



Prof. Karunagaran Devarajan

Dept: Biotechnology

IIT-Madras

MOLECULAR CELL BIOLOGY

BIOTECHNOLOGY

Module: 9

Molecular basis of cancer, oncogenes
and tumor suppressor genes



What is Cancer?





- Cancer was first described by Hippocrates, the Greek physician who lived during 460–370 BC
- He coined the term carcinoma. In Greek *karcinos* means “crab”. This is because tumors often have a central cell mass with extensions radiating outward that mimic the shape of a Crab
- The Roman physician, Celsus, who lived during 28-50 BC, later translated the Greek term into *cancer*, the Latin word for crab.
- Galen (130-200 AD), another Roman physician, used the word *oncos* (Greek for swelling) to describe cancers
- Study of cancer - oncology; cancer specialists - oncologists.

What is Cancer?

- The common phenomenon observed is the deregulation of growth processes caused by multiple changes in gene expression
- Deregulation occurs not only in cell proliferation but also in cell death
- Evolution of a population of cells that can invade tissues and metastasize to distant sites, causing significant morbidity
- If left untreated, this disease is fatal.



Types of cancers



Solid



Liquid

Solid cancers

- **Carcinomas** are solid cancers/solid tumors) (90%) that arise from the epithelial cells
- **Sarcomas** are solid cancers that arise from the connective tissue cells such as muscle and bone

Liquid cancers

- arise from the bone marrow or lymphatic system, which carries fluids throughout the body.
- **leukemia** (cancer of the blood or bone marrow)
- **lymphoma** (cancer in the lymphatic system)
- **multiple myeloma** (cancer of the plasma cells in the blood).

Tumors

- A tumor is any abnormal mass or swelling in the body
- It can be a **benign (noncancerous) tumor** . It is generally harmless but a large tumor in certain locations like brain can be harmful
- or a **malignant (cancerous)** tumor
- All tumors are believed to begin with mutations in a single cell that alters its DNA and that of its offspring thus initiating functional aberrations upon accumulation of these changes

Mutations

- **Sporadic mutations** occur spontaneously during the lifespan of a cell
- It may be **due to errors in cell cycle** when a cell copies its DNA prior to dividing the **incorrect repair** of a damaged DNA molecule or **chemical modification** of the DNA each of this interferes with expression of the genetic information.
- **Inherited mutations** are present in the DNA contributed by the sperm and/or egg at the moment of conception.
- To date, 90–95% of diagnosed cancers appear to be sporadic in nature and thus have no heredity basis.

Common cancers

World scenario

- About 12.7 million cancer cases and 7.6 million cancer deaths occurred in 2008; 56% of the cases and 64% of the deaths from developing world.
- Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths.
- Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths.
- Although overall cancer incidence rates in the developing world are half those seen in the developed world in both sexes, the overall cancer mortality rates are generally similar.

Indian scenario

- 1.5 to 2 million cancer cases at any given point of time.
- Over seven lakh new cases of cancer and 3 lakh deaths occur annually due to cancer
- leading sites of cancer are oral cavity, lungs, oesophagus and stomach amongst men
- cervix, breast and oral cavity amongst women
- Breast cancer is now leading in incidence in urban centres, a shift from the previous decades during which the first place was held by cervical cancer.

GEOGRAPHIC DIFFERENCES IN CANCER INCIDENCE

Nasopharyngeal cancer	China, Hong Kong, Taiwan and Singapore
Esophageal carcinoma	Asia stretching from Europe and Russia to eastern China
Stomach cancer	Japan (10X rate Caucasian Americans)
Colorectal cancer	United States (3-4X more common than Japan India, Africa or Latin America)
Liver cancer	Sub-Saharan African, China and Japan
Breast cancer	Europe and North America (5-6X higher than African or Asia)
Cancer of the cervix	low socioeconomic status up to 25X higher incidence

CAUSES



- Carcinogenesis – is the process of cancer development. It is a multistep process thriving with mutations, epigenetic changes and a conducive microenvironment
- The factors/agents that induce/cause cancer are called carcinogens. Most carcinogenic agents cause **genetic damage** and induce **neoplastic transformation** of cells
- They include **chemicals, radiation and microbes** aided by a host of risk factors. Thus this list includes external/environmental and internal factors which may act together
- Hereditary – Inherited cancer syndromes
 - Retinoblastoma, Li-Fraumeni syndrome, Multiple Endocrine Neoplasia (MEN) type 1 and 2, Hereditary Non-Polyposis Colon Cancer (HNPCC)

Many Risk Factors have been identified that increase the risk

Diet and Tobacco play a major role



Sexual behavior

Occupational hazards

Alcohol

Pollution

Industrial products

Medical products/procedures

Sedentary living

Chemical Carcinogens

- **Sir Percival Pott** – in the 18th century, related the high incidence of scrotal skin cancer in chimney sweeps to chronic exposure to soot – bathing daily controlled the cancer! – First known correlation between a cancer and a chemical / environmental agent.
- Mutagenic potential of chemicals assessed by **Ames test** – Ability of the chemical to induce mutations in *Salmonella typhimurium*; Most carcinogens are mutagens

Major Chemical Carcinogens

Alkylating agents	Acylating agents	Polycyclic and heterocyclic aromatic hydrocarbons	Aromatic amines, Amides, Azo dyes	Plant and microbial products
<ul style="list-style-type: none">•B-propiolactone•Dimethyl sulfate•Diepoxybutane•Anticancer drugs!! (cyclophosphamide, chlorambucil, nitrosoureas, etc)	<ul style="list-style-type: none">•1-Acetyl – imidazole•Dimethyl carbamyl chloride	<ul style="list-style-type: none">•Benz(a)anthracene•Benzo(a)pyrene•3-Methylchloranthrene	<ul style="list-style-type: none">•2-Naphthylamine•Benzidine•Dimethyl aminoazobenzene (butter yellow)	<ul style="list-style-type: none">•Aflatoxin B1•Griseofulvin•Cycasin•Safrole•Betel nuts
Others <ul style="list-style-type: none">•Nitrosamine and amides•Vinyl chloride, Nickel, Chromium•Insecticides, fungicides				

- **Cigarette smoke** contains **43 known carcinogens**, including PAHs, Polonium 210, N' -Nitrosonornicotine (NNN)
- A major cause of cancer of lung, larynx, oral cavity

Radiation

- **Hiroshima and Nagasaki** – Increased incidence of Breast and thyroid cancer years after the bombings
- **Chernobyl disaster**– Thyroid carcinoma
- **Marshall and Rongelap Islands** – Near nuclear weapons testing sites → high incidence of Thyroid carcinoma

Radiation

- Types
 - UV rays – from the sun; → Skin cancers
 - UVC – more mutagenic but filtered out by Ozone
 - UVB – Pyrimidine dimers (corrected by Nucleotide Excision Repair → *Xeroderma Pigmentosum* a case in point)
- Ionizing radiation
 - X-rays
 - γ rays
 - Particulate (α , β , protons, neutrons)

Microbes

- Viruses
 - Human Papilloma Virus (HPV) – cervical cancer, oral cancer
 - Epstein Barr Virus (EBV) – Burkitt Lymphoma
 - Hepatitis B Virus – Liver cancer
 - Human T-Cell Leukemia Virus Type 1 (HTLV-1) - Leukemia
- Bacteria
 - *Helicobacter pylori* – stomach cancer
- Other non-microbial pathogens
 - Schistosoma (bladder fluke) → Inflammation → bladder cancer

The Neoplastic Phenotype

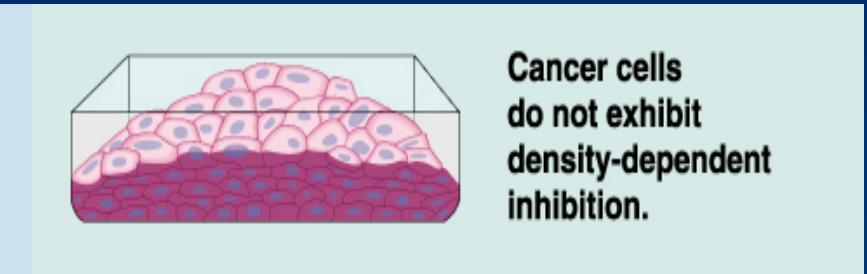
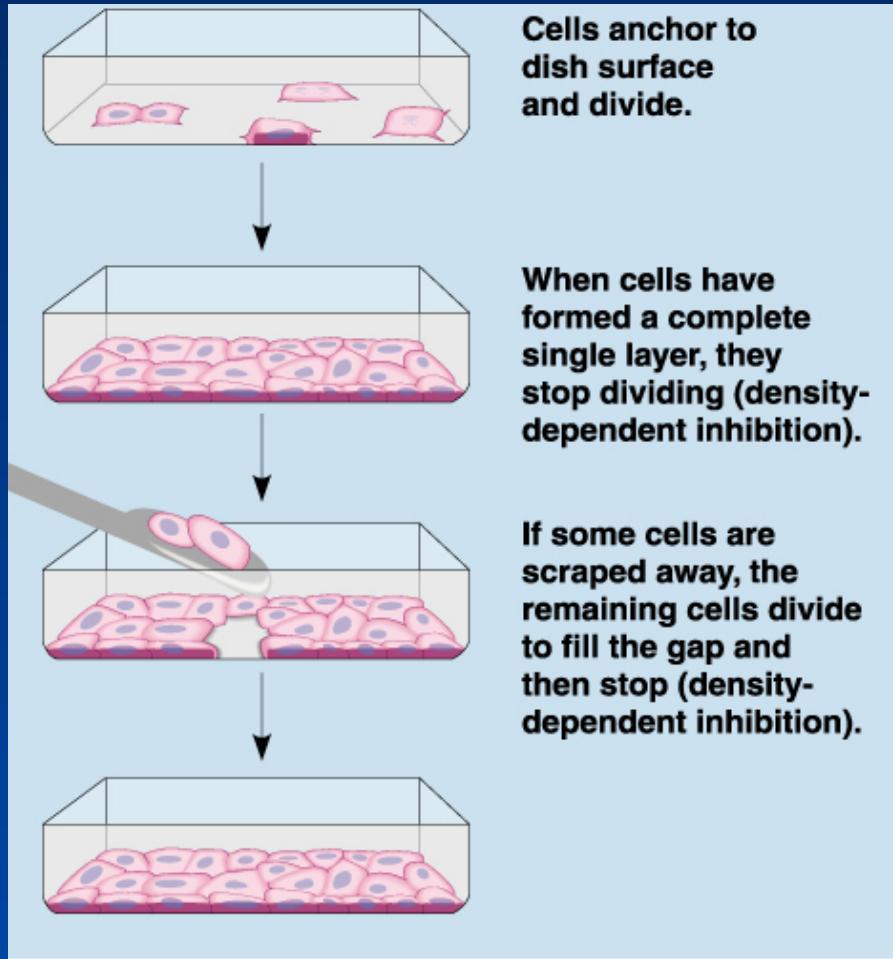
Terms used

- **Anaplasia**
lack of differentiation – a hallmark of malignant transformation
- **Dysplasia**
A loss in uniformity of the individual cells as well as a loss in architectural orientation (abnormal structural change)
- **Hyperplasia**
increase in cell number; regulated and physiological
- **Hypertrophy**
increase in cell size

Metastasis

- is the condition in which the cells from the original primary tumor migrate to either local or distant locations in the body where they will divide and form secondary tumors.

The Neoplastic Phenotype

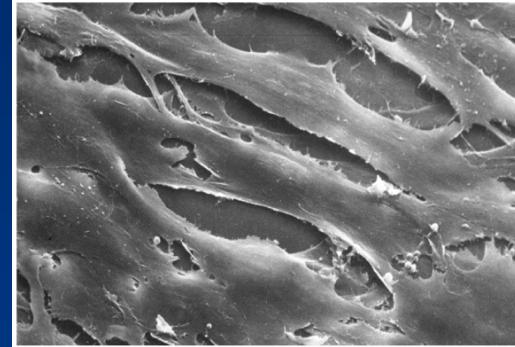


- Cancerous cells are immortal
- Normal cells divide 20-50 times
- Cancerous cells can divide indefinitely (Telomerase activity)

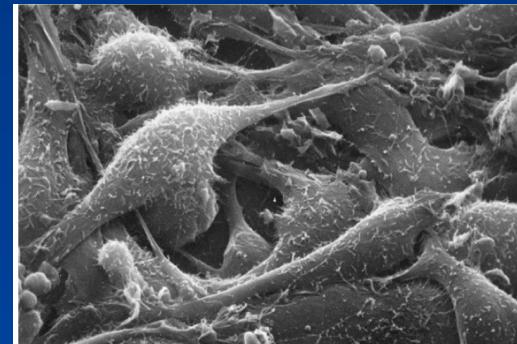
The Neoplastic Phenotype

Features of cancer cells

- Increased nuclear/cytoplasmic ratio
- More DNA content
- More mitotic figures
- Variable chromosome number
- Loss of contact inhibition
- Loss of anchorage dependence
- Secretion of growth factors
- Expression of growth factor receptors

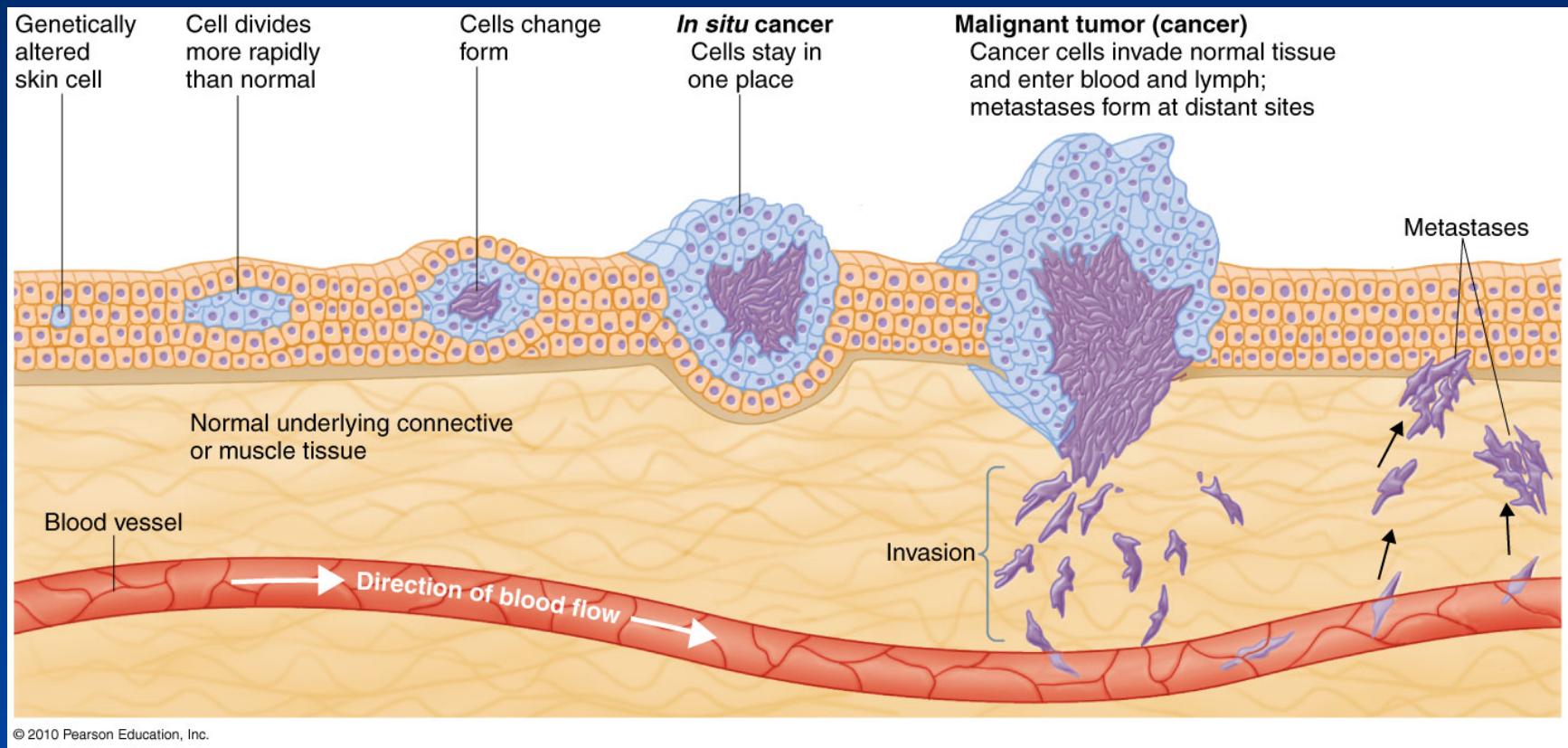


Normal cells



Cancer cells

Development of a malignant tumor



Development of a malignant tumor



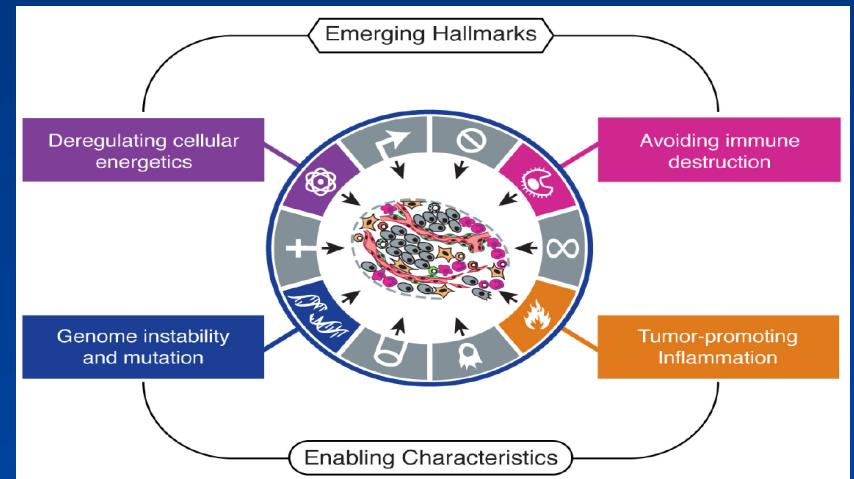
Most cancers occur in
highly proliferating cells (epithelial, stem cells)
or cells that can come in contact with
chemicals/viruses/environment

Cancers of the heart and brain

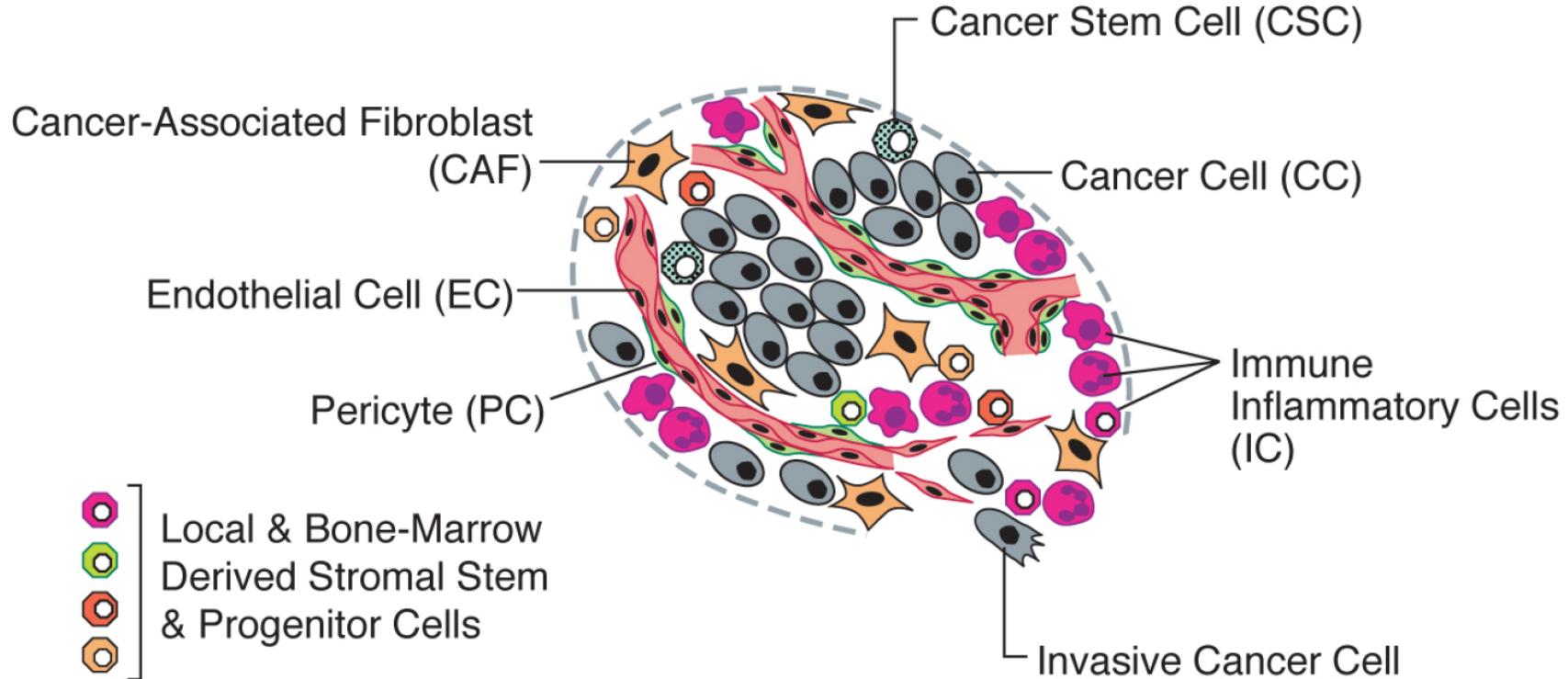
- “Heart cancer” – listed as a “Rare Disease” by the National Institutes of Health (NIH), USA. Affects less than 200,000 people in the entire US population.
- Cardiac sarcoma, rhabdomyosarcoma, angiosarcoma
- We know that nerve cells can not reproduce well. Then how do people have brain tumors?
- Many tumors in the brain are not composed of (transformed) neurons, but rather other cell types, like glia, astrocytes and schwann cells

Hallmarks of cancer

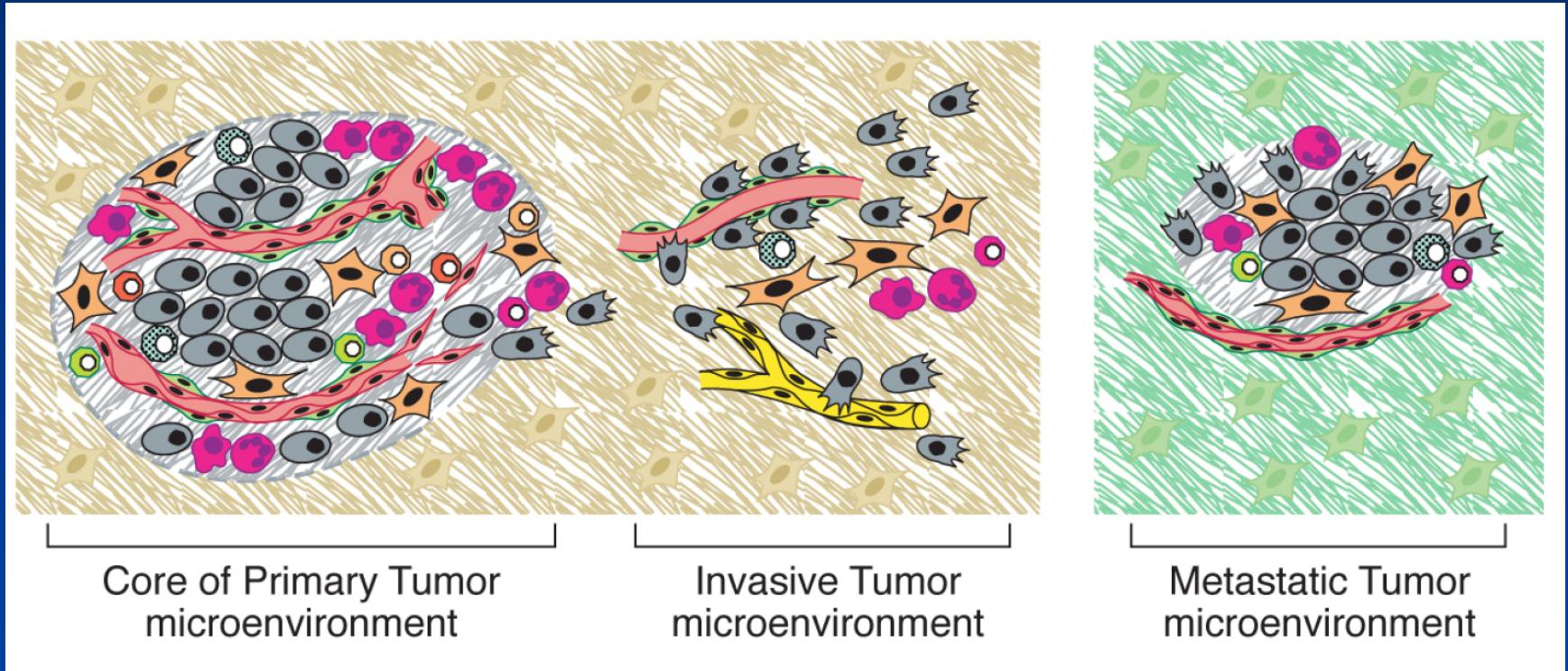
- Hallmarks/essential alterations acquired by cancer cells
- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Evasion of apoptosis
- Defects in DNA repair
- Limitless replicative potential
- Sustained angiogenesis
- Invasion and metastasis



Tumor microenvironment



Tumor microenvironment

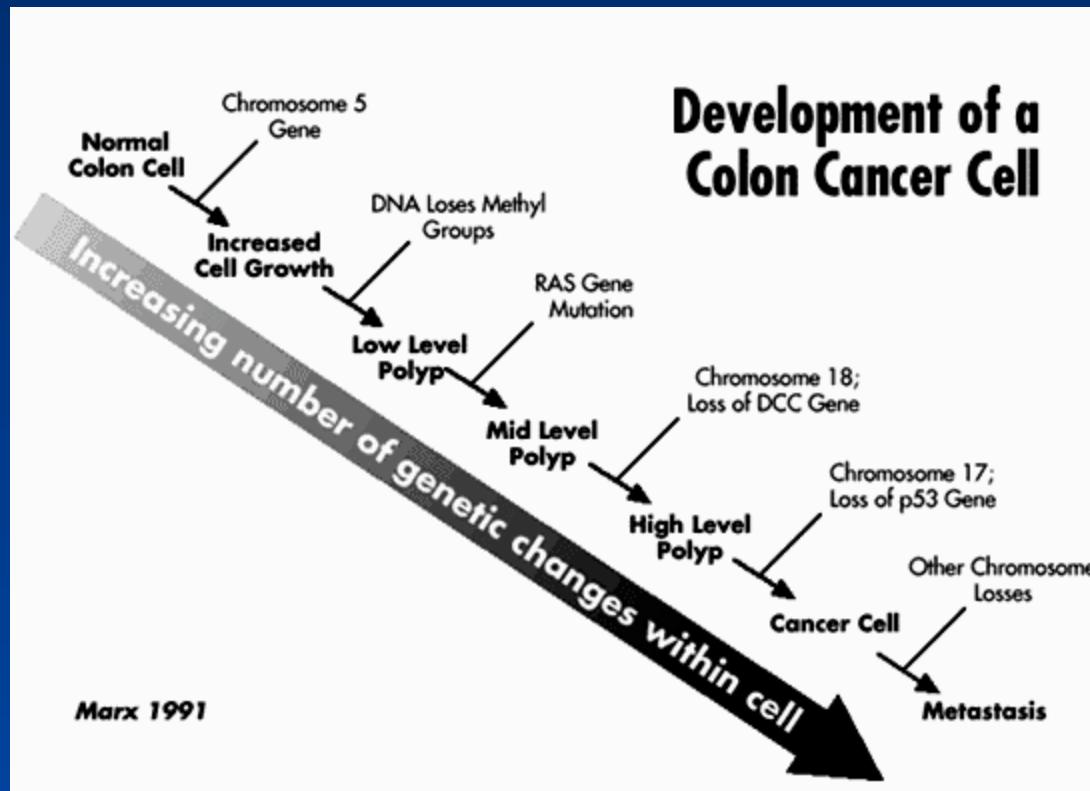


Core of Primary Tumor
microenvironment

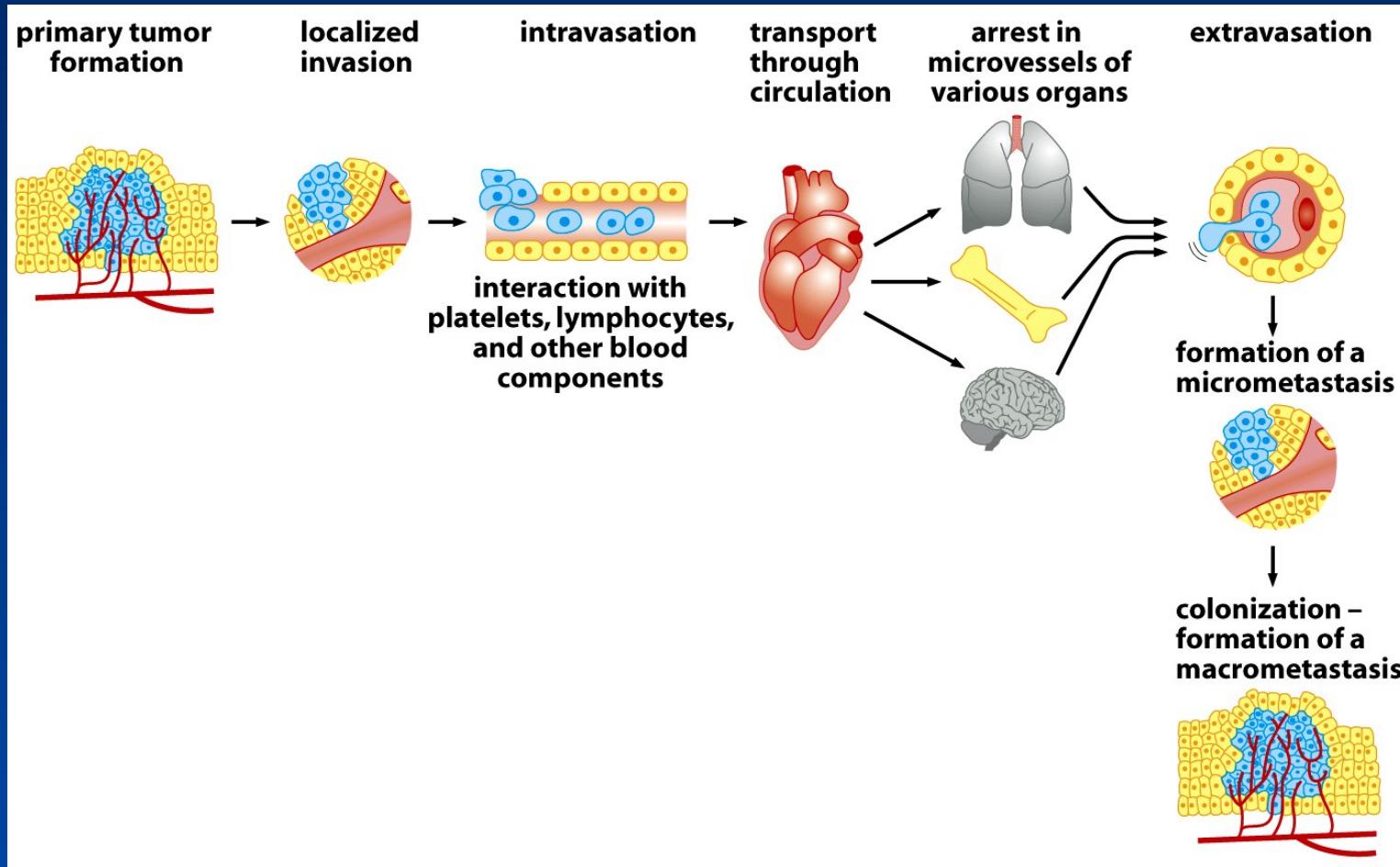
Invasive Tumor
microenvironment

Metastatic Tumor
microenvironment

Development of a Colon Cancer Cell



The Invasion-Metastasis Cascade



Six steps to metastasis

- Breach of basement membrane
- Intravasation
- Transport to distant tissues
- Arrest at target organs and extravasation
- Formation of micrometastases
- Colonization at distant sites

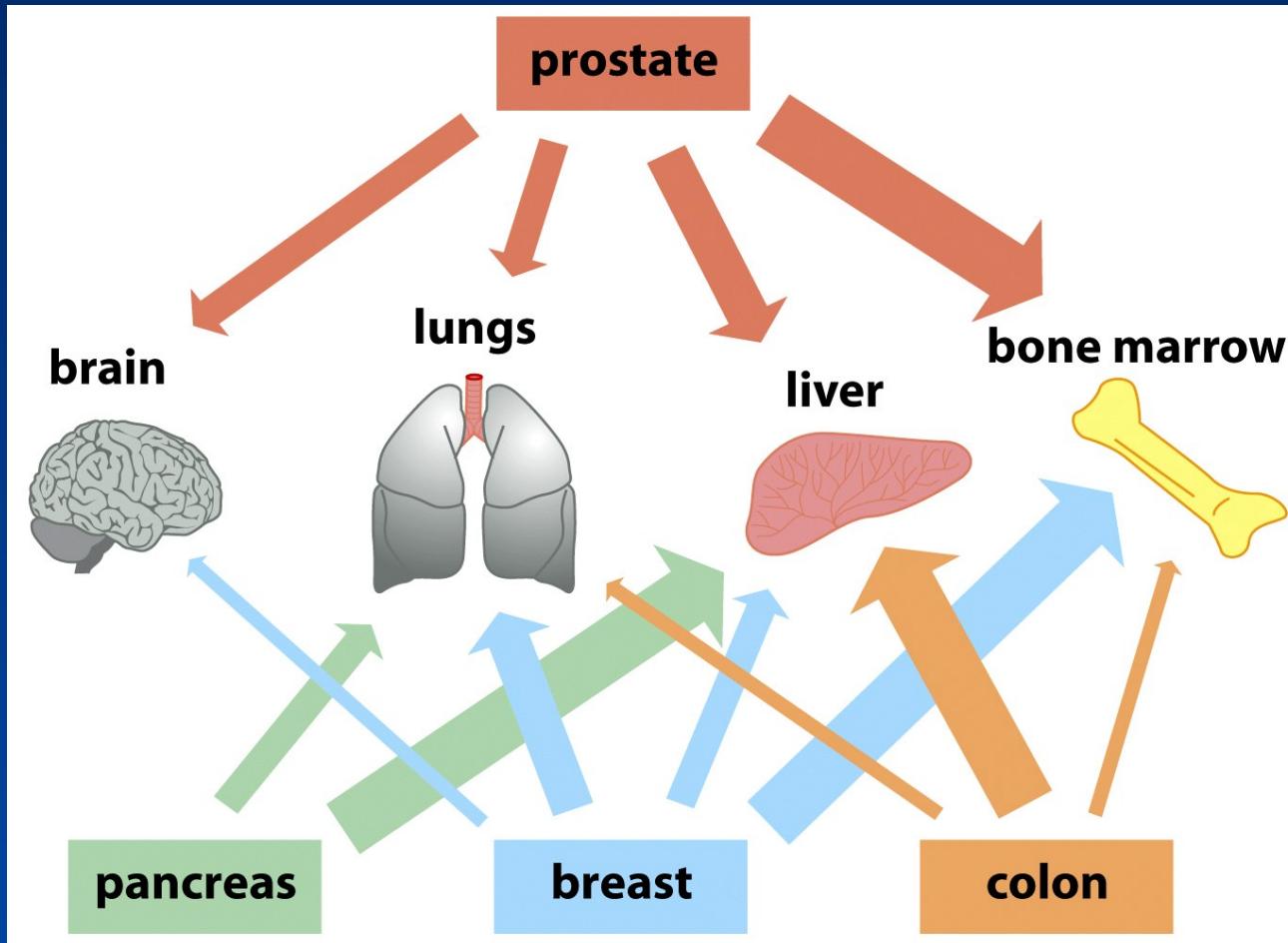
Routes

- Lymphatic spread
 - Although tumors have no lymphatic supply, surrounding areas have lymphatic vessels
 - Most common way of spread
 - Eg: Breast cancer and axillary lymph nodes.

Routes

- Hematogenous spread
 - **Liver, lungs, bone marrow** most commonly involved, because of extensive blood supply
 - Veins more easily penetrated by tumor than arteries (because of thinner walls)
 - Cancer cells are much larger than RBCs and WBCs and not easily deformable; they get **trapped in capillary beds, esp. in the lungs**

Certain Cancers have a Tendency to Metastasize to Specific Organs – Metastatic Tropism



Theories of carcinogenesis



- **Early theories**

Humoral origin – “black bile” (Hippocrates, Galen)

Lymphatic origin (John Hunter)

- **Modern theories**

Somatic Mutation Theory

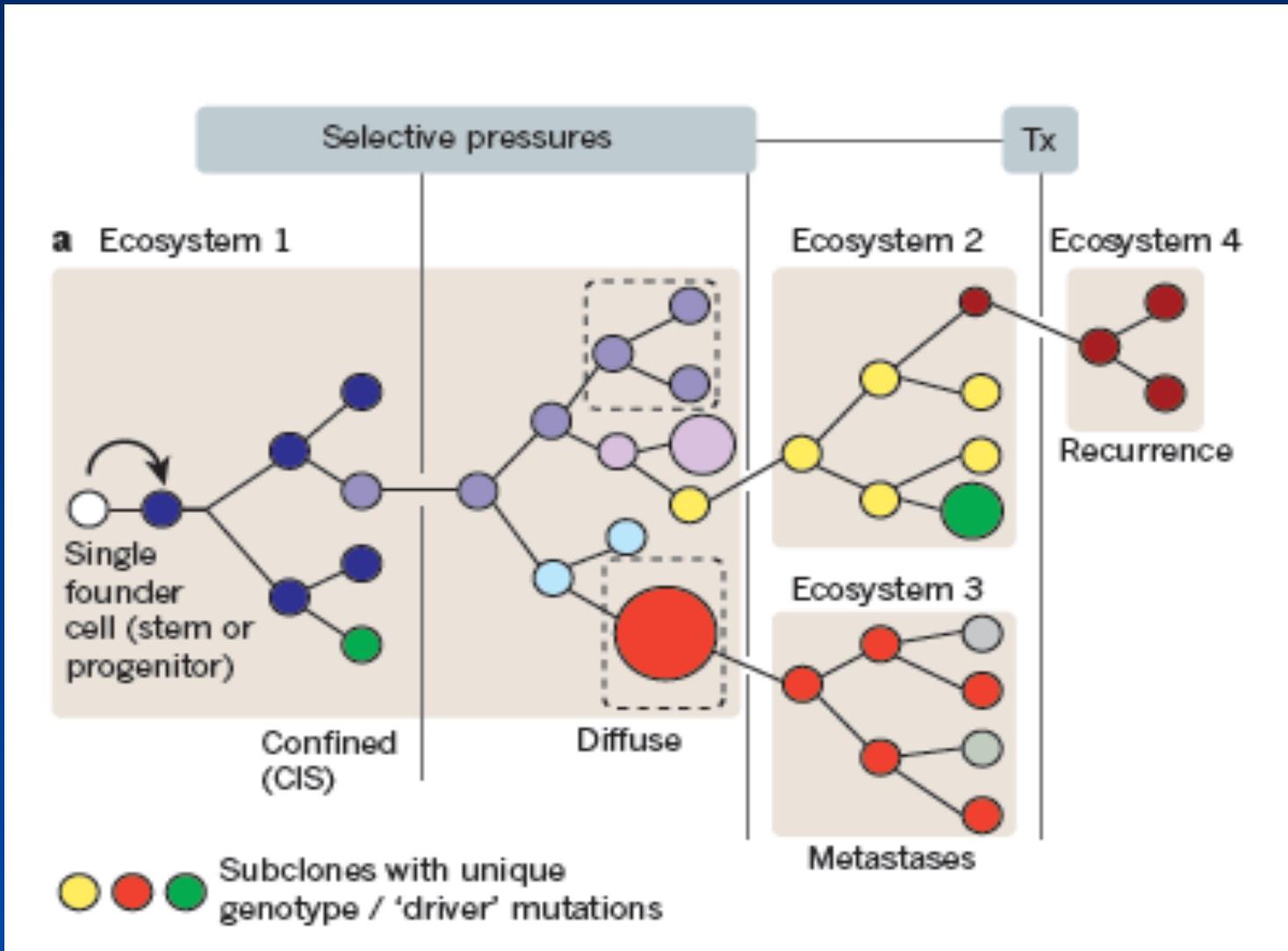
Origin from a single cell with multiple mutations in its DNA (*clonal origin*)

Stem cell theory

Tissue Organization Field Theory

“Carcinogenesis is a problem of tissue organization, comparable to organ formation during early development”

Theories of carcinogenesis



Theories on metastasis



The Anatomic Model

Secondary tumors occur in the organs which they come across first during their journey into the blood/lymphatic circulation from the primary tumor

Tumor cells from colon first pass through the capillary bed of the liver that provides a suitable environment for the growth of these secondary tumors

The Seed and Soil Hypothesis

In 1889 Stephen Paget observed that breast cancer patients often had secondary metastatic tumors in the liver. For him selective accessibility of the liver by the blood supply was not acceptable as many other organs are equally accessible for the blood supply. He hypothesized that tumor cells (seeds) can only grow in selective organs (soil) that provided suitable growth environment.

Modern theories on metastasis



1. Tumour cells in the blood and lymphatic systems have equal access to all organs, but multiply only in those organs that have the appropriate growth factors

2. Endothelial cells lining the blood vessels in target organs express adhesion molecules that act as brakes to stop the circulating tumour cells in those organs

Modern theories on metastasis



3. chemoattraction theory

organ-specific attractant molecules (chemokines) enter the circulation

They attract the circulating tumour cells containing the corresponding chemokine receptors

This stimulates them to invade the walls of blood vessels and enter the organs.

- Higher expression of CXCR4 receptor in breast-cancer tissue than normal breast tissue
- CXCL12 chemokine is expressed in many metastatic sites/organs of breast cancer, such as lymph nodes, bone marrow and lungs



Therapy

- Conventional therapies include
- Surgery
- Radiation
- Chemotherapy
- No conventional drug is without side effect
- With our understanding on the molecular biology of cancer, now researchers have developed many targeted therapies
- Combination therapy

Summary



- What is cancer?
- Types of cancers
- What is the cancer burden in India and the world
- Molecular basis of cancer
- Causes of cancer
- Metastasis
- Theories of carcinogenesis
- Modern theories on metastasis
- Therapy

END