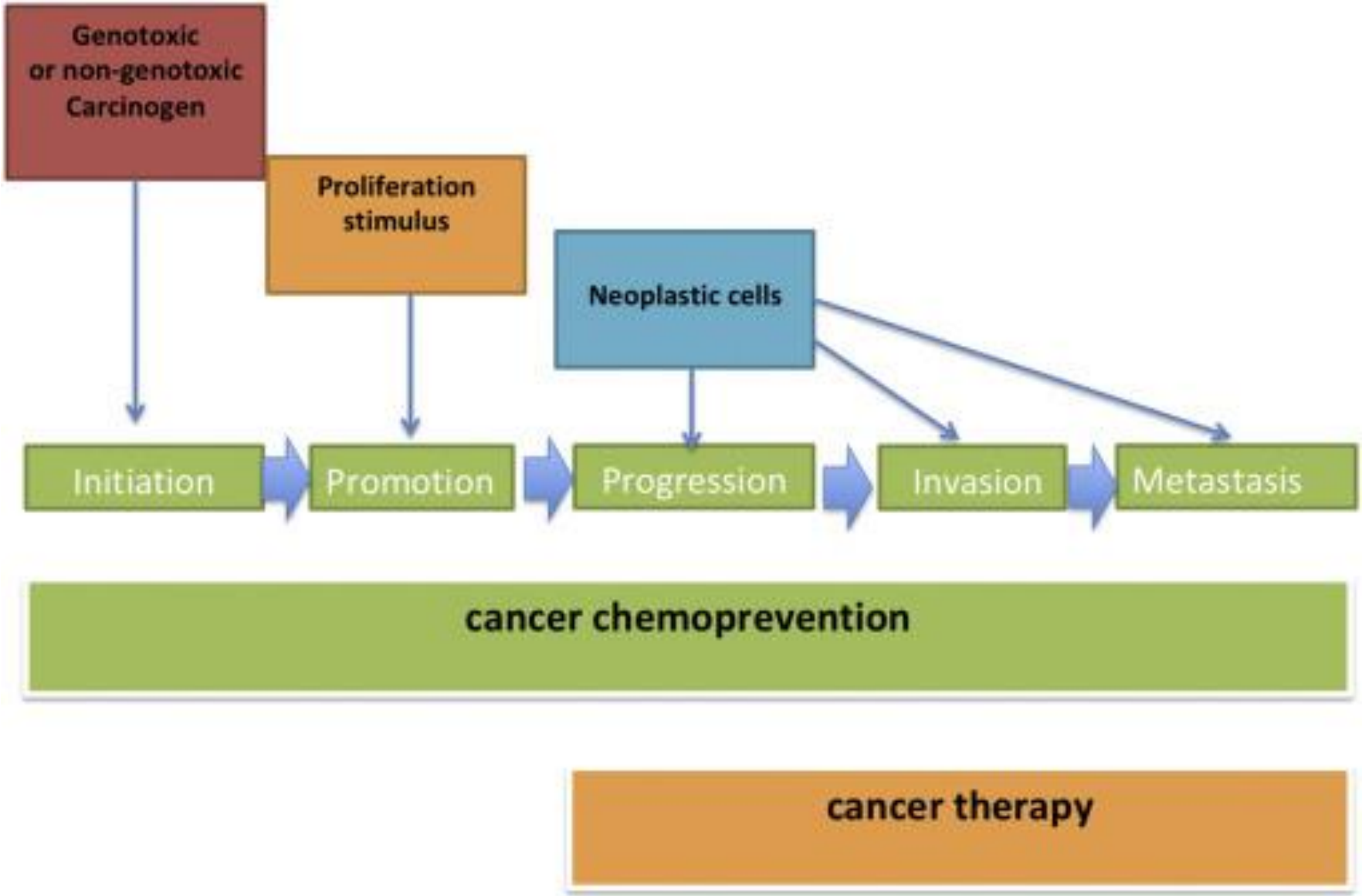
Somatic mutation theory



Mechanisms of carcinogenesis

- Initiation
- Promotion
- Progression

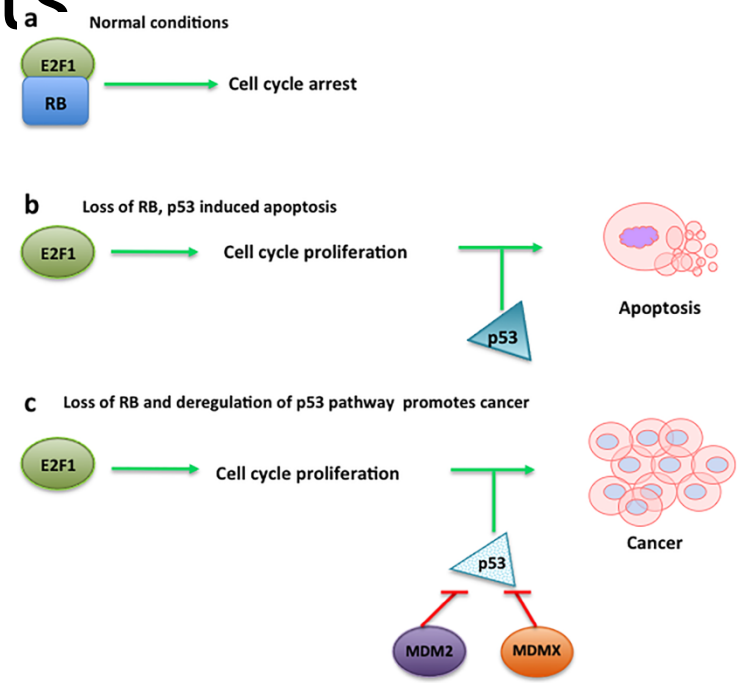


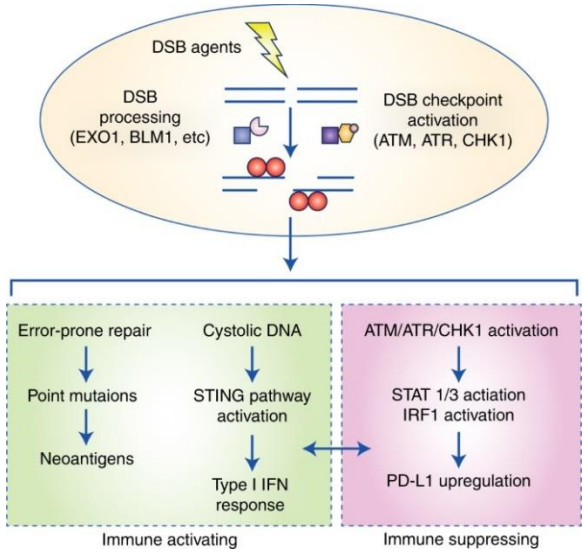

Genotoxic
or non-genotoxic
Carcinogen
Proliferation
stimulus
Neoplastic cells
Initiation
Promotion
Progression
Invasion
Metastasis
cancer chemoprevention
cancer therapy

Check point in cancer

Check points

- All key stages in cell cycle progression are subject to stringent “checkpoints” that determine if various steps in the cell cycle, such as DNA replication, duplication, and partitioning of chromosomes have been successfully completed.
- If a problem is detected then the cell cycle is arrested until it is corrected, or failing that the cell may die or irreversibly exit from cell cycling (senescence).
- These checkpoints are monitored by, amongst others, important tumor suppressors, including RB, p53, and various CKIs, and two damage-sensing pathways – the ATM and the ATR-CHK1 signaling pathways.





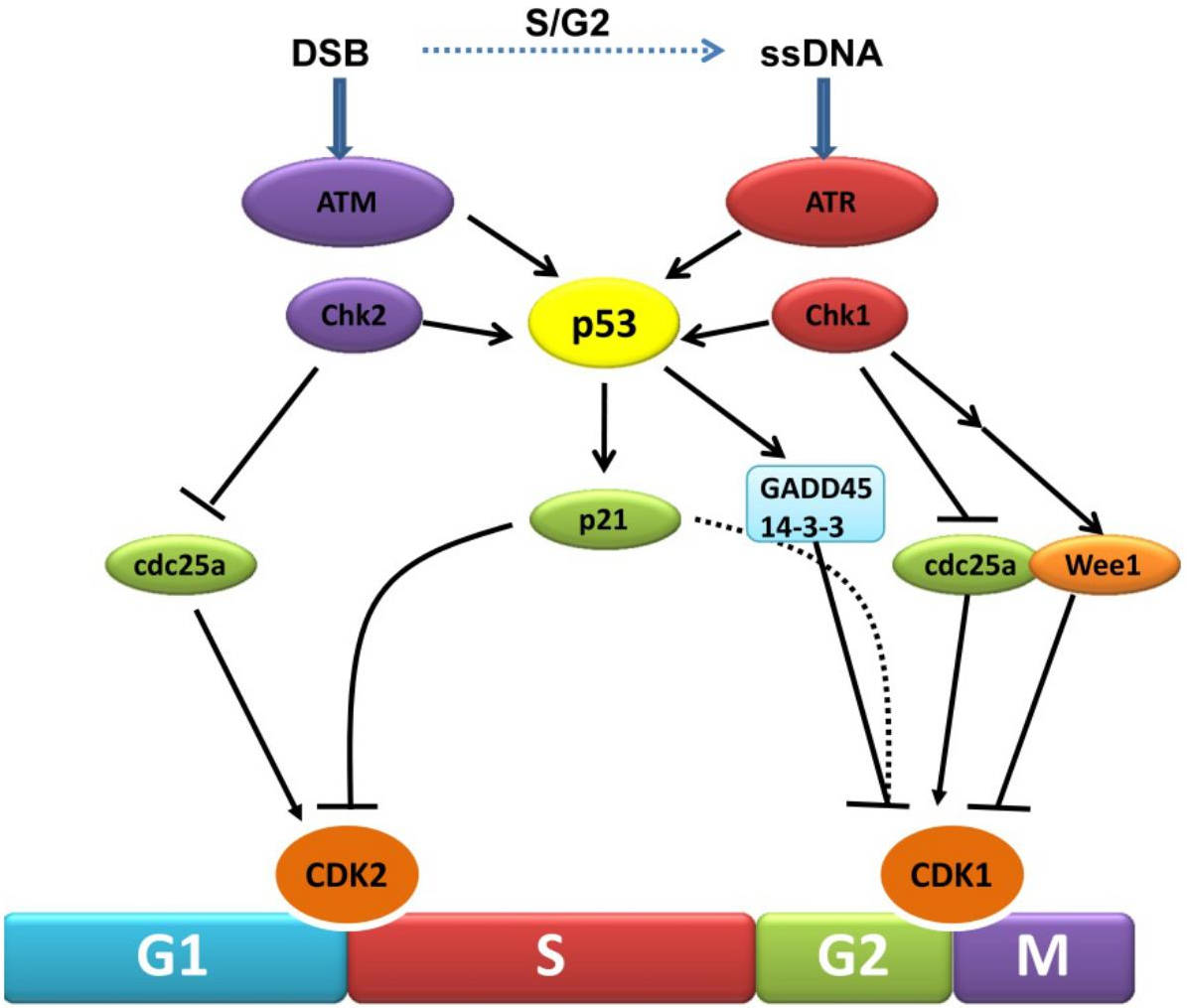
Checkpoint kinase

- **Maintaining the integrity of the genome** is a crucial task of the cell cycle checkpoints.
- Two checkpoint kinases, called Chk1 and Chk2 (also called Cds1), are involved in checkpoint controls that affect a number of genes involved in maintenance of genome integrity
- Chk1 and Chk2 are activated by DNA damage and initiate a number of cellular defense mechanisms that modulate DNA repair pathways and slow down the cell division cycle to allow time for repair.
- If DNA is not successfully mended, the damaged cells usually undergo cell death via apoptosis.
- This process prevents the defective genome from extending its paternity into daughter cells

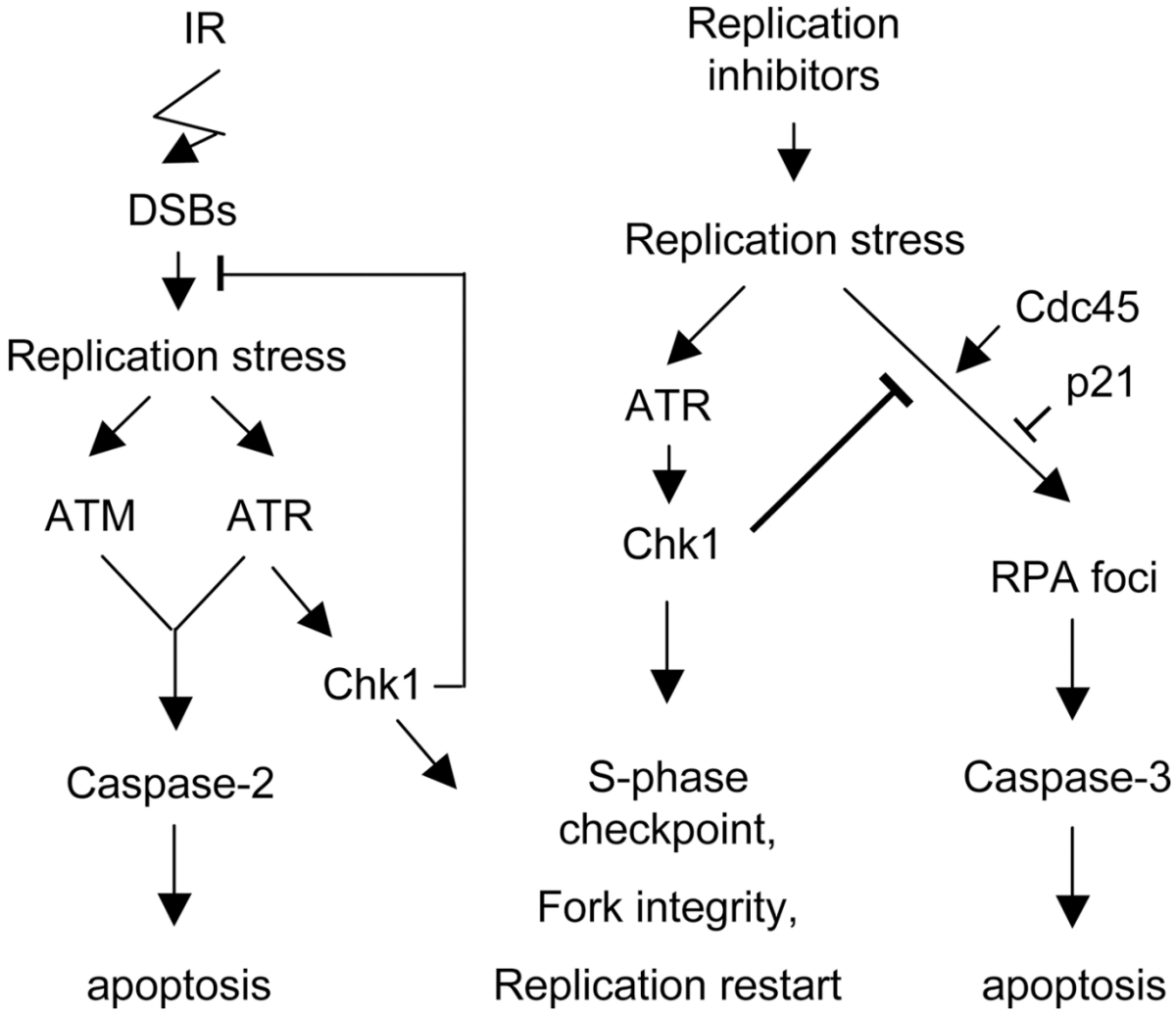
The ATM and ATR-CHK1 signalling pathway

- DNA damage is a key factor both in the evolution and treatment of cancer.
- **Genomic instability** is a common feature of cancer cells, fuelling accumulation of oncogenic mutations, while radiation and diverse genotoxic agents remain important, if imperfect, therapeutic modalities.
- **Cellular responses to DNA damage** are coordinated primarily by **two distinct kinase signaling cascades**, the **ATM–Chk2 and ATR–Chk1 pathways**, which are activated by DNA double-strand breaks (DSBs) and single-stranded DNA respectively

The ATM and ATR-CHK1 signalling pathway

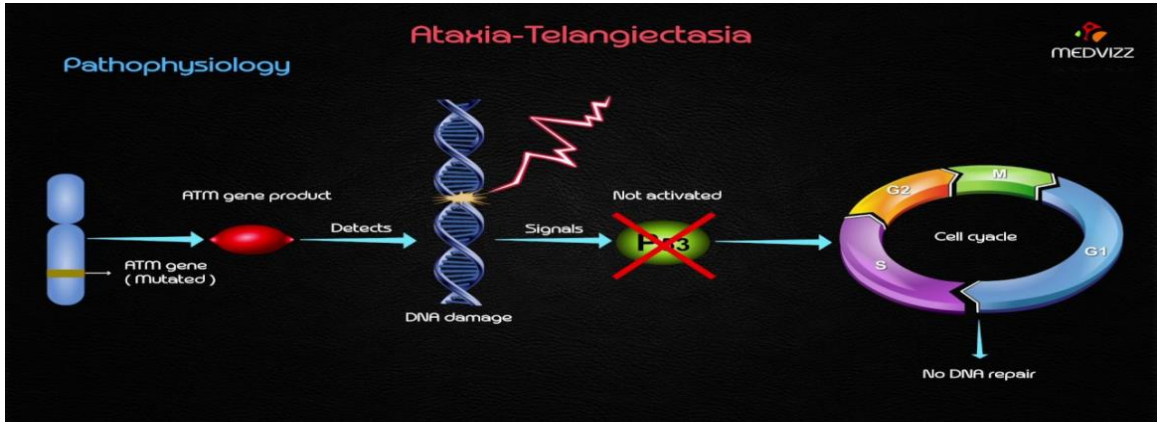


The ATM and ATR-CHK1 signalling pathway



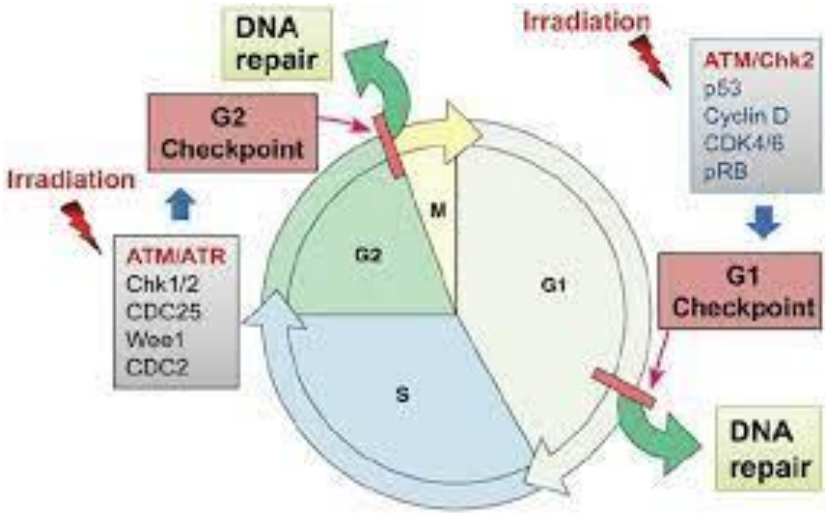
Discovery of ATM

- A-T is a rare inherited autosomal-recessive genetic condition (2nd most common), characterized by dilated blood vessels (telangiectasia) and progressive neurological decline, resulting in a lack of voluntary movement coordination, including gait abnormality (ataxia).
- A-T patients also display immunodeficiency and predisposition to malignancies, especially lymphoid tumors.



Discovery of ATM

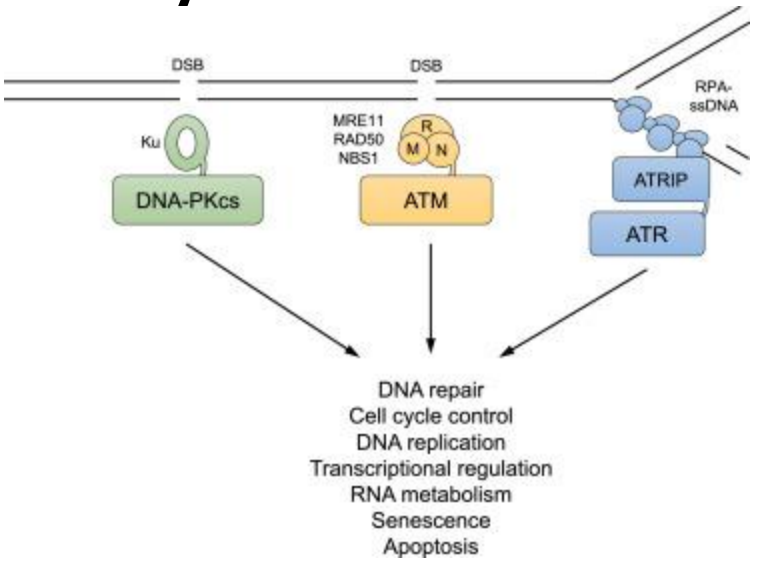
- Later work showed that A-T cells are defective in establishing both the G1/S and G2/M cell-cycle checkpoints in response to IR
- A major insight into why the G1/S checkpoint is defective in A-T cells came when it was found that the tumor suppressor protein p53 is not induced properly in these cells after IR
- When the A-T mutated (ATM) gene was identified it was found that the C terminus of the predicted ATM protein contained a PI3K-like kinase domain.

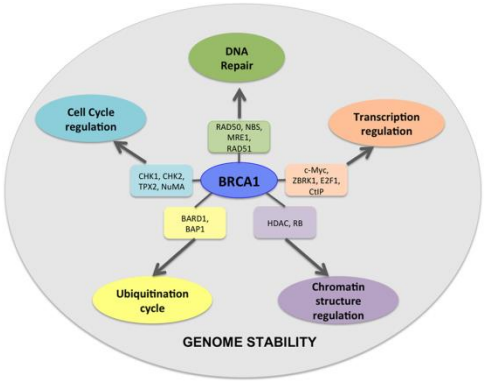


- Although this initially suggested that ATM might function in phospholipid signaling, we now know that it, like DNA-PKcs, is a protein kinase.
- Compared to proteins known at the time, ATM was found to be most homologous to Tel1, a budding yeast protein involved in controlling telomere length and now considered to be the yeast ATM ortholog
- Significantly, ATM was also found to share homology with two other yeast proteins implicated in DNA repair and cell-cycle checkpoint control: budding yeast Mec1/Esr1/Sad3 and fission yeast Rad3

The ATM – CHK2 and ATR-CHK1 signalling pathway

- In response to DSBs, ATM is required both for ATR–Chk1 activation and to initiate DNA repair via homologous recombination (HRR) by promoting formation of single-stranded DNA at sites of damage through nucleolytic resection.
- Interestingly, cells and organisms survive with mutations in ATM or other components required for HRR, such as BRCA1 and BRCA2, but at the cost of genomic instability and cancer predisposition

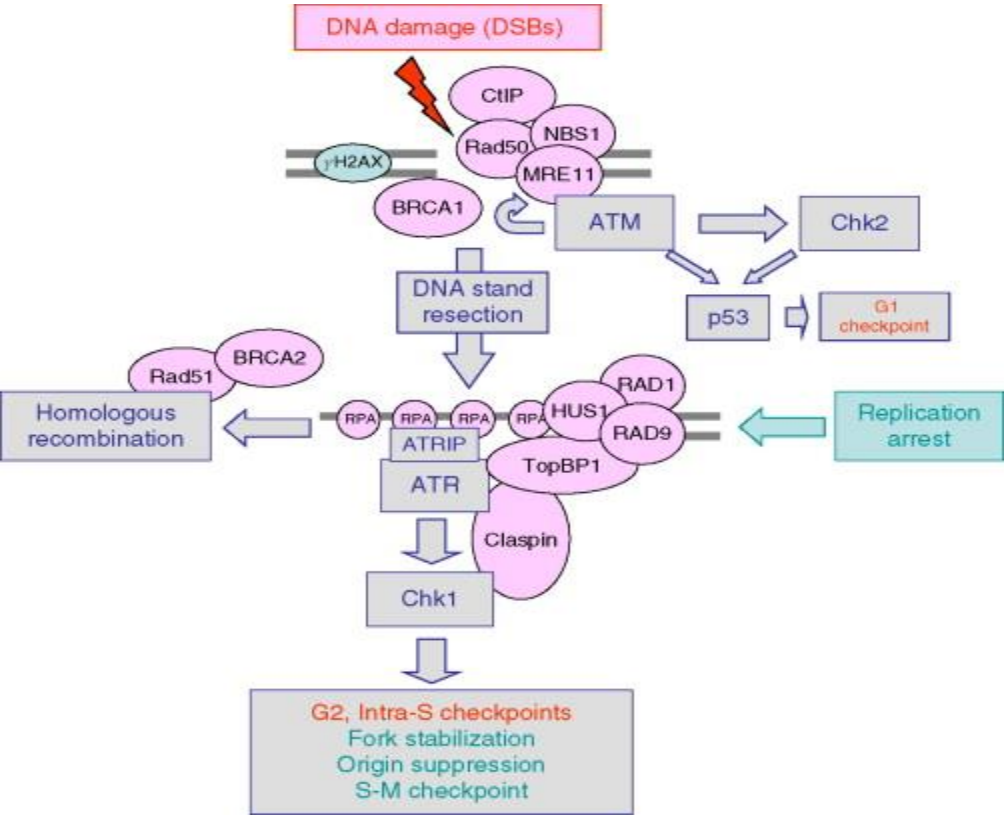


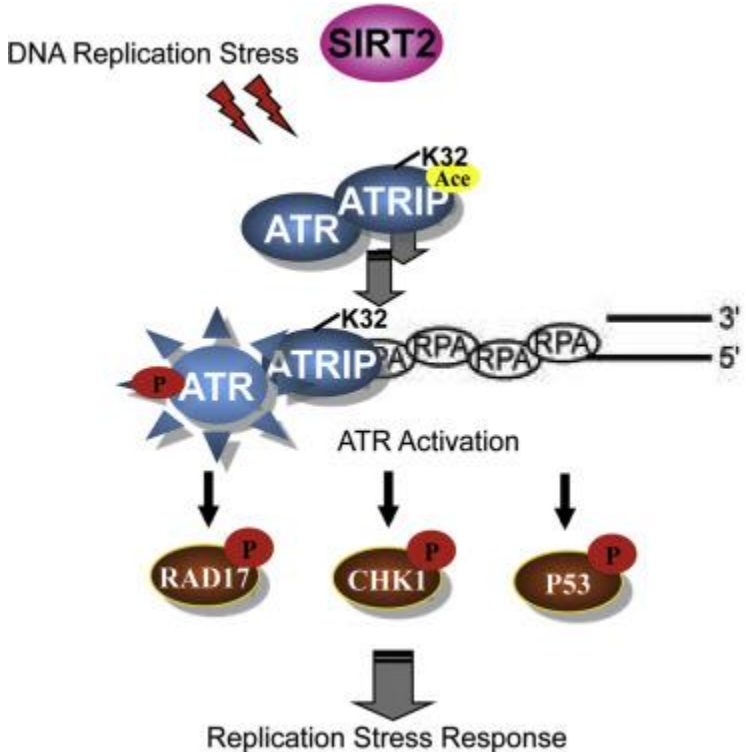


ACTIVATION OF THE ATM–CHK2 AND ATR–CHK1 DNA PATHWAYS

- In vertebrates, the two main signaling pathways activated by DNA damage consist of the ATM–Chk2 and ATR–Chk1 protein kinases
- ATM and ATR are large kinases with sequence similarity to lipid kinases of the phosphatidylinositol-3-kinase (PI3K) family, but which phosphorylate only protein substrates.
- Key among these substrates are the **serine–threonine checkpoint effector kinases,** Chk1 and Chk2, which are selectively phosphorylated and activated by ATR and ATM respectively to trigger a wide range of distinct downstream responses

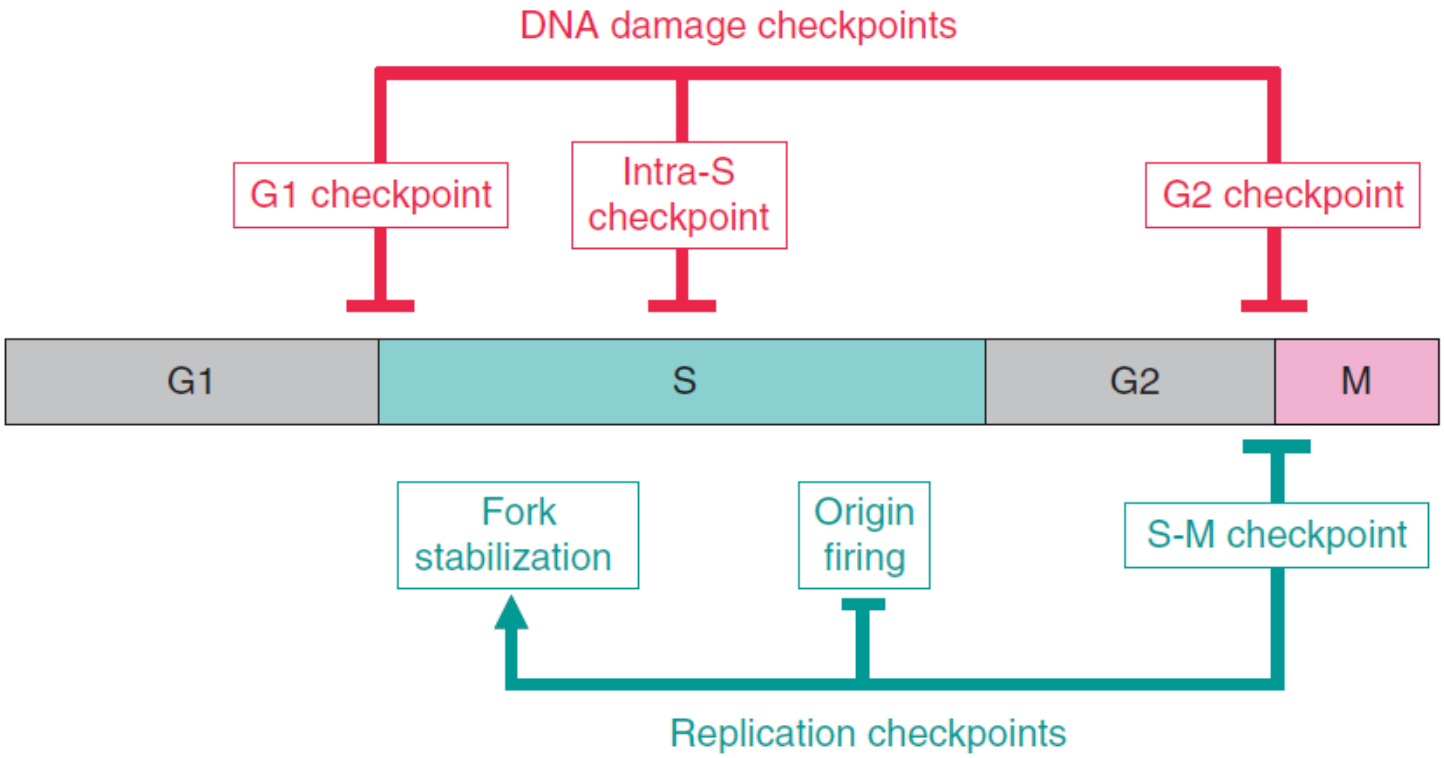
- The ATM–Chk2 and ATR–Chk1 pathways respond to different aberrant DNA structures; ATM is recruited to and activated primarily at DNA double-strand breaks (DSBs) in conjunction with the MRE11:RAD50: NBS1 (MRN) sensor complex), whereas ATR is activated via recruitment to tracts of single-stranded DNA (ssDNA) in association with its partner protein, ATRIP

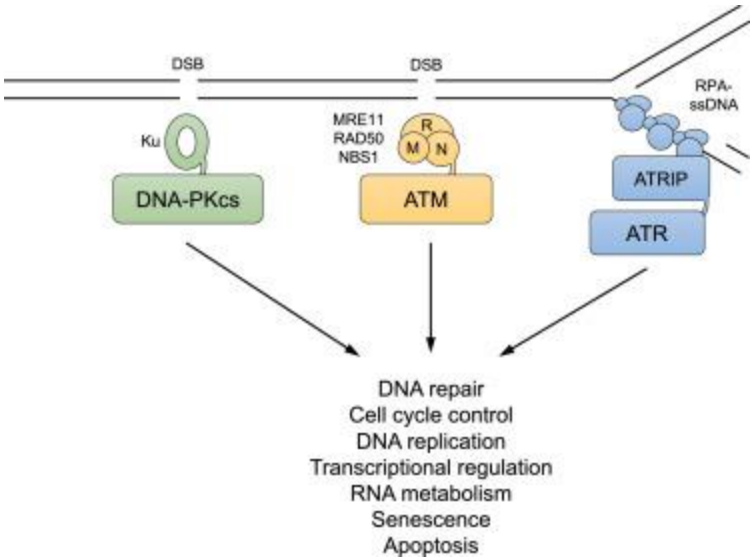




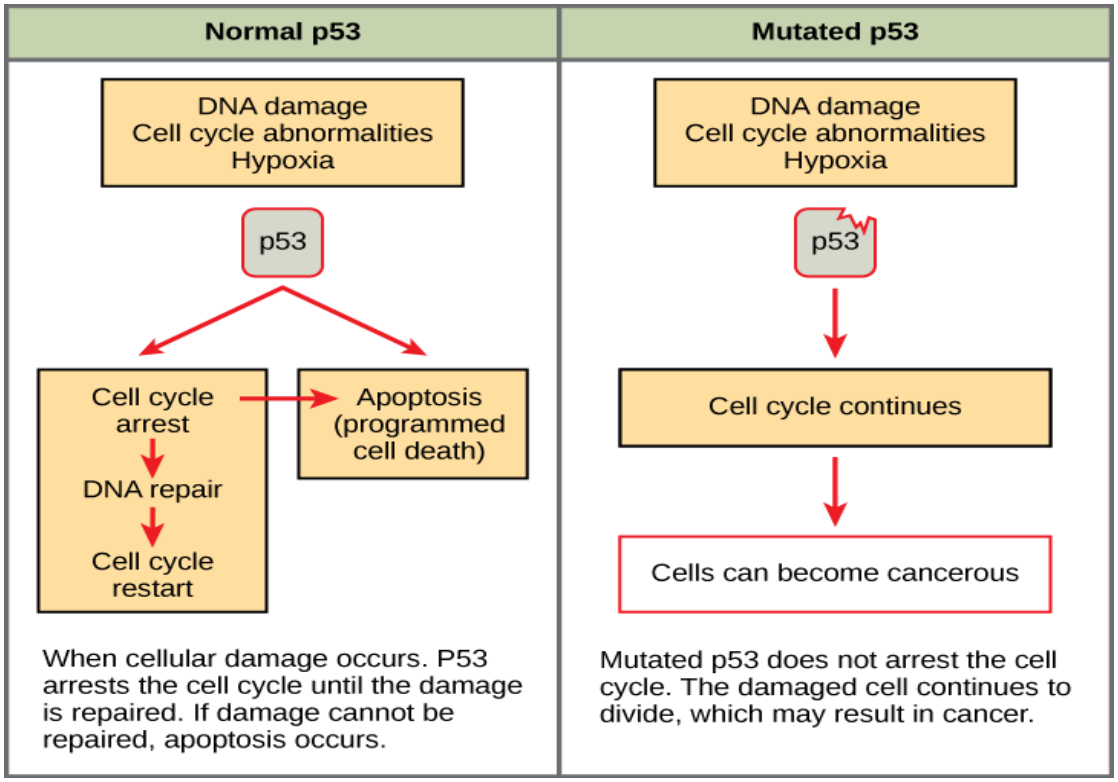
Activation of the ATM–Chk2 and ATR–Chk1 pathways

- The ATM–Chk2 and ATR– Chk1 pathways are activated selectively by DSBs and tracts of ssDNA complexed with RPA respectively.
- **Phosphorylation** events are indicated by (P) in red, **acetylation** by (Ac) in yellow.
- DSBs in chromatin stimulate ATM autophosphorylation and acetylation but full activation also requires recruitment to sites of damage in conjunction with the MRN complex where ATM modifies multiple substrates including the downstream effector kinase, Chk2, leading to Chk2 activation and downstream signal transduction.
- ATR is recruited to tracts of ssDNA-RPA through its interacting partner, ATRIP, where it phosphorylates and activates Chk1 in conjunction with the TopBP1 and Claspin mediator proteins.
- Two additional mediator proteins, Timeless and Tipin, also contribute to ATR–Chk1 activation


DNA damage checkpoints
G1 checkpoint
Intra-S checkpoint
G2 checkpoint
G1
S
G2
M
Fork stabilization
Origin firing
S-M checkpoint
Replication checkpoints


DSB
DSB
Ku
DNA-PKcs
MRE11
RAD50
NBS1
R
M
N
ATM
RPA-ssDNA
ATRIP
ATR
DNA repair
Cell cycle control
DNA replication
Transcriptional regulation
RNA metabolism
Senescence
Apoptosis

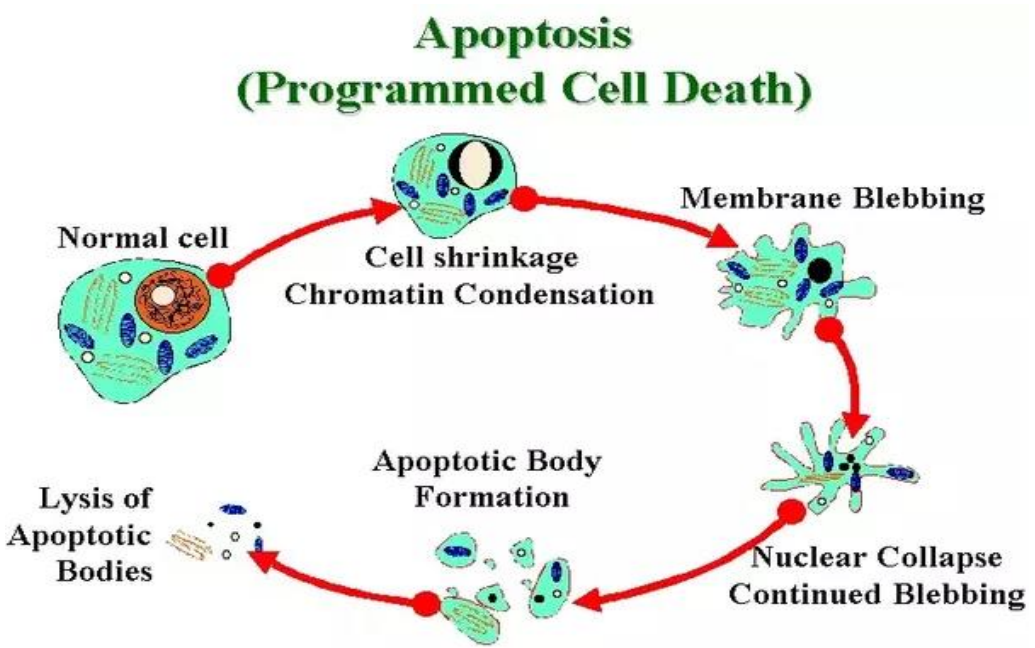
- An important checkpoint involves the tumor suppressor **p53**, which ensures that the S phase is blocked after DNA damage.
- This key checkpoint prevents replication of mutated DNA until the damage has been repaired or the cell is eliminated by its own death (Apoptosis).



‘osis’ in cancer

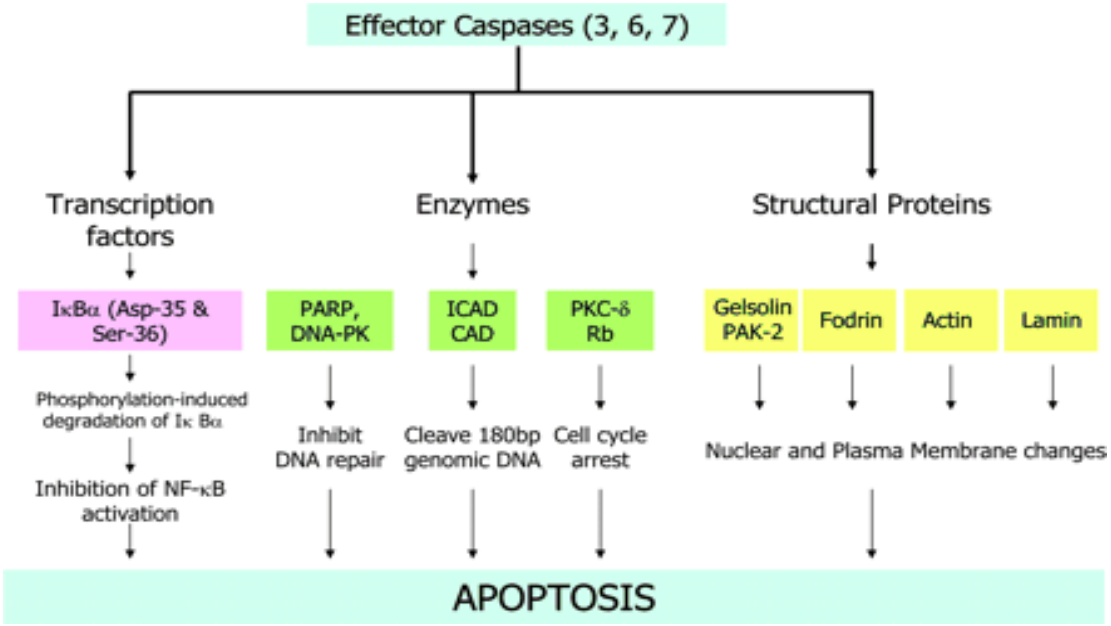
Apoptosis

- Programmed cell death
- cell suicide mechanism that enables multicellular organisms to regulate cell number in tissues and to eliminate unneeded or aging cells as an organism develops



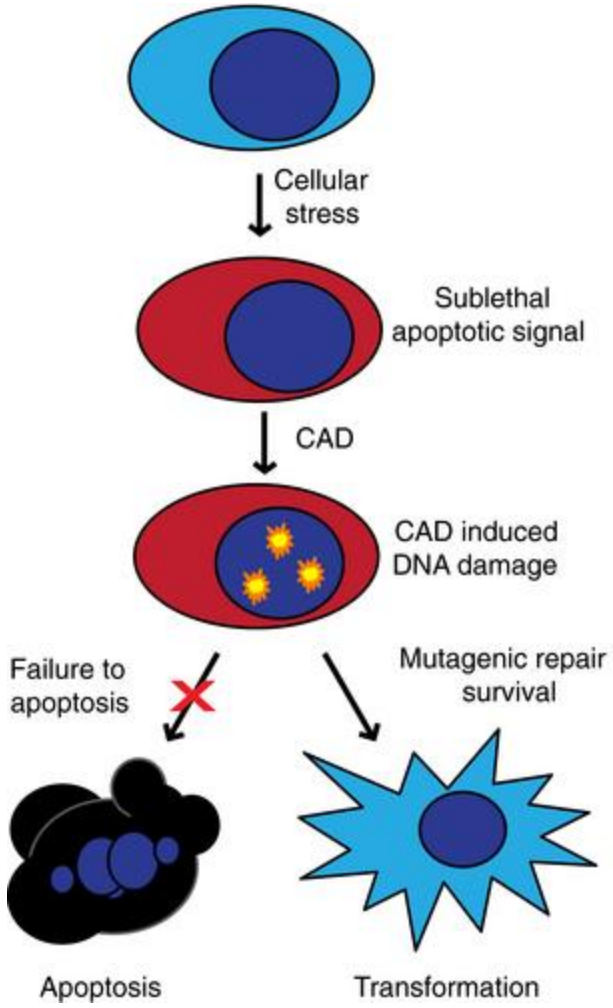
The apoptosis pathway

- involves a series of positive and negative regulators of proteases called caspases, which cleave substrates, such as poly (ADP-ribose) polymerase, actin, fodrin, and lamin.



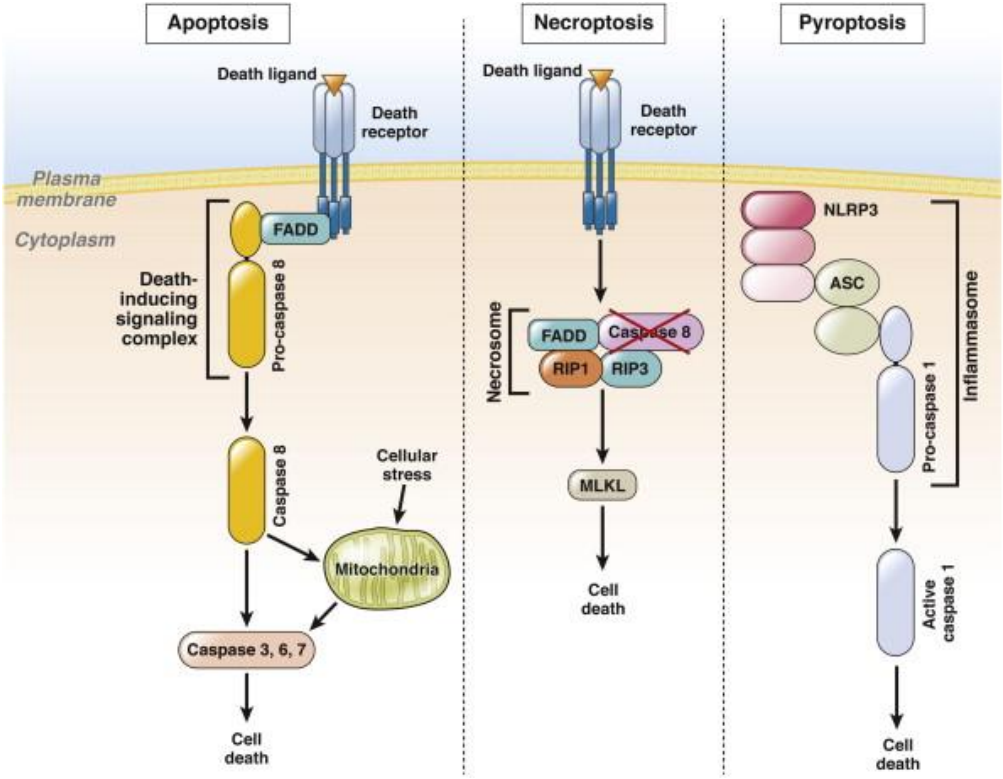
The apoptosis pathway

- Apoptosis is accompanied by the intranucleosomal degradation of chromosomal DNA, producing the typical DNA ladder seen for chromatin isolated from cells undergoing apoptosis.
- The endonuclease responsible for this effect is called caspase-activated DNase, or CAD.



Death receptors

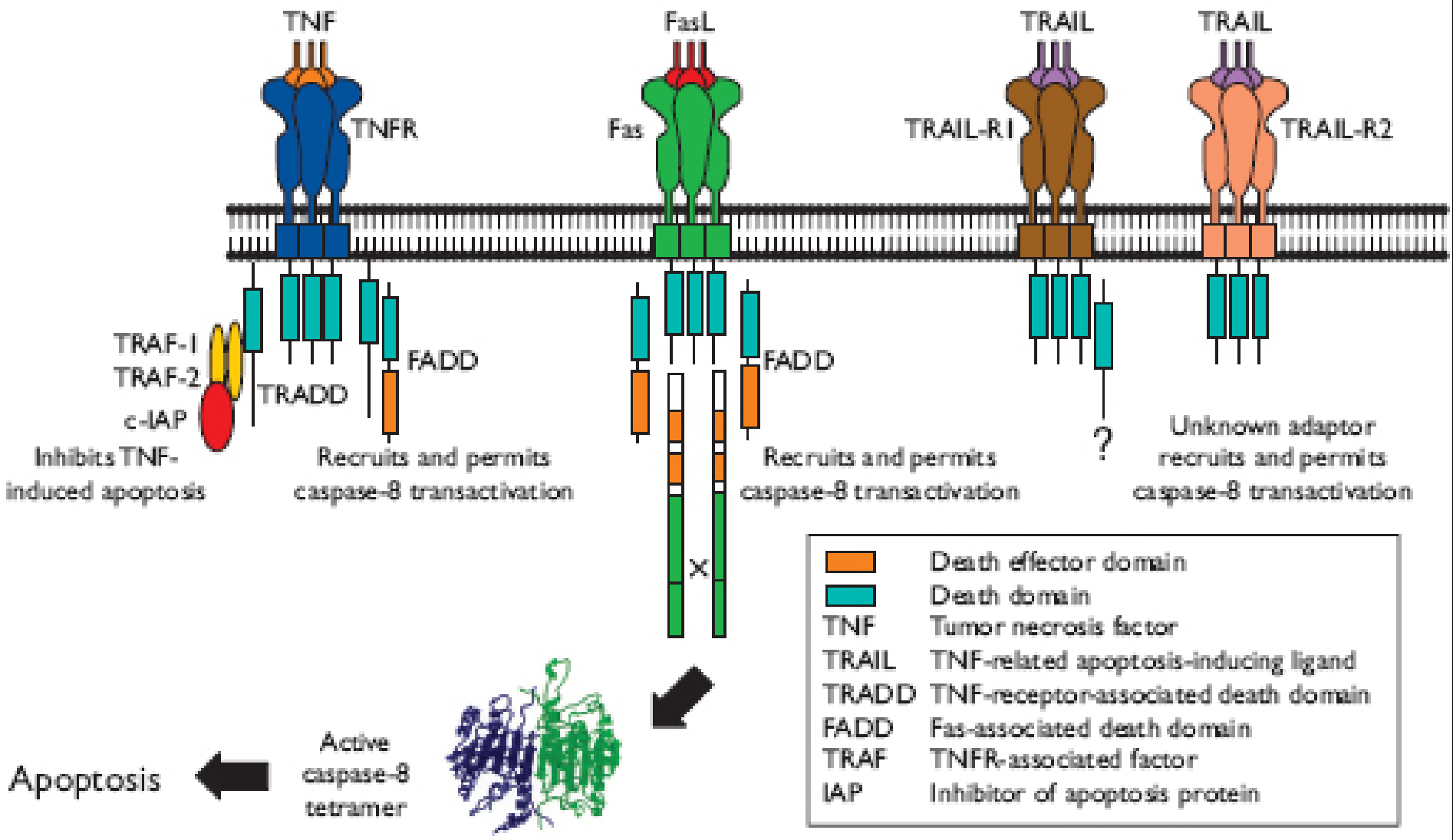
- cell surface receptors that transmit apoptotic signals initiated by death ligands.
- The death receptors sense signals that tell the cell that it is in an uncompromising environment and needs to die.
- These receptors can activate the **death caspases** within seconds of ligand binding and induce apoptosis within hours.



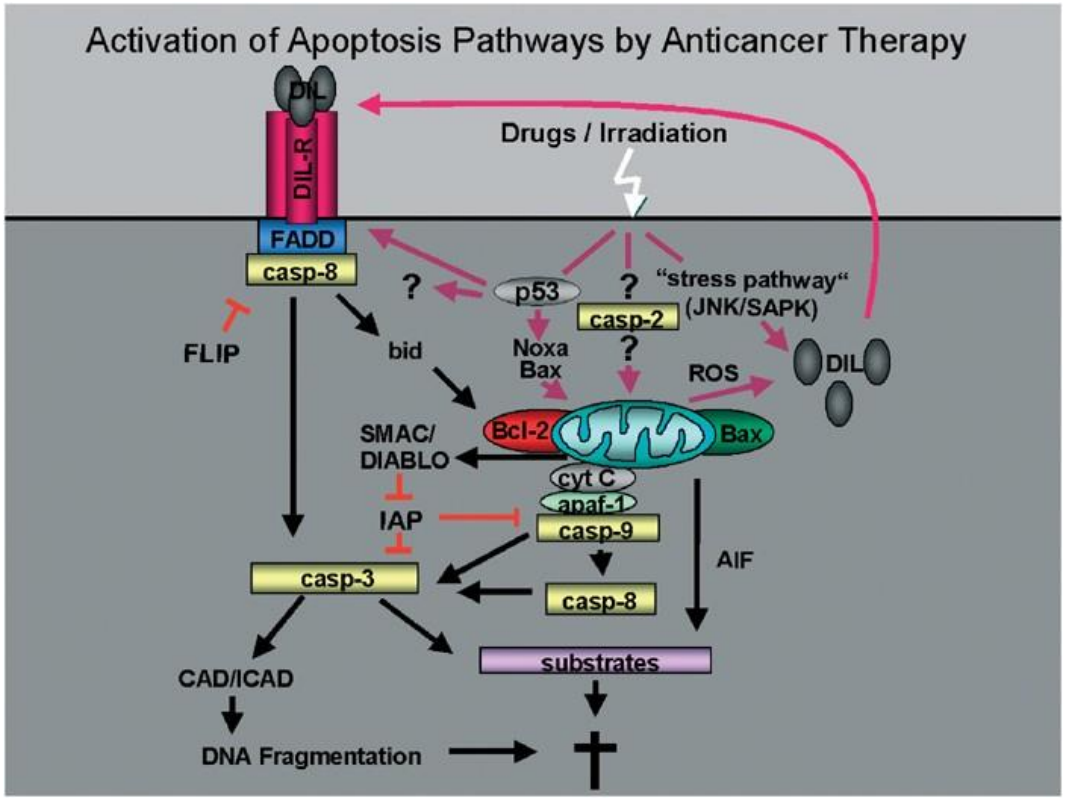
Death receptors

- belong to the tumor necrosis factor (TNF) receptor gene superfamily and have the typical cystine rich extracellular domains and an additional cytoplasmic sequence termed the **death domain.**
- The best-characterized death receptors are **CD95** (Fas or Apo1) and TNF receptor TNFR1 (p55 or CD120a).
- **TNFRI / P55 /CD120a**
- The importance of the apoptotic pathway in cancer progression is seen when there are mutations that alter the ability of the cell to undergo apoptosis and allow transformed cells to keep proliferating rather than die.

TNF-family death receptors



- Such genetic alterations include the **translocation of the bcl-2 gene** in lymphomas that prevents apoptosis and promotes resistance to cytotoxic drugs.
- Other genes involved as players on the apoptosis stage include c-myc, p53, c-fos, and the gene for interleukin-1b-converting enzyme (ICE).
- Various oncogene products can suppress apoptosis. These include adenovirus protein E1b, ras, and n-abl



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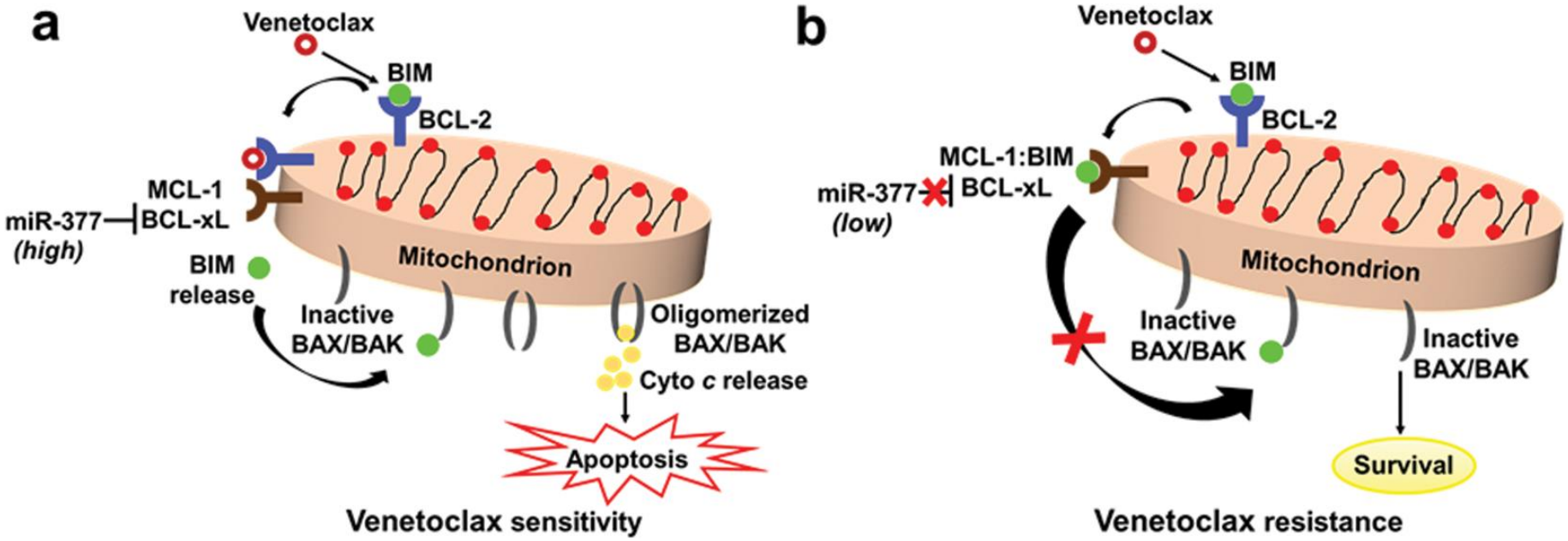

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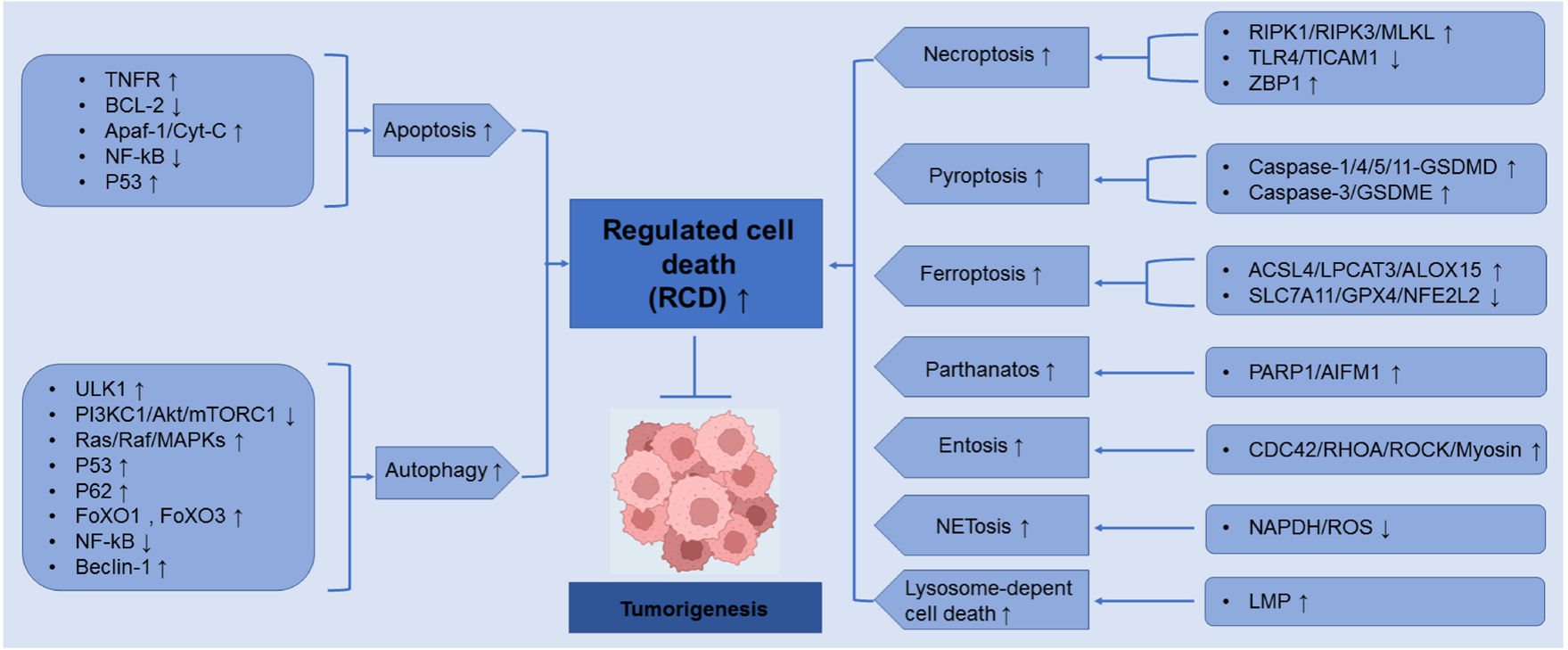
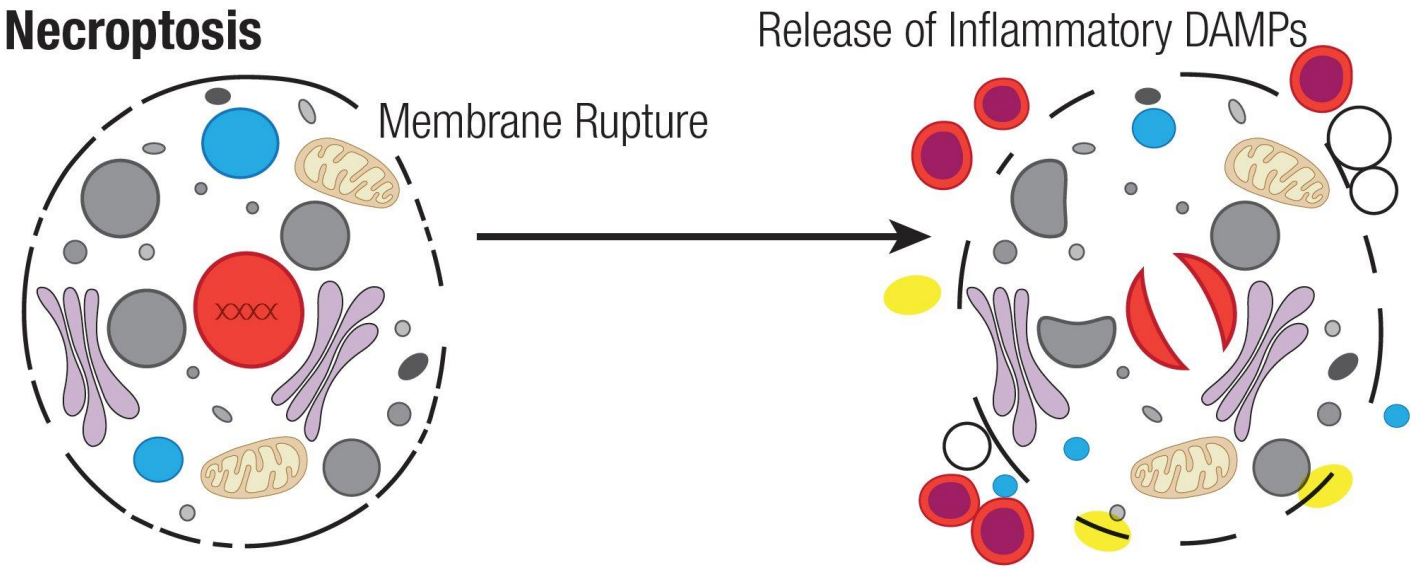
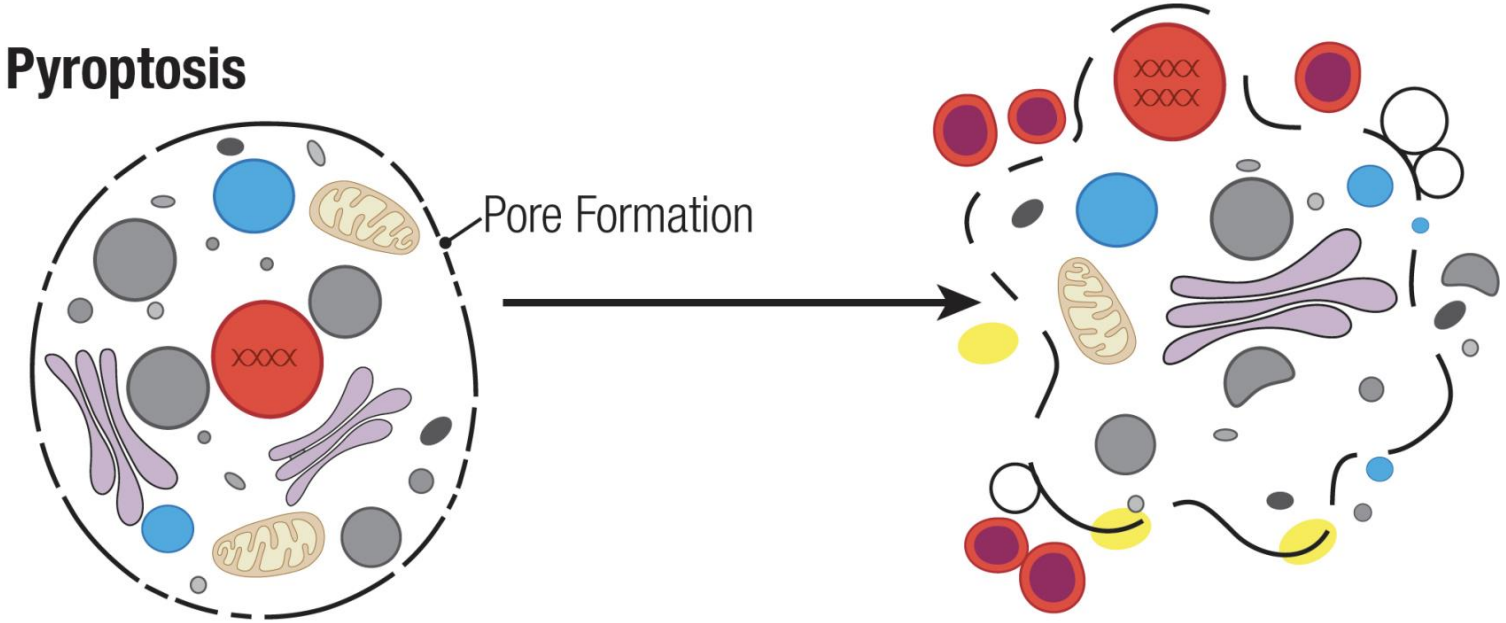


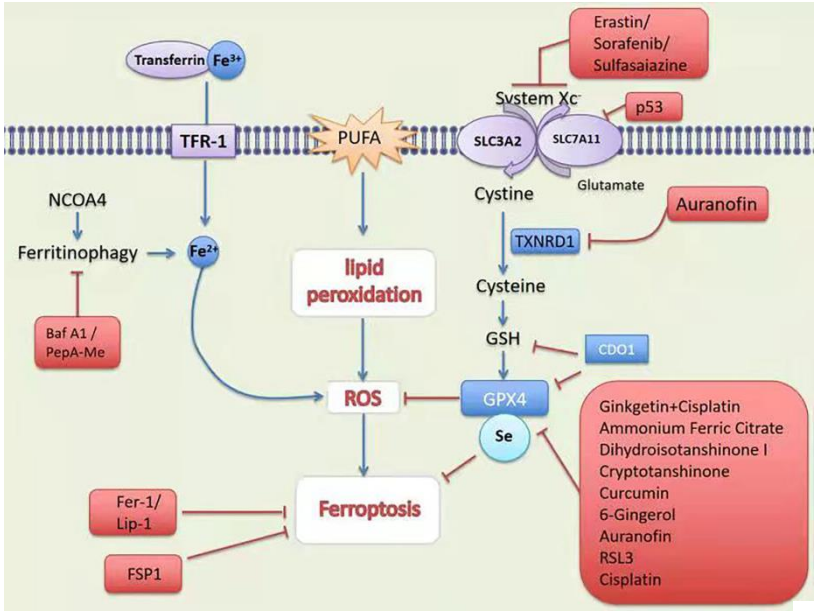
Necrosis

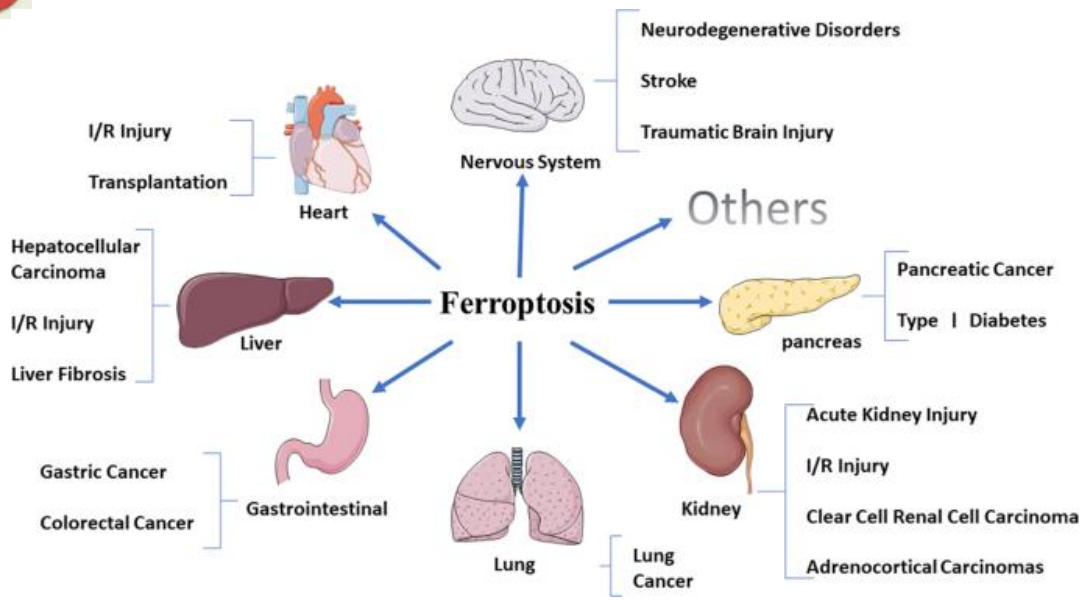

Necroptosis
Membrane Rupture
Release of Inflammatory DAMPs

Pyroptosis

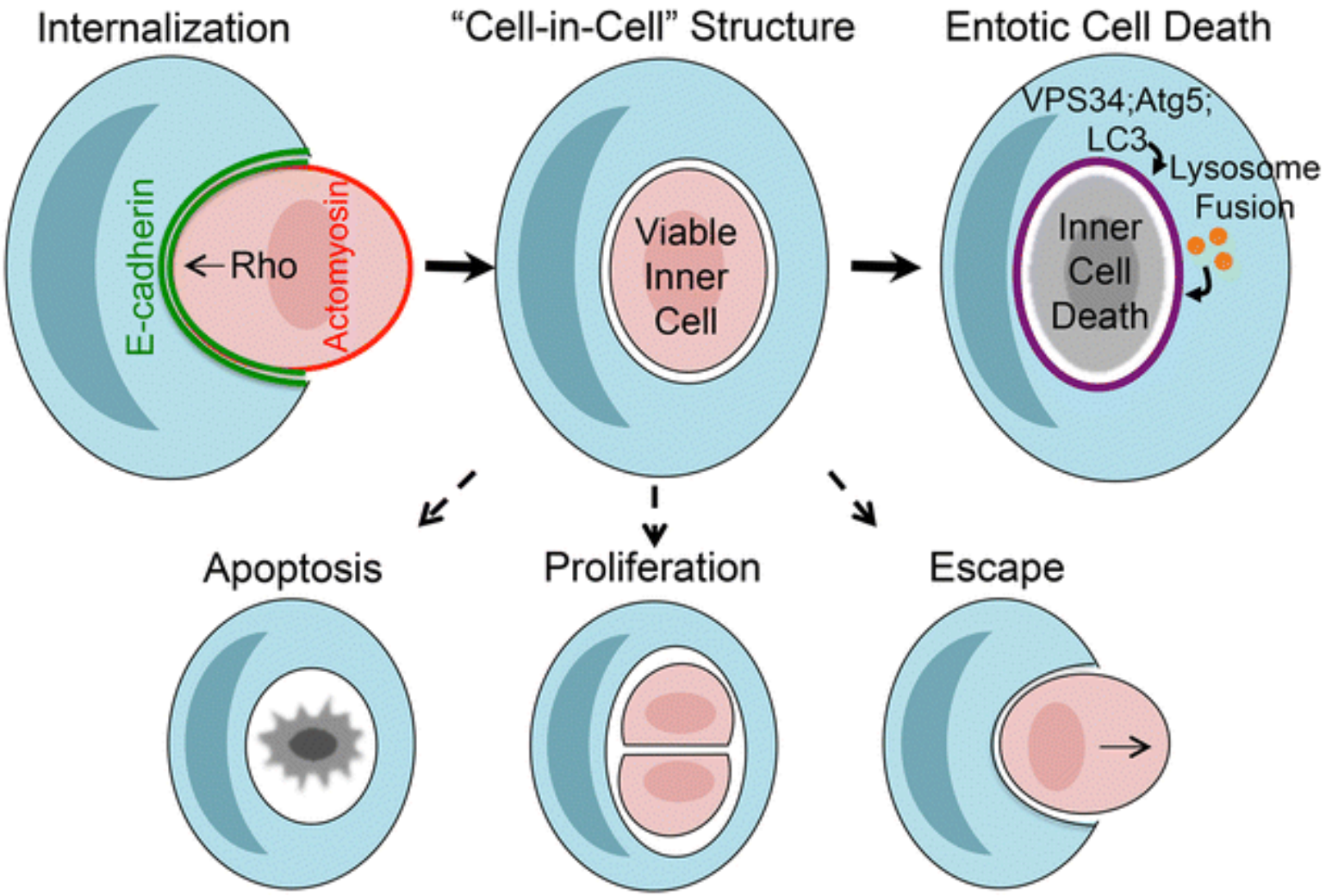


ferroptosis

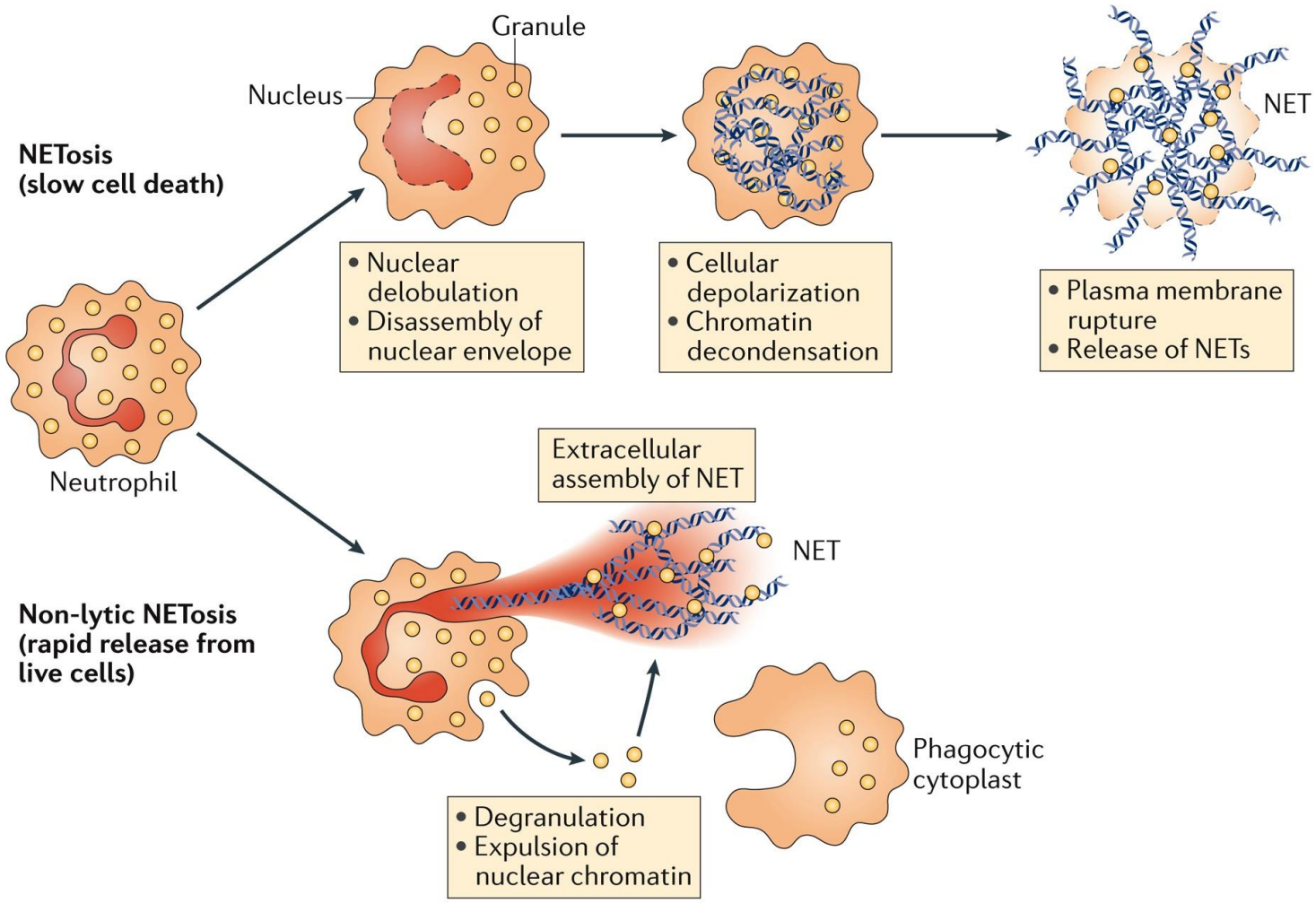




Entosis


Internalization
"Cell-in-Cell" Structure
Entotic Cell Death
E-cadherin
Rho
Actomyosin
Viable Inner Cell
VPS34;Atg5;
LC3
Lysosome Fusion
Inner Cell Death
Apoptosis
Proliferation
Escape

Netosis



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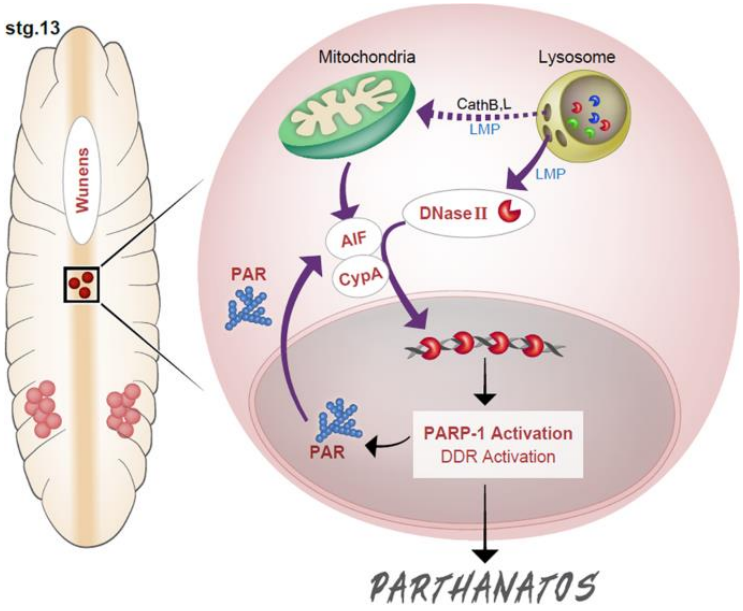
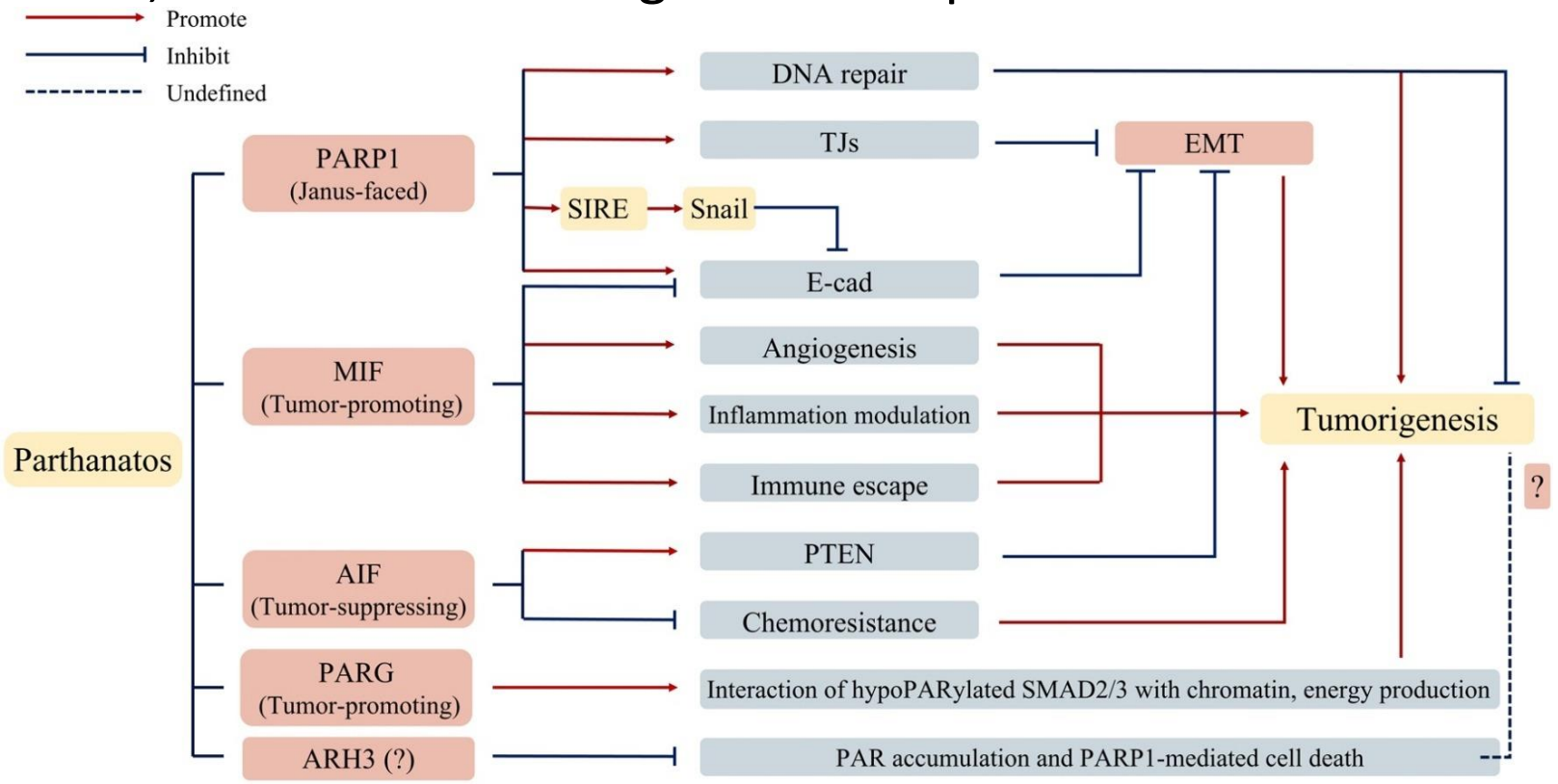
Parthanatos

- Parthanatos is a PARP1-dependent, caspase-independent, cell-death pathway that is distinct from apoptosis, necrosis, or other known forms of cell death.
- Parthanatos is a multistep pathway that plays a pivotal role in tumorigenesis



- There are many molecules in the parthanatos cascade that can be exploited to create therapeutic interventions for cancer management, including PARP1, PARG, ARH3, AIF, and MIF.
- These critical molecules are involved in tumor cell proliferation, progression, invasion, and metastasis.
- Therefore, these molecular signals in the parthanatos cascade repr



- Apoptosis occurs in most, if not all, solid cancers.
- Ischemia, infiltration of cytotoxic lymphocytes, and release of TNF may all play a role in this.
- It would be therapeutically advantageous to tip the balance in favor of apoptosis over mitosis in tumors, if that could be done.
- It is clear that a number of anticancer drugs induce apoptosis in cancer cells.
- The problem is that they usually do this in normal proliferating cells as well.
- Therefore, the goal should be to manipulate selectively the genes involved in inducing apoptosis in tumor cells.
- Understanding how those genes work may go a long way to achieving this goal