BioScience in the 21st Century

Cell Cycle, Cell Division and Stuff
Chromosomes condensed

Sister chromatids segregate away

Mitosis in a Newt Lung Epithelial Cell

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Chromatid motility involves some fibrous component
Mitosis: condensed chromosomes, NEB and microtubule spindle apparatus
Chromosomes must duplicate at some point . . .
Cells incorporate nucleotide components

H³-thymidine
Cells incorporate nucleotide components

H$^3$-thymidine

BrDU
Bromo-deoxyuridine used in place of thymidine

Very narrow window of time does NOT overlap with mitosis . . .
Careful analysis showed that S-phase and Mitosis (M-phase) were separated by additional Gap phases.
Mitosis

Interphase

G1

G2

Synthesis or S-phase
Proportions? What are the relative contributions of each phase to the cell cycle . . ?

How do cells respond to challenges?

Mitosis

Interphase

Synthesis or S-phase

G1

G2
Synchrony

Timing – clock-like mechanism
Changes in cell cycles: developmental regulation
Not all cycles are created equal

- Growth without division
  - oocyte grows without dividing (months)
- Division without Growth
  - fertilized egg divides without growing (hours)

1 mm

sperm
tadpole feeds, grows, and becomes an adult frog
Directionality of the cell cycle . . . Which way to go?

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

G1 cell is competent to enter S
Directionality - clocks go in only one direction

No going in reverse (S-phase cell does not induce G2 cell to re-enter S-phase) -> DIRECTIONALITY!

G2 cell is Inhibited from Re-entering S

Only G1 cells Are competent to enter S
Directionality - clocks go in only one direction

G2 cell can not induce G1 cell to replicate DNA

G2 cells have lost the S-phase promoting factor

Molecular mechanism
For ‘losing’ and ‘gaining’ an Activity . . .
Random mutagenesis allows for identification of genes required for cell cycle regulation/progression

Conditional mutations

Two choices:

Die ‘where’ you are or . . .
Termed: Cell Division Cycle genes or CDCs

random death vs specific cell cycle staged defects

Conditional mutations
Yeast – a model system in which generation of Conditional mutant cells is easy

Cell morphology
Cell morphology and DNA content provide detailed information regarding cell cycle distribution.
Now what???
Analysis of **Cell Division Cycle** genes or CDCs, coupled with biochemical analysis of cycling egg extracts from clams and sea urchins and frogs

All identified the SAME regulators of the cell cycle
Master Regulator of the Cell Cycle:

Cyclin-dependent Kinase (CDK)

Cell cycle progression requires CDK activity

Budding yeast -
only 1 CDK = Cdc28

Fission yeast
only 1 CDK = Cdc2

Partners in crime:
Cyclin binds/activates Kinase subunit

Hmm . . .
but regulate G1, S, G2, M
Names for different cyclins

Some cell systems have a single CDK gene – we have many

But there are many and cell cycle-specific types of Cyclins
Cyclin-dependent Kinase (CDK)

Cell cycle progression requires CDK activity

Different cyclins - different substrates

- Condense chromosomes (Histone 1)
- Microtubule re-organization (MAPs)
- Nuclear envelope breakdown (Lamins)
- Transcription of DNA replication factors (Polymerase, RFCs)
- Initiate DNA replication (ORC)
Directionality comes from degradation

Mitotic cyclin degradation = Anaphase Promoting Complex or APC

S-phase cyclin degradation
SCF (Skp1-Cullin-F box complex)
Responding to cues

Cell divisions in good times
Responding to cues

Cell divisions in good times

Cells delay cell cycle entry typically by arresting in G1/G0

Cell divisions in bad times?
Think of G1 as a state of CDK inactivity . . . the longer you keep CDK inactive, the more your cell grows

1. APC1 activity stays high to get rid of CDK

   X turn off APC

2. Transcriptional inhibition of G1 and S-phase cyclins

   X turn ON expression of G1 cyclin

   That means to
   Exit G1 and enter
   Cycle . . . .

This transition of exiting G1 and entering Cell Cycle is termed START or Restriction Point
G1 (and S) cyclin-CDK expression induced by external cues

MITOGENS

PDGF
  Platelet-derived growth factor
EGF
  epidermal growth factor
TGF-β
  Transforming growth factor
G1 cyclin-CDK activated by external cues: Mitogens!!

Releasing the brakes that keep cells in G1

Mitogen receptor activates signal transduction pathway

PDGF

EGF

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

Mitogen receptor activates signal transduction pathway

PDGF

EGF

TGF-β

Kinase turns on TFs to induce MYC expression

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

1. Express G1 cyclins

Get a rise in CDK activity!
Actions of MYC:

1. Express G1 cyclins
   - Get a rise in G1-CDK activity! Enter the Cycle . . .
   
2. Express E2F
   - Get a rise in S-CDK activity!
If Mitogens drive G1 cyclin-CDK and ultimately S cyclin-CDK activity . . .

What about loss of control . . .
Cells that divide without external cues?
Imagine unregulated and HIGH levels of Myc

Or Mitogen receptors that ‘fire’ without mitogen . . . Potential contributors to cancer.
If time is the problem . . .

Identity and Time are problems . . .

Then GLUE is the solution!

Chromosome segregation

DNA Replication

Then Glue Is the Solution
Different activities throughout cell cycle are coupled
Don’t smoke
Use sunscreen

THANKS!