1 Cell cycle

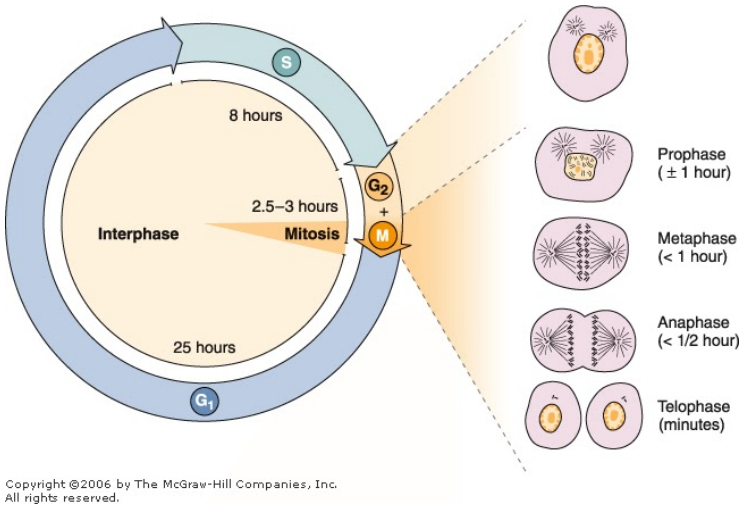

Figure 1: `https://dehistology.blogspot.com/2011/06/cell-cycle.html`

1.1 Cdks

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

1.2 Cyclins

Cyclins activate the CDKs (partially) by forming complexes. See table.

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).

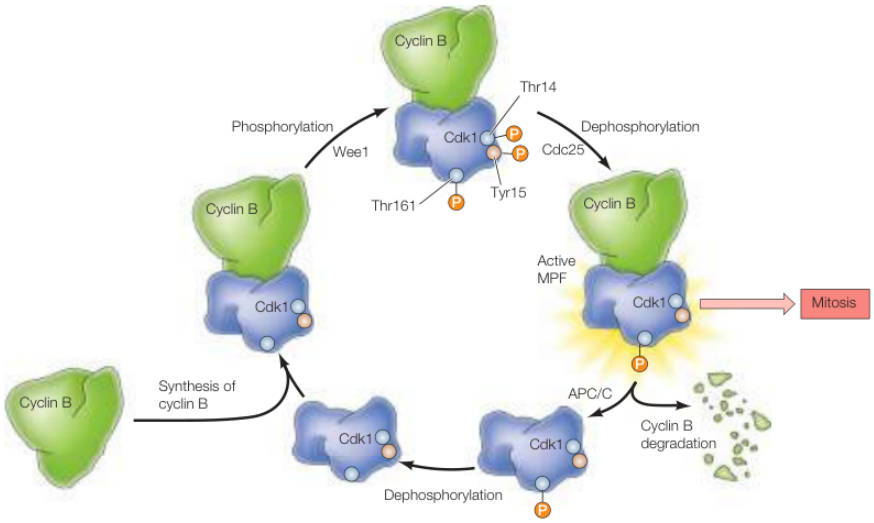

Figure 18.12 MPF regulation Cdk1 forms complexes with cyclin B during G_2. Cdk1 is then phosphorylated on threonine-161 (Thr161), which is required for Cdk1 activity, as well as on tyrosine-15 (Tyr15)—and threonine-14 (Thr14) in vertebrate cells—which inhibits Cdk1 activity. Dephosphorylation of Tyr15 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

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

[1] albert, p. 1093

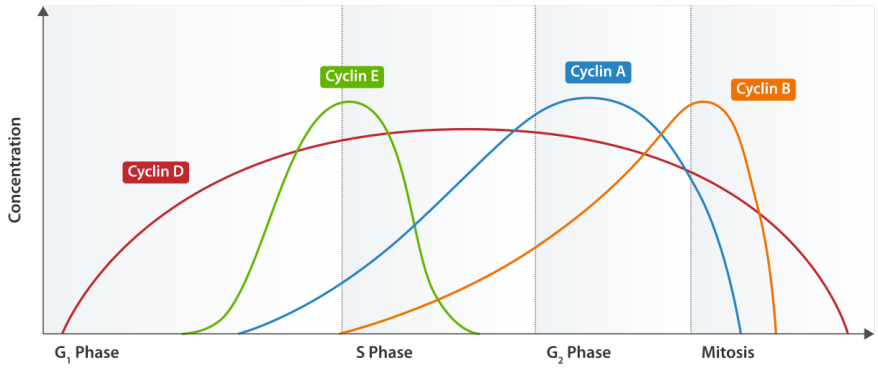

Figure 3: Concentration of the cyclins during the cell cycle (wikipedia)

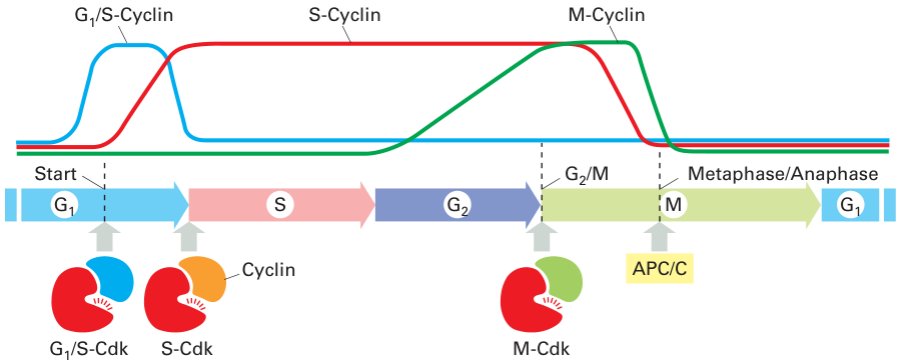

Figure 4: Concentration of the cyclins during the cell cycle (alberts)

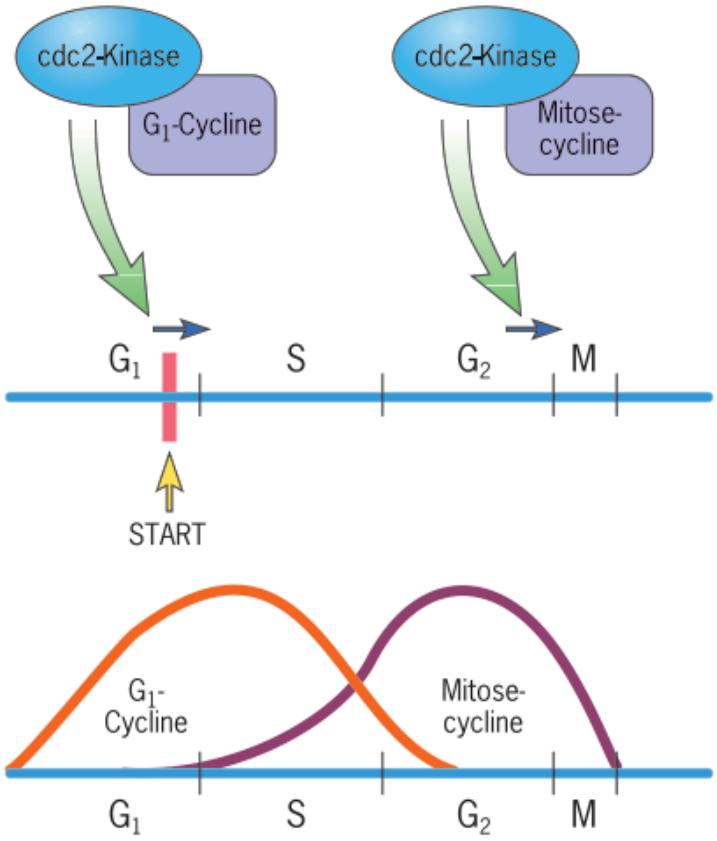

Figure 5: Concentration of the cyclins during the cell cycle (karp). cdc2 = cdk1

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

Another ubiquitin ligase. CF 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:

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

[2] alberts, p. 178

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.