Molecular Genetics of Cancer

Oncogenes

Proto-oncogenes

Tumor Suppressor Genes

Oncogenes - when inappropriately activated or over-expressed, promote unregulated cell division.

Proto-oncogenes - normal cellular versions that can be mutated to become oncogenes

Many proto-oncogenes are in signal transduction pathways

Growth factors

Growth factor receptors

Intracellular signaling proteins

Transcription factors

(Regulators of apoptosis)

(Cell cycle regulators)

Tumor Suppressor Genes

normally function to

- promote apoptosis
- inhibit cell proliferation

block the cell cycle

temporary – cell cycle arrest or exit

permanent – cell cycle exit (aka senescence)

Molecular Genetics of Cancer - Tumor Suppressor Genes

p53 protein

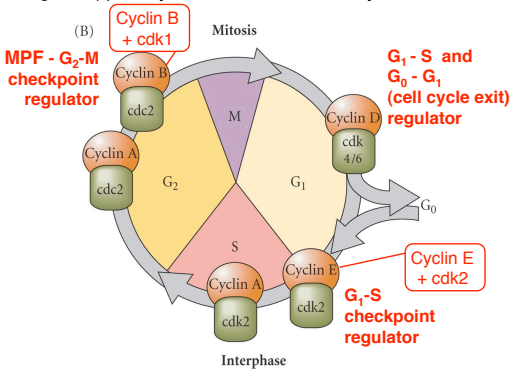
- regulates progression through the cell cycle, especially at the G1-S checkpoint.
- blocks entry into S phase if DNA is damaged, allowing time for repair
- if repair fails, then p53 promotes apoptosis

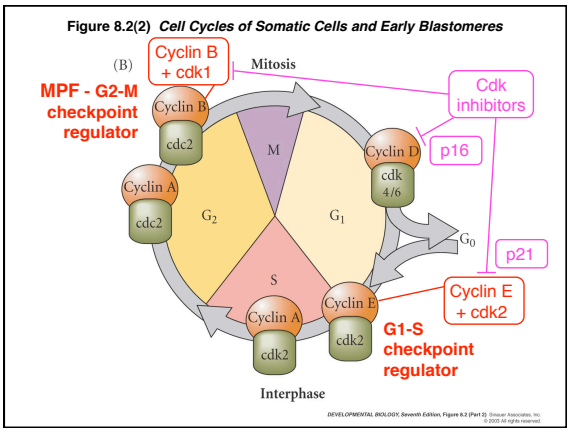
Molecular Genetics of Cancer - Tumor Suppressor Genes

p53 protein

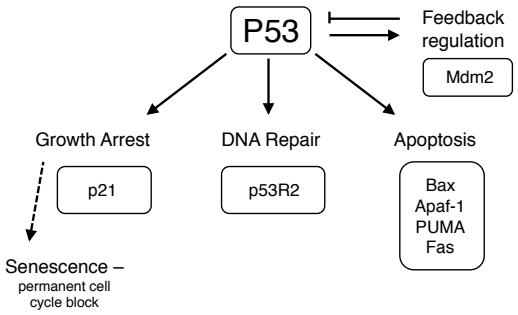
- transcription factor
- turns on p21 - a cyclin-dependent kinase inhibitor
- p21 blocks activity of cyclinE-cdk2 (among others), the main regulator of entry into S phase.

Figure 8.2(2) ***Cell Cycles of Somatic Cells and Early Blastomeres***

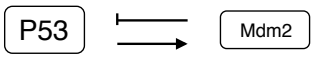




p53 Functions & Targets



p53 Feedback Regulation

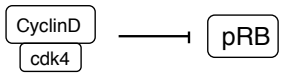


P53 protein as TF turns on *mdm2* gene

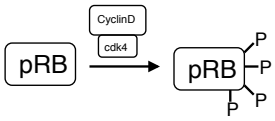
MDM2 protein ubitinates P53 protein

[ubiquitin targets proteins for degradation]

Cell Cycle Regulation by pRB



CyclinD/cdk4 inhibits Rb function



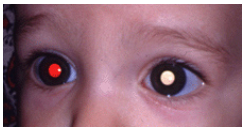
pRB is phosphorylated to inhibit its function

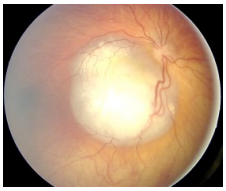
- this promotes cell cycle progress
(which unphosphorylated pRB blocks)

RB – Retinoblastoma

Retinoblastoma – 1st human tumor suppressor gene discovered

Mutations in Rb gene cause eye tumors (esp. in children)





Molecular Genetics of Cancer - Tumor Suppressor Genes

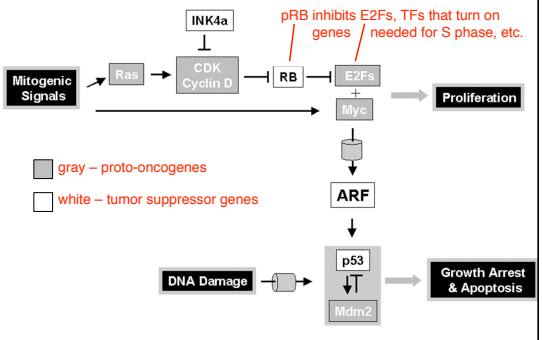
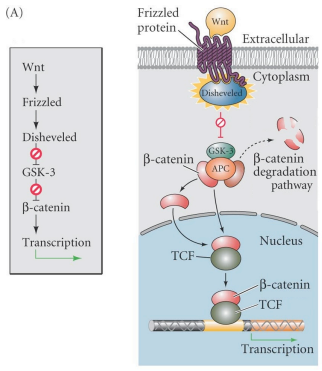


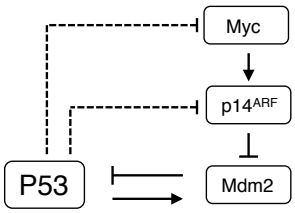
Figure 6.24(1) ***The Wnt Signal Transduction Pathway***



Both *myc* and *cyclinD* are target genes

p53 Regulation

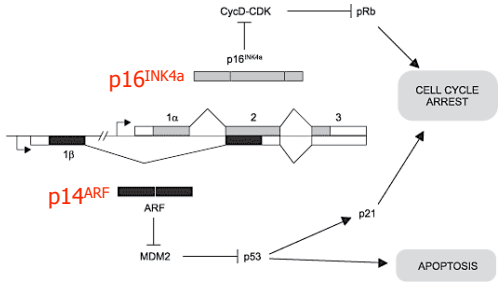
- ARF checks proliferative signals (e.g., from Myc)
- P53 also regulates (indirectly) ARF & Myc



Molecular Genetics of Cancer - Tumor Suppressor Genes

An amazing genetic locus: INK4A

– 2 unrelated proteins from the same gene



ARF: 'alternate reading frame'