BioScience in the 21st Century

Cell Biology of Cancer: an Intro to Cell Division.

Prof. R. V. Skibbens
August 31, 2018
Cell growth and division – What are the goals?

1. Cell growth - response to trauma

2. Cell growth - development

Cell growth during wound repair and development are different

Unregulated cell division -> tumor growth and cancer
Cell division

I Cell Cycle
what is this?

II Altering the Cell Cycle
to achieve different outcomes

III Masters of the cell cycle! Regulating
cell cycle stages
Cell growth and division – What are the goals?

- response to trauma
- need for growth
- ≠ growth in development

I  Cell Cycle
what is this?

II  Altering the Cell Cycle
different outcomes

III Regulators – Masters of the cell cycle!
Duplicate information

Segregate information
Cell cycle contains 4 Phases:

$G_1$, $S$, $G_2$ and $M$

S Phase or Synthesis Phase

Each chromosome (linear sequence of nucleotides: ATGC) is replicated to produce two identical sister chromatids
DNA = The Cook Book of Life

Chromosome

Identical Sister Chromatids

Vertebrate cells analyses

$H^3$-thymidine

Cells incorporate ‘tagged’ nucleotides (or nucleotide analogs) only during S-phase
Also during S phase – **Cohesins**
‘Glue’ proteins that hold sister chromatids together

Identifies sister chromatids over time!

M Phase or Mitosis
(Sister chromatid Segregation)

The two identical sister chromatids are moved away from each other into newly forming daughter cells
Mitosis – a mechanical process to move chromosomes

Microtubule – ‘Rope’ to help move sisters apart

Cohesin

Cohesin removal
Mitosis
Mitosis

Kinetochore: Microtubule-Chromatid attachment site
Mitosis in a Newt Lung Epithelial Cell

L. Cassimeris and E.D. Salmon

University of North Carolina
What are the relative contributions of each phase to the cell cycle . . ? And are these regulated in some way?

Gap 2 – growth and maturation separates S from M

Cohesin removal - Sister chromatids segregate toward daughter cells

DNA replication
-> 2 sister chromatids (tethered together)

Gap 1 – growth phase, separates M from S
I  Cell Cycle
   what is this?

II  Altering the Cell Cycle
   different outcomes during cell division

III Regulators – Masters of the cell!

IV Regulating the Regulators . . .
Cell division control is critical for both cell growth (trauma) and Development.

Timing - clock
Clock changes -> different outputs
Different portions of the cell cycle (clock) are altered to produce different outcomes.

Growth without division

- oocyte grows without dividing (months)

Division without Growth

- fertilized egg divides without growing (hours)

How do we regulate the clock (what activities comprise the clock?)
Cell fusion experiments -> ‘Directionality’ of the cell cycle . . .

3 Possibilities upon cell fusion:
- shared cytoplasm . . .
  1. G1 nucleus will stay G1, S will stay S
  2. G1 nucleus will transition to S
  3. S nucleus will return back to a G1 state
Directionality of the cell cycle . . .

S-phase promoting **activity** in ‘S’ cell triggers DNA replication in G1 cell

G1 cell is competent to enter S

S phase activity rises and falls!
Directionality - clocks go in only one direction

3 Possibilities upon cell fusion:

- Shared cytoplasm...
- G2 stays in G2, S stays in S
- G2 enters S
- S enters G2 state
Directionality - clocks go in only one direction

No going in reverse (S activity can not drive G2 cell to re-enter S-phase) -> DIRECTIONALITY!

You can’t rush S . . . cells must monitor for complete DNA replication!

Checkpoints - surveillance
Directionality - clocks go in only one direction

G2 cell can not induce G1 cell to replicate DNA

G2 cell has lost the S-phase promoting activity

Molecular mechanism
For ‘losing’ and ‘gaining’ an Activity . . .
I Cell Cycle
what is this?

II Altering the Cell Cycle
different outcomes during cell division

III Regulators – Masters of the cell!
The Nobel Prize in Physiology or Medicine 2001
"for their discoveries of key regulators of the cell cycle"

Fission yeast  
Budding Yeast  
Urchin  
Sea clam  

Model organisms ROCK  
Conservation through Evolution
Identify genes, when mutated, that arrests cells in a particular phase

CDCs -
Cell Division Cycle Mutants . . .

Master Regulators of the Cell Cycle
Master Regulator of the Cell Cycle:

Cyclin-dependent Kinase (CDK)

Cell cycle progression requires CDK activity

Kinase subunit turns off/on various protein functions required for cell cycle progression

Partners in crime:

Cyclin binds/activates kinase subunit
Cyclin-dependent Kinase (CDK)

Cell cycle progression requires CDK activity

Different cyclins - different parts of the cell cycle

Nuclear envelope breakdown
Condense chromosomes
Microtubule re-organization

Transcription of DNA replication factors
Initiate DNA replication
Keeping CDK low keeps our cells in prolonged G_1 . . .

Quiescence (G_0) state

Exiting G_1/G_0 to re-enter the cell cycle requires external cues

Understanding cancer involves understanding how cells Re-enter the cell cycle in the absence of proper cues!
I  Cell Cycle
   what is this?
II  Altering the Cell Cycle
   different outcomes during cell division
III Regulators – Masters of the cell!
IV  Regulating the Regulators . . .
Remember that $G_1/G_0$ is a LOW CDK state - New cyclin-CDK expression induced by external cues

**Mitogens!!**

**MITOGENS**

PDGF  
Platelet-derived growth factor

EGF  
epidermal growth factor

TGF-β  
Transforming growth factor
G1 cyclin-CDK activated by external cues: Mitogens!!

1. Wound/trauma activates platelets -> release PDGF

2. PDGF receptor activates Kinase signal transduction pathway
G1 cyclin-CDK activated by external cues: Mitogens!!

1. Wound/trauma activates platelets
   -> release PDGF

2. PDGF receptor activates Kinase signal transduction pathway

3. Kinase turns on transcription factors -> gene expression
G1 cyclin-CDK activated by external cues: Mitogens!!

1. Wound/trauma activates platelets -> release PDGF

2. PDGF receptor on neighboring cells activates Kinase signal transduction pathway

3. Kinase turns on transcription factors -> gene expression

Tada!! The target of Mitogen activation . . .
Actions of MYC:

Express G1 cyclins

Get a rise in G1-CDK activity! Enter the cell cycle.
Cancer - Unregulated and HIGH CDK activity

Cell cycle no longer regulated by external cues (such as PDGF)
Expansion of genes that regulate cell cycle progression:

Myc proto-oncogene amplification homogenously staining regions (HSR)
What if the PDGF receptor is mutated??

Always ‘ON’
even without
PDGF
Overexpressing mitogen receptor provides inappropriately high response to low mitogen . . .

Her2 – EGF-like mitogen receptor

[Diagram showing regulation of cell proliferation by activation of PDGF receptor with annotations for Her2 dimerization and E-receptor HER2, as well as estrogen response element (ERE).]
Her-2 over-expressed
Accounts for 20-30% of all breast cancers
Herceptin: Ab that blocks Her2 dimerization

Tamoxifen

Aromatase

Estrogen

HER2

ERE

Estrogen response element

Regulation of cell proliferation by activation of PDGF receptor

EGF-like receptor

Her2 dimerization

Names change

Therapeutic TARGETS!!!
Cancer pathways:

Oncogene –

mutation that over-responds to or falsely signals mitogen is present -> cell division

Driver Education car: 2 of everything

Oncogene – stuck accelerator
Cells not only have accelerators . . . they have brakes!
Cancer pathways:

(A) overactivity mutation (gain of function)

![Diagram of normal cell with a single mutation event creating an oncogene]

(B) underactivity mutation (loss of function)

![Diagram of normal cell with a mutation event inactivating the tumor suppressor gene, leading to no effect of mutation in one gene copy, and a second mutation event inactivating the second gene copy]

Tumor Suppressors – Brakes
Slow car down! – Driver ED car = 2 brakes!

Need mutations in both
Cancer requires the accumulation of mutations
Multi-hits take time . . .