Coordinating Cell Division and Growth

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Lecture 1: Why Cycle? and Discovery of a cell cycle

Lecture 2: A brief history of the cell cycle

Cyclin dependent kinases

The frogs and the yeast meet, cyclins and hysteresis

What’s the point of a Cell Cycle?

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Double cellular contents

Make new cell

Why Bother to Make a New Cell?

Why Bother to Make a New Cell?

Humongo cell seems like a bad idea!

Can 1 nucleus generate enough RNA for a football field-sized cell?

Goal??? Surface area to volume?

Biomass to genetic material

Why maintain biomass to genome ratio?

Why maintain biomass to genome ratio?

Too low genome/biomass: genome limiting and can’t support exponential biomass increase

How can a cell monitor its genome/biomass ratio?

- Easy problem from outside the cell with a balance/ruler, but from within the cell?
- Compare something that correlates with biomass with something that correlates with genome

How to measure biomass to genetic material?

How to measure biomass to genetic material:

Assume: production of a DNA binding-protein varies directly with the number of ribosomes

Genome: fixed number of sites

Rule: replicate DNA with site filled

Then, you'd double the genome with mass

Problem: stochastic chromosome replication! DNA replicates once and only once

But if we want constant and exact ploidy?

But if we want a constant and exact ploidy?

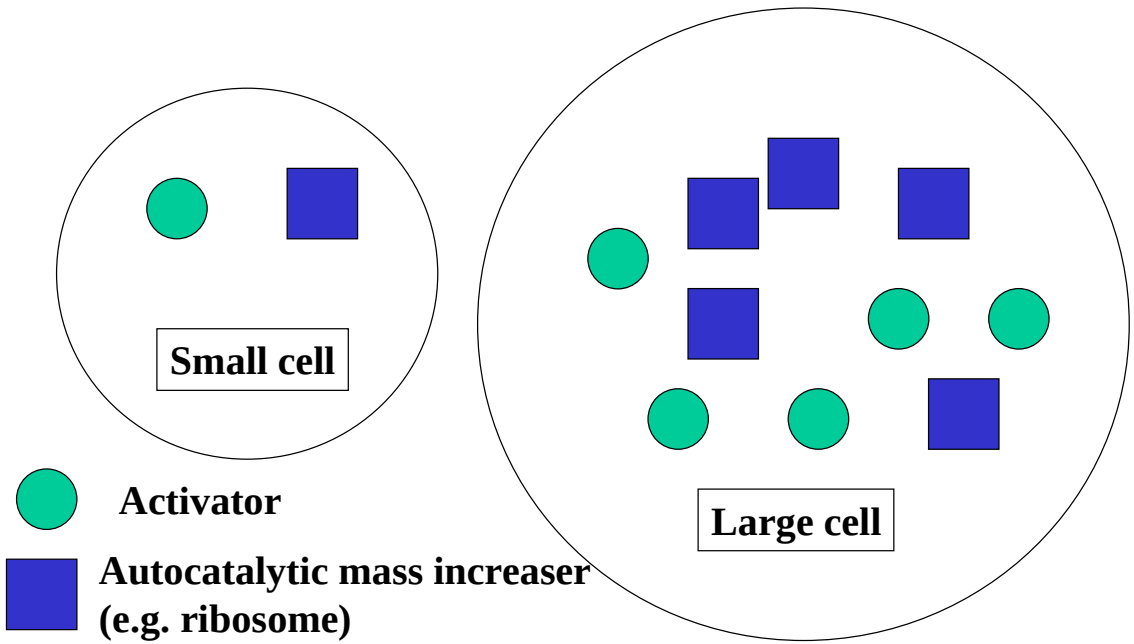
- Separate, cell-wide indicator that it’s time to divide
- G1 cyclin: global activator of genome replication
- Synthesized so its abundance (number of molecules per cell) directly correlates with biomass
- How can we do this???

Instability!

- Cyclins are very unstable, so their level is very reflective of how much is made right now

But just increasing synthesis of a cyclin doesn't solve our problem

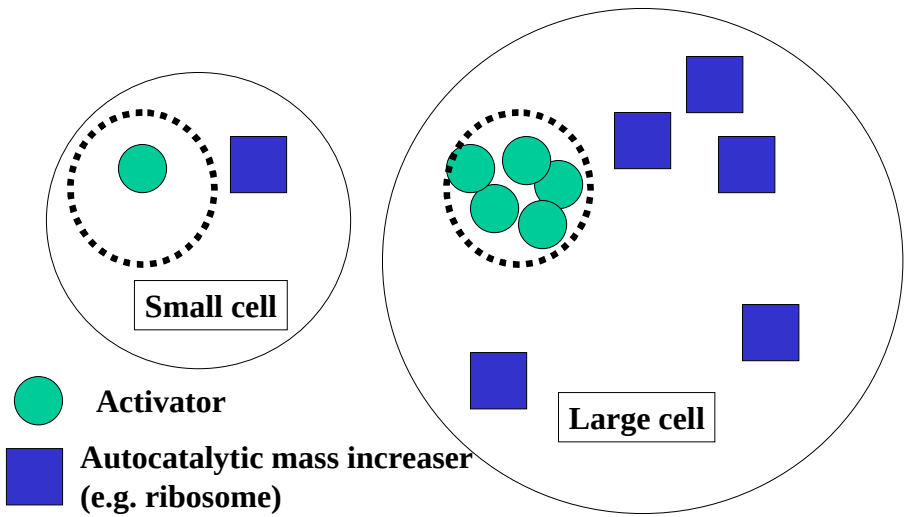
Problem: Continuous synthesis of an activator will not cause increasing concentration in the cell, because the cell gets larger as the amount of activator increases



How can we determine the amount of biomass without dilution?

One solution: Keep in the nucleus

Solution: sequester the activator in a compartment of constant volume (like the nucleus)



Controlling chromosome duplication

Don’t want imbalance in chromosome number (trisomy 21, for instance, is a problem)

Over or underrepresentation of a single gene can lead to problems (cancer)

Coordinating chromosome duplication with cell duplication

Make a cell cycle so DNA is faithfully passed down

Assume a cell with a small genome: single replication origin

Failures: aploid, polyploid

How can we coordinate chromosome duplication with cell division?

Coordinating chromosome duplication with cell duplication

- An inelegant solution (why?)
- Replicate the chromosome many times
- Select just one copy for transmission at mitosis

Coordinating chromosome duplication with cell duplication

Seems unnecessarily complicated and wasteful

wouldn’t scale well for more complex genomes

How to couple synthesis and division if you synthesize only one copy?

Coordinating chromosome duplication with cell duplication

- Better solution: require that one complete duplication of the genome obligately alternate with mitosis

- How?

Coordinating chromosome duplication with cell duplication

Couple initiation of replication at the replication origin to some event that only occurs only once each cell cycle, such as reaching a critical cell mass, or perhaps mitosis itself

Replication begins each time that event occurred

What if cell division begins before replication finishes?

What if cell division begins before replication finishes?

When nutrients are plentiful, only replicate genes near origin

When nutrients are limiting and cycle is slower, have time for the rest of the genome to catch up

Or make the cell wait

Or make the cell wait

Establish a safeguard to prevent mitosis until the genome is fully copied

Make the cell wait for replication to finish before proceeding with mitosis

What could be the trigger for mitosis?

Possible mitosis triggers

Possible mitosis triggers

Inhibition by:

Unreplicated DNA

The replication fork

A signal from the replication fork

Single stranded DNA

What if the genome is big?

What if the genome is big?

Alternative:

Make many replication forks

DNA from each decreases so it goes faster

Now the genome can get bigger and you can keep your ploidy

If we didn’t have multiple forks, could take days or weeks to copy a genome

Starting S phase

Starting S phase

So couple initiation of replication to something that occurs once per cycle

Some cell cycle event activates replication

How?

For multiple forks, need a global activator of DNA synthesis

Example of a global synthesis activator:

A. Protein essential for copying DNA is turned on by the global activator

(DNA pol? Protein that recognizes origins?)

B. The chromatin changes so that proteins already there can now replicate it

Initiating synthesis once

Activator of cell division accumulates in the nucleus and is converted into an all or none trigger of DNA synthesis

Suppose there’s an inhibitor

When you have enough of the activator to overcome the inhibitor, then DNA replication proceeds

Initiating synthesis once

Now suppose the activator destroys the inhibitor

Then, once you have enough activator, you'll overcome the inhibitor and destroy it

Positive feedback

Burst of functional activity

Need to do something to reset the cycle

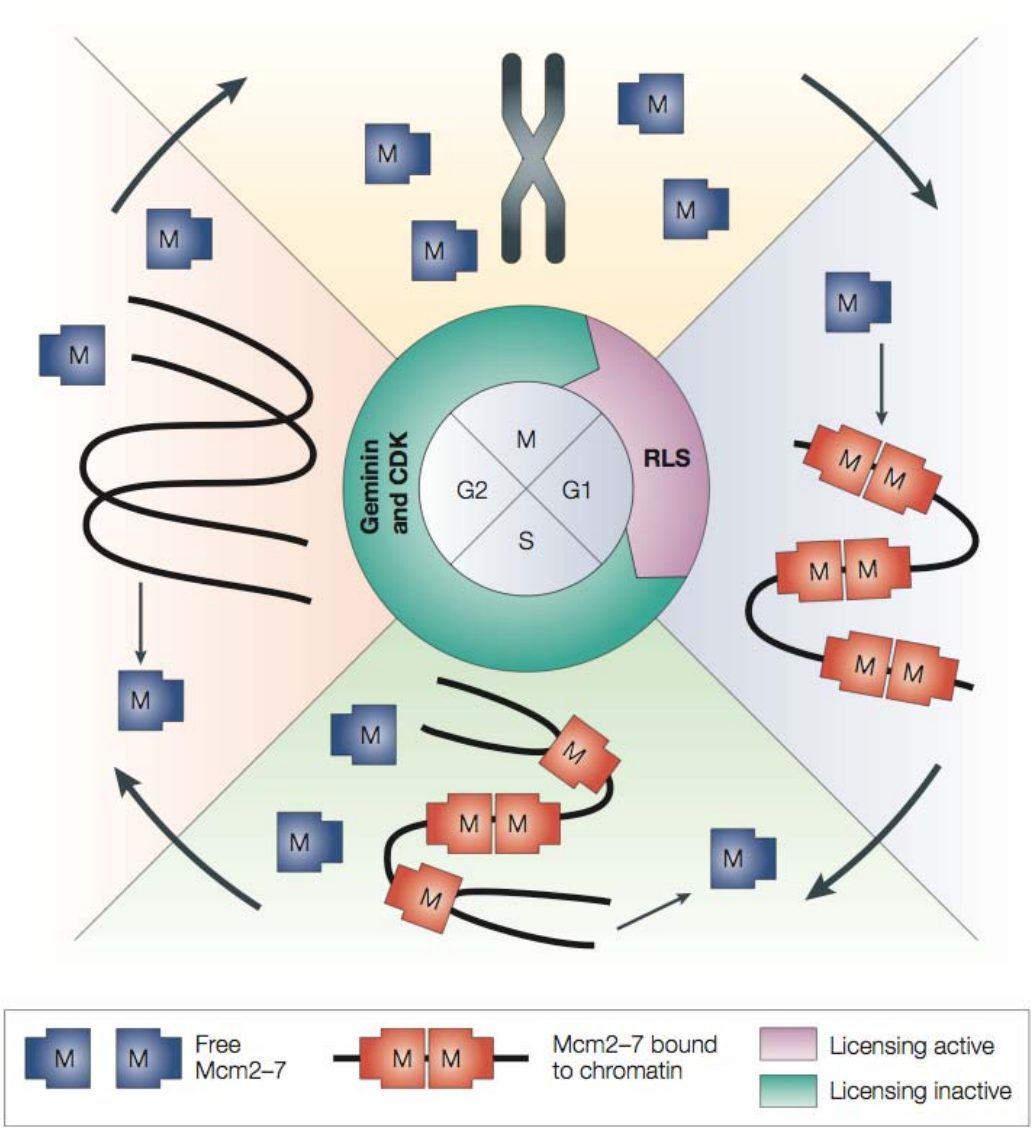
If the global activator says “go!”, how do we prevent re-replication from the same fork?

How do we prevent rereplication?
Once the proteins are active, why don’t they keep replicating DNA over and over?

Preventing re-replication

- “Licensing” origins of replication must be “licensed” in order to be used, and licensing only occurs in a specific phase of the cell cycle: global
- Passage of the replication fork makes origins no longer functional for replication: fork specific

Preventing re-replication:



Preventing re-replication:

Regulated loading and unloading of helicase MCM2-7 during the cell cycle

Small segment of chromosomalDNA encompassing 3 replication origins

End of mitosis, replication licensing system activated, causes minichromosomal maintenance proteins MCM2-7 to be loaded onto potential replication origins: origin licensing

Preventing re-replication:

Licensing system is turned off at the end of G1

(different mechanisms for yeast and mammals)

During S phase, Mcm2-7 complexes are displaced from replicated DNA by moving ahead of the replication fork, and are removed from DNA at fork termination

Replicated DNA cannot undergo further initiation events until passage through mitosis

Why study the cell cycle?

Stem cells

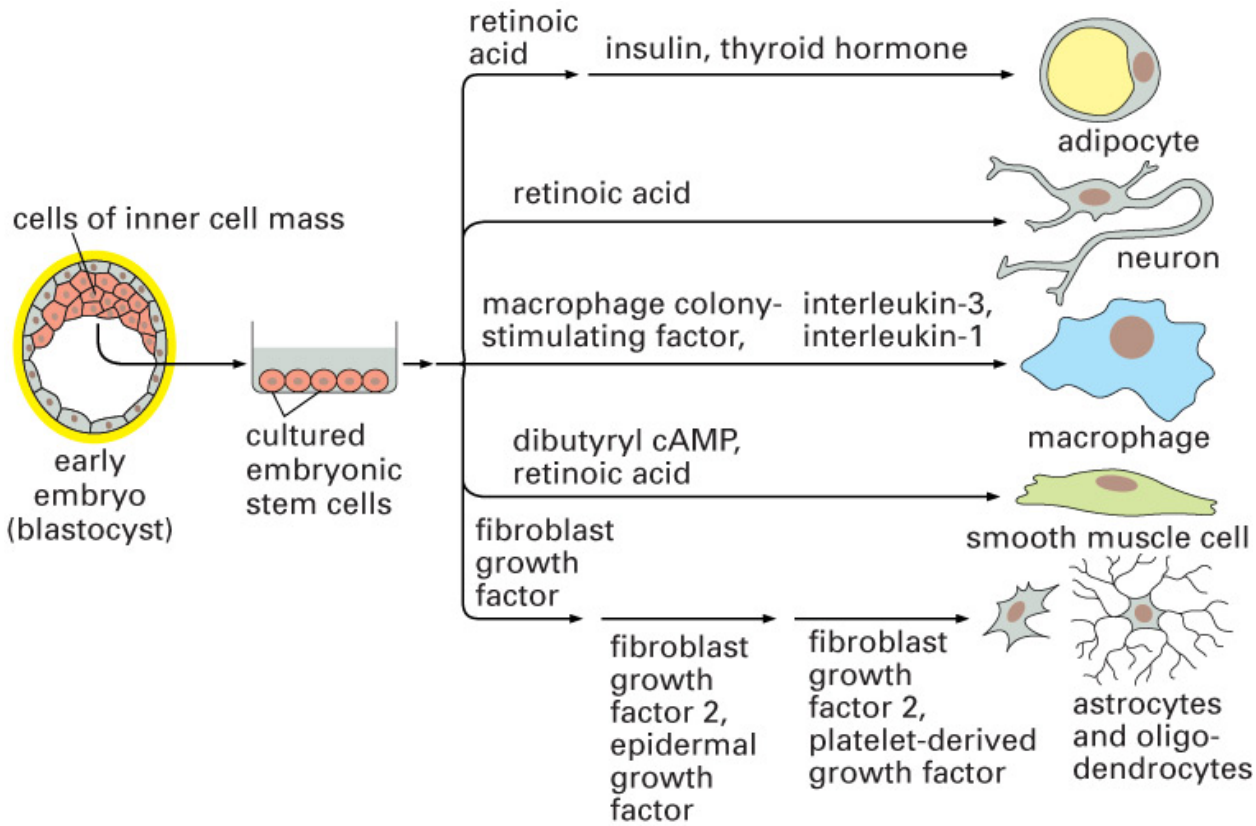
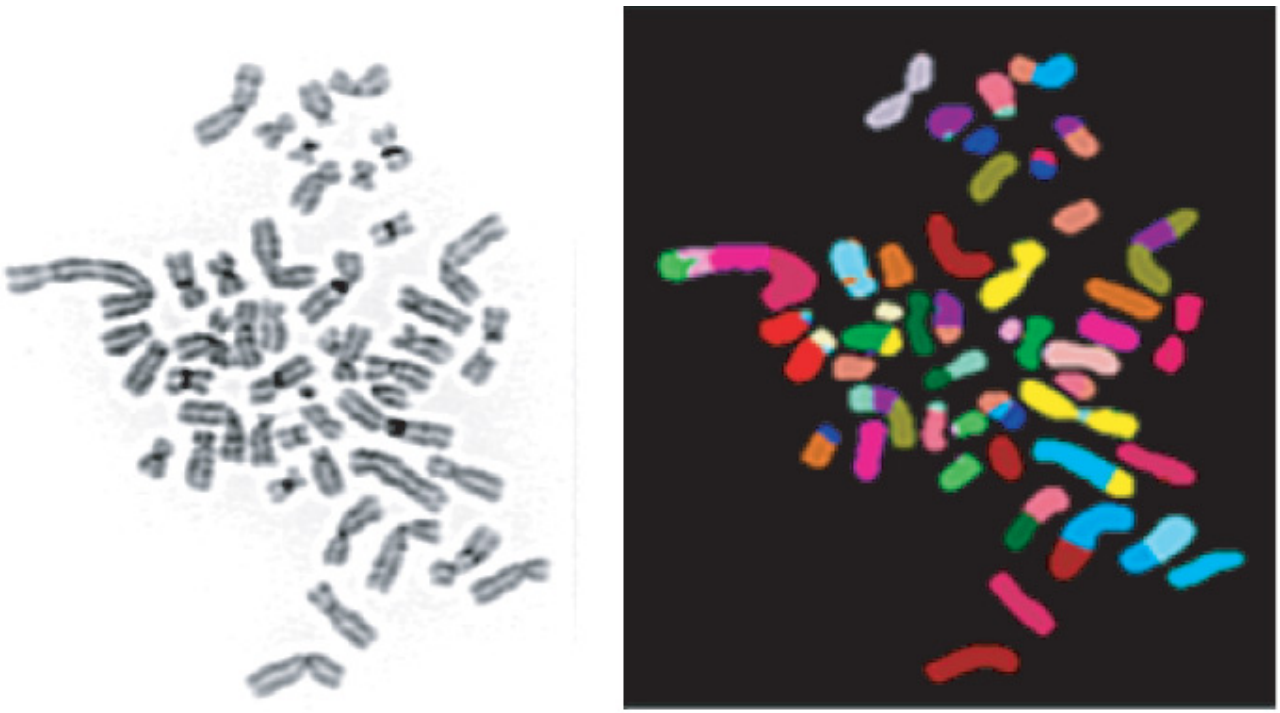


Figure 22–57. Molecular Biology of the Cell, 4th Edition.

Why study the cell cycle?

Cancer



(A) (B)

Figure 23–12. Molecular Biology of the Cell, 4th Edition.

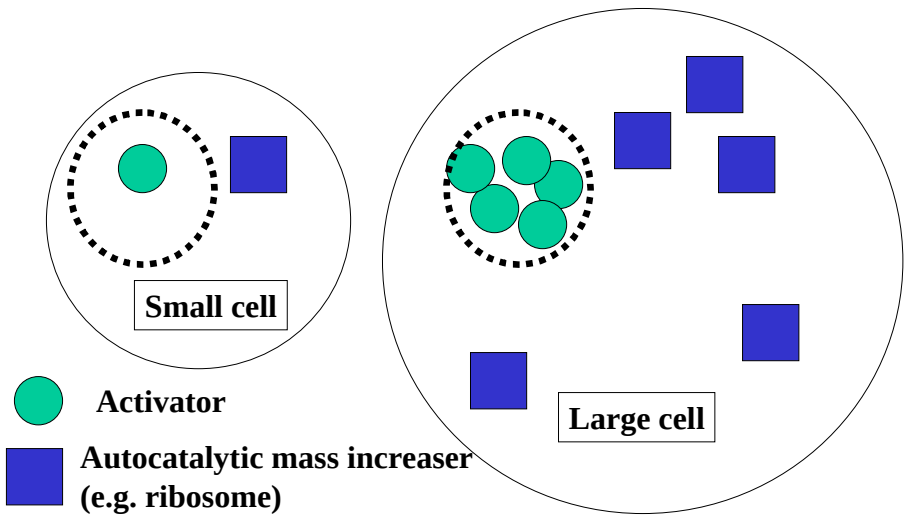
Wrap up of Class I

Good reason to cycle: maintain ratio of biomass to genetic material

Have a “cyclin” that measures biomass and constrain to the nucleus

One solution: Keep in the nucleus

Solution: sequester the activator in a compartment of constant volume (like the nucleus)



Wrap up of Class I

To coordinate genome synthesis with cell division

Couple initiation of DNA synthesis to something that happens once

(biomass trigger?)

Wrap up of Class I

Multiple replication forks for big genomes

Global inhibitor of synthesis and global activator: activator inhibits the inhibitor: feedback to create a burst of activity

Couple mitosis to the end of DNA synthesis

Wrap up of Class I

Prevent re-replication

For multiple replication forks, cannot be a global mechanism:

Initiation proteins are altered so that rereplication is impossible

Preventing re-replication: