# Computational Systems Biology: Biology X

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**L#5**:(October-18-2010)
Cancer and Signals

# Outline

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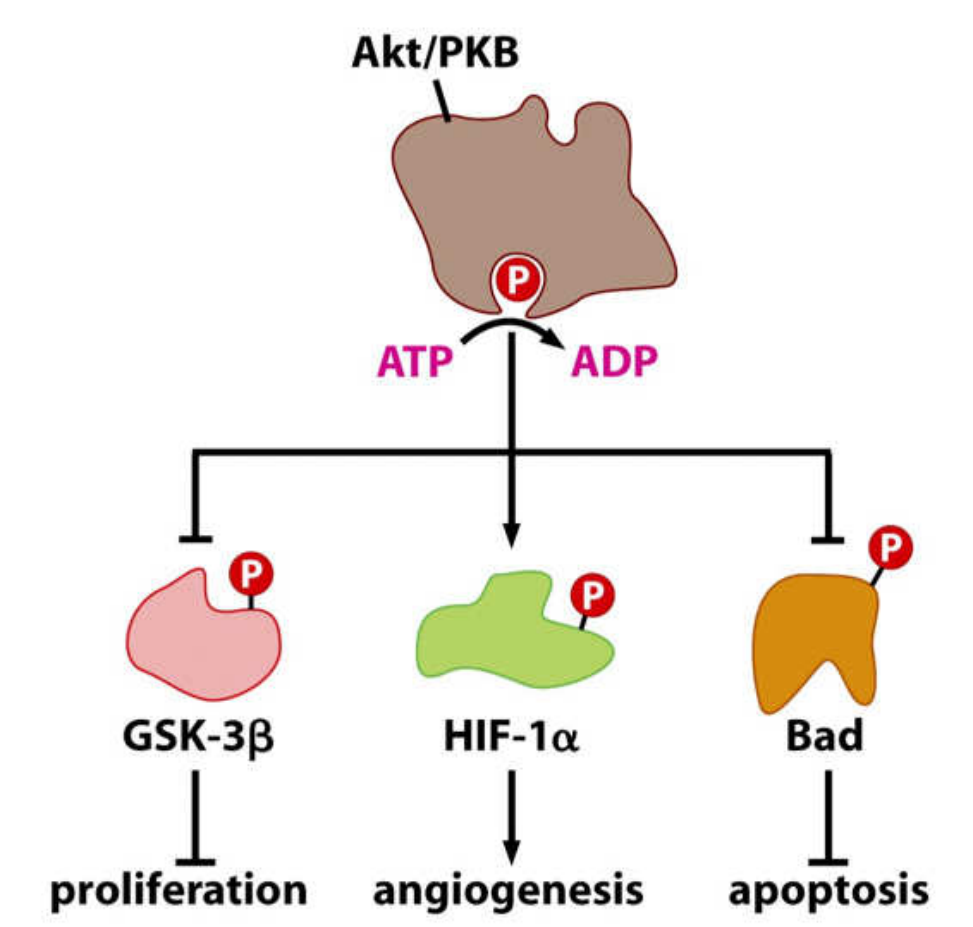
# Cancer is a disease of “malfunctioning” cells.

- **Cell Lineage**: Adult cells in an organism trace back to a single fertilized egg.
- Adult cells retain their ability to (i) proliferate, (ii) participate in morphogenesis, and (iii) repair of wounds and replacement of cells.
- Multicellularity is built on several processes: (a) Stem cell differentiation, (b) Autophagy and growth signals, (c) apoptosis and necrosis
- *Tumors derive directly from the normal tissue... Cells in the population malfunction by choosing defection over cooperation*

# Apoptosis vs. Proliferation



# Classification of Growth

- Depends on their presumed tissue of origin
- Depends on clinical behavior of tumor: **Benign**: (invading adjacent tissues) and **Malignant**: (invading nearby tissues and can spawn metastasis)
- Great majority of primary tumors are benign. Often, they are responsible for increase in certain hormones:
  - Thyroid Adenomas: thyroid hormones
  - Pituitary Adenomas: growth hormones (cause excessive growth of certain tissues)

# Tissues of Origin

- Epithelial Tissues:
  - Epithelia are sheets of tissues that line the walls, cavities and channels in a body
  - It sits on top of (a) *Basement Membrane* (Basal Lamina), separating it from (b) *Stroma*
  - It needs ECM (extra-cellular matrix) for its growth and proper function
- Endothelial Tissues
  - Inner linings of capillaries and larger vessels

# Carcinoma

- **Carcinoma**: Most common human cancers originating on epithelia
  - (a) Skin (basal cell carcinoma)
  - (b) Breast (mammary glands
  - (c) Pancreas
  - (d) Prostrate
  - (e) Lung
  - (f) Gastrointestinal tract (mouth, esophagus, stomach, intestine)
  - (g) Liver, Ovary, Gall Bladder, etc.

# Embryonic Cell Layers

- In embryonic development, there are three layers: (1) *Ectoderm* (skin, outer layer), (2) *Mesoderm* (ovary, etc., middle layer) and (3) *Endoderm* (lungs, pancreas, stomach, intestine, etc., making up the inner layer)
- **Carcinoma** is the cancer of the epithelia and is classified as
  - (1) **Squamous Cell Carcinoma**: Affects squamous cells that seal the channels/cavities and protect the underlying cell population.
  - (2) **Adenocarcinoma**: Affects the epithelial cells secreting substances into ducts or cavities
- A carcinoma could be pure (either squamous cell carcinoma or adenocarcinoma) or a mixture

# Non-epithelial Cancers

- (a) **Sarcomas**: cancer of the connective tissues or mesoderms... they derive from mesenchymal cell types: Fibroblast (collagen), Adipocytes (storing fat) or Osteoblasts
- (b) **Leukemia and Lymphoma**: Affect hematopoietic tissues and B and T lymphocytes. In Leukemia the cancer cells circulate in the blood; lymphoma is characteriized by solid tumors.
- (c) **Neuroectodermal Tumors**: Glioma, Glioblastoma, Neuroblastoma, Schwannomas, Medulloblastoma, etc.

# Further Exceptions

- **Melanoma**: Affects melanocytes, the pigmented cells that derive from neural crests
- **Small-Cell Lung Carcinoma (SCLC)**: Affects neuro-secretory cells
- In both cases, metaplasia (transdifferentiation) or anaplasia (dedifferentiation) may be involved. EMT (Epitehelial to mesenchymal transition)... Cells ay move from one differentiation lineage into another.

# Cancer Progression

Cancer involves a complex multi-step process...

- - **a) Hyperplasia**: Deviates minimally from normal... Characterized by just excessive number of cells...
- - **b) Metaplasia**: One type of normal cell layer is displaced by another... (More frequent in epithelial transition zones, where one type meets another type of epithelial cells.) For example, in pancreatic cancer, the transition is from acinar to ductal cells (secretory to squamous)
- - **c) Dysplasia**: Transitional state between benign and malignant. Characterized by: (i) variable nuclear size, (ii) increased mitotic activities, (iii) lack of normal cytoplasmic features... Examples: Adenomas, Polyps, Paillomas, Warts (all in situ)
- - **d) Neoplasia**: Disparate collection of growths (combining both benign and malignant)
- - **e) Metastasis**

# Tumor Growth

- **Monoclonal vs. Polyclonal**
- **Homogeneous vs. Heterogeneous**
- **Geometry and Distribution**

# Outline

# Growth Factors, Receptors and Cancer

- A variety of cell phenotypes are concomitantly altered by oncoproteins... such as Src and Ras
- The machinery for such alteration already exist in normal cells: Normal cells receive growth stimulatory signals from their surrounding.... These signals are processed and integrated by complex circuits within a cell... cell decides which strategy (growth, division, etc.) is appropriate.
- Extracellular signal (arrives at the cell surface) $\mapsto$ Effects of the signal is transferred to cytoplasm. There are many challenges in crossing the lipid bilayer.

- How are these related to the origin of multi-cellularity (in metazoan around 600 - 700 mya)? The structure in terms of senders and receivers. Siganling game involving oncoproteins... Resulted in cooperation among large group of cells... Coordinated growth (using growth factors (GFs)) plays an important role.

# Growth Factors (GFs)

- Growth factors play an important role in deciding between growth vs. no-growth... thus, welfare of the entire tissue or organism.
- They stimulate proliferation (Mitogens)
- Or they release growth-inhibitore factors.
- **Wound Healing**: Orchestrated by PDGF (Platelet-Derived Growth Factors). PDGF attracts fibroblasts into wound sites and stimulates their proliferation.

# Epidermal Growth Factor (EGF)

- **Epidermal Growth Factor (EGF)**: Used in signaling a cell to carry out mitosis.
- Oncogene-encoded protein...
- EGF-R is the signaling molecules needed to sense the presence of growth factors; they convey the signaling information into the cell interior, where the information is processed.

# Src Proteins

- Src Protein (coded by *v-src* oncogene) is a tyrosine-kinase, playing an important role in many cancers.
- *v-src* oncogene is a retro-viral gene first discovered in the context of Rous sarcoma, affecting chicken (non-receptor TK).
- When *v-src* was cloned, it was found to have 533 aa sequence, which is translated into a 60kD protein (polypeptide chain)
- When a cell is transformed by *v-src*, it alters the cell's shape and leads to (1) Rapid glucose absorption, (2) Growth in an anchorage independent manner, (3) Loss of contact-inhibition and (4) Tumor formation

# Src Proteins

- Using anti-bodies that bind to Src, it was found that the antibody is phosphorylated. This suggested that Src is used as a protein kinase – It removes a phosphate from ATP and transfers it to a target protein.
- It was also found that Src is a phosphoprotein: Substrate for phosphorylation. Another kinase or it uses itself as a substrate. One possibility is that it is involved in **Autophosphorylation** leading to a positive-feedback process.
- As a kinase, Src phosphorylates one (or more) substrate proteins and alters their functional properties. Thus it can be **Pleiotropic**: perturbing multiple phenotypes.
- Note: Phosphorylation can target different amino acid residues: serine, theronine or tyrosine (usually uncommon). A tyrosine kinase phosphorylates a tyrosine to make a phosphotyrosine, which plays an important role in *mitogenic signaling pathway*.

# EGF (Epidermal Growth Factor)

- It has mitogenic effect on a variety of epithelial cells. It binds to surface of a cell. EGF-R (receptor) cell surface protein, which is 622 aa.
- It consists of (a) Ectodomain (protrudes into extra-cellular space), (b) Trans-membrane Domain (23 aa, hydrophobic), (c) Cytoplasmic Domain (542 aa, homologous to *src*), and (d) *C*-terminal Tail.
- EGF binds to EGF-R ectodomain... Cytoplasmic domain is activated... Src-like kinase in cytoplasm is activated. The cascade is involved in *mitogenic pathway*.
- Other signaling involved in (a) cell shape, (b) cell survival, and (c) cell motility.

# EGF-R (Epidermal Growth Factor Receptor)

- EGF-R was found to be homologous to *erbB* oncogene (avian erythroblastosis) virus.
- *erbB* oncogene lack *N*-terminal ectodomain of the EGF-R.
- Truncated EGF-R sends growth-stimulatory signals in a constitutive manner.

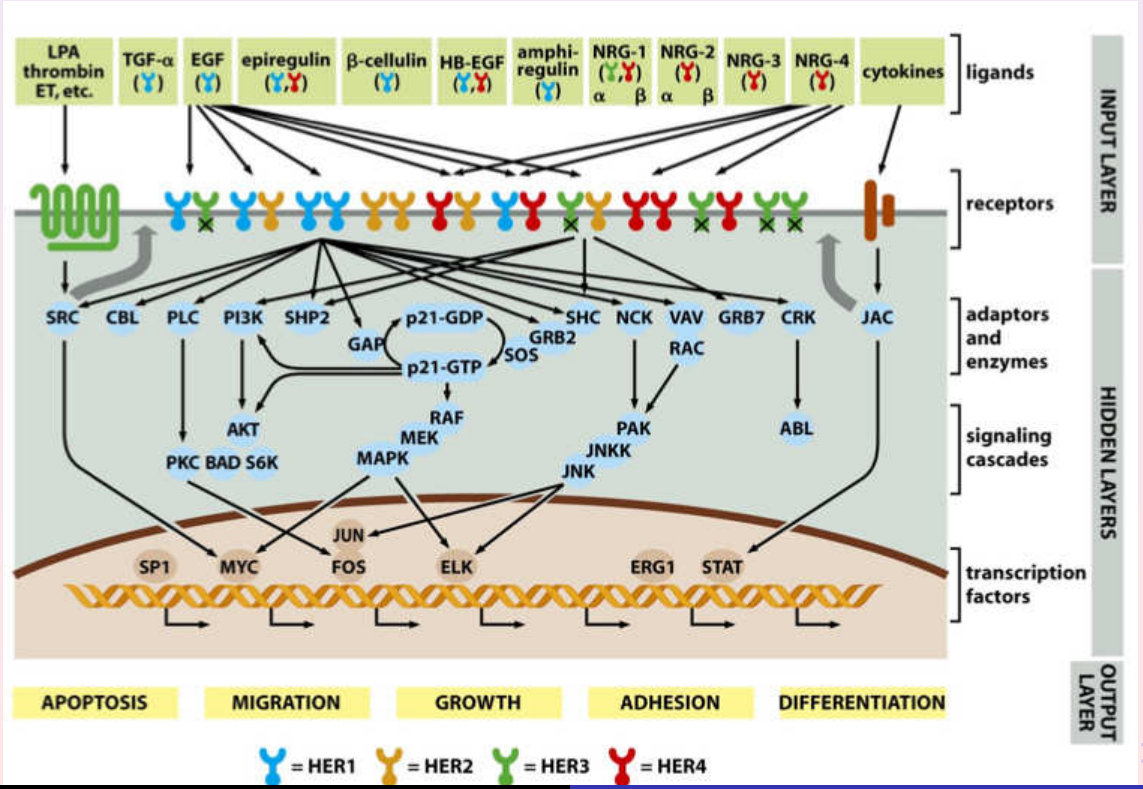
# Platelet-Derived Growth Factors (PDGFs)

- PDGF (platelet-derived growth factor) ... homologous to *v-sis* (simian sarcoma)
- PDGF stimulates mesenchymal cells... fibroblasts, adipocytes, smooth muscle cells and endothelial cells
- *sis*-oncogene in an infected cell produces PDGF-like Sis protein, which then binds to PDGF-R (of the same infected cell)
- Positive feedback in activation signaling of mitogeneic pathway in mesenchymal cells

# Signaling

- **Paracrine Signaling**: Growth factor signal from one type of cells to another.
- **Endocrine Signaling**: Growth factor signal from cells in one tissue to another.
- **Autocrine Signaling**: Growth factor signal from one type of cells to itself or same type.
- In aggressive lung cancer, 3 different autocrine signalings have been found to occur simultaneously: TGF-$\alpha$ (Tumor Growth Factor $\alpha$), SCF (Stem Cell Factor) and IGF (Insulin-like Growth Factor).

# Cancer Signal



# [End of Lecture #5]