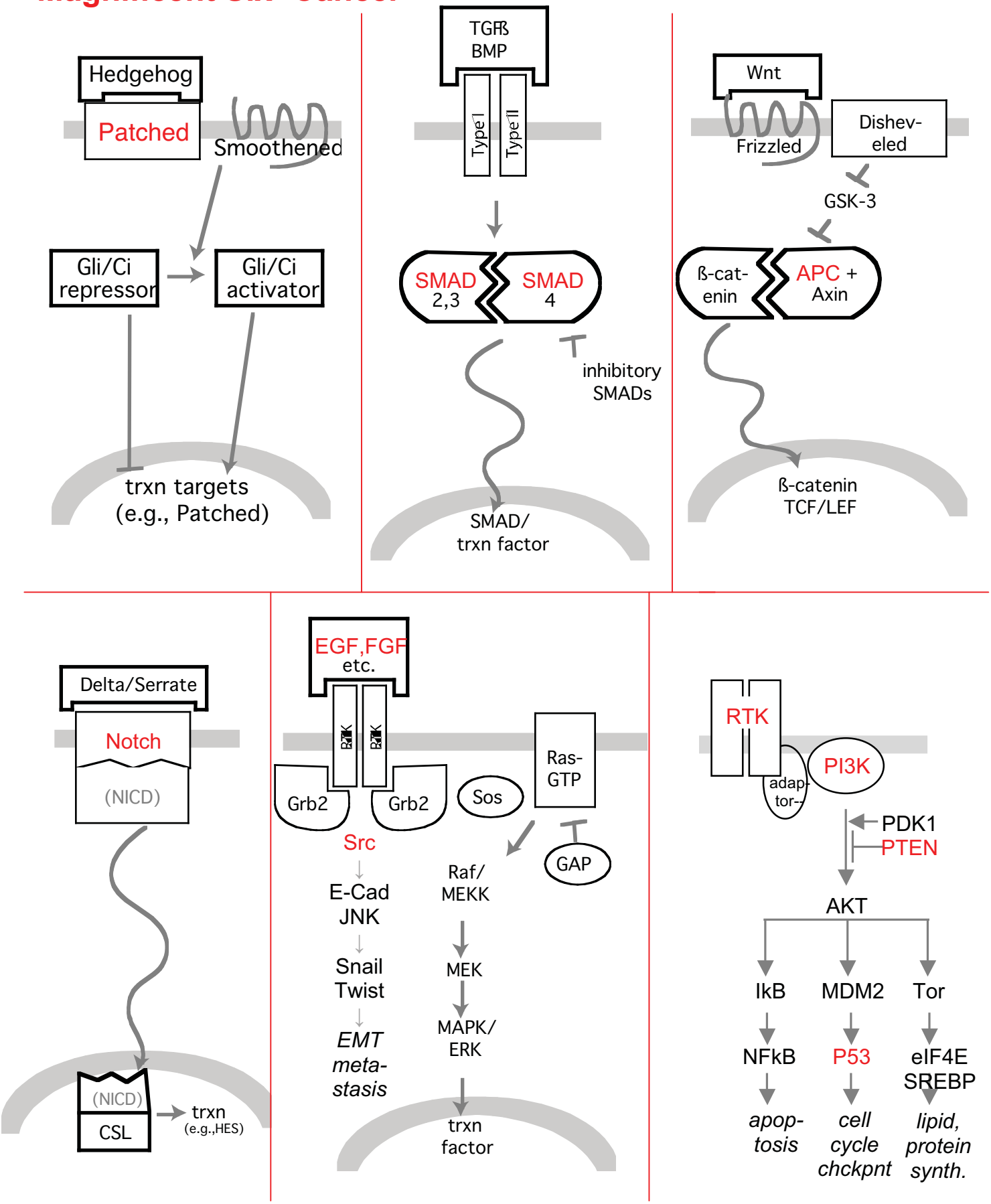
# Magnificent Six- Cancer



**Cancer means "crab"; Named by Greeks such as Hippocrates**

• Carcinoma (epithelial tumor): Greek *carcinos* --> Latin *cancer*, also meaning crab and *oma* for 'swelling'.

- This name comes from the appearance of the cut surface of a solid malignant tumour, with "the veins stretched on all sides as the animal the crab has its feet, whence it derives its name"
  - This was strictly head-and-neck tumors, since the Greeks did not believe in cutting people open

• *Oncos* also means 'swelling' (--> "oncology")

• 1600 BC in Egypt: 8 cases of ulcers of the breast that were treated by cauterization, with a tool called "the fire drill."

• 17th Century: English surgeon Percival Pott noted that chimney sweeps had high rates of scrotal cancer
- combated by emphasizing daily showering
- first example that environment can play a role

**Certain genes are mutated more often:**

• breast cancer:

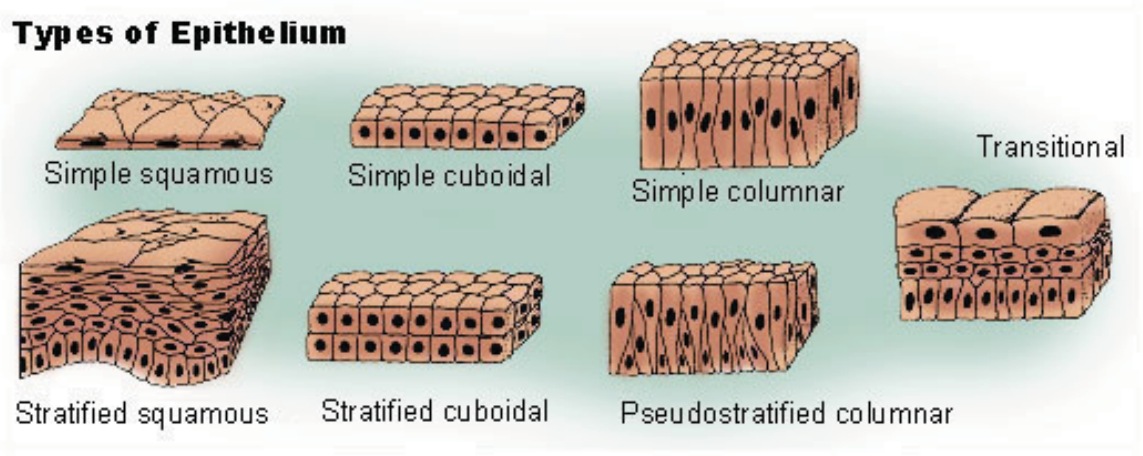
| 1 | 2 | 3 | # of observations/138 |
|---|---|---|---|
| KRAS | LRP1B | TP53 | 8 |
| KDR | KRAS | TP53 | 4 |
| INSRR | KRAS | TP53 | 4 |
| EPHA3 | LRP1B | TP53 | 4 |
| EPHA3 | KRAS | TP53 | 4 |

• colorectal:

| Triple combinations | Quadruple combinations |
|---|---|
| $Ras1^{V12}$ $Pten^{RNAi}$ $Apc^{RNAi}$<br>$Ras1^{V12}$ $P53^{RNAi}$ $Pten^{RNAi}$<br>$EGFR^{act}$ $P53^{RNAi}$ $Pten^{RNAi}$<br>$Med^{RNAi}$ $P53^{RNAi}$ $Pten^{RNAi}$<br>$Apc^{RNAi}$ $P53^{RNAi}$ $Pten^{RNAi}$ | $Ras1^{V12}$ $Pten^{RNAi}$ $Apc^{RNAi}$ $P53^{RNAi}$<br>$Ras1^{V12}$ $Med^{RNAi}$ $Apc^{RNAi}$ $P53^{RNAi}$<br>$EGFR^{act}$ $Med^{RNAi}$ $Apc^{RNAi}$ $P53^{RNAi}$ |

**Cancer Module of the Systems Biomedicine course- Cancer Signaling**

Most cancers are of epithelial origin




- Differentiated, with apical/basal polarity, junctions, basement membrane
- 80% of cancer deaths are due to epithelial tumors termed *carcinomas*
    - sarcomas (mesoderm-derived) make up ~1% of tumors
        - includes tumors of the bone, fat (adipocytes), muscle
    - leukemias and lymphomas- hematopoietic derived
        - leukemias: circulating parts of immune system
        - lymphomas: B&T lymphocytes that aggregate to form solid masses
    - neuroectodermal tumors (1.3% of tumors; 2.5% of tumor deaths)
        - gliomas, neuroblastomas, schwannomas, medulloblastomas

- two major types of carcinomas:
    - Adenocarcinomas- from cells that secrete substances, to nourish or protect the body
        - lung, colon, breast, pancreas, stomach, prostate, ovary
    - Squamous cell carcinomas- derive from thinly layered cells that act as a sheet to protect underlying structure
        - skin, larynx, lung, esophagus, cervix
    - Other carcinomas-
        - small/large cell lung carcinoma, hepatocellular carcinoma, renal cell carcinoma

**Core signaling pathways also mediate cancer: (SEE SHEET)**

- RTK/Ras (includes cytoplasmic kinase cascades Ras, PI3K, Src, etc)
    - PDGFR, FGFR- endothelial & mesenchymal, glial tumors,
    - NGF/Trk- neuronal tumors
    - IGF-R1- many types of tumors
    - Kit- hematopoietic tumors
    - EGFR- many types of carcinomas
        - ErbB1-4; HER1-4
        - factors that bind its intracellular domain:
            - Stat3/5, PLC-g, Shc, Cbl, Jak2, Grb2, Gab-1, Shp1, PTP1
        - popular drug target: chemical, antibody drugs
            - resistance is a problem
- Notch
- BMP/TGFß
- Wnt
- Hedgehog
- Jak/Stat
- cell cycle/checkpoint: p53, Rb, cyclins

These factors interact with targets through *modular domains*

- Partial list:
    - SH2, SH3, PDZ, PTB, 14-3-3, SAM, DD, DED, CARD, PB1, FYVE, WW, WD40, MH2, Bromo, UBA, EVH1
- These are therapeutic targets

**Methods of activating signaling**

- mutating coding sequence
    - example: $Ras^{G12V}$ (glycine-to-valine)
        - eliminates Ras's GTPase activity→ activation of Raf etc.
        - frequency of mutated Ras:
            - lung (35%), colorectal (45%), thyroid (60%), pancreas (90%)
    - example: MEN2 and Ret (M918T, C→S)
    - example of deletion: Notch receptor in ALL

- epigenetic- just being worked out now
- amplification of expression
    - major method for activating *myc*, *src*, *cyclins*, *akt-1*, *erB1/2*
    - can occur by chromosomal duplication, mutating promoter sites, retrotransposon or viral insertion, or translocations
- gene fusion
    - examples for receptors:
        - Ros/Fig
        - PDGFRa/BCR; PDGFRß- 5 different partners
        - FGFR1/FIM.FOP.Cep110.BCR
        - Ret/(9 different fusion partners)

Signaling

- Major signaling pathways for cancer are shared with development

    Q: why would that be?

## Molecular steps towards tumor progression: initiating & sustaining tumorigenesis

- **Anti-apoptosis and Abrogation of Programmed Cell Death**
    - Normal cells kill themselves by apoptosis when:
        - unrepaired genetic damage,
        - do not receive tissue-specific survival signals
        - receive death signals from immune cells
    - Genetic changes that abrogate the normal cell death response commonly occur in tumors.

- **Hypermutation and Chromosomal Instability**
    - Cells in most tumors have widespread genomic changes in chromosome number and arrangement
    - often arise from increases in double-strand DNA breaks or failure to repair such breaks,
    - several tumor suppressors mediate this repair

- **Cell-Cycle Checkpoints and Accelerators**
    - Cell-cycle checkpoints block progress through the cell cycle in the absence of appropriate external growth signals or in response to internal damage
    - these brakes on cell division often fall in the class of tumor suppressors—genes with products that can suppress uncontrolled cell division.
    - Unlike oncogenes, tumor suppressors typically require loss of both copies
        - Example: Rb blocks transition into the S phase of the cell cycle, during which the cell copies its DNA in preparation for splitting into two daughter cells
            - Only a proper combination of other cell-cycle controls can release the retinoblastoma block, providing a check that the cell is ready for the complex process of DNA replication.
    - Unlike tumor suppressors, oncogenes stimulate cell division
        - Example: nondividing cells express little of the *myc* gene
        - external growth signals→ increase expression of *myc,* which in turn stimulates expression of many growth-related factors→ high growth

- **Avoiding Cellular Senescence**
    - Most cells can divide only a limited number of times
        - With each cell division, the chromosome ends (telomeres) shorten because they are not copied by the normal DNA replication enzymes.

- After forty or so divisions, the special telomeric caps have worn down.
- Normal cells will not continue to divide.
- Normal germ & stem cells telomerase to regenerates the full telomere during each replication cycle.

- Late-stage cancer cells usually express telomerase
  - why is not entirely clear; perhaps mutations direct expression or the cells were originally stem cells

- **Resource Acquisition and Stromal Ecology**
  - A solid tumor cannot grow beyond 1–2mm without obtaining a blood supply.
    - To progress, the tumor must overcome angiogenic repression and stimulate the growth of a blood supply.
      - they do this by collaborating with cells in the ‘stroma’: fibroblasts, immune cells, and blood-vessel cells, together forming the stroma

- **Invasiveness and Neglect of Death Signals**
  - A solid tumor also needs to cut through the extracellular matrix (MMPs)
  - Most cells die by ‘anoikis’; successful tumor cells must overcome this
  - distant tissues typically kill off ‘unlike’ tumor cells. Migrating tumor cells often have high mutation rates or rapid genomic changes, which may help them to adapt to the new conditions required for growth.

**Signaling by tumor to its surrounding**

- attract blood supply
  - note what Erdem sees with colorectal model
  - during development, FGF is secreted to attract blood supply and VEGFR is used to induce branching into tumor; HIF regulates branching by ‘reading’ oxygen levels
  - cutting off blood supply is a popular drug target
    - VEGFR inhibitors didn’t work- tumor found other blood supplies
    - recent VEGFR inhibitors work synergistically by promoting leaky blood vessels to improve drug uptake

## Let's follow the flow of signaling:

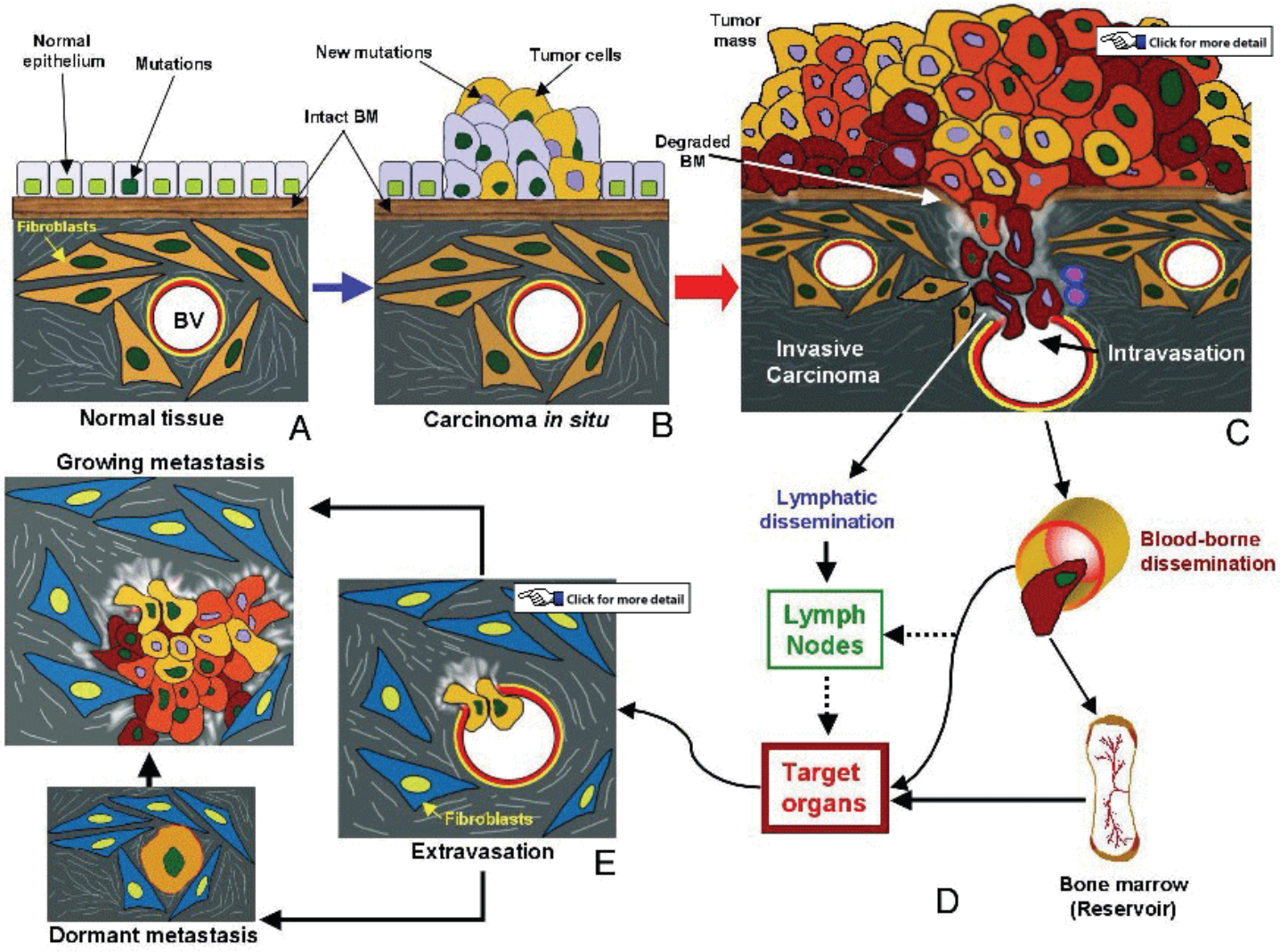
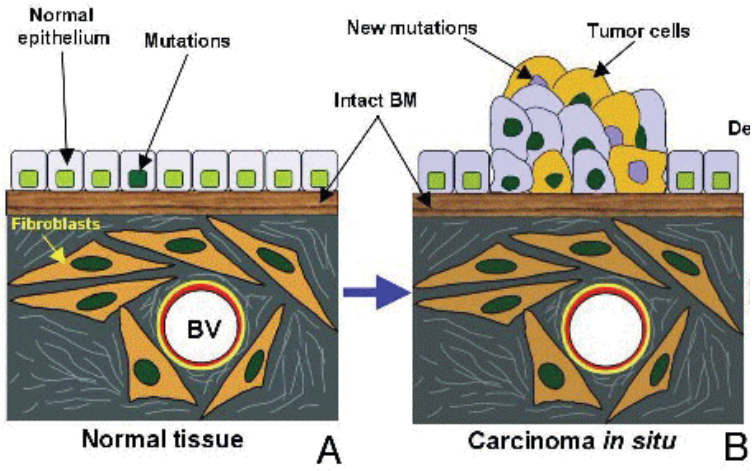



**Fig1. Tumor formation and progression to metastasis. (A)**

Carcinoma forms in the epithelial compartment, which has a distinct polarized organization maintained through cadherin based cell-cell junctions and integrin-based cell-matrix attachments. The cells rest on a basement membrane. Nutrients are provided by blood vessels in the stromal compartment (**Normal tissue**). **(B)**, Mutations and accumulating epigenetic changes alter cell morphology and cause loss of polarized architecture. The proliferative compartment increases. Proteases may, or may not be expressed, but the basement membrane remains intact (**In situ carcinoma**). **(C)**, Further genetic or epigenetic events lead to the acquisition of motile and invasive properties (strong, self-generated mitogenic signaling, active integrins and proteases), the cells degrade the basement membrane, invade the underlying stroma. The heterogeneity within the tumor increases. Invading tumor cells interact with fibroblasts (brown) or immune cells (blue and pink) and matrix component different from those in basement membrane. Angiogenesis may occur (not shown) and tumor cells (in cooperation with stromal cells) degrade the matrix and the vascular walls (yellow) and disseminate through arterial or lymphatic routes (**Invasive carcinoma**), **(D)**. The cells arrest in lymph nodes, bone marrow, or in blood vessels of target organs, where they extravasate into the organ parenchyma by interacting with the endothelium and degrading the vessel wal **(E)**. In the new environment tumor cells can rapidly form growing, detectable metastases or they can remain dormant for variable time periods (months to decades) until new signals are generated that activate the cells to resume their growth **(E)**.

**1. Growth of primary tumor**




A. Normal epithelium-

- polarized, intact basement membrane, apical junctions
- receives nutrients from underlying stromal layer, blood vessels, etc.

B. "*in situ* carcinoma"

- mutations occur within tumor
- lose polarity as cells stack up, show some de-differentiation
- stroma can signal through TGFß, Hedgehog, *etc.*

## 2. Invasion/intravasation, migration

A. "Invasive carcinoma"

a. Growth continues

i. RTKs (autocrine loops), cell cycle genes

b. Motility pathways are activated

i. integrins→ Rho pathway→ rearrangement of cytoskeleton

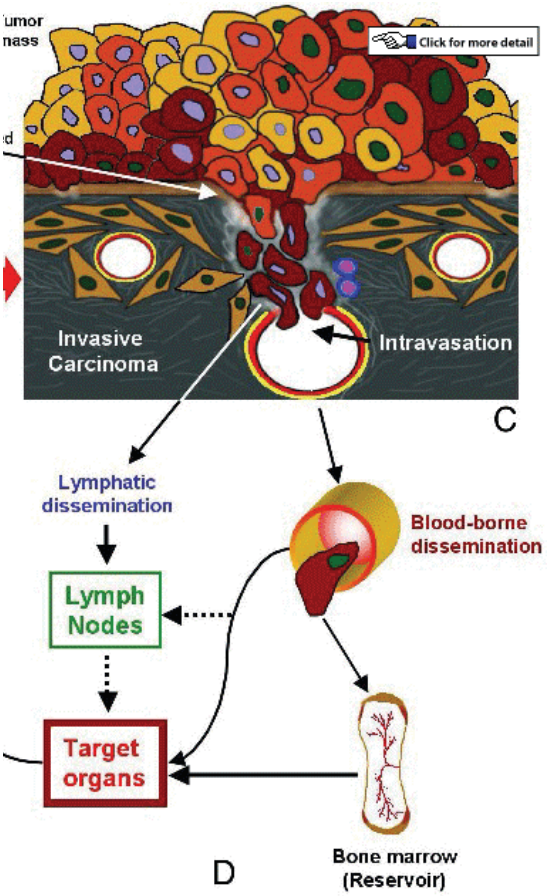
ii. leads to 'invadopodia" as a migratory front

c. MMPs (MMP-2, TIMP-2) expression rises to degrade the basement membrane and vascular walls

i. tumor invades the underlying stroma

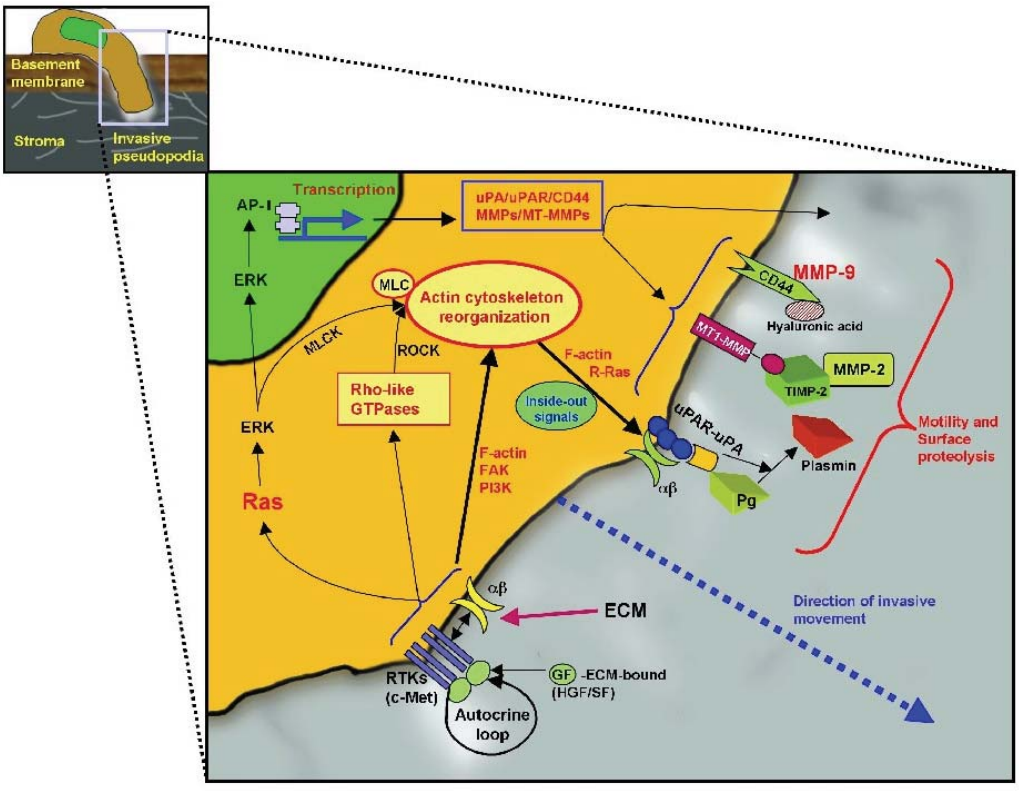
ii. tumor degrades vascular walls to invade into arterial or lymphatic routes

1. often done in cooperation with stromal cells

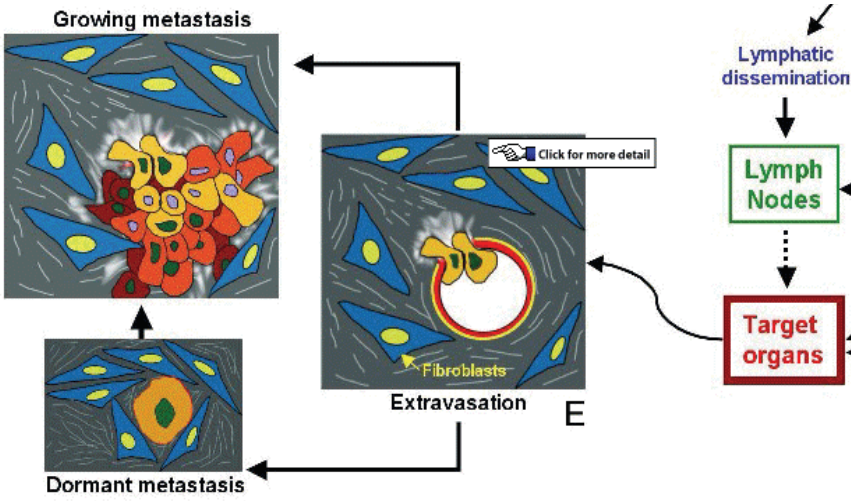



d. More intimate interactions with stroma including fibroblasts, immune cells, matrix components

i. Angiogenesis (VEGF) may occur to feed the tumor



**3. Attachment → Spreading → extravasation**




A. 1/1M cells makes it to a second site. Most get 'stuck' or phagocytosed by macrophages, etc.

i. different tumors use different signals to target particular tissues.

ii. For example: breast tumor cells use TGFß signaling to target bone, Hedgehog signaling to target lung (describe Hh inhibitor expt.)

iii. Q: Why do these invasion pathways exist?

B. After traveling, cells slow and eventually arrest in lymph nodes, bone marrow, or in blood vessels of target organs

i. they use sugars and glycoproteins (e.g., Sialyl Lewis, Mucins) to stick to endothelial wall (E-, P-, Selectins)

ii. This interaction is stabilized by integrin (tumor)-VCAM binding (endothelia)

C. They "extravasate" into the organ by interacting with the endothelium:

i. Homophilic N-Cad binding leads to ↓ of endothelial VE-Cad → creates opening

ii. Also, tumor/endothelial GAP junctions (Connexin26) are formed to pass further information

iii. ↑ MMP expression → "extravasation" into organ

D. In the new environment they can:

i. grow into detectable metastases

ii. remain dormant for months to decades

a. what triggers re-growth?