XV) cell cycle (Alberts Ch. 17)

A) Phases of the cell cycle (M, G1, S, G2)

1) M = Mitosis

2) G1, S, and G2 make up interphase

B) review of mitosis

1) M phase includes mitosis and cytokinesis

2) several events occur during mitosis

3) M phase can be divided into 6 stages

a) prophase

b) prometaphase

c) metaphase

d) anaphase

e) telophase

f) cytokinesis

C) Cell cycle time varies

D) Regulation of the Cell Cycle by cell growth and extracellular signals

1)G1 restriction point

a) occurs late in G1

b) controls progression from G1 to S

c) first defined in Saccharomyces cerevisiae - START

d) passage through START in yeast is highly regulated

e) most animal cells have a G1 restriction point analogous to START

2) Some cell cycles are controlled via a G2 restriction point

a) Schizosaccharomyces pombe

b) oocytes

E) Checkpoints

1) G2 checkpoint

a) senses unreplicated DNA

b) senses damaged DNA

2) G1 checkpoint

a) also recognizes damaged DNA

b) mediated by p53

3) M phase checkpoint

F) Identification of MPF

1) experiments with xenopus oocytes

2) experiments in mammalian cells

3) experiments in yeast

4) studies in sea urchin embryos

G) purification and characterization of MPF from xenopus

1) MPF contains two components

a) a cyclin dependent kinase (CDK) called Cdc2

b) a mitotic cyclin - cyclin B

2) MPF activity cycles

H) MPF (CyclinB/cdc2) controls G2-M transition

1) Cyclin B synthesis begins in S phase

2) Cyclin B accumulates and forms complexes with Cdc2 throughout S and G2

3) Cdc2 is phosphorylated on three regulatory positions

4) Thr 15 and Tyr 15 get dephosphorylated by cdc25

5) active cdc2 phosphorylates a variety of target proteins

a) nuclear lamins

b) Histone H1

c) MAPs

d) other targets

6) Cdc2 activity also triggers the degradation of cyclin B

7) cdc2 is then inactivated

8) cells exit mitosis, undergo cytokinesis, return to interphase

I) Cyclin B and cdc2 are members of large families of proteins

1) yeast contain multiple cyclins

2) higher eukayrotes have multiple cyclins and cdc2 related kinases (CDKs)

J) The activities of the Cdks are regulated by multiple mechanisms

1) association of the Cdks with their cyclin partners

2) stimulatory phosphorylation sites

3) inhibitory phosphorylation sites

4) binding of inhibitory proteins (CKIs - Cdk inhibitors)

K) Growth factors and the D type cyclins

1) cells require growth factors to pass from G1 to S

2) Cyclin D synthesis is induced in response to growth factors

3) Cyclin D concentration falls if growth factors are removed

4) Cyclin D/Cdk4 drives cells through the restriction point

5) Cyclin D overexpression is associated with cancer

6) CKIs such as p16 can inhibit Cdk4/Cyclin D complexes

L) Rb is a key substrate of cyclin D1

1) Rb is a product of the gene responsible for retinoblastoma

2) Rb is also associated with other cancers

3) Rb is a tumor suppresser gene

4) Rb phosphorylation is regulated throughout the cell cycle

5) Rb becomes phosphorylated by Cdk4/Cyclin D complexes as cells pass through G1 restriction point

6) unphosphorylated Rb binds members of the E2F family

7) binding Rb inhibits E2F's ability to activate transcription

8) phosphorylation of Rb results in its dissociation from E2F

9) E2F then activates target genes

M) p53 acts to stimulate expression of p21

1) p21 inhibits the cell cycle progression in two ways

a) it is a CKI that inhibits several Cdk/cyclin complexes

b) It may also directly inhibit DNA replication in S phase

2) expression of the p21 gene is induced by p53

N) TGFβ inhibits cell proliferation in many epithelial cells

1) TGFB arrests cells at G1

2) TGFB induces the CKI p15 and p27

3) p15 and p27 bind Cdk4/Cyclin D

4) In the absence of Cdk4 activity, Rb phosphorylation is blocked and the cell cycle is arrested at G1

Figures from Alberts:
17-14, 17-19, Panel 18-1