HALLMARKS OF CANCER

What are ‘ hallmarks of cancer ‘ ?

- Biologic capabilities acquired by cancer cells during the multistep process of development of human tumors
- ***Essential Alterations In Cell Physiology That Collectively Lead To Malignant Growth Of A Normal Cells.***
- Described by Douglas Hanahan & Robert Weinberg in 2000

Originally *six* hallmarks of cancer proposed :

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory (antigrowth) signals.
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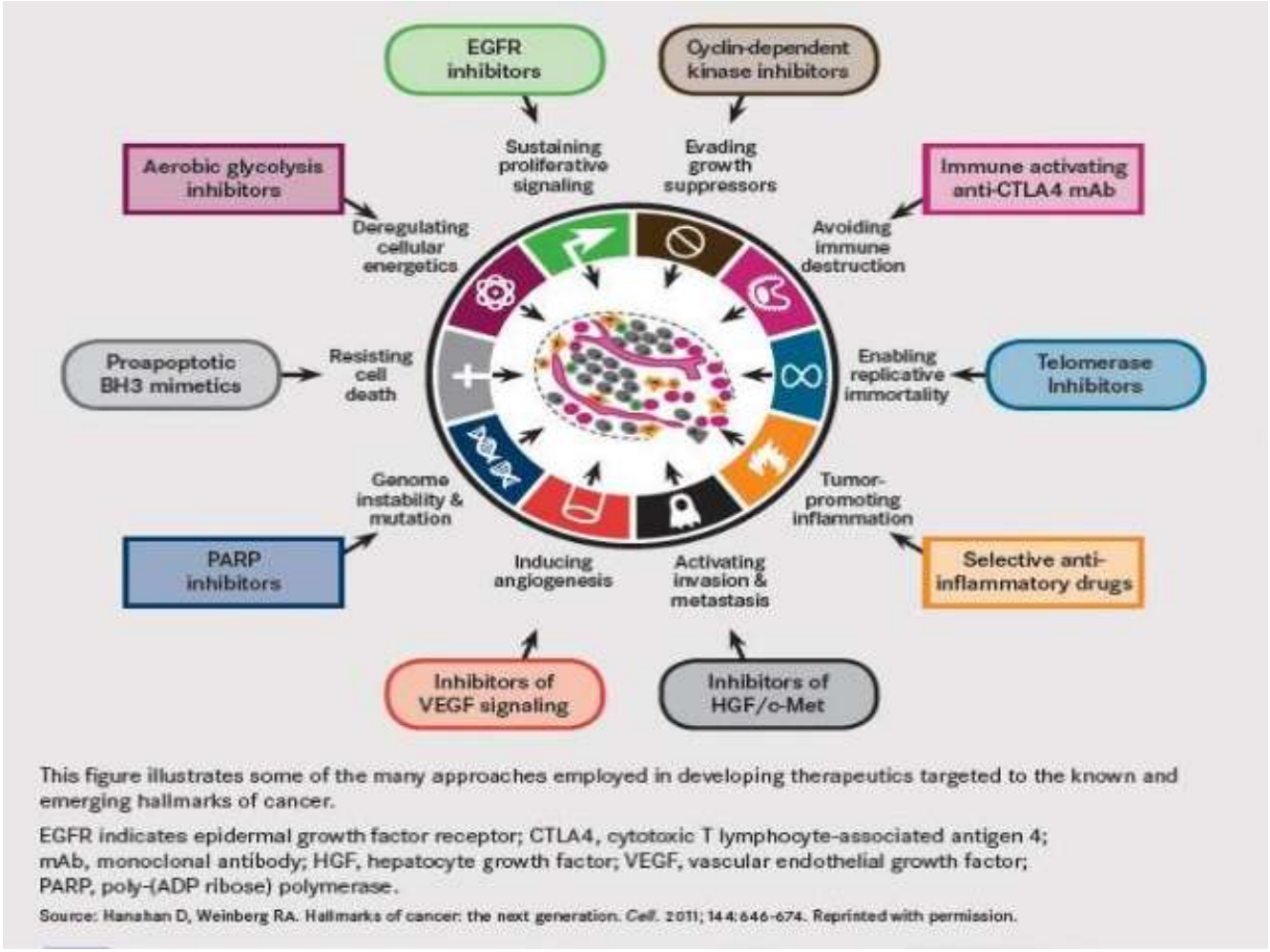
- Evading apoptosis.
- Limitless replicative potential.
- Sustained angiogenesis.
- Tissue invasion and metastasis.

- With development in genetics and epigenetics Hanahan and Weinberg again redefined "Hallmarks of cancer" in 2011.

Two additional hallmarks of cancer are:

- Evading immune destruction.
- Deregulating cellular metabolism or energetics.



This figure illustrates some of the many approaches employed in developing therapeutics targeted to the known and emerging hallmarks of cancer.

EGFR indicates epidermal growth factor receptor; CTLA4, cytotoxic T lymphocyte-associated antigen 4; mAb, monoclonal antibody; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; PARP, poly-(ADP ribose) polymerase.

Source: Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144:646-674. Reprinted with permission.

1. Sustained Proliferative Signalling

- Cancer cells : 'master of their own destinies'
- Normal cells require growth signals to enter from a quiescent state into an active proliferative state.
- These signals are transmitted into the cell through transmembrane receptors that binds to a particular class of signaling molecules.
- Tumor cells generate their own growth signals and thereby reducing their dependence on external stimulation from their normal tissue microenvironment.

Over express receptors

Sustained Proliferative Signaling

Alteration of extracellular growth signals	• Many cancer cells acquire the ability to synthesize abundance of GFs to which they are responsive, creating a positive feedback signaling loop
Alternation of transcellular receptor of those signals	• Receptor overexpression may enable the cancer cell to become hyperresponsive to ambient levels of GF that normally would not trigger proliferation
Alternation of intracellular circuits that translate those signals into action.	• Alterations in components of the downstream cytoplasmic circuitry that receives and processes the signals emitted by GF receptors can release a flux of signals into cells, without ongoing stimulation by their normal upstream regulators

Sustained Proliferative Signaling

- **Somatic Mutations activate additional downstream pathways that promote sustained growth**

- RAS-RAF-MAPK PATHWAY
- 90% Pancreatic adenocarcinomas carry mutant K-RAS alleles
- 40% melanomas contain activating mutations affecting B-RAF

Sustained Proliferative Signaling

Disruptions of Negative-Feedback Mechanisms that Attenuate Proliferative Signaling –

- Defect in negative feed back mechanism leads to uncontrolled proliferative signaling .
- The prototype of this type of regulation involves the RAS oncoprotein.
- The oncogenic mutations of RAS genes impair the intrinsic GTPase activity of RAS that normally serves to turn its activity off, ensuring that active signal transmission is transient.

Sustained Proliferative Signaling

Excessive Proliferative Signaling Can Trigger Cell Senescence

- Excessively elevated signaling by oncoproteins, such as RAS, MYC, and RAF in a normal cell provoke protective response such as **induction of cell death.**
- Alternatively, cancer cells expressing high levels of these oncoproteins may be forced to enter into the nonproliferative but viable state called **senescence.**
- Whenever these tumor cells get the favorable microenvironment they enter into proliferative phase.

2. Evading Growth Suppressors

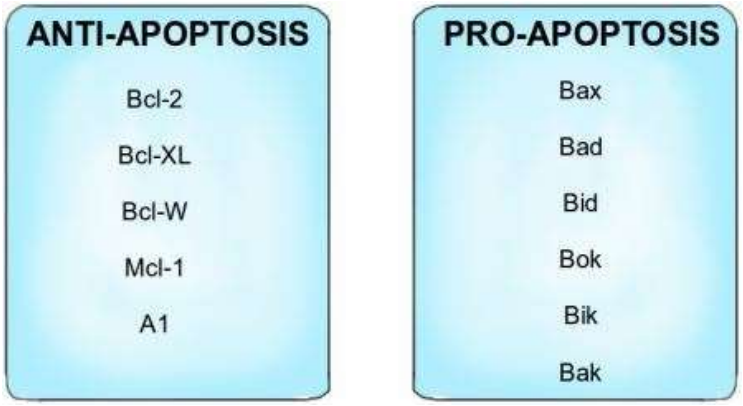
- Growth suppressors are acting as the break mechanism to overrule the initiation or "turning off" of cell division.

- The two prototype tumor suppressor genes encode the retinoblastoma **(RB)**-associated and **P53** proteins.

- The RB protein integrates signals from diverse extracellular and intracellular sources and, in response, decides whether or not a cell should proceed through its growth and division cycle.

3. Resisting Cell Death

- Normally when cells become old or damaged they are programmed to die in a process called apoptosis.
- But cancer cells escapes normal cell death and continue to accumulate in the body.
- Tumor cells develops a variety of strategies to escape apoptosis.



Controlled by fine balance between pro-apoptotic and anti-apoptotic proteins.

Resisting Cell Death

Cancer cells acquires anti apoptotic regulators:-

- Most common is the loss of P53 tumor suppressor function, which eliminates this critical damage sensor from the apoptosis-inducing circuit.
- Alternatively, tumors may escape apoptosis by increasing the expression of antiapoptotic regulators (Bcl-2, Bcl-XL Mcl-1).
- By downregulating proapoptotic Bcl-2–related factors (Bax, Bim,Apaf-1).

Resisting Cell Death

Autophagy Mediates Both Tumor Cell Survival and Death –

- Nutrient starvation, radiotherapy, and certain cytotoxic drugs can induce elevated levels of autophagy that apparently protect cancer cells via resistance to apoptosis.

- Moreover, severely stressed cancer cells have been shown to shrink via autophagy to a state of reversible dormancy.

- This particular survival response may enable the cancer cells to survive during anticancer therapy or during shortage of nutrition.

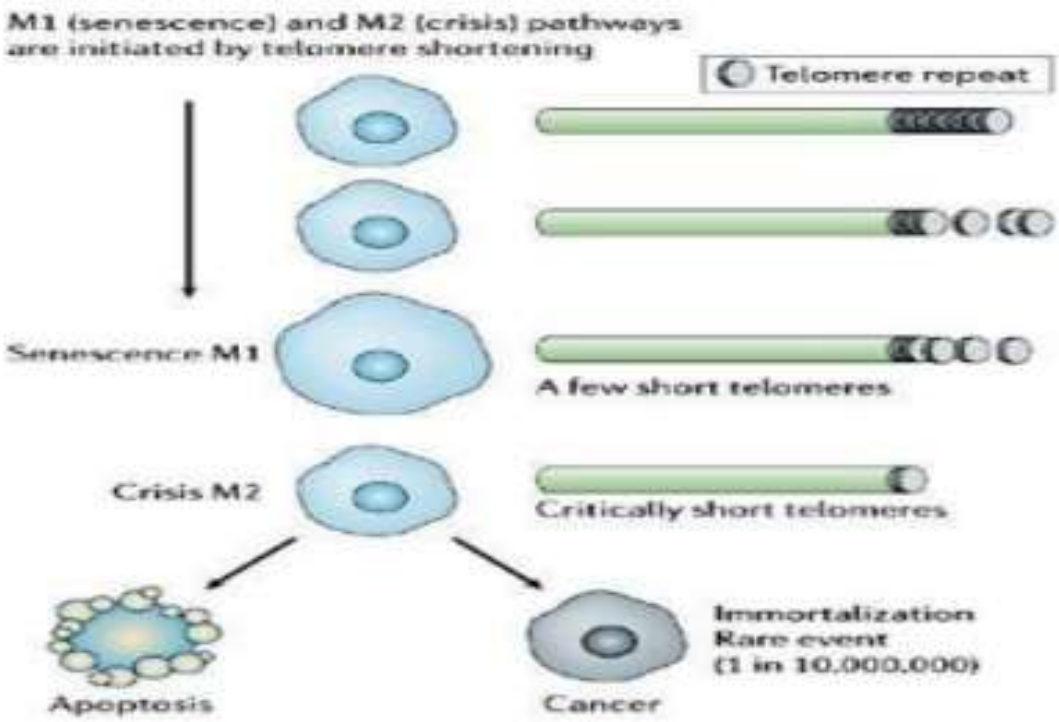
Resisting Cell Death

Necrosis has proinflammatory & tumor promoting potential

- Necrotic cells can release bioactive regulatory factors which can directly stimulate viable neighbouring cells to proliferate

4. Enabling Replicative Immortality

- In normal cell division, a small portion of the end of each chromosome called telomere, is lost every time DNA is copied.
- Loss of telomere reaches a critical point and cell will no longer divide and replicate and undergo p53 dependent cell cycle arrest or apoptosis. In this way healthy cells self limit their replication.
- But in cancer cells activation of an enzyme called telomerase can maintain telomeres and allow cells to replicate limitlessly.



5. Inducing Angiogenesis

The formation of new blood vessels out of pre-existing capillaries.

ANGIOGENIC SWITCH OF TUMORS

INVOLVES : Sprouting

Splitting

Remodeling of the existing vessels

WHY IT IS IMPORTANT?

- Supply of oxygen and nutrients
- Removal of waste products

Cytokines
Vascular endothelial growth factor =VEGF
Basic fibroblast growth facto=bFGF)

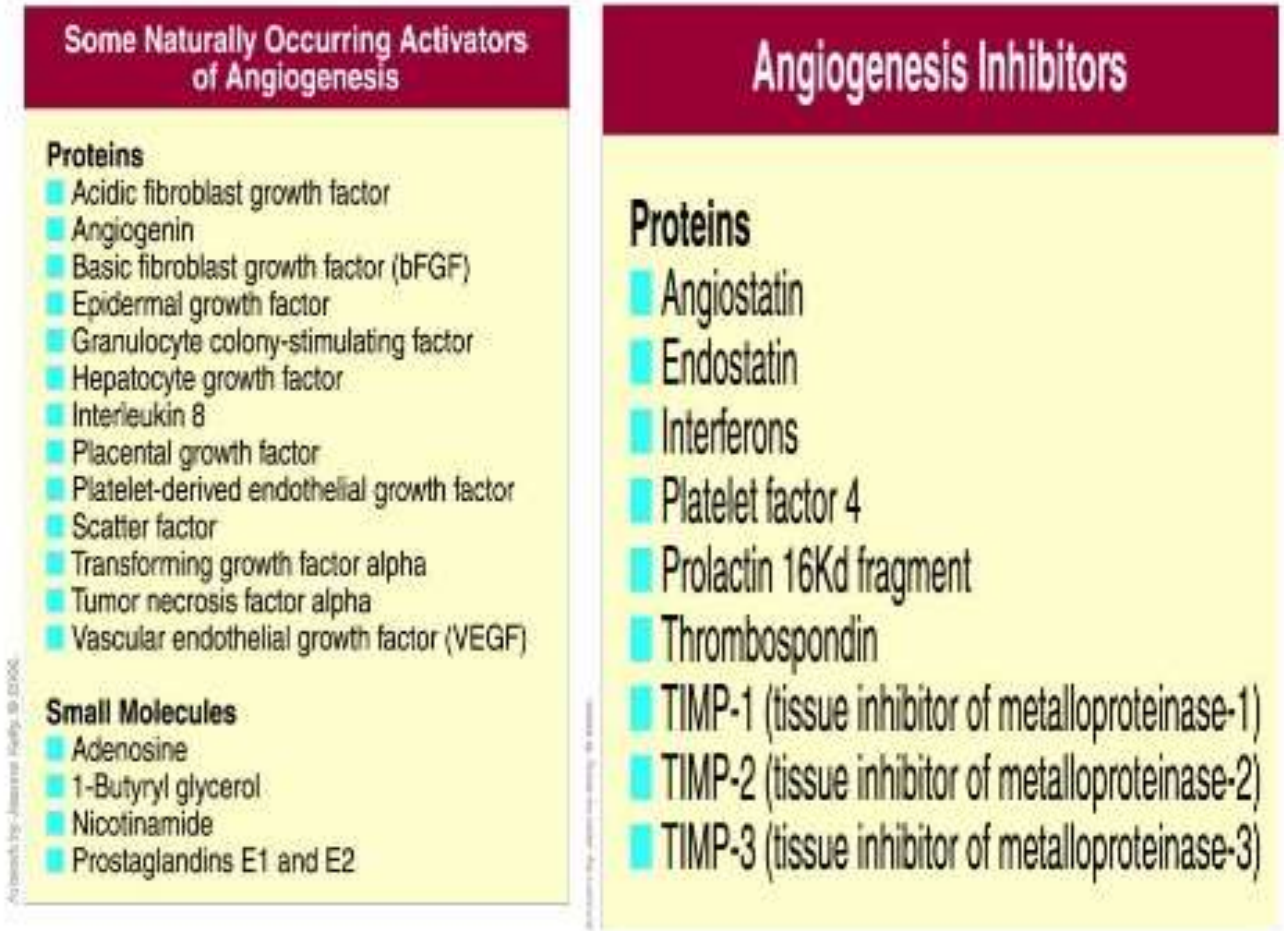
TUMOR ANGIOGENESIS

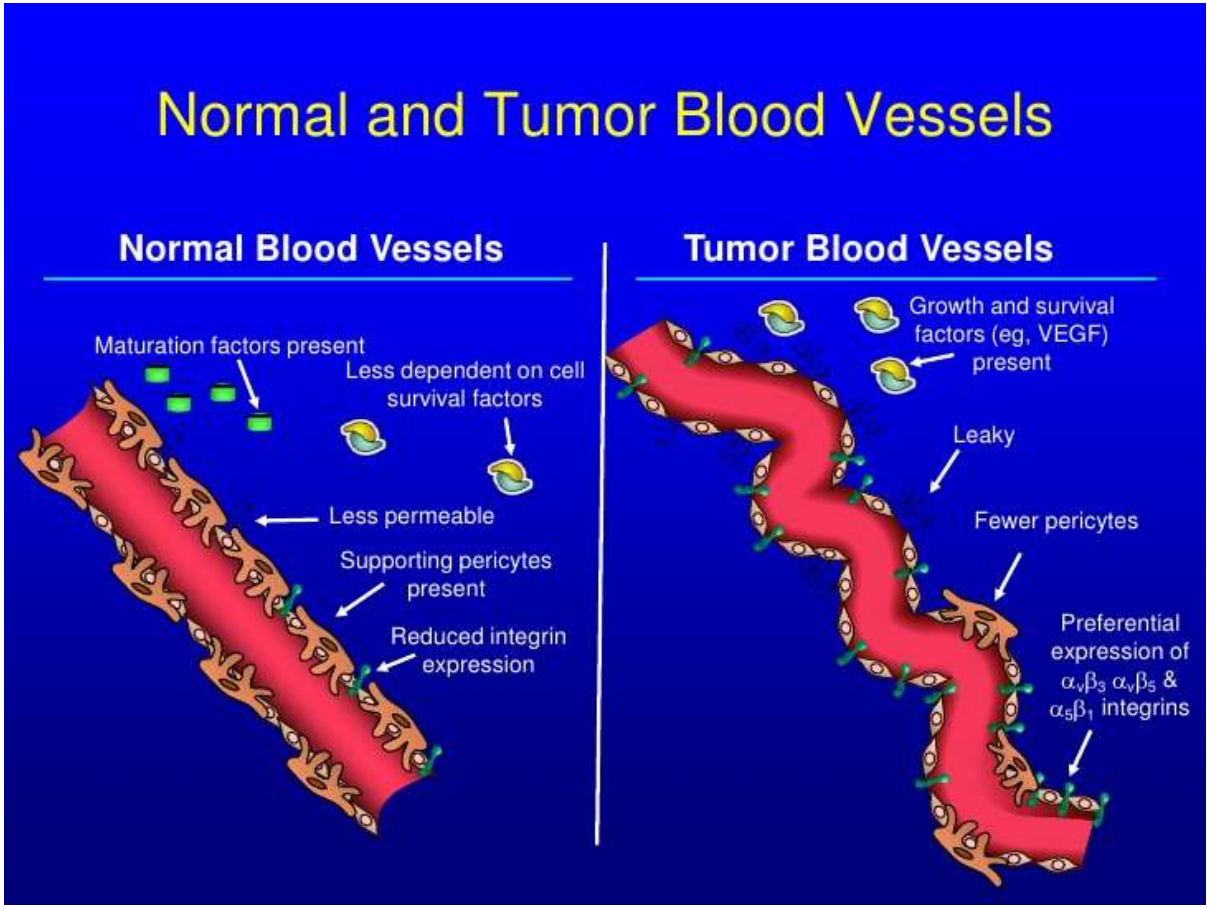
Three major steps

(A) Initiation of the angiogenic response.

(B) Endothelial cell(EC) migration, proliferation and tube formation.

(C) Finally the maturation of the neovasculature.


Some Naturally Occurring Activators of Angiogenesis
Proteins
Acidic fibroblast growth factor
Angiogenin
Basic fibroblast growth factor (bFGF)
Epidermal growth factor
Granulocyte colony-stimulating factor
Hepatocyte growth factor
Interleukin 8
Placental growth factor
Platelet-derived endothelial growth factor
Scatter factor
Transforming growth factor alpha
Tumor necrosis factor alpha
Vascular endothelial growth factor (VEGF)
Small Molecules
Adenosine
1-Butyryl glycerol
Nicotinamide
Prostaglandins E1 and E2
Angiogenesis Inhibitors
Proteins
Angiostatin
Endostatin
Interferons
Platelet factor 4
Prolactin 16Kd fragment
Thrombospondin
TIMP-1 (tissue inhibitor of metalloproteinase-1)
TIMP-2 (tissue inhibitor of metalloproteinase-2)
TIMP-3 (tissue inhibitor of metalloproteinase-3)


Normal and Tumor Blood Vessels
Normal Blood Vessels
Maturation factors present
Less dependent on cell survival factors
Less permeable
Supporting pericytes present
Reduced integrin expression
Tumor Blood Vessels
Growth and survival factors (eg, VEGF) present
Leaky
Fewer pericytes
Preferential expression of $\alpha_v\beta_3$ $\alpha_v\beta_5$ & $\alpha_5\beta_1$ integrins

5. Avoid Immune destruction

Majority of small tumor destroyed by immune system

Lage tumor avoid detection- evade destruction by immune system

Greater incidence of cancer in immune compromised or immunosuppressed individual. E.g HCV, HBV, Herpes virus.

6. Tumor promoting inflammation

Chronic inflammation (autoimmune, bacterial, viral, parasitic etc.) cause normal cells to develop pro-neoplastic mutation and resistance to apoptosis.

COX_2 (Cyclooxygenase) generate prostaglandin E_2(PGE_2) which is an inflammatory mediator. COX_2 is overexpressed in tumor cells.

Inflammation recruit leukocytes such as neutrophils and macrophages to the tumor environment.

Macrophage release cytokines and growth factors that nourish tumor.

7. Deregulating cellular energetics

- Chronic cell proliferation requires adjustment of energy metabolism
- Normal cells use glucose via glycolysis under anaerobic conditions but favor oxidative phosphorylation under aerobic conditions
- Cancer cells can reprogram glucose metabolism to favor glycolysis even under aerobic conditions
- Glycolysis is much less efficient than oxidative phosphorylation
- Cancer cells compensate by up-regulating glucose transporters (GLUT1) to increase glucose uptake into the cell
- Use of glycolysis is associated with activated oncogenes (RAS, MYC), with mutant tumor suppressors (p53) and can be further increased in the setting of hypoxia, present in many tumors

8. Genome instability and mutation

- Tumor cell continuously evolves
- BRCA1 +BRCA 2 (in hereditary breast and ovarian cancer)
- P53 gene
- RB1 (The retinoblastoma protein is a tumor suppressor protein that is dysfunctional in several major cancers. One function of Rb is to prevent excessive cell growth by inhibiting cell cycle progression until a cell is ready to divide)
- Diseases associated with **RB1** include Retinoblastoma and Small Cell Cancer Of The Lung.
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9. Deregulating cellular energetics

- Tumor cell undergoes aerobic glycolysis less efficiently
- It convert glucose into lactate (85%) or CO_2 (5%) in absence or presence of oxygen.
- Increase expression og GLUT1 AS compensation.
- Facilitate biosynthesis of macromolecules (amino acids & nucleic acid precursors) for formation of tumor daughter cells.

10. Activation of invasion and metastasis

- 80 to 90% cancer deaths are because of metastasis of cancer.----2ndary tumor-lungs, brain etc.
- Breakdown of cell-cell adhesion (E-cadherin)
- Degradation of extracellular matrix(MMP=Matrix metalloproteinases)
- Increased motility of cancerous cells(chemotaxis)

Invasion-Metastasis Cascade Adapted from Fidler, Nat. Rev. Cancer 3: 453-458, 2003