PATHO-PHYSIOLOGY OF CANCER & SPREAD

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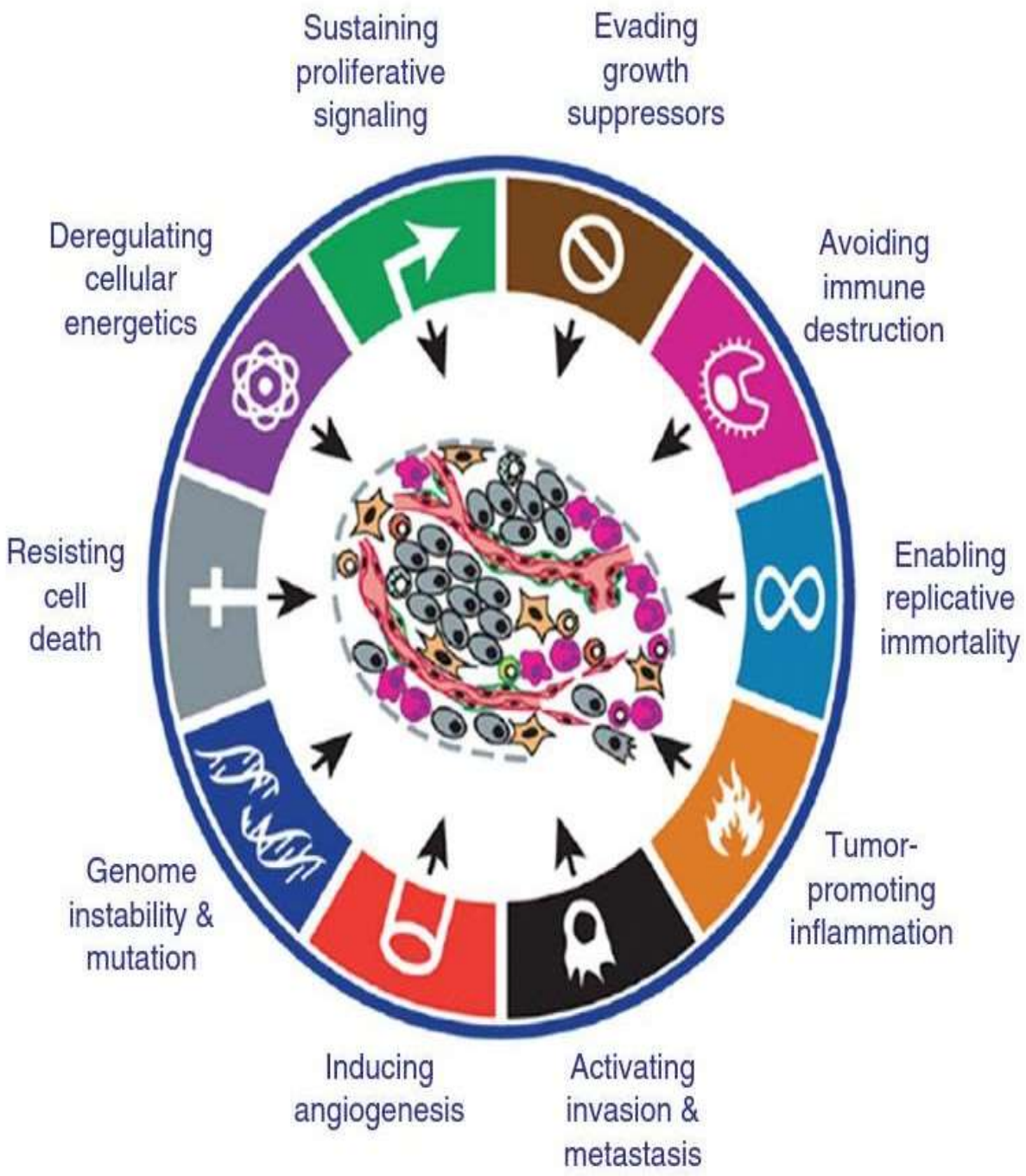
- cancer is, in essence, a genetic disease, and that accumulation of molecular alterations in the genome of somatic cells is the basis of cancer progression.

Physiologic changes associated with progressive conversion of normal cells into malignant tumor cells.



A. Sustaining Proliferative Signaling

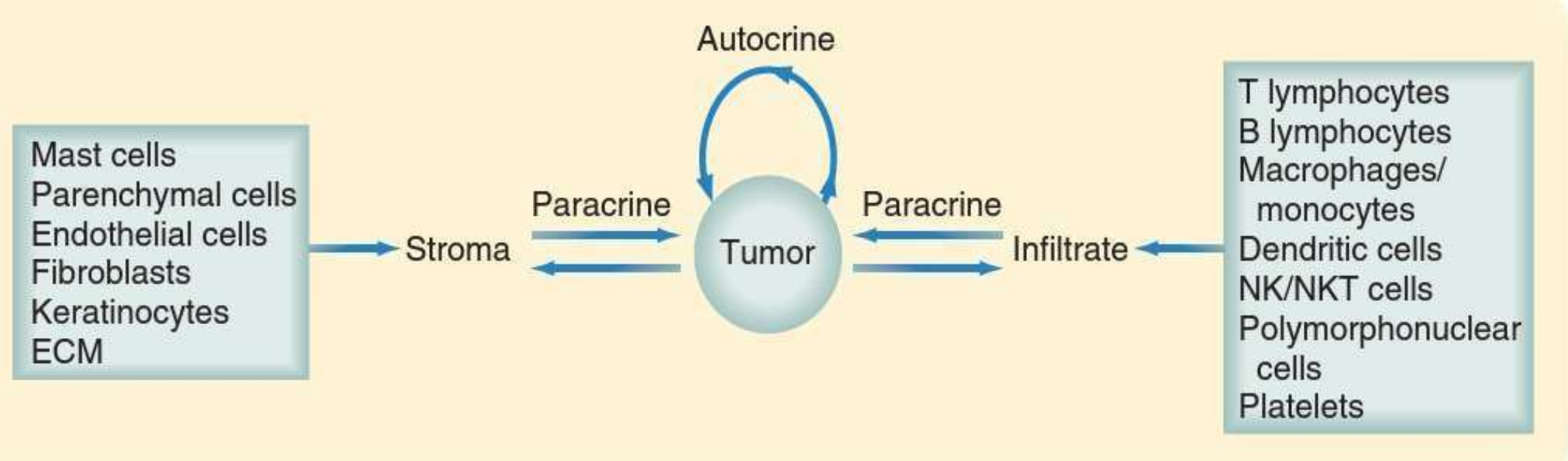
1.By Autocrine, Paracrine and Acrine Signaling:-

- Tumor cells and stroma produce factors (autocrine and paracrine factors) that influence tumor development. These factors include angiogenesis factors, growth factors, chemokines, cytokines, hormones, enzymes, and cytolytic factors.

- Paracrine growth mechanisms are dominant during the early development of tumor.

- Autocrine growth mechanisms become more prominent as tumors further develop. EX: Loss of hormone responsiveness in advanced breast cancers.

- It is even possible for a tumor to grow completely autonomously (acrine state).



- **Paracrine and Autocrine Growth Mechanisms.**
- Both stromal cells and infiltrating cells secrete paracrine factors that affect tumor development. In addition, tumor cells secrete autocrine as well as paracrine factors that in turn act on stromal cells and infiltrating cells.

TABLE 28-2 Cells and Soluble Factors Affecting Tumor Development

CELLS	SOLUBLE FACTORS
Stroma	
Parenchymal cells Endothelial cells Fibroblasts Mast cells Extracellular matrix Keratinocytes	Growth factors, growth inhibitors, nutritional factors, hormones, degradative enzymes, cytokines, angiogenesis factors
Infiltrate	
T lymphocytes B lymphocytes Natural killer cells Natural killer T cells Macrophages-monocytes Dendritic cells Polymorphonuclear cells Platelets	Cytokines, chemokines, cytolytic factors, angiogenesis factors, growth (inhibitory) factors, degradative enzymes, cytostatic factors, antibodies
Tumor	
	Chemokines, cytokines, angiogenesis factors, degradative enzymes, growth (inhibitory) factors

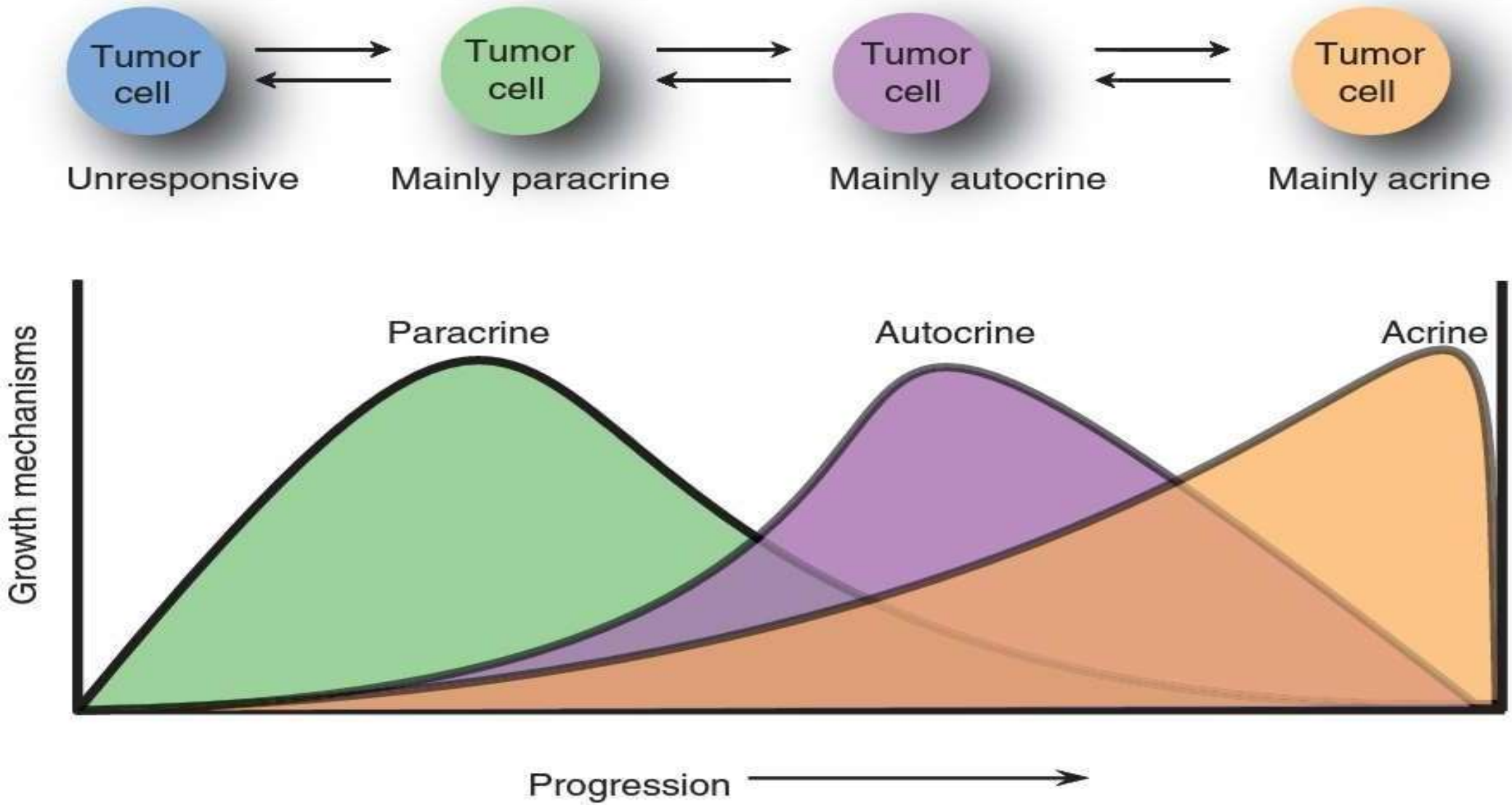


FIGURE 28-6 Changes in Contribution of Growth Mechanisms to Tumor Development. During tumor progression, the contribution of paracrine growth mechanisms decreases, and the tumor becomes more dependent on autocrine growth mechanisms. At later stages, the tumor may even become independent of growth mechanisms (acrine state).

2.By Altering growth signaling pathways :-

- Alteration of extracellular growth signals, of transmembrane transducers of those signals, or of intracellular signaling pathways that translate those signals into action.

3.By Overexpression of growth factor receptors :-

- Response of cancer cell to low levels of growth factor that normally would not trigger proliferation. Ex , EGFR and the HER2/neu receptor are overexpressed in breast and other epithelial cancers.

- Gross overexpression of growth factor receptors can elicit growth factor–independent signaling. Ex , truncated versions of EGFR that lack much of its cytoplasmic domain and are constitutively activated.

4.By altering stromal environment including ECM :-

- Through secretion of factors such as basic fibroblast growth factor, PDGF, TGF-β etc. ECM components, such as collagens, fibronectins, laminins, and vitronectins, may bind to two or more receptors.
- The matrix molecule– receptor interaction induces signals that influence cell behavior, including entrance into the active cell cycle.

5.By autonomous cell proliferation independent of external signals.

Ex, Activating mutations in *KRAS.*

- ***6.Disruption of*** **Negative feedback mechanisms :-**
- This enhance proliferative signaling.

B.Evading Growth Suppressors

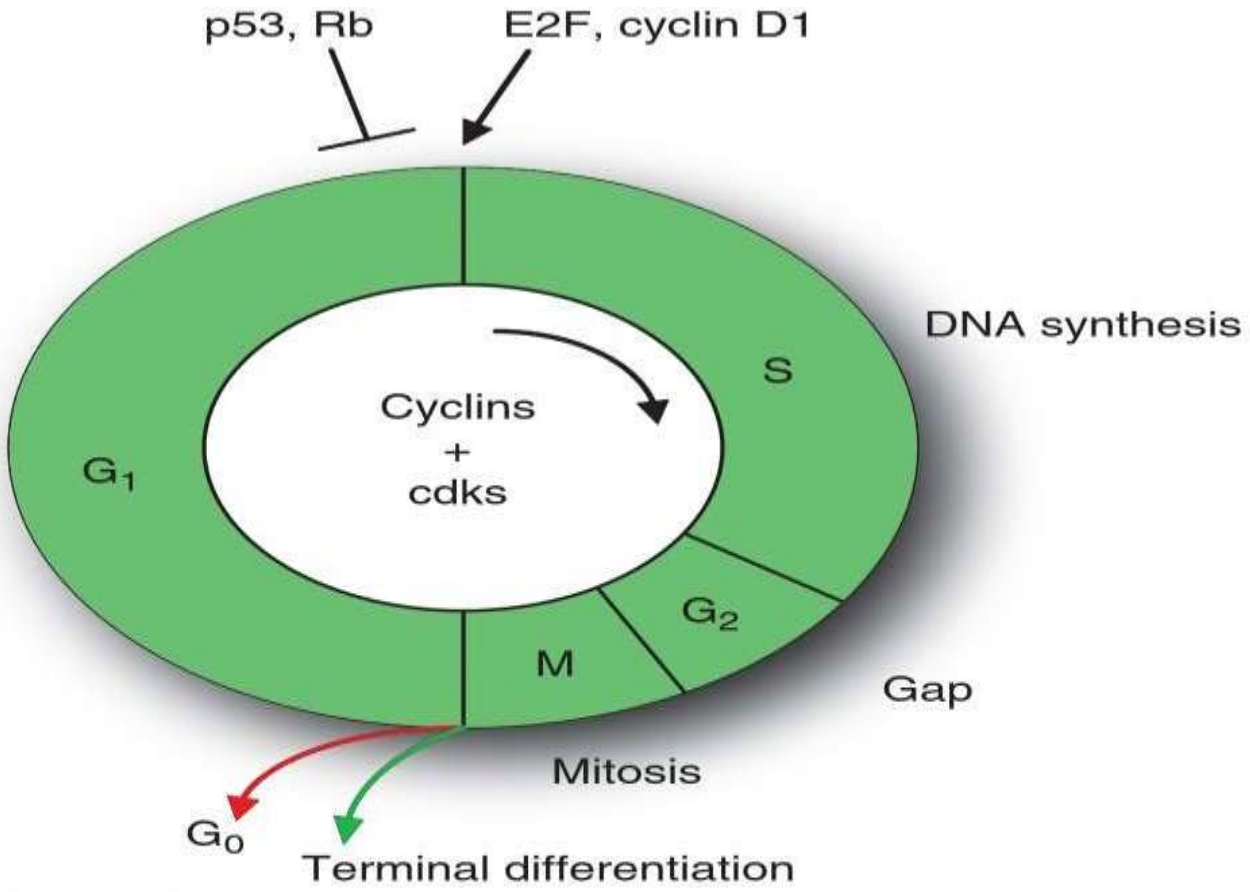


FIGURE 28-7 Schematic Overview of the Cell Cycle. Cell division is governed by cyclin proteins and cyclin-dependent kinases (cdks). After mitosis, a cell can terminally differentiate, enter a quiescent state, or re-enter the cell cycle. A critical point in the cell cycle control is the transition from G_1 to S. After passing this checkpoint, the cell is committed to division. Tumor suppressor genes such as the retinoblastoma *(Rb)* gene and *p53* block G_1 to S transition, whereas oncogenes such as cyclin D1 and E2F promote transition.

- At the molecular level, many and perhaps all antiproliferative signals involve the retinoblastoma protein (pRb) and its two family members, p107 and p130.

- In quiescent cells, pRb is hypophosphorylated and blocks cell division by binding E2F transcription factors that control the expression of many genes essential for progression from G1 into S phase.

- growth-stimulatory signals induce phosphorylation of pRb that does not bind E2F factors and is considered functionally inactive.

- TGF-β prevents the phosphorylation of pRb that inactivates pRb and thereby blocks advance through G1.

- In breast, colon, liver, and pancreatic cancers, TGF-β responsiveness is lost.

- In colon, lung, and liver cancers, the cytoplasmic Smad4 protein, which transduces signals from ligand-activated TGF-β receptors to downstream targets, may be eliminated through mutation of its encoding gene.

- In cervical carcinomas induced by human papillomavirus, the viral oncoprotein E7 binds pRb and thereby induces dissociation of E2F and subsequent transcription of genes necessary for cell cycle progression.

- Cancer cells can also turn off expression of integrins and other cell adhesion molecules (CAMs) that send antigrowth signals.

- Cyclin–cyclin-dependent kinase complexes, essential for cell cycle progression, are regulated by two families of cyclin–cyclin-dependent kinase inhibitors in normal cells.

- In tumor cells, these regulatory proteins, such as the p16 member of the INK4 family, are frequently deleted, allowing tumor cells to bypass cell cycle arrest.

- Tumor cells may also avoid terminal differentiation.

- Overexpression of the oncogene c-*myc*, which encodes a transcription factor regulating expression of cyclins and cyclin-dependent kinases, or through upregulation of Id (short for inhibitor of DNA-binding/differentiation) family members.

- During human colon carcinogenesis, mutations of *APC*, a negative regulator of β-catenin, lead to the constitutive activation of Wnt/β-catenin signaling, which serves to block the terminal differentiation of enterocytes in colonic crypts.

C.Resisting Cell Death

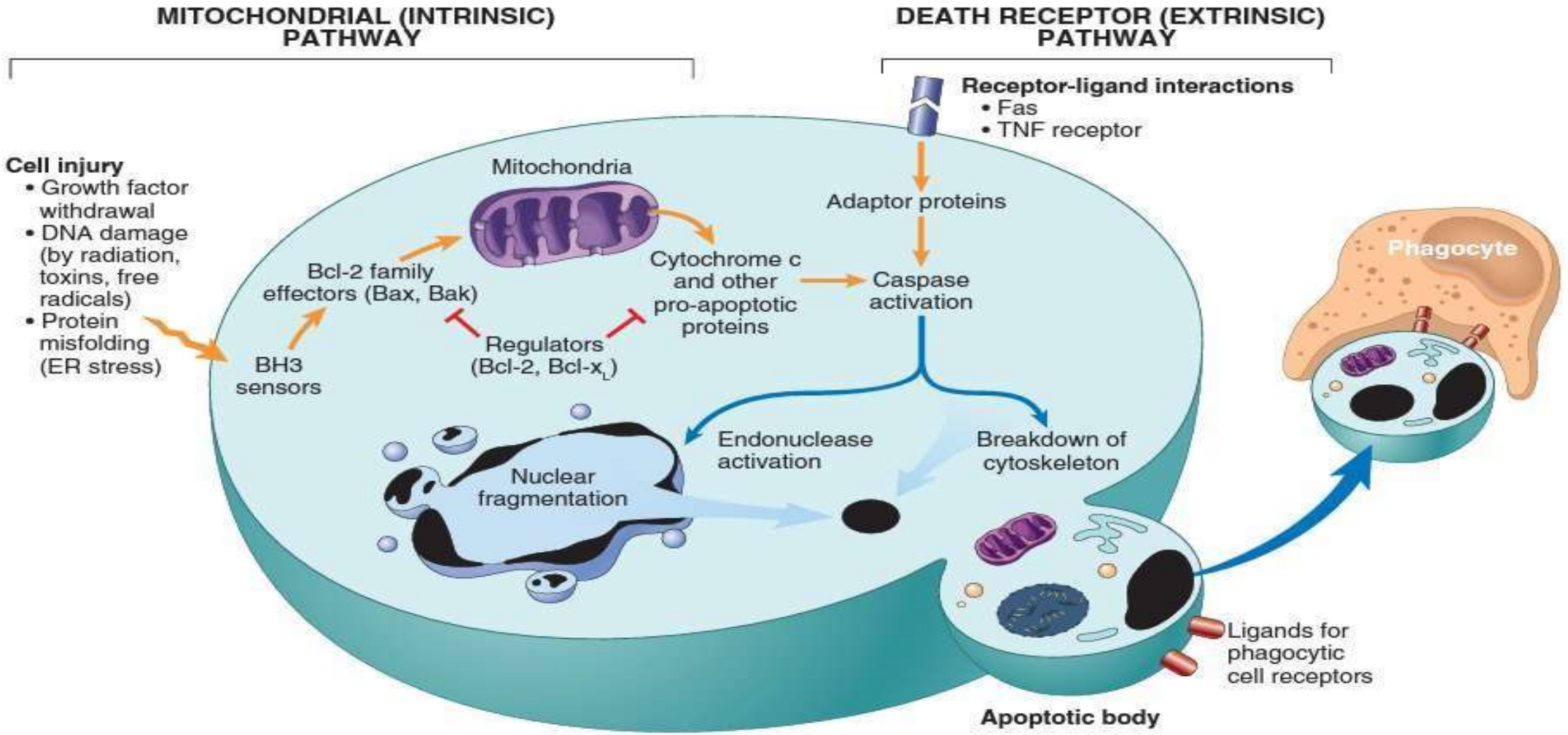


Fig. 2.12 Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of caspases. In the mitochondrial pathway, BH3-only proteins, which are related to members of the Bcl-2 family, sense a lack of survival signals or DNA or protein damage. These BH3-only proteins activate effector molecules that increase mitochondrial permeability. In concert with a deficiency of Bcl-2 and other proteins that maintain mitochondrial permeability, the mitochondria become leaky and various substances, such as cytochrome c, enter the cytosol and activate caspases. Activated caspases induce the changes that culminate in cell death and fragmentation. In the death receptor pathway, signals from plasma membrane receptors lead to the assembly of adaptor proteins into a "death-inducing signaling complex," which activates caspases, and the end result is the same.

- extracellular and intracellular stresses, such as growth factor withdrawal, hypoxia, DNA damage, and oncogene induction.

- death receptor pathways are the Fas receptor and death receptor 5 that bind the extracellular Fas ligand and TRAIL, respectively.

- Activation of caspase 8

- promotes the cascade of procaspase activation

- release of cytochrome *c* from mitochondria and eventually apoptosis.

- Receptor-independent pathways involve translocation of proapoptotic molecules from the cytoplasm to the mitochondria, causing mitochondrial damage and release of cytochrome *c*.

Cytochrome *c* is directly involved in the activation of caspase 9, which activates caspase 3, which then leads to apoptosis.

- *bcl-2* oncogene(antiapoptotic activity)-Bcl-2 promotes formation of B cell lymphomas through a chromosomal translocation linking the *bcl-2* gene to an immunoglobulin locus which results in constitutive activation of *bcl-2*, driving lymphocyte survival.

- P53(altering components of the apoptotic Machinery)-sensing DNA damage that cannot be repaired and subsequent activation of the apoptotic pathway.

- phosphatidylinositol 3-kinase/AKT pathway(alterations in cell survival pathways)- Transmits antiapoptotic survival signals, by extracellular factors such as insulin-like growth factors I and II or interleukin-3 (IL-3), by intracellular signals from Ras, or by loss of the pTEN tumor suppressor that negatively regulates the phosphatidylinositol 3-kinase/AKT pathway.

Nonsignaling decoy receptor(dilutes the death signal mediated through FAS) for FAS ligand in a high fraction of lung and colon carcinoma cell lines.

- Nonapoptotic types of cell death that can promote tumor growth include necrosis, autophagy, and mitotic catastrophe.

- Aberrant mitosis caused by failure of the G2 checkpoint to block mitosis when DNA is damaged can lead to cell death, known as mitotic catastrophe.

- MDM2 oncogene, which negatively regulates expression of p53, results in inadequate expression of p53 and thereby loss of tumor suppressor function.

- Deletion of the autophagy regulating gene *becklin-1* in high percentages of ovarian, breast, and prostate cancers.

D. Enabling Replicative Immortality

- By maintaining a telomere length above a critical threshold, the tumor cells have unlimited proliferative potential and are considered immortal.

- Cancer stem cells (CSCs)-CSCs may generate tumors through self-renewal as well as through differentiation into multiple cell types. Various cell surface markers have been used to define CSCs, such as CD44, CD133, and CXCR4

E. Inducing Angiogenesis

- microscopic tumors lack the ability to induce angiogenesis.

- naturally occurring endogenous angiogenesis inhibitors (interferon-α,thrombospondin, tumstatin,canstatin, endostatin, and angiostatin)prevent tumors from expanding.

- Angiogenic activity is induced by growth factors such as vascular endothelial growth factor (VEGF), basic and acidic fibroblast growth factor, and platelet-derived growth factor.

- bcl-2 activation leads to significantly increased expression of VEGF and angiogenesis.

- plasmin, a proangiogenic component of the clotting system, can cleave itself into an angiogenesis inhibitor form called angiostatin.

- angiogenesis inhibitor, endostatin, is an internal fragment of the basement membrane collagen XVIII.

- Endothelial cells produce angiogenesis promoting factors these include proinflammatory cytokines such as IL-6, VEGF, and hematopoietic growth factors such as colonystimulating factors that recruit and activate bone marrow–derived progenitor cells.

- Myeloid precursors that further promote the proinflammatory responses at the tumor and actively contribute to angiogenesis by producing matrix metalloprotease-9, a critical regulator of tumor angiogenesis through the induced release of VEGF.

- APC function is lost, as is the case in many colon cancers or in the case of Wnt activation, β-catenin is not degraded but instead translocates to the nucleus, where transcription is activated of genes involved in cell proliferation and tumor progression, such as c-myc, cyclin D1, CD44.

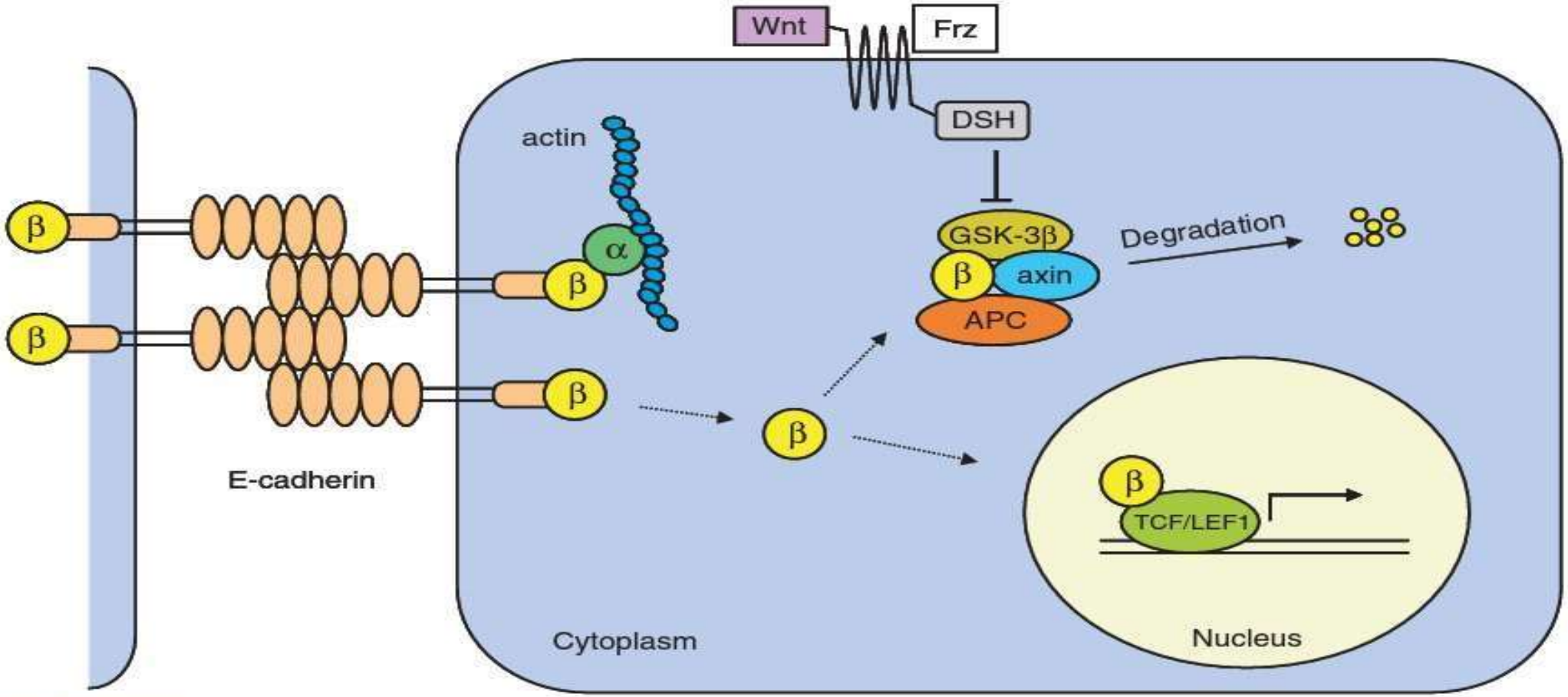


FIGURE 28-9 Loss of E-Cadherin Permits Tumor Progression. Functional loss of E-cadherin to sequester β-catenin leads to accumulation of β-catenin in the cytoplasm. Likewise, Wnt signaling inactivates GSK-3β, which leads to stabilization of β-catenin instead of its degradation. Also, loss of *APC* function may result in accumulation of β-catenin in the cytoplasm. This leads to translocation of β-catenin to the nucleus, where it binds the T cell–specific transcription factor/lymphoid enhancer factor-1 (TCF/LEF-1), inducing a genetic program that leads to tumor progression. *α,* α-catenin; *APC,* adenomatous polyposis coli; *β,* β-catenin; *Frz,* frizzled (transmembrane receptor for Wnt growth factors); *DSH,* disheveled; *GSK-3β,* glycogen synthase kinase 3β.

- Overall expression of N-CAM is reduced in In invasive pancreatic cancer and colorectal cancers.

- Alterations in the expression level of selectins or their ligands, such as the E- and L-selectin ligand CD44, have been associated with increased invasiveness and poor survival in several malignant neoplasms, such as breast cancer and colorectal cancer.

- Changes in integrin expression are also evident in invasive and metastatic cells.

- ex: expression of α4β1, which binds fibronectin, correlates with progression of melanoma.

- Changes in integrin expression may also be essential for expansion of the tumor stem cell compartment by inhibiting differentiation or apoptosis.

- Tumors can alter the functionality of infiltrating immune cells, causing functional leukocytes to become anergic or even immunosuppressive.

- Macrophages isolated from tumors, such as pancreatic cancer, are potently immunosuppressive and prevent antitumor immune responses by T cells.

CANCER SYMPTOMS:

- Depends on the types
- General symptoms are,

Fatigue Weight loss

Pain

Skin changes Unusual

bleeding Persistent cough

Fever

TREATMENT:

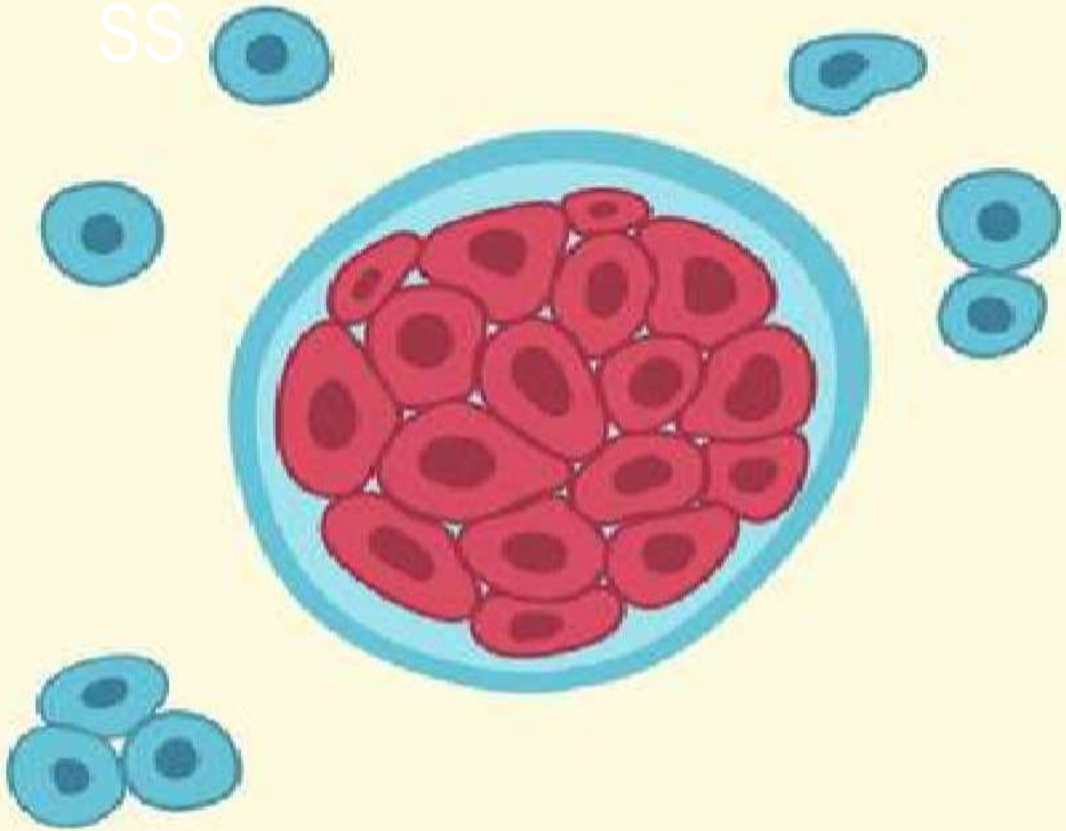
- Chemotherapy,
- Radiation
- Surgery General

term:

Benign – non cancerous tumor

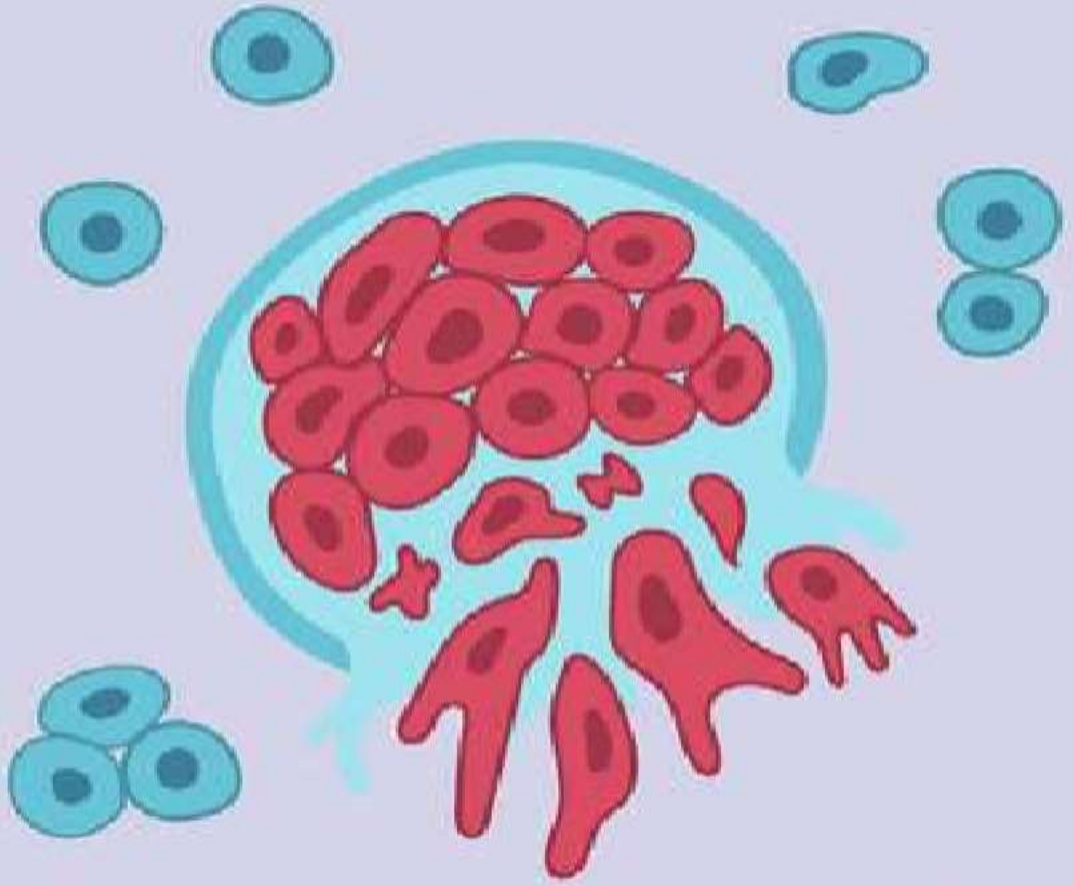
Malignant – cancerous tumor

Benign Tumor



Cells are not cancerous and won't spread.

Malignant Tumor



Cells are cancerous and can spread to other tissues and organs.

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