

BIOL 2030, Lecture 10/27,
Problems Ch. 6: 30-32; Ch. 7: 13, 14; Ch. 19:4-10, 12, 14-17, 22-24

I. Recombination Mechanism

- A. Gene conversion
- B. Holliday Jct., branch migration and heteroduplex formation
- C. double strand break model of recombination

II. DNA repair

- A. Mutants in repair genes highly sensitive to mutagens
- B. Types of repair
 - 1. Damage reversal
 - photoreactivation
 - alkyltransferases
 - 2. Damage removal
 - base excision repair
 - nucleotide excision repair
 - transcription-coupled repair
 - mismatch repair
 - 3. DSB repair
 - NHEJ
 - SSA
 - SDSA

III. Mutations in repair genes

- A. Xeroderma pigmentosum – NER defects
- B. Ataxia telangiectasia – damage sensing defect
- C. Bloom's syndrome – replication errors?
- D. BRCA1 – repair pathways

IV. Cancer – unregulated, uncontrolled proliferation of cells

- A. Phenotypes of cancer cells
 - 1. “unlimited” replication
 - 2. loss of contact inhibition
 - 3. loss of anchoring mechanisms
 - 4. angiogenesis
 - 5. self-sufficient for growth
 - 6. resistant to cell death (apoptosis)
- B. Cancer results from accumulation of mutations in several genes (usually >5)
 - 1. Oncogenes – genes in which dominant, activating, mutations contribute to cancer
 - 2. tumor suppressor genes – loss of fx, recessive → cancer
 - 3. checkpoint proteins – monitor state of cell (chromosomes) to ensure cell cycle proceeds only when appropriate

V. Control of cell cycle

- A. Phases of cell cycle
- B. Analysis of cell cycle mutations in yeast
- C. Genes controlling cycle
 - 1. cdk's – kinases that regulate proteins involved in executing cell cycle specific functions (cdk – cyclin dependent kinase)
 - 2. cyclins – partners of cdk's that are required for cdk fx, concentration varies during stages of cell cycle
- D. Tumor suppressors: Rb – retinoblastoma – a key target of cdk phosphorylation
 - 1. Rb complexes with E2F to keep E2F turned off
 - 2. phosphorylation of Rb by cdks causes dissociation – active E2F drives cell into and through S phase
- E. Cell-signalling and oncogenes - oncogenic defects can result at many steps in pathways that signal cells to divide/not divide
 - 1. growth factors
 - 2. receptors
 - 3. G-proteins (GTP binding – control kinases)
 - 4. kinases
 - 5. transcription factors
- F. Checkpoints – detect defects in chromosome structure/fx and halt cell cycle, allowing time for repair, e.g. – chk1, chk2 transduce signal from damaged DNA (via ATM/R) to activate p53
 - 1. p53 – trx factor that controls arrest/repair/cell death functions

2. loss/mutation of p53 is most common defect in human cancers