Directionality – The Cell Cycle clock goes in only one direction

S-phase cells have a S-phase promoting activity

G1 nuclei are receptive
Directionality – The Cell Cycle clock goes in only one direction

S-phase cells have a S-phase promoting activity

G1 nuclei are receptive

G2 nuclei aren’t
Directionality – The Cell Cycle clock goes in only one direction

S-phase cells have a S-phase promoting activity

G1 nuclei are receptive

G2 nuclei aren’t

G2 have lost that S-phase promoting activity
Directionality - clocks go in only one direction

Molecular mechanism for ‘gaining’ and then ‘losing’ Cell Cycle Progression Activities . . .

S-phase cells have a S-phase promoting activity

S

G1

G2

G1 nuclei are receptive

G2 nuclei aren’t

G2 have lost that S-phase promoting activity
Master Regulator of the Cell Cycle:  
Cyclin-dependent Kinase (CDK)

Cell cycle progression requires CDK activity

Partners in crime:  
Cyclin binds/activates KINASE enzyme
Names for different cyclins

Some cell systems have a single CDK gene – we have many
Cyclin-dependent Kinase (CDK)

Different cyclins - different substrates

Initiate DNA replication

Condense chromosomes

Organize spindle

NEB
Directionality comes from degradation

Mitotic cyclin degradation = Anaphase Promoting Complex or APC

S-phase cyclin degradation
SCF (Skp1-Cullin-F box complex)
Not all cycles are created equal

Growth without division

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

Division without Growth

- sperm
- tadpole feeds, grows, and becomes an adult frog
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
Quiescence $G_1/G_0$ are periods of **LOW CDK** activity

Most of our cells won’t divide (exit $G_1/G_0$) until they receive an **external** signal to divide.

Cancer involves cell re-entry into the cell cycle in the absence of those external cues!
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!
Imagine unregulated and HIGH levels of Myc
Expansion of genes that regulate cell cycle progression:

Myc proto-oncogene amplification
homogenously staining regions (HSR)
Expansion of genes that regulate cell cycle progression:

Examples of
Myc proto-oncogene amplification
homogenously staining regions (HSR)
Double minute chromosomes

More MYC -> more expression of Cyclin

less reliance on Mitogens -> faster accumulation of CDK!
Cancer pathways:

Oncogene – a stuck accelerator in a Driver’s Ed Car . . .
(2 of everything)

Causes:
mutation that falsely signals mitogen dosage – too much
Overactive Accelerators – loss of control receptor active without mitogen

Regulation of cell proliferation by activation of PDGF receptor

PDGF receptor No longer needs PDGF for Activation
Overactive or too Many Accelerators – over-active signaler

HER2 receptor - transmembrane tyrosine kinase (EGF-like R) can be either over-expressed or
No longer needs mitogen for
activation

Her-2 OE accounts
20-30% of all
breast cancers

Herceptin: Ab that
blocks Her2 dimerization

ER-positive cells
Estrogen
ER-receptor
ERE

Tamoxifen
Cancer pathways:

Cells not only have accelerators . . . they have brakes!
Cancer pathways:

(A) overactivity mutation (gain of function)

(B) underactivity mutation (loss of function)

Rb, p53, viruses and BRCA1
Rb binds E2F to keep it INACTIVE
(No E2F . . . No Cyclin E expression)

Mutations in Rb bypass Mitogen dependency
Need to get rid of BOTH Rb copies

**Healthy cell with only 1 normal Rb gene copy**
- Mutation at Rb locus in maternal chromosome
- Normal Rb gene in paternal chromosome

**Possible ways of eliminating normal Rb gene**
- Nondisjunction (chromosome loss)
- Nondisjunction and duplication
- Mitotic recombination
- Gene conversion
- Deletion
- Point mutation

**Loss of heterozygosity (LOH)**
mutation need not be the same!!
DNA replication trims DNA ends
removes protective DNA cap sequence
DNA synthesis + Telomerase
The Nobel Prize in Physiology or Medicine 2009
Elizabeth H. Blackburn, Carol W. Greider, Jack W. Szostak

Photo: U. Montan
Elizabeth H. Blackburn

Photo: U. Montan
Carol W. Greider

Photo: U. Montan
Jack W. Szostak
**p53** - gatekeeper of the cell

p53 mutated in ~1/2 of all cancers . .

p53 highly unstable

Associates with Mdm2 degradation factor

Made for destruction
p53 - gatekeeper of the cell

DNA damage-induced p53 phosphorylation

p53 - Mdm2 release

-> stabilization by p53 kinase

ATM = ataxia telangiectasia mutated
ATR = ATM related

patients with predisposition to cancer and extremely UV sensitive
p53 - gatekeeper of the cell

p53 is transcription factor
induces p21 expression

p21 is a CKI!! CDK-Inhibitor

BRAKES!!!
cell locked in G1
Viral mechanisms of cancer progression

papilloma virus genome stably maintained in epithelial cells

viral proteins required for controlled replication of the virus

host chromosome

chromosome of papillomavirus

BENIGN GROWTH OR WART
Viral mechanisms of cancer progression

Papilloma virus genome stably maintained in epithelial cells

Viral E5 co-assembles with PDGF receptor
- mediates receptor dimerization...

Viral E7 upregulated
- binds and inactivates Rb (E2F is free!)

Viral E6 upregulated
- drives proteolysis of phos-p53 (No brake)
Don’t smoke
Use sunscreen

THANKS!