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Pharmacology : Antineoplastic

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definition

- **Antineoplastic**: Acting to prevent, inhibit or halt the development of a **neoplasm (a tumor**)

https://www.medicinenet.com/antineoplastic/definition.htm

- **Antineoplastic drugs** are medications used to treat cancer.
- **Antineoplastic drugs** are also called anticancer, chemotherapy, chemo, cytotoxic, or hazardous **drugs**

https://www.cdc.gov/niosh/topics/repro/antineoplastic.html

Cancer

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- **Cancer** A term for diseases in which abnormal cells divide without control and can invade nearby tissues.
- **Cancer** cells can also spread to other parts of the body through the blood and lymph systems.
- **Cancer**: An abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread).
- **Cancer** can involve any tissue of the body and have many different forms in each body area

Most Common Types of Cancer

- Breast cancer
- Prostate cancer
- Basal cell cancer
- Colon cancer
- Lung cancer
- Leukemia
- Lymphoma

US 2016 cancer cases

FEMALE			
Cancer Site	**New Cases**	**Risk Factor/Carcinogen**	**Driver Mutations**
Breast	266,120	Estrogen, obesity, BRCA1/2	potential drivers
Lung&bronchus	112,350	smoking	EGFR, KRAS, EML4ALK
Uterine (cervical)	76,470	Estrogen (HPV)	
Colon, Rectum	47,530	high fat diet, socioeconomic	APC,TP53
Thyroid	40,900	radiation	Multiple[Ras-Erk,cyclin D pathways]
Melanoma	36,120	UV exposure	BRAF V600E
NH-Lymphoma	32,950		
Pancreas	26,240	?, smoking, diabetes	KRAS
Leukemia	25,270	Radiation/benzene	Depends on subtype
Kidney&renal	22,260		
Ovary	22,240	Parity (ovulation), BRCA1/2	?, TP53 in subtypes

MALE			
Cancer Site	**New Cases**	**Risk Factor/Carcinogen**	**Driver Mutations**
Prostate	164,690	Age, race, diet (calcium)	AR, TP53, ETS, PTEN
Lung&bronchus	112,350	smoking	EGFR, KRAS, EML4ALK
Colon, Rectum	49,690	High fat diet, socioeconomic	APC, TP53
Urinary bladder	62,380	smoking	
Melanoma	55,150	UV exposure	BRAF V600E
Kidney&renal	42,680	smoking	
NH-Lymphoma	41,730		
Oral cavity	37,160	Tobacco, alcohol/betel nut	?
Leukemia	35,030	Radiation/benzene	
Liver& bile duct	30,610	Alcohol, HBV	TP53, TERT, various
Pancreas	29,200	?, smoking, diabetes	KRAS

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Cancer

Cancer is one of the most common diseases in the developed world. There are over 100 different forms of cancer

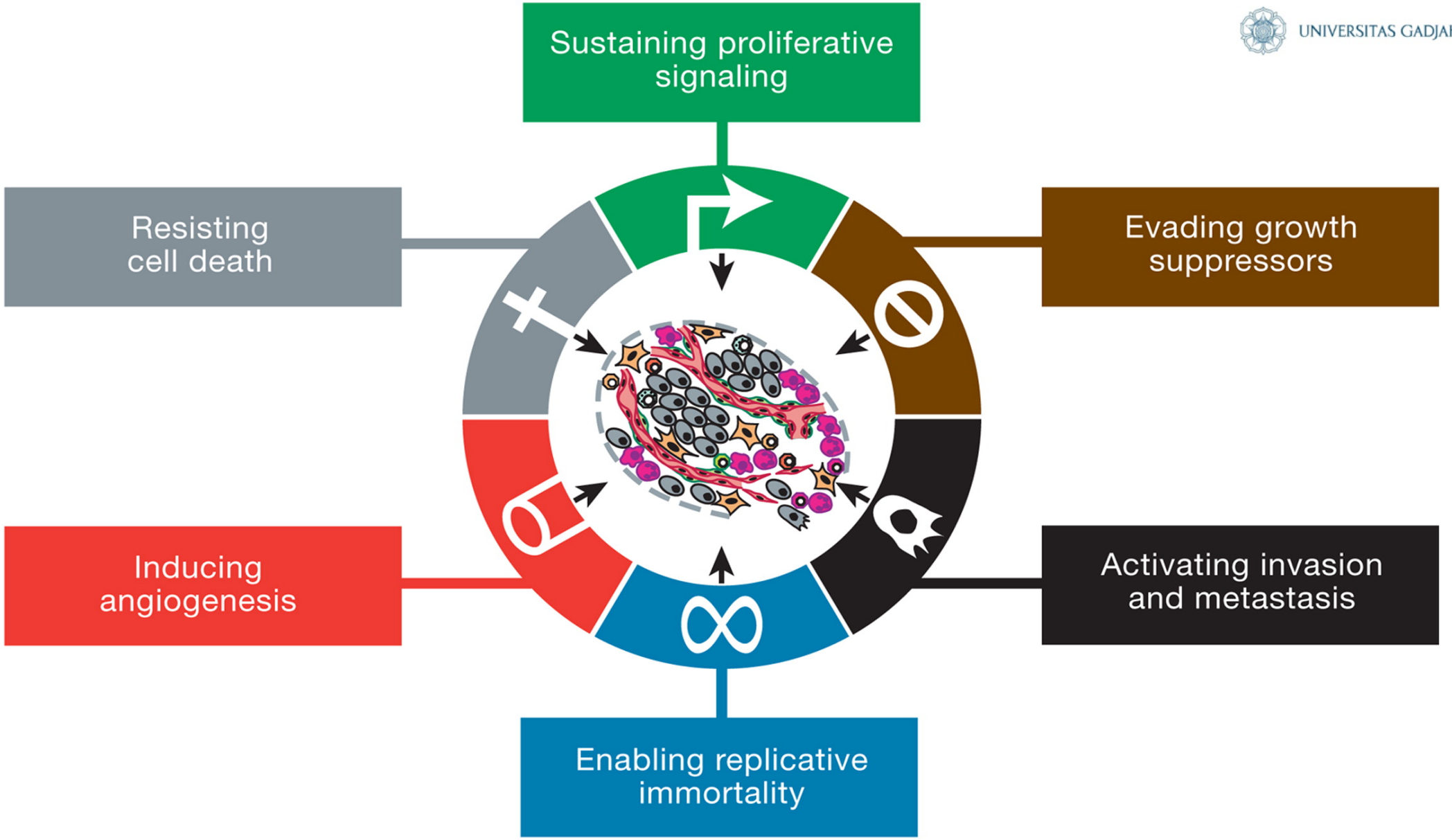
CARGINOGENESIS

- Carcinogenesis is a multistep process that drives normal cells to evolve progressively towards a **malignant**, neoplastic state, and ultimately to acquire metastatic features.

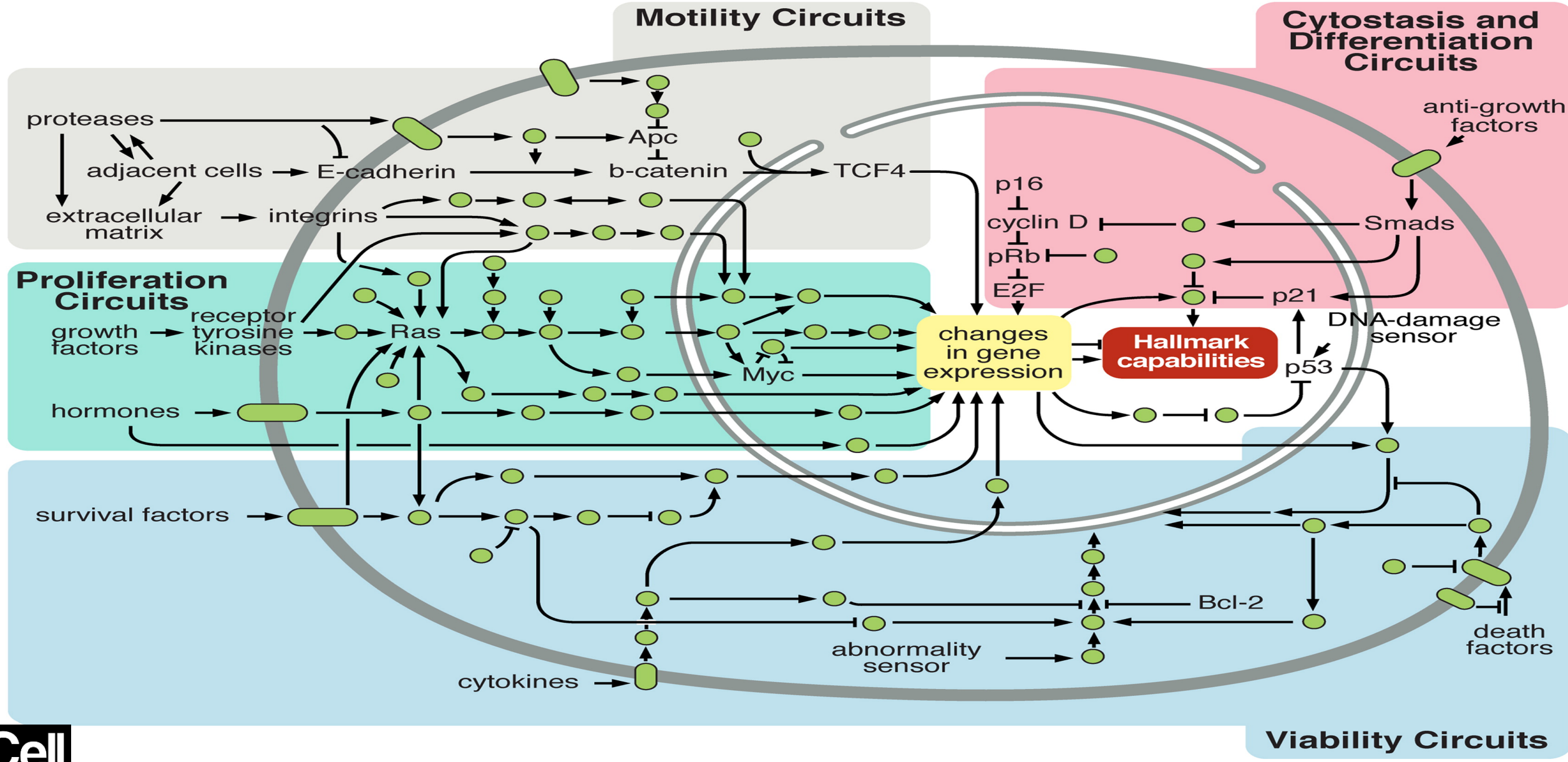
- During this process non-cancer cells develop stepwise various **biological capabilities** that enable them to acquire their tumorigenic potential.

Note: sometimes the word carcinogenesis and oncogenesis are used interchangeably

Tumorigenesis: formation of a tumor



Cell 2011 144646-674DOI: (10.1016/j.cell.2011.02.013)



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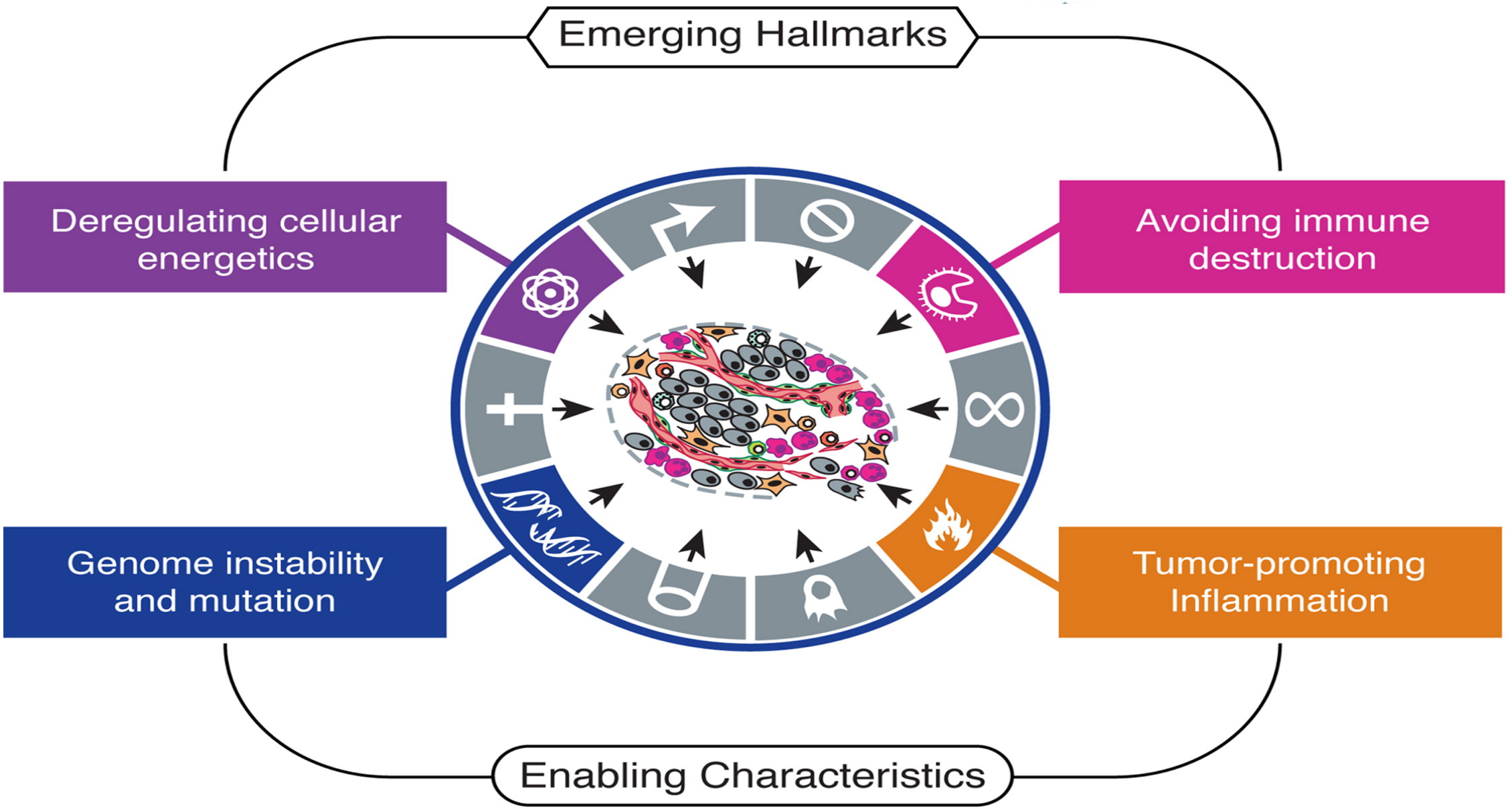

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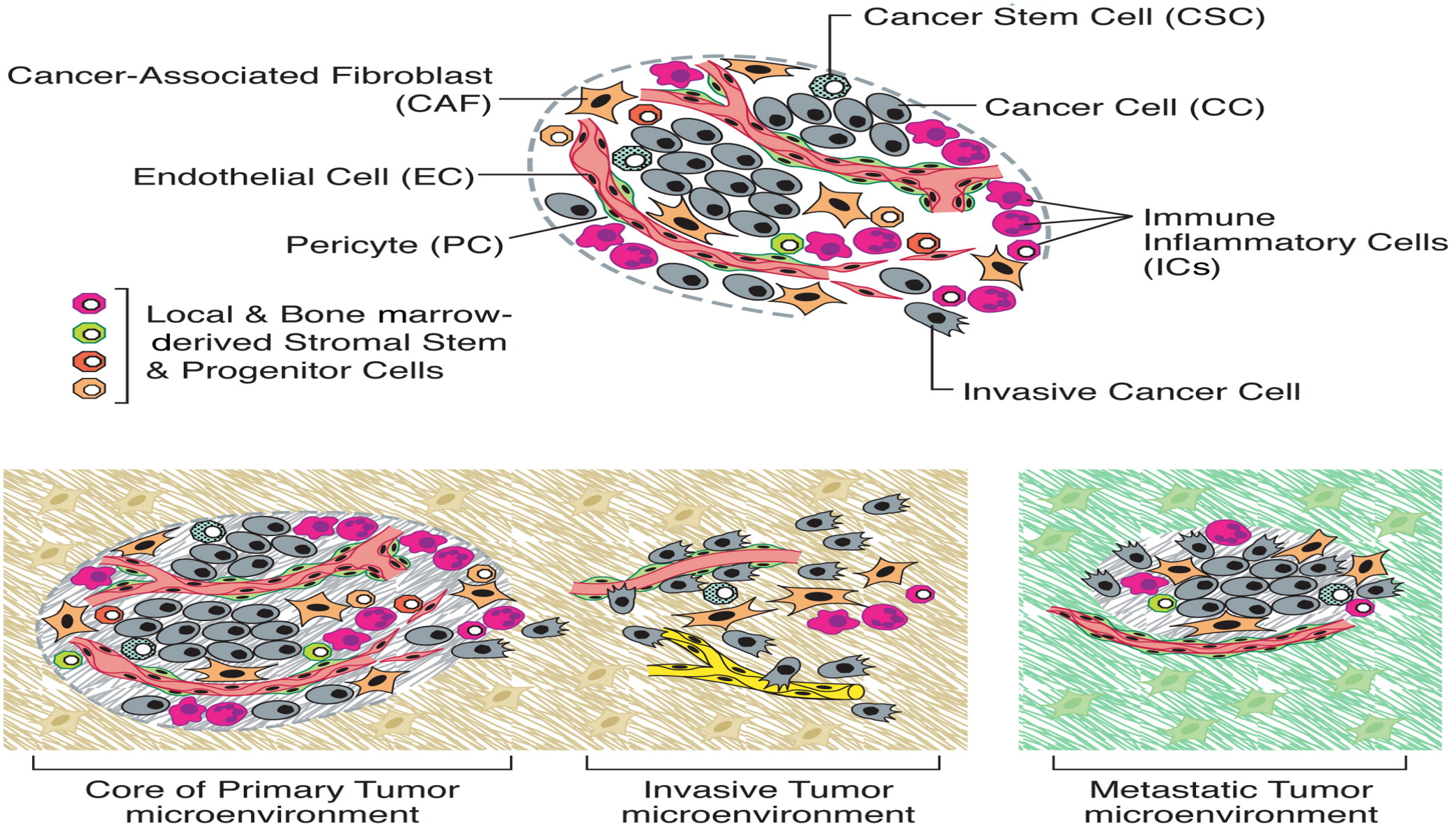

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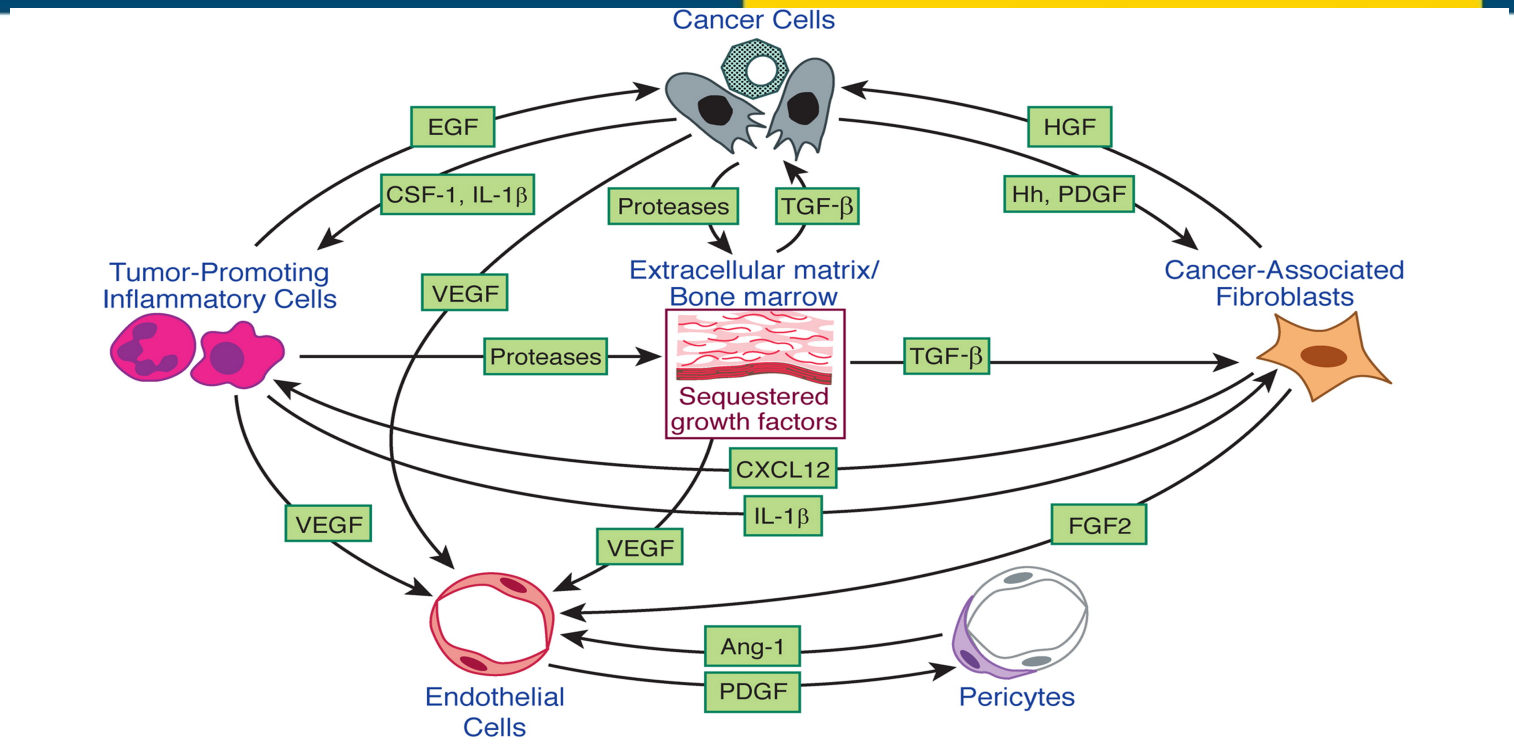
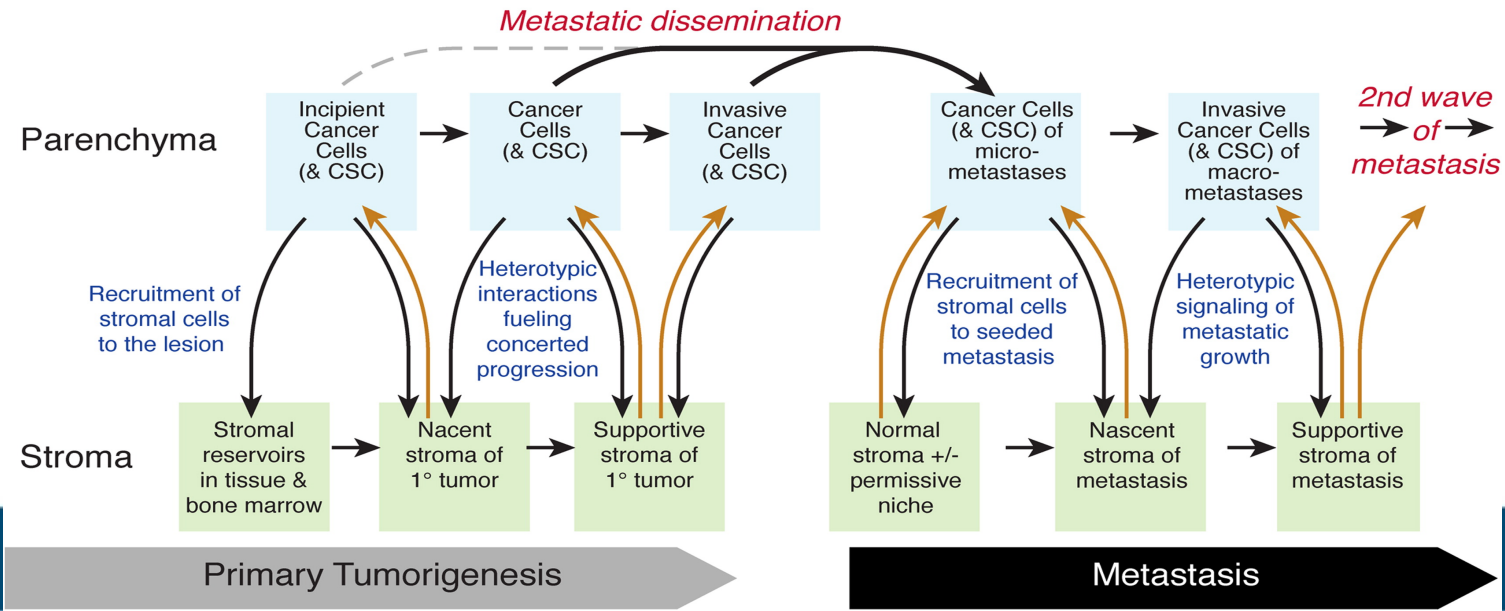
GENETIC INSTABILITY and CANCER

- Cancer arises from the **mutation** of a normal gene.

- It is thought that **several mutations** need to occur to give rise to cancer
- These mutations allow cancerous cells do not self destruct and continue to divide rapidly producing millions of new cancerous cells.
- These mutations “fix” the cell in the transformed state
- Additional factors such as growth factors, together with aberrant cell signalling because of additional mutations lead to enhanced proliferation, angiogenesis, lack of immune regulation, invasion and metastasis. This is usually a result of:

INCORRECT SIGNAL REGULATION & FAULTY SIGNAL TERMINATION





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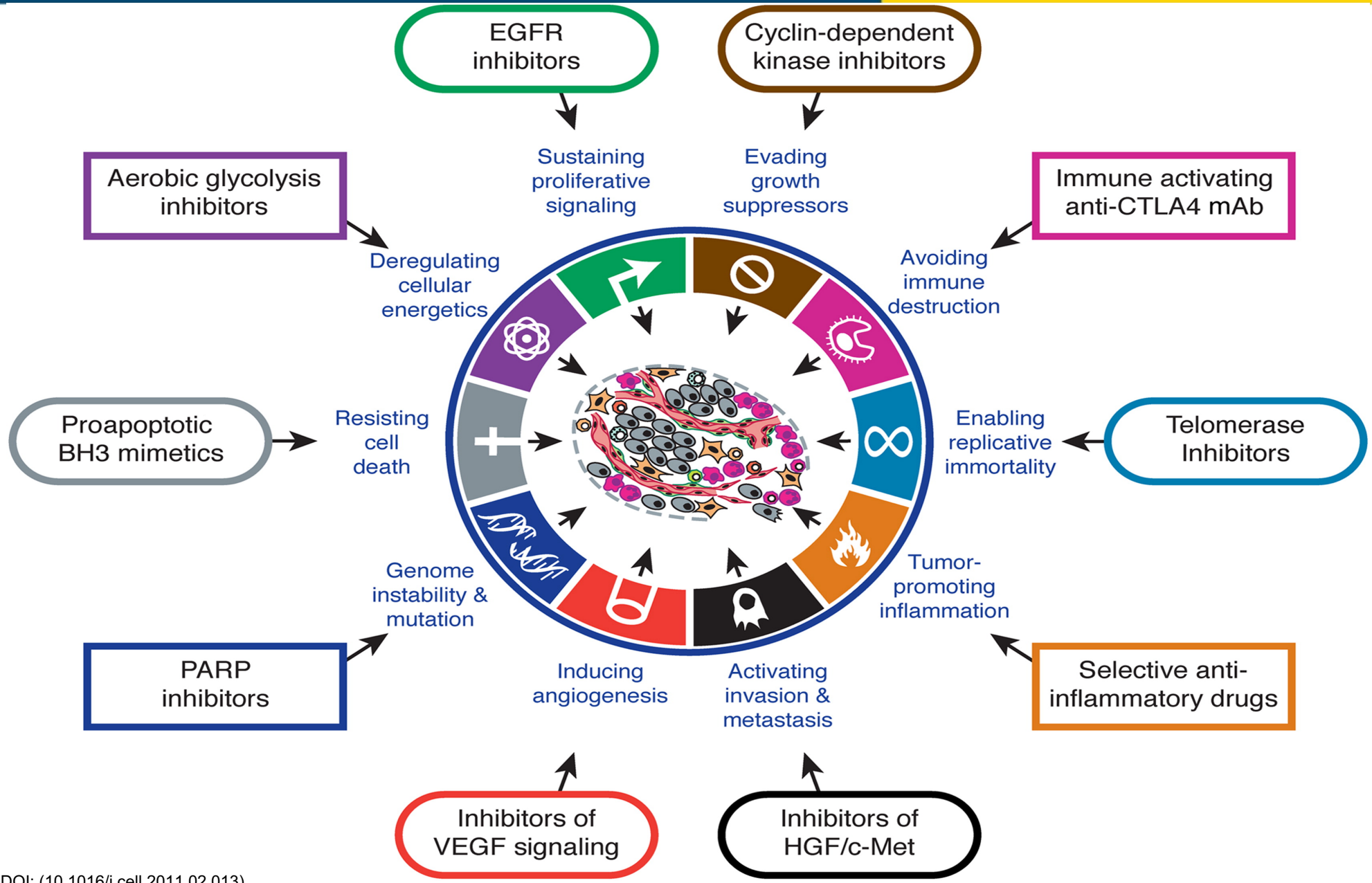

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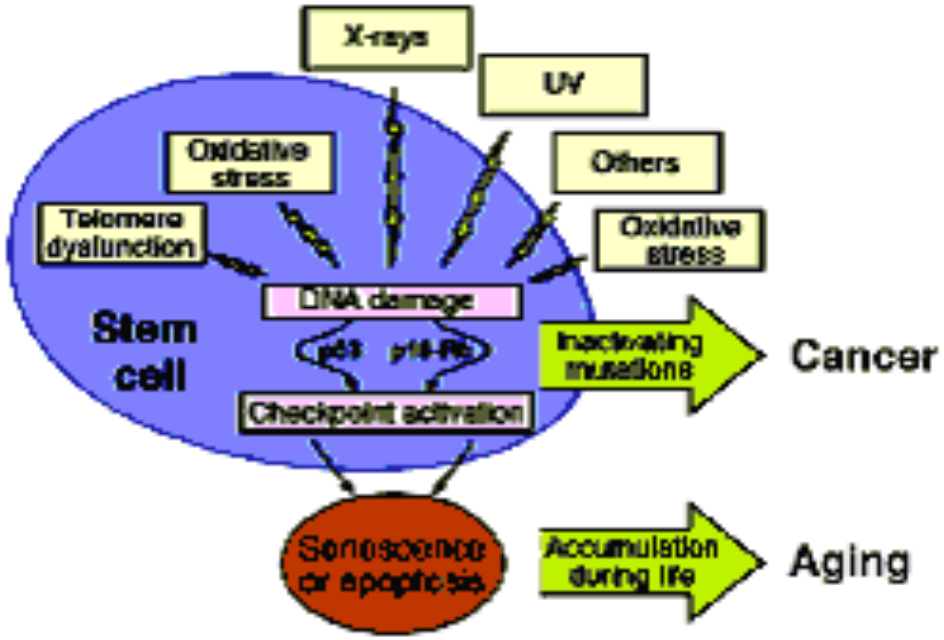
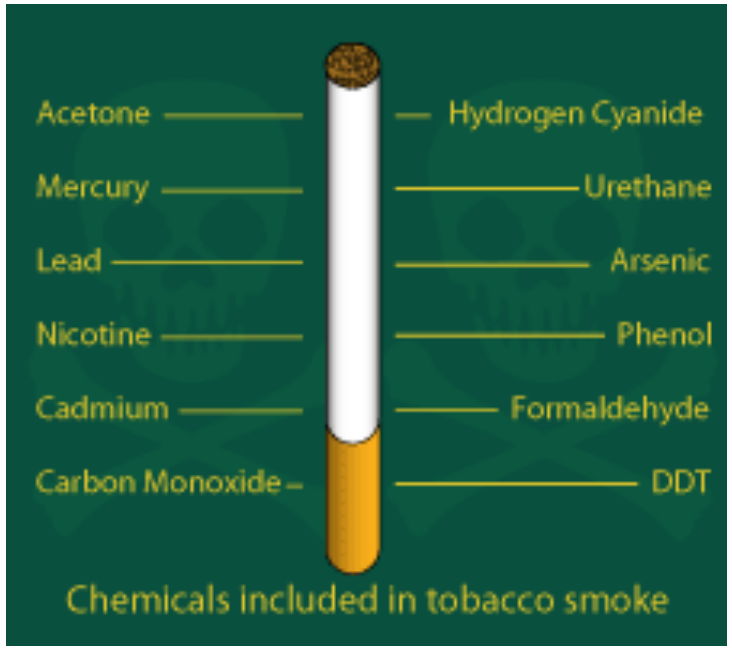
Faktor Penyebab Kanker

- Virus
- Hormon
- Penyinaran yang berlebih
- Senyawa kimia
- Makanan tertentu
- Kelemahan genetis pada sel-sel tubuh





Proto-oncogenes ⇒ oncogenes:

Proto-oncogenes

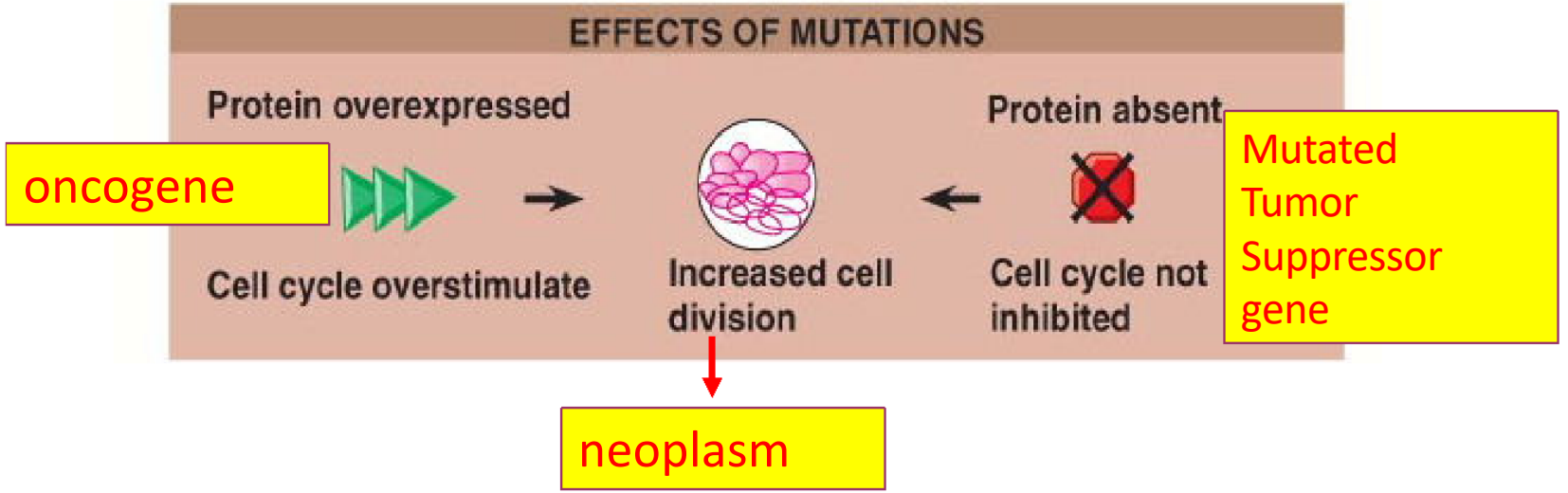
- Proto-oncgenes are genes that possess normal gene products and stimulate normal cell development.

Oncogenes

- Oncogenes arise from **mutant proto-oncogenes**.
- Oncogenes are more active than normal or active at inappropriate times and stimulate **unregulated cell proliferation**.

Cancer Mutations

- **Proto-oncogenes** form **active oncogenes** by
  - being misplaced (e.g. by **translocation**) to a site where the **gene is continually expressed** resulting in **overproduction of a protein that stimulates cell division** (e.g. in Chronic Myeloid Leukemia)
  - By **mutating** to a form that is **over expressed**.
- **Cancer causing Mutations** in **Tumor Suppressor genes inactivate the genes** so normal protein product is not formed.



GENES THAT BECOME MUTATED IN CANCER:

Two classes of genes are frequently mutated in cancer:

- **Proto-oncogenes (⇒ oncogenes)**
  - **Oncogenes result from mutation which turns on (activates) protooncogene to drive cancer**

- **Tumor suppressor genes**
  - **Tumor suppressors help cause cancer when they are turned off (inactivated) by mutation**

Gene Mutations That Cause Cancer

Mutations in 4 types of genes cause Cancer

- **Proto - oncogenes:** genes that code for normal proteins used in cell division
  - **–Growth factors**
  - **–Membrane Receptors** for Growth Factors
  - **–Signaling Proteins** (e.g. **ras proto- oncogene** mutates in 30% of cancers).
- **Tumor Suppressor genes:** gene that code for proteins that help prevent uncontrolled cell division by blocking key steps (e.g. DNA replication).
  - **Retinoblastoma susceptibilty (RB) gene**
  - **p53** gene mutates in >50% of cancers.

- **DNA Repair genes**
- **Genes for Apoptosis**

Resume

- Mutasi DNA, sel, gen apoptosis (p53), tumor supresor gen
- Menurunnya ekspresi dan fungsi tumor supresor gen shg sel tdk sensitif thdp sinyal anti pertumbuhan
- Kesalahan dlm mitosis
  - Tdk ada kontrol pertumbuhan (memiliki kemampuan replikasi tdk terbatas)
  - Pertumbuhan sel kanker bersifat keseimbangan positif (jumlah sel yg dibuat > jumlah sel yg mati, kecepatan proliferasi sel > mekanisme apoptosis)
- Meningkatkan ekspresi dan fungsi onkogen

Mempunyai mekanisme angiogenesis (indikator adanya potensi metastasis)

mampu melakukan metastasis & invasi

Cell cycle

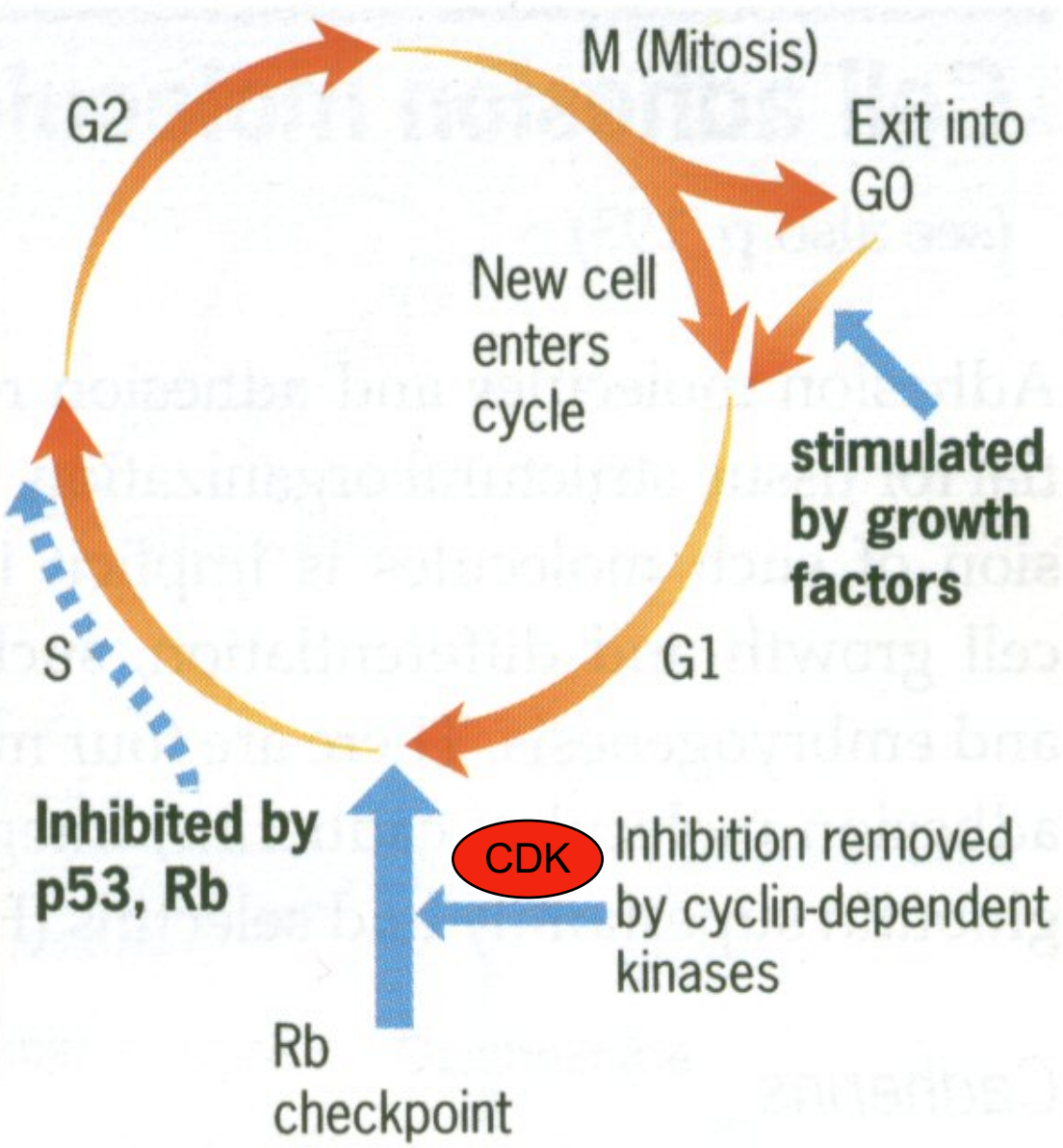
G0 non-cell replication phase

G1 Preparation phase for DNA synthesis i.e. transcription of proteins necessary for DNA replication

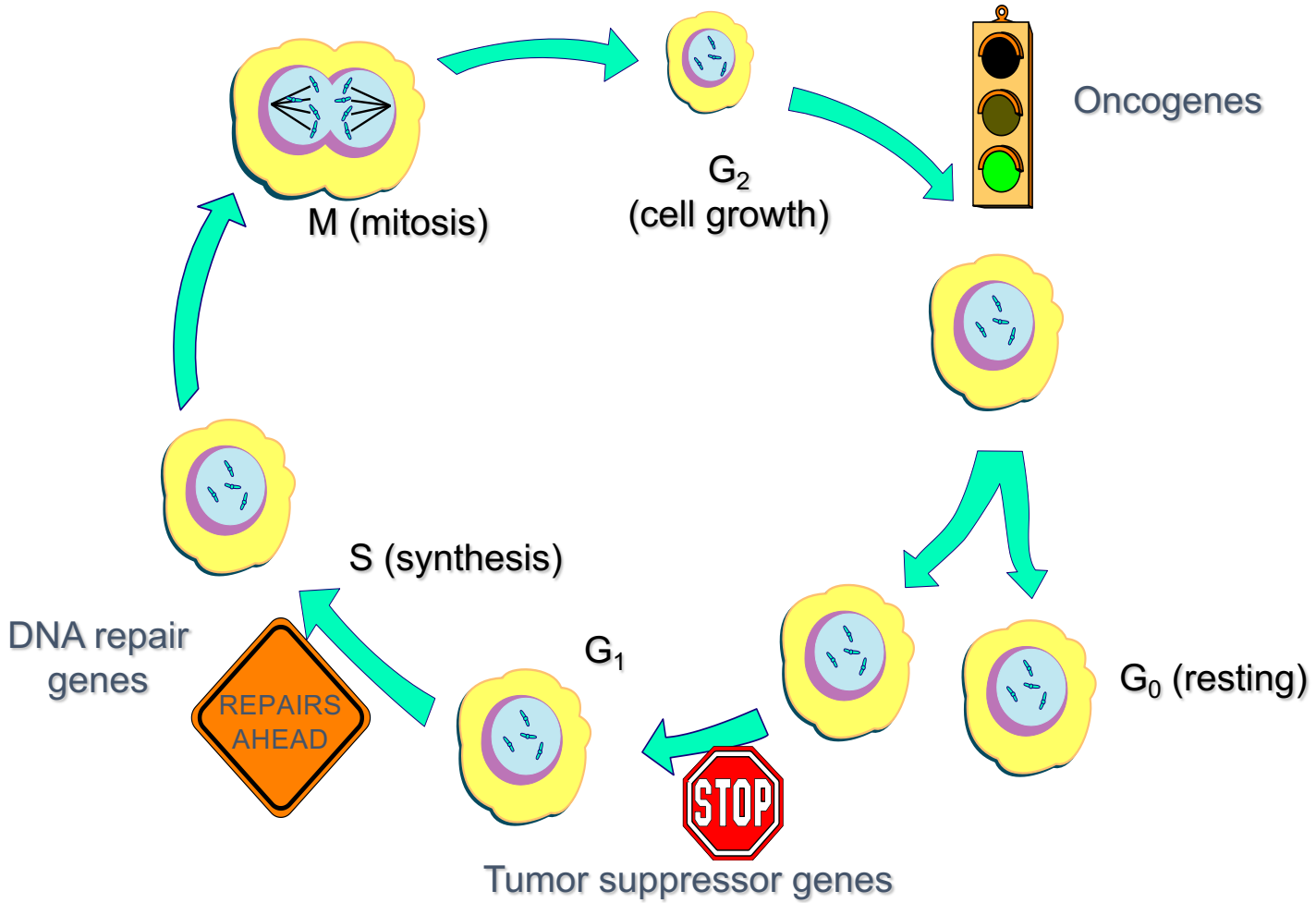
S DNA synthesis (genome replication)

G2 preparation phase for separating diploid chromosomes into two daughter cells

M mitosis + formation of two daughter cells



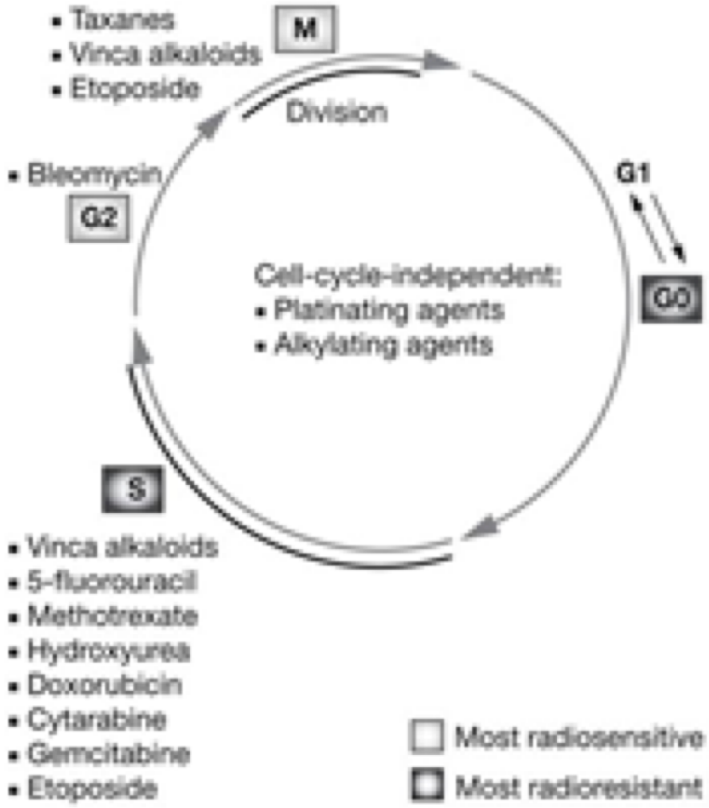
The Cell Cycle



Proto – oncogenes/ oncogenes induce cell cycle progression , while tumor suppressor genes inhibit it

Cell-cycle schematic and respective sensitivity to chemotherapeutic agents

antineoplastic agents are classified according to their structure or cell cycle activity - either cell cycle phase specific or cell cycle phase non-specific

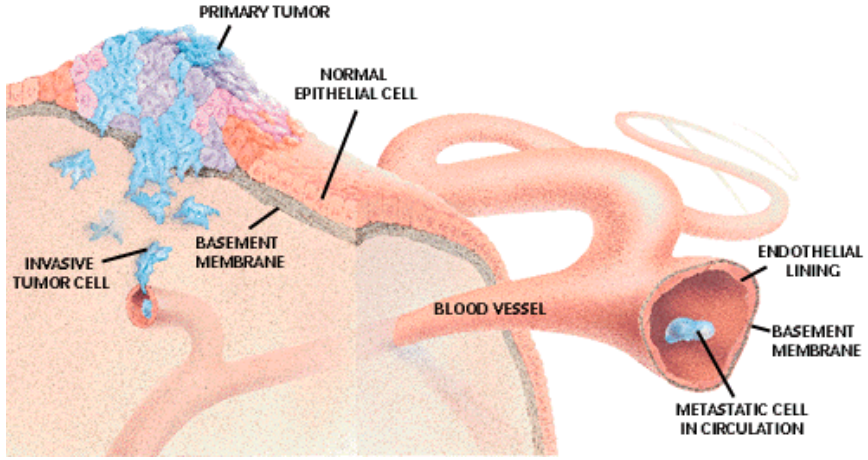


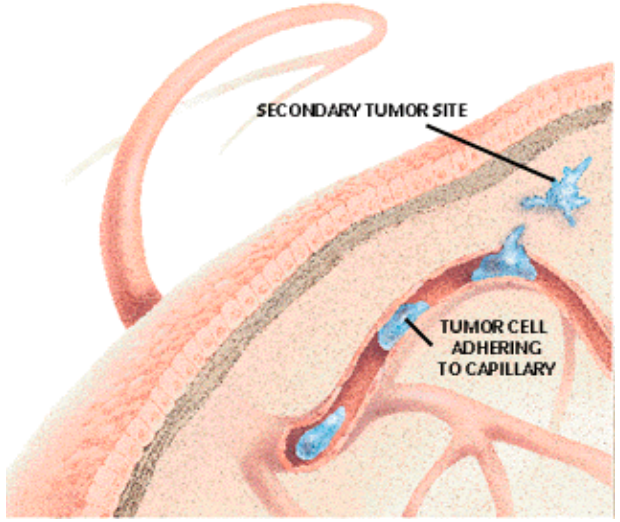
Selwert TY *et al.* (2007) The concurrent chemoradiation paradigm—general principles. *Nat Clin Pract Oncol* 4: 86–100 doi:10.1038/ncponc0714 copyright (2007)
http://www.nature.com/nrclinonc/journal/v4/n2/full/ncponc0714.html

nature CLINICAL PRACTICE ONCOLOGY

Fase karsinogenesis

- Inisiasi
  - Tahap awal karsinogenesis
  - Tjd perubahan genetik dlm sel yg (krn mutasi gen/sel, kesalahan selama proses mitosis, zat karsinogenik) menyebabkan abnormalitas proliferasi sel tunggal tp blm menimbulkan kanker
- Promosi
  - Sel tumbuh sangat cepat membtk sebuah formasi kecil (tumor, benigna)
  - Tjd peningkatan kecepatan proliferasi yg dpt menyebabkan kerusakan sel (ekspresi COX-2 tinggi)
- Progresi
  - Sel tumbuh mjd sebuah kumpulan sel yg besar dgn tingkat kecepatan proliferatif yg tinggi
  - Tjd peningkatan mobilitas
  - Terbentuk angiogenesis
- Metastasis
  - Masuknya sel kanker ke sirkulasi darah, jaringan limfatik, dan tjd perlekatan sel kanker pd permukaan jaringan baru dlm tubuh
  - Menyebar ke jaringan tetangga dan tumbuh di sana





Klasifikasi kanker menurut jenis jaringan asal pertumbuhannya

- Karsinoma
  - Kanker yg tumbuh dr jar.epitel yg meliputi membran mukosa dan kelenjar
  - Kanker payudara, paru2, ovarium
- Sarkoma
  - Kanker yg tumbuh dr jar.mesodermal yg meliputi dr jar.ikat, tulang, sel otot
- Blastoma
  - Kanker yg tumbuh dr sel hemopoetik dan jar.darah yg meliputi jar.limfoid, sel erithroid
- Leukimia
  - Kanker yg tumbuh dr leukosit

Pengobatan Kanker

Kemoterapi (sitostatika), pembedahan (operasi), penyinaran (radioterapi), imunoterapi (meningkatkan daya tahan tubuh), pengobatan dgn hormon

tujuannya :

- Menghilangkan semua sel kanker di tubuh, bahkan saat telah menyebar
- Memperpanjang harapan hidup dengan membatasi pertumbuhan dan penyebaran kanker
- Menyembuhkan gejala dan meningkatkan kualitas hidup

Sitostatika

- Tumbuh → sintesis DNA, sintesis protein

  ⇨ anti pertumbuhan (anti EGFR)
- mekanisme kematian sel kanker = apoptosis

  ⇨ induksi apoptosis
- Proliferasi sel ⇨ antiproliferatif (doxorubucin, tamoxifen (mengeblok estrogen shg tdk terikat dgn reseptornya, flavopiridol, genistein)
- Perkembangan pembuluh darah (angiogenesis)
  - pensuplay oksigen dan nutrisi ke dalam sel melalui pembuluh darah → sel kanker dengan cepat mengalami pertumbuhan, perkembangan, serta pembelahan

  ⇨ antiangiogenesis (inhibitor angiogenesis)

- *Chemoprevention* ⇨ antioksidan (vit.C, vit.E, resveratrol, genistein, epigallocathecin-3-gallate (EGCG), gingerol, kurkuminoid, betakaroten, flavonoid)
- COX-2 inhibitor (coxib drugs, meloksikam, tenoksikam)
- Analgetik opioid
- Bekerja pada *cell cycle* ???

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