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DEPARTMENT OF BIOTECHNOLOGY
FACULTY OFENGINEERING & TECHNOLOGY

LT1. Cell cycle regulation

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What is cell cycle?

The cell cycle is the process a cell undertakes to replicate all of its material and divide into two identical cells. In this article, we will look at the different stages of the cell cycle and what happens in each stage.

Phases of the Cell Cycle

•The cell cycle is a 4-stage process consisting of Gap 1 (G1), Synthesis, Gap 2 (G2) and mitosis. An active **eukaryotic** cell will undergo these steps as it grows and divides. After completing the cycle, the cell either starts the process again from G1 or exits the cycle through G0. From G0, the cell can undergo terminal differentiation.

•The stages in the cell cycle between one mitosis and the next, which include G1, S and G2, are known collectively as the **interphase**.

G1 phase

Cell increases in size

Cellular contents duplicated

S phase

DNA replication

Each of the 46 chromosomes (23 pairs) is replicated by the cell

G2 phase

Cell grows more

Organelles and proteins develop in preparation for cell division

M phase

Mitosis followed by cytokinesis (cell separation)

Formation of two identical daughter cells

G0 phase

While some cells are constantly dividing, some cell types are at rest. These cells may exit G1 and enter a resting state called G0. In G0, a cell is performing its function without actively preparing to divide. G0 is a permanent state for some cells, while others may re-start division if they get the right

cyclins and cyclin-dependent kinases (CDKs) : The master regulator of cell cycle

•CDKs are important master regulators of the cell cycle. Their role is to phosphorylate proteins on either S or T amino acids and thereby regulate the activity of those proteins. Yeast have just one CDK (Cdk1), while 'metazoans' (animals) like us have nine, of which four are really critical to the cell cycle.

•The levels of these proteins remain pretty constant throughout the cell cycle, yet their levels of *activity* rise and fall cyclically. CDKs need to hydrolize ATP for energy in order to perform phosphorylation. They have an ATP binding cleft whose ability to bind ATP is regulated by two mechanisms. First, CDKs have a 'flexible T loop' which contains a threonine (T) residue which normally blocks the ATP binding cleft, but not when the T is phosphorylated. Second, cyclins bind CDKs and induce a conformational change that also helps to expose the ATP binding cleft. Therefore a fully active CDK is one which is both phosphorylated at the T on the T loop *and* is bound to a cyclin.

The various activities of the cell cycle, then, are determined by the combination of cyclins and CDKs that are active at each stage, as shown in the following table:

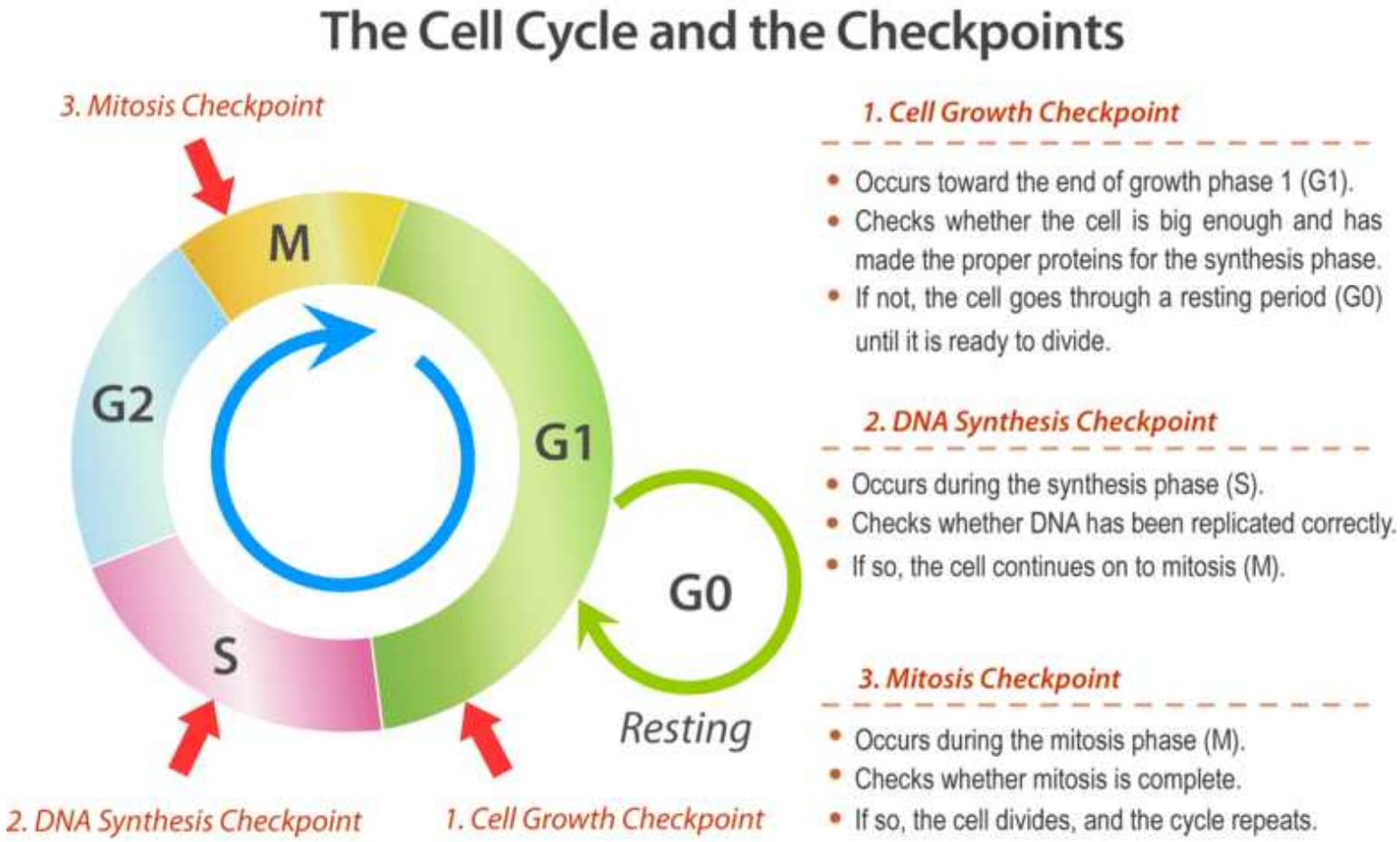
cell cycle stage	cyclins	CDKs	comments
G1	Cyclin D	CDK4&6	Can react to outside signals such as growth factors or mitogens.
G1/S	Cyclins E & A	CDK2	Regulate centrosome duplication; important for reaching START
S	Cyclins E & A	CDK2	Targets are helicases and polymerases
M	Cyclins A & B	CDK1	Regulate G2/M checkpoint. The cyclins are synthesized during S but not active until synthesis is complete. Phosphorylate lots of downstream targets.

All cyclins contain a conserved 100 amino acid 'cyclin box.' Cyclin/CDK complexes regulate the cell cycle both by promoting activites for their respective stages, and by inhibiting activites for future cell cycle stages that must not yet be reached. Therefore cyclins must be able to be both generated *and* degraded in order for the cell cycle to proceed.

Cell-Cycle checkpoints

•Cell proliferation is the process that results in an increase of the number of cells, and is defined by the balance between cell divisions and cell loss through cell death or differentiation. (Nature)

•Cell proliferation is regulated by a coordinated entry into the cell cycle



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Regulation of cell cycle

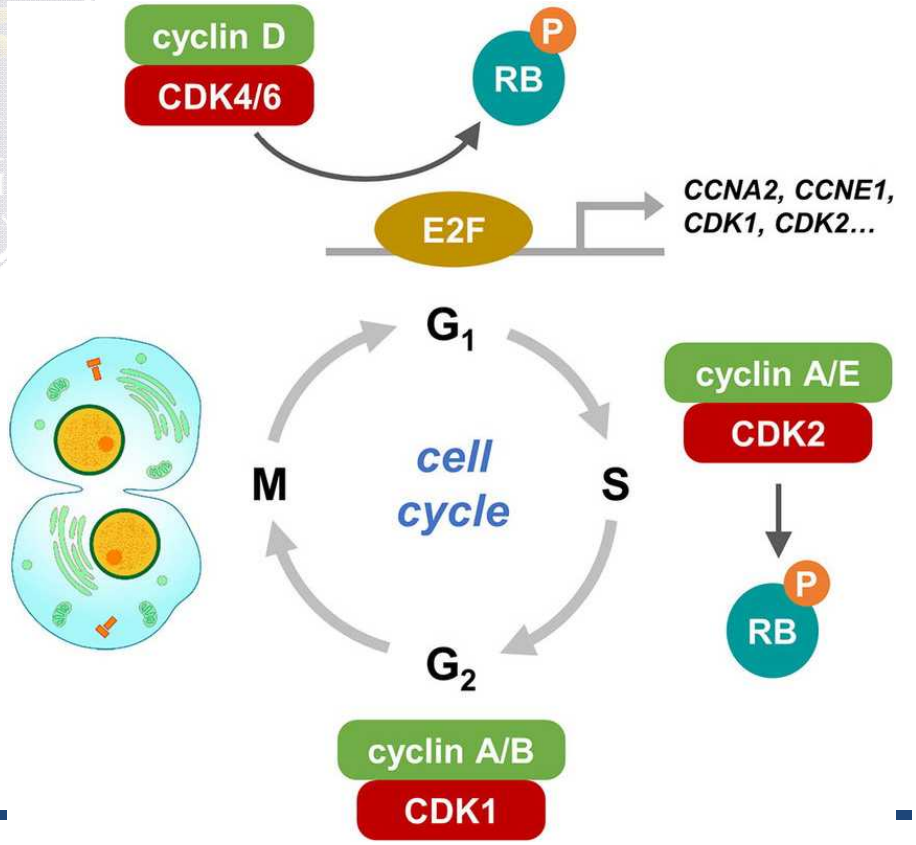
•It is during G1 that the cell is particularly susceptible to control of cell cycle progression at a number of restriction points, which determine whether the cell will re-enter the cycle, withdraw from it, or withdraw and differentiate.

•Checkpoints at the beginning of DNA synthesis and in G2 determine the integrity of the DNA and will halt the cell cycle to allow DNA repair or entry into apoptosis if repair is impossible

➢Control of proliferation is regulated by extracellular factors as well as intracellular factors.

➢Extracellular factors is related to environmental condition provided to cells.

➢Extracellular control are regulated by mitogenic growth factors, such as epidermal growth factor (EGF), fibroblast growth factors (FGFs), or platelet-derived growth factor (PDGF).



Example of extracellular signal

•Low cell density permit entry of cells into cell cycle, or negative acting such as high cell density which signals inhibition of proliferation of normal cells

Intracellular regulation of cell proliferation

•Intracellular control is mediated by positive-acting factors such as the cyclins.

•cell cycle progression are the cyclin-dependent kinases (CDKs). These are serine/threonine protein kinases that phosphorylate key substrates to promote DNA synthesis and mitotic progression.

•Cyclin-binding allows inactive CDKs to adopt an active configuration akin to monomeric and active kinases.

•Negative-acting factors such as p53, p16 and p21 or the Rb gene product block cell cycle progression at restriction points or checkpoints.

Role of regulatory gene elements in cell cycle regulations

p53: *p53*, also known as TP53 or tumor protein is a gene that codes for a protein that regulates the cell cycle and hence functions as tumor suppression. If damaged DNA is detected at any checkpoint, activation of the checkpoint results in increased **protein p53** production. In the cell, p53 protein binds DNA, which in turn stimulates another gene to produce a protein called p21 that interacts with a cell division-stimulating protein (cdk2). When p21 is complexed with cdk2 the cell cannot pass through to the next stage of cell division.

p21: *p21* mediates its various biological activities primarily by binding to and inhibiting the kinase activity of the cyclin-dependent kinases (CDKs) CDK2 and CDK1 (also known as CDC2) leading to growth arrest at G1/S phases in the cell cycle

pRb: The Rb protein is a tumor suppressor, which plays a pivotal role in the negative control of the cell cycle and in tumor progression. It has been shown that Rb protein (pRb) is responsible for a major G1 checkpoint, blocking S-phase entry and cell growth. t regulates cell growth and keeps cells from dividing too fast or in an uncontrolled way.

Test your understanding

Which of the following statements regarding cyclin-dependent protein kinase is not correct?

a. Their activity is regulated by cyclins
b. They can alter the activity of proteins involve in the progression of cells through cell cycle
c. Their activity fluctuates during cell cycle
d. Each type of cell contains one specific form

Cdk2/cyclinE functions in _____

a. G_2/M transition
b. G_2
c. M
d. G_1/S transition

In which phase of cell cycle is DNA replicated

a. G_1 phase
b. S phase
c. G_2 phase
d. M phase

Cyclin dependent kinases which control progression through cell cycle checkpoints are totally activated by which of the following?

a) Binding to cyclin, plus phosphorylation by a Cdk activating protein kinase
b) Binding to cyclins
c) Phosphorylation by Cdk activating protein kinase
d) Phosphorylation by a tyrosine kinase

At which cell cycle checkpoint, cell cycle is halted if cell's DNA is damaged?

a) G_1 – S
b) S – G_2
c) G_2 – M
d) G_0 – G_1

References & Further reading

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