NEOPLASIA : 2
METASTASIS

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METASTASIS

- Tumor spread discontinuous from primary

- About 30% of tumours present with metastases
- Unequivocally marks a tumor as malignant except gliomas & basal cell carcinoma of skin

- More aggressive, more rapidly growing, larger & poorly differentiated tumors more likely to spread
- Metastatic spread strongly reduces possibility of cure

Liver metastases from a primary breast carcinoma

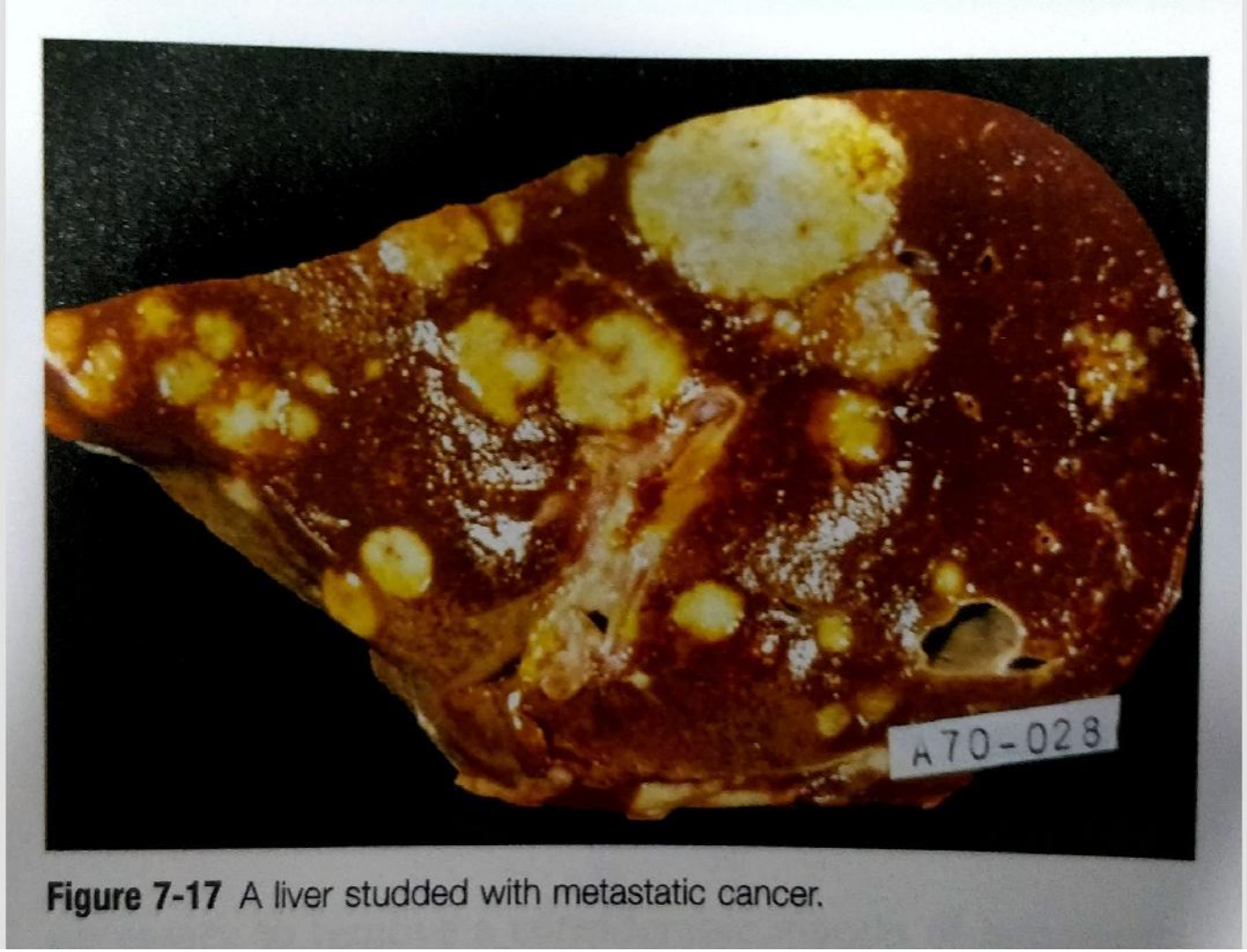


Figure 7-17 A liver studded with metastatic cancer.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

PATHWAYS OF SPREAD

- **Lymphatic spread**

  -usual route for carcinomas

  -regional lymph nodes

- **Haematogenous spread**

  - usual route for sarcomas
  - usual route for late stage tumors (carcinomas)

- **Transcoelomic (body cavity spread)**

  -seeding of cavities/surface by tumor

- Seeding of body cavities and surfaces- neoplasm penetrates into a natural “open field” viz. peritoneal, pericardial, pleural, subarachnoid spaces & joint space

  e.g. pseudomyxoma peritonei, krukenberg tumor of ovary

- Transplantation- Mechanical transport of tumor fragments by instruments & along needle tracks following aspiration biopsy.

LYMPHATIC SPREAD

- Most common pathway for spread of carcinomas.
- Cancer cells when they reach the lymphatic channels actively migrate through interendothelial junctions
- The pattern of L.N. involvement follows the natural route of drainage.
- In many cases the regional L.N.s serve as effective BARRIERS to the further dissemination. so, reactive changes
- Cells after arrest in the L.N.s are destroyed by a tumor specific immune response. NK cells may also be involved
- .Skip metastasis – local L.N. bypassed due to venous- lymphatic anastomosis or inflammatory /radiation obliterate lymphatic channels
- Sentinel LN biopsy imp- 1st LN in regional lymphatic basin that receives lymph flow from primary tumor
- Mapping done by injection of radio labeled tracers or blue dye
- Also used for detecting spread of melanoma, colon cancer etc.

HEMATOGENOUS SPREAD

- Typical of sarcomas
- Arteries less readily penetrated than veins due to thicker wall
- Arterial spread occur when lung is involved via pulmonary capillary bed or A-V shunt
- Venous invasion the tumor cells follow the venous drainage of the primary site.
- Thus, in such spreads liver (portal area) and lungs (caval area) would be most frequently secondarily involved.
- Cancers in close proximity to the vertebral column spread through paravertebral veins. i. e. thyroid & lung

Certain cancers may involve veins themselves. E.g. Renal cell ca often invades the renal vein due to which it grows in a snakelike fashion sometimes reaching upto the right side of the heart.

EVENTS INVOLVED IN METASTASIS

PRIMARY NEOPLASM

↓

Progressive growth

↓

Vascularization (angiogenesis)

↓

Invasion

↓

Detachment

↓

Embolization

↓

Survival in circulation

↓

Arrest

↓

Extravasation

↓

Evasion of host defence

↓

Progressive growth

↓

METASTASIS

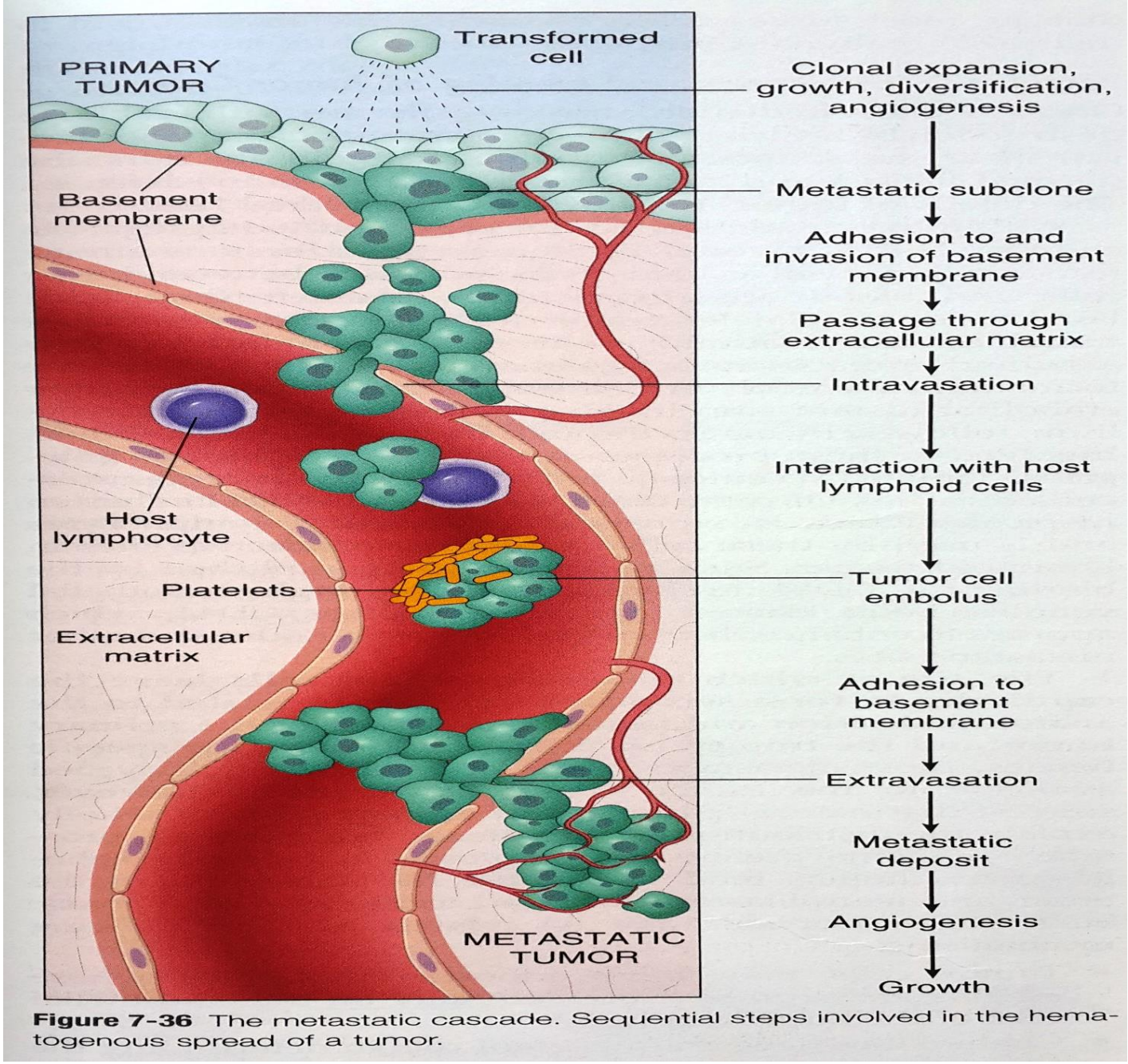


Figure 7-36 The metastatic cascade. Sequential steps involved in the hematogenous spread of a tumor.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

INVASION OF THE ECM

(1) Detachment of tumor cells from each other- Normal cells are glued to each other by transmembrane glycoproteins e.g. Cadherins.

E- cadherins linked to cytoskeleton by catenins

(in Adenocarcinoma of the colon th*ere is down regulation of the E-cadherin expression*)

(2) Attachment to matrix components- Normal epithelial cells express high affinity receptors- integrin family for the basement membrane LAMININ that are polarized to their basal surface. Also cancer cells have receptors for fibronectin & collagen.

(3) Degradation of ECM- It is achieved by proteolytic enzymes produced by tumor cells (or even host cells like stromal fibroblasts & infiltrating macrophages)

3 classes of proteases- Serine, Cysteine, Metalloproteinase.

E.g.–type IV collagenase which is a metalloproteinase

–Cathepsin D which is a cysteine protease

–Urokinase type plasminogen activator which is

a serine protease

(4) Migration of tumor cells- i.e. locomotion. It is mediated by tumor cell derived cytokines.

- *cleavage products of some ECM components have Growth promoting , angiogenic & chemotactic activities for tumor cells*
- *Collagen IV degradation also produce endostatin & tumstatin - antiangiogenic*

Vascular dissemination & Homing of tumor cells

- After invasion of the vascular or lymphatic channels the cells may either grow at the site of penetration or because of their loss of cohesiveness, be swept away as individual cells or small embolic clumps.
- Here they are vulnerable to the immune (CMI and humoral) as well as non-immune (NK cells, activated macrophages) responses.

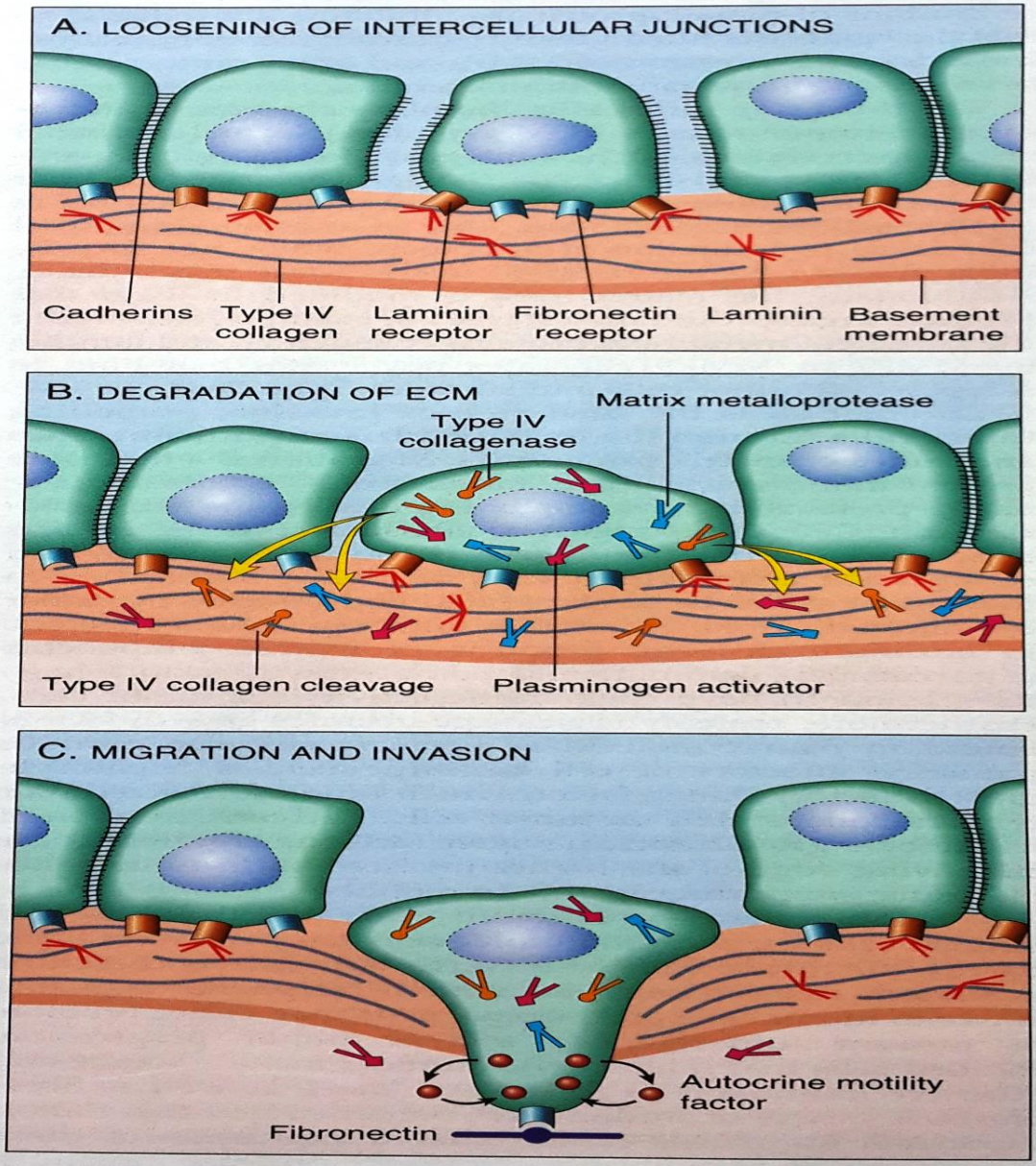


Figure 7–37 Sequence of events in the invasion of epithelial basement membranes by tumor cells. Tumor cells detach from each other because of reduced adhesiveness and attract inflammatory cells. Proteases secreted from tumor cells and inflammatory cells degrade the basement membrane. Binding of tumor cells to proteolytically generated binding sites and tumor cell migration follow.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

VASCULAR DISSEMINATION AND HOMING OF TUMOR CELLS- MECHANISMS

- Within circulation, tumor cells tend to aggregate in clumps which may be:

  -Homotypic- adhesions between tumor cells

  -Heterotypic- adhesions between tumor cells and lymphocytes or platelets. Enhance tumor cell survival & implantability

- Arrest and extravasation of the tumor emboli at distant sites involves adhesion to the endothelium followed by passage through the basement membrane.
- CD44 (adhesion molecule) expressed on the

  T lymphocytes enhance migration to selective sites in

  L. N. It also accomplished by binding to the endothelial venules. Overexpression of CD44 favor metastatic spread

- The cells that survive then arrest in capillary beds of distant organs either by adherence to the endothelial cells or attachment to the vascular basement membrane.
- Thereafter the metastases must avoid the host immune response, develop its own vascularization in the same way and produce a secondary implant.

PREFERENTIAL HOMING OF TUMOR CELLS

- Prostatic carcinoma spreads to bone
- Bronchogenic carcinoma to adrenals
- Neuroblastomas to liver and bones
- Mechanisms for ORGANOTROPISM -

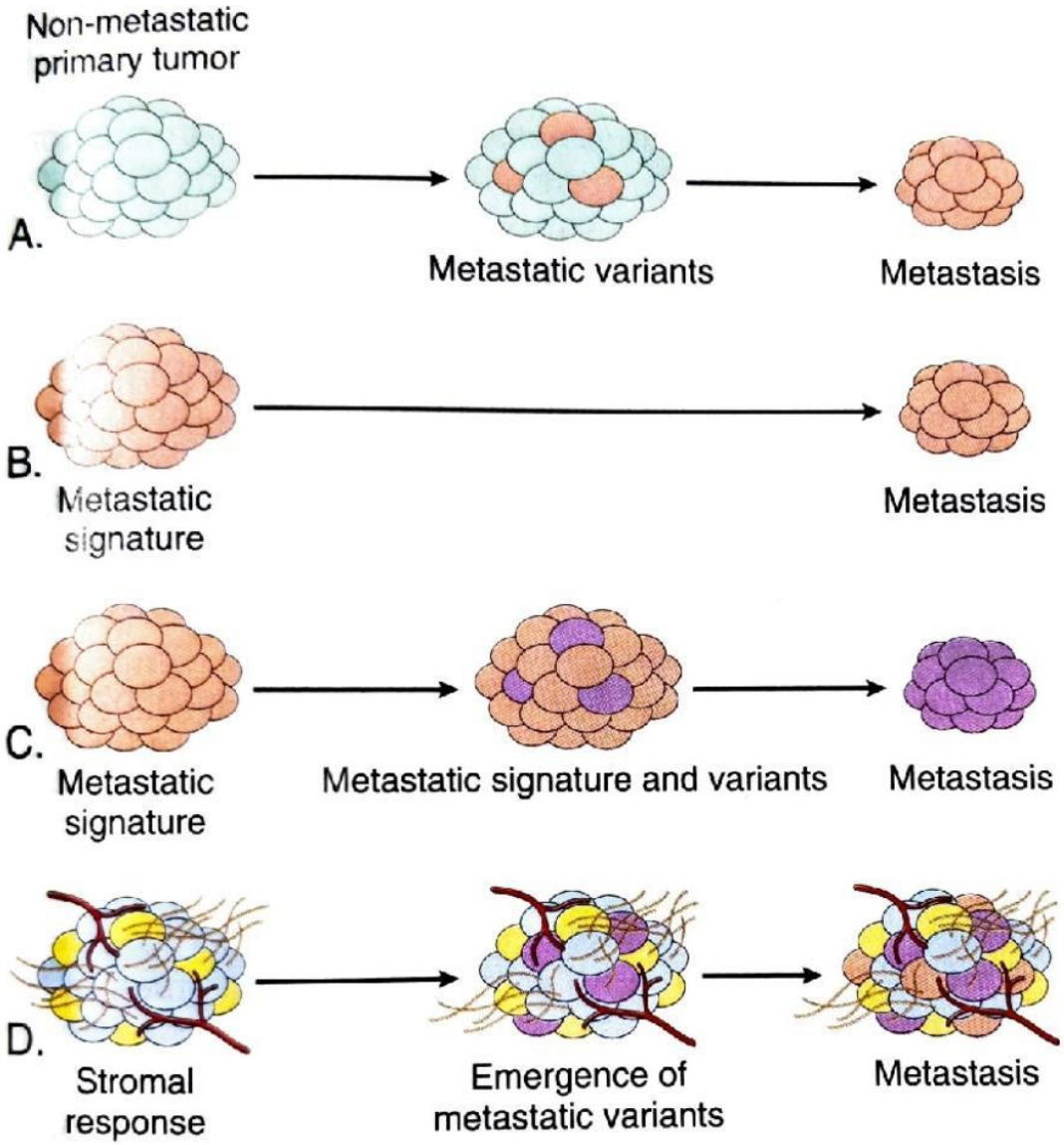
1. Tumor cells may express adhesion molecules whose ligands are expressed preferentially on endothelial cells of target organs
2. Some target organs liberate chemoattractants that tend to recruit tumor cells to the site.
3. In some cases, the target tissue may be an unpermissible environment for the growth of tumor seedlings e.g. inhibitors of proteases could prevent the establishment of tumor colony.

CANCER PROGRESSION TO THE METASTATIC STATE --- SUMMARY

1. Primary tumor growth, angiogenesis
2. Loss of cell-cell adhesion
3. Altered cell-ECM interactions
4. Cell polarization and invasion, motile phenotype
5. Remodeling of the ECM, proteolytic enzyme secretion
6. Entry into the vasculature, intravasation
7. Travel and survival through the blood vessels and lymphatic vessels. Avoidance of host immune system.
8. Arrest in organ sites. Specific adhesion to endothelium and basement membranes
9. Extravasation, Invasion of new site, proteolytic enzyme secretion, cell motility
10. Colonization, proliferation and establishment of secondary tumor

Positive/negative regulation by new organ-derived factors

ROLE OF ANGIOGENESIS



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