

REGULATION OF CELL CYCLE: RAS PATHWAY

26 Nov 03, 1 Dec 03: BKH 5th, p 555-572, 7th: 591-594

G1 checkpoint: **restriction point:**
See page 563 for general model for Cell Cycle Regulation.

MITOGENS growth factors stimulate, many by stimulating passage thru G-1 checkpoint

platelet-derived growth factor (PDGF)	proliferation of connective tissue and smooth muscle leads to wound healing
Epidermal growth factor (EGF)	Isolated by Stanley Cohen in 1987 (Nobel prize) stimulates wide variety of tissue growth, development

RAS PATHWAY (p 592): growth factors bind to receptors, causes activation of tyrosine kinase, leads to cascade:

- 1: **growth factor binds** to receptor
- 2: **phosphorylation of tyrosine** residues on cytosol side of receptor
- 3: leads to **activated G protein** (*Ras*) binding GTP
- 4: cascade of **phosphorylation reactions in cytoplasm** (*Raf*, then MEK, then **mitogen-activated protein** kinases (MAPK))
- 5: **MAP Kinase enters nucleus**, phosphorylates regulatory transcription factors
- 6: **Early genes transcribed**, produce delayed genes including **E2F which controls entry into S phase**.
- 7: **other late genes include Cdk and cyclin**.

Some **factors can be inhibitory:**

p15 suppresses activity of Cdk-cyclin
p21 prevents S phase in cells with damaged DNA

mutant hyperactive Ras cells enter S phase even without growth factor

Three classes of cancer inducing genes: oncogenes
tumor suppressor genes
DNA repair genes

Oncogenes: presence can induce cancer, identified by oncogene transfection: DNA from tumor transfected into normal cells, look for transformation

50 oncogenes, most mutant forms of normal genes such as *src*, *myc*, *ras*, etc
mutant can be point mutation, gene amplification, or translocation

Oncogenes usually are mutated genes for growth factor signaling pathways, often over active:

- 1: growth factor
- 2: receptor
- 3: G protein
- 4: protein kinase
- 5: transcription factor
- 6: Cdk-cyclin (over production by amplification)

Tumor suppressor genes: genes normally control growth, become mutated/inactivated

Rb: retinoblastoma: Rb gene part of checkpoint inhibition from G1 to S
Normally, **Rb inhibits E2F**. **Cdk-cyclin inactivates Rb by phosphorylation**
Mutated Rb does not inhibit E2F induction of transcription factor synthesis

p53: most frequent (50%) human mutated cancer gene: (p 569)

A: Extensive **DNA damage causes increased ATM**, a kinase

B: **ATM activates p 53** by phosphorylation.

C: **Activated p53 dissociates from Mdm2** which inhibits p53 action.

D: free activated p53 action;

- 1) activates p21 which inhibits Cdk-cyclin, blocking G1 to S
- 2) causes apoptosis (cell death) by mitochondrial breakdown etc.