The Cell Cycle and Cancer

October 7, 2013
BioScience in the 21st Century
The Cell: Basic Unit of Life
Duplicate and Equally Segregate
1 cell

Embryo

10 trillion divisions later

~100 trillion cells

Einstein
Cell Division - an ongoing process

- Development
- Tissue Maintenance
- Cancer

Wound repair

NIH.gov
Cell divisions in your body
Every cell from a cell

- Bone marrow stem cells: > 1,000,000 divisions per minute
- Skin stem cells
- Intestinal stem cells
- Muscle satellite cells
- Liver cells
When cells go bad -

Cancers proliferate by clonal selection

| Normal cells | A cell sustains a mutation in a growth-regulating gene | Mutant cell's descendants proliferate more rapidly than normal cells | Additional mutation causes the cancer cells to grow even faster |

from Lewin’s Cells

Cancer cells proliferate without environmental cues

Monday, October 7, 13
Cell Division Cycle - not just Mitosis

1/24th of cell cycle

- **G1**
- **G2**
- **S**
- **M**

**Interphase**

- **Centrosomes**
- **Chromatin**
- **Nucleolus**
- **Nuclear envelope**
- **Plasma membrane**
- **Spindle**

**Mitosis**

- **Prophase**
- **Prometaphase**
- **Metaphase**
- **Anaphase**
- **Telophase and Cytokinesis**

- **Aster**
- **Centromere**
- **Kinetochore**
- **Nonkinetochore microtubules**
- **Daughter chromosomes**
- **Nucleolus forming**
Figure 17-3. Molecular Biology of the Cell, 4th Edition.
Figure 17–14. Molecular Biology of the Cell, 4th Edition.
Checkpoints are “WAIT” signals

Damage is repaired before cycle continues
Errors in the cell cycle may lead to cell death or cancer.
General Cell Cycle Controls

CDK inhibitors

CDK’s
One Example: DNA damage

X-rays

p53

CKI ➔ WAIT
p53 (detector) is often mutated in cancer

The structure of the core domain of the p53 protein (light blue) bound to DNA (dark blue). The six most frequently mutated amino acids in human cancers are shown in yellow - all are residues important for p53 binding to DNA. Red ball: zinc atom. [Reproduced from Cho, Y., et al. (1994) Science, 265, 346-355, with kind permission.]
Without p53, some of the brakes are missing
Cancer results from inappropriate “GO” or not enough “STOP”

General mutations that disrupt normal balance:

- Over-active mutation: too much “GO”
- Under-active mutation: too little “STOP”

Source of mutations: inherited or acquired
Other sources of cell-cycle disruption

Viral proteins

Gene Rearrangements

“Brakes are out”

Too much GO
“Gas pedal stuck”

Not enough STOP
A damaged cell’s last resort
Apoptosis = programmed cell death
Treating Cancer

Combinations of:

1. Surgery
2. Radiation
3. Chemotherapy (most target cell cycle)
   a. DNA synthesis/damaging agents
   b. Metabolic disruptors
   c. mitotic disruptors
Mitotic disruptors cause cell death

Compounds
- Taxol*
- Vincristine*
- Vinblastine*
- Nocodazole
- Colchicine*

*=natural compound or derivative

Side Effects
- Myleosuppression
- GI bleeding/ulcers
- Nausea/vomiting
- Alopecia
- Nephrotoxicity
- Teratogenesis
- Immunosuppression
- Carcinogenicity
- Neuropathy
At the frontier

Finding alternative cell cycle targets (outside mitosis)  Selectively targeting cancer cells
-p53

No Stathmin $\rightarrow$ cell death
Summary

- basic unit of life is the cell
- cell’s division is regulated by environmental and internal cues
- loss of regulation can lead to cancer
- cancer therapies target cell division/cell cycle mechanisms
- next generation of therapy - better targets, selectivity