Contents

1 Cell cycle

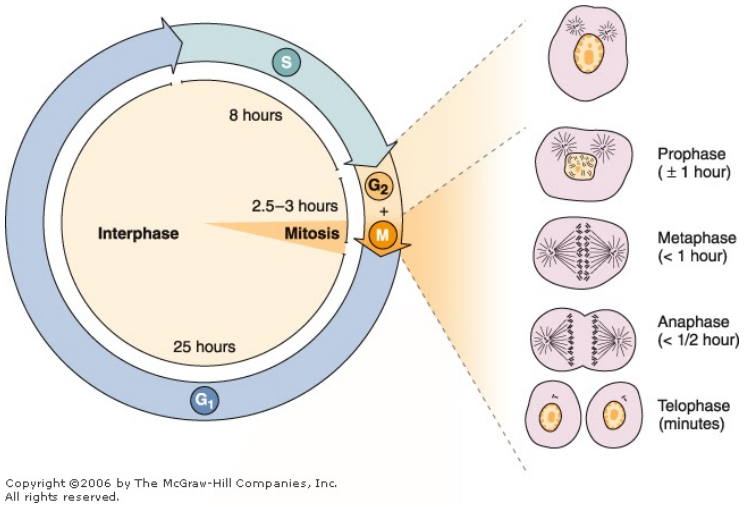

Figure 1: `https://dehistology.blogspot.com/2011/06/cell-cycle.html`

1.1 Cdks

Cyclin-Dependent Kinases (CDKs) phosphorylate proteins that drive the cell through the cell cycle. This is regulated by

1. Synthesis rate of the Cyclins

2. Ubiquitylation rate of the cyclins (marking them for proteolysis/degradation)
3. Phosphorylation of the Cdks
4. CKIs

1.2 Cyclins

Cyclins activate the CDKs (partially) by forming complexes (see table). There are 4 types of cyclins (A, B, D and E) with various related forms (i. e. D1, D2 and D3 in humans). When characterized by the state of the cell cycle they are active in, they can further be divided into 4 groups: G1/S-Cyclins, S-Cyclins, M-Cyclins and G1-Cyclins.

Cyclin	Cdks	Complex
Cyclin-D	(Cdk4/Cdk6)	G1-Cdk
Cyclin-E	Cdk2	G1/S-Cdk
Cyclin-A	(Cdk2/Cdk1)	S-Cdk (MPF)
Cyclin-B	Cdk1	M-Cdk (MPF)

Table 1: Cyclines and the Cdks they form complexes with

- G1/S-Cdk initiates the cell cycle in the dormant G1 phase (yeast: START, mammals: restriction point)
- S-Cdk triggers transition from the G1 to the S phase
- M-Cdk triggers transition from the G2 to the M phase

The resulting complex when Cyclin A or B bind to Cdk1/Cdk2 is called the maturation promoting factor (MPF).

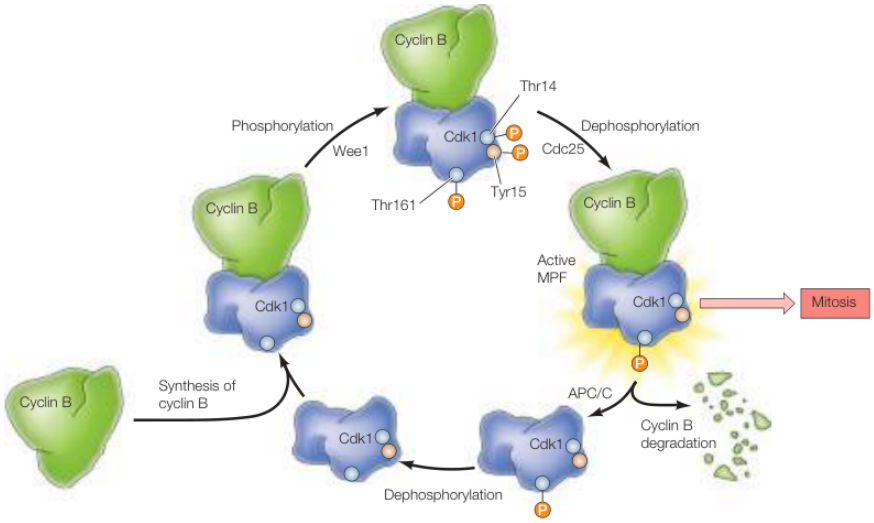

Figure 18.12 MPF regulation Cdk1 forms complexes with cyclin B during G_2. Cdk1 is then phosphorylated on threonine-161 (Thr161), which is required for Cdk1 activity, as well as on tyrosine-15 (Tyr15)—and threonine-14 (Thr14) in vertebrate cells—which inhibits Cdk1 activity. Dephosphorylation of Tyr15 and Thr14 activates MPF at the G_2 to M transition. MPF activity is then terminated toward the end of mitosis by proteolytic degradation of cyclin B, which is followed by dephosphorylation of Cdk1.

Figure 2: MPF Regulation. The "Phosphorylation" step is carried out by CAK

Cdk concentration remains mostly constant.[1] Concentration of cyclins changes during the cell cycle (see images).

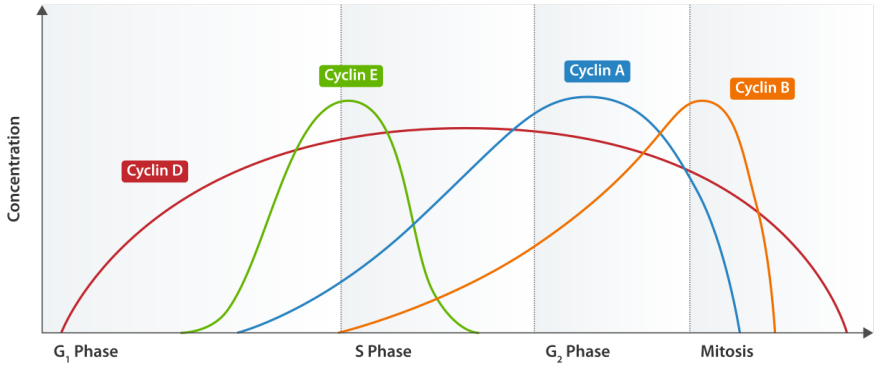

Figure 3: Concentration of the cyclins during the cell cycle (wikipedia)

[1] albert, p. 1093

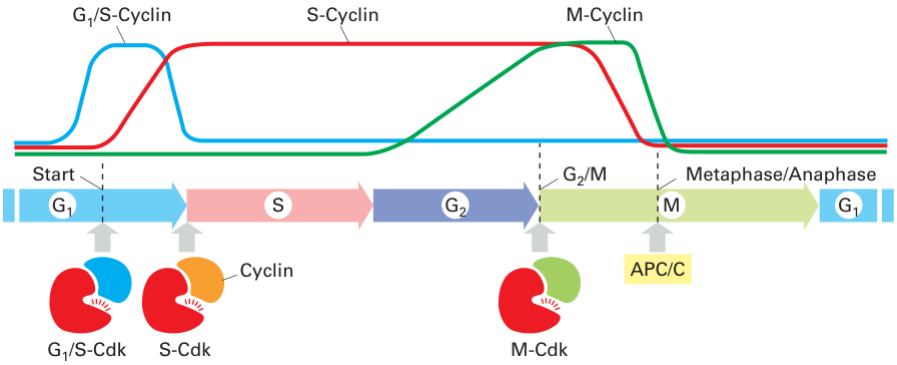

Figure 4: Concentration of the cyclins during the cell cycle (alberts)

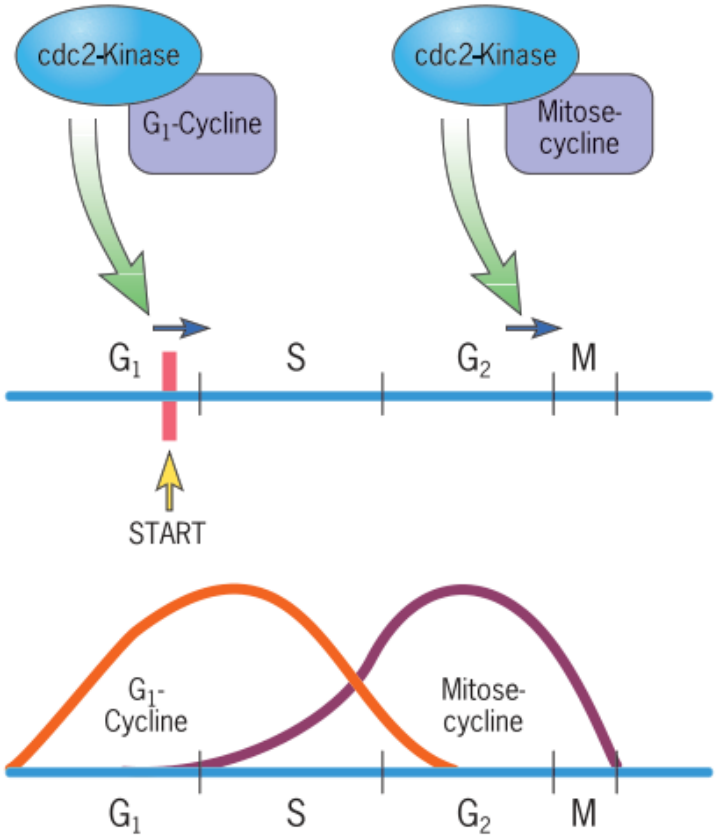

Figure 5: Concentration of the cyclins during the cell cycle (karp). cdc2 = cdk1

1.3 Wee1

Wee1 inhibits Cyclin-Cdk complexes by phosphorylation, causing a delay of the M-Phase so that the cell can grow. If Wee1 is defective, the cells transition directly from S- to M-Phase without the growth in the G2 phase, resulting in *wee* little cells :)

1.4 Cdc25

Cdc25 activates the MPF that was previously inactivated by Wee1. It dephosphorylizes Thr14 and Tyr15. Mammals have 3 related forms Cdc25A, B and C.

1.5 APC/C

The anaphase-promoting complex/cyclosome (APC/C) is a ubiquitin ligase and triggers transition from the metaphase to the anaphase by ubiquitylation of securin and Cyclin-A/Cyclin-B, marking them for proteolysis. Once they are destroyed, the MPF is no more.

1.5.1 Cdc20

Binds with APC/C in mitosis to specify target proteins.

1.5.2 Cdh1

Binds with APC/C in late mitosis/G1 to specify target proteins.

1.6 SCF

Skp, Cullin, F-box containing complex is another ubiquitin ligase. SCF ubiquitylates CKIs in the late G1 phase, thus activating S-Cdks; it's also responsible for proteolysis of G1/S-Cdks in the early S phase. Marks p27. Typically requires phosphorylated targets.

1.6.1 F-Box-Proteins

Exchangeable part of the SCF, specifying the target protein. There are more than 70 genes coding for F-Box-Proteins.[2]

1.7 CKIs

Cdk inhibitors (CKIs) inhibit Cyclin-Cdk complexes by binding to them (mostly G1/S- and S-Cdks). There are 2 families of CKIs, binding to different Cdks and Cyclin/Cdk complexes:

[2] alberts, p. 178

Table 18.1 Cdk Inhibitors

Inhibitor	Cdk or Cdk/ cyclin complex	Cell cycle phase inhibited
Ink4 family (p15, p16, p18, p19)	Cdk4 and Cdk6	G_1
Cip/Kip family (p21, p27, p57)	Cdk2/cyclin E	G_1
	Cdk2/cyclin A	S, G_2

Figure 6: CKI families and their targets

1.7.1 p27

Inhibits Cdks in G1. Gets phosphorylated by Cdk1, causing it to be marked for proteolysis (by SCF or APC/C?).

1.7.2 p21

Inhibits G1/S-Cdk und S-Cdk if DNA damage occured.

1.7.3 p16

Inhibits G1-Cdk in G1. Frequently inactive in cancer cells.

1.8 CAK

CDK-activating kinase (CAK) activates the cyclin-CDK complex.[3]

[3] https://en.wikipedia.org/wiki/CDK-activating_kinase