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Lecture IV: Pathways Of Cancer Progression

March 24, 2003 1:00-2:00 PM

Lecture Outline:

- I. Multi-step model of carcinogenesis
 - A. Colorectal cancer
 - B. ARF and p53
 - C. Myc and ras

- II. Epithelial-Mesenchymal Transition

- III. Tumor growth and metastasis

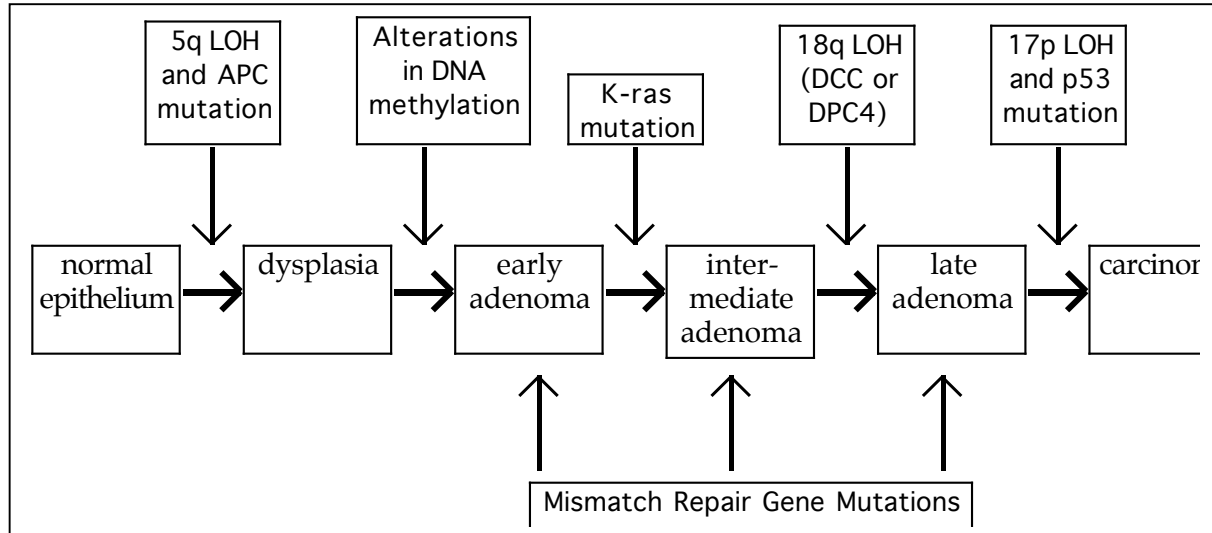
Required Reading:

Markowitz, S.D., Dawson, D.M., Willis, J., and Willson, J.K.V. (2002) Focus on colon cancer. *Cancer Cell* 1, 233-236.

Chambers, A.F., Groom, A.C., and MacDonald, I.C. (2002) Dissemination and growth of cancer cells in metastatic sites. *Nature Reviews Cancer* 2, 563-572.

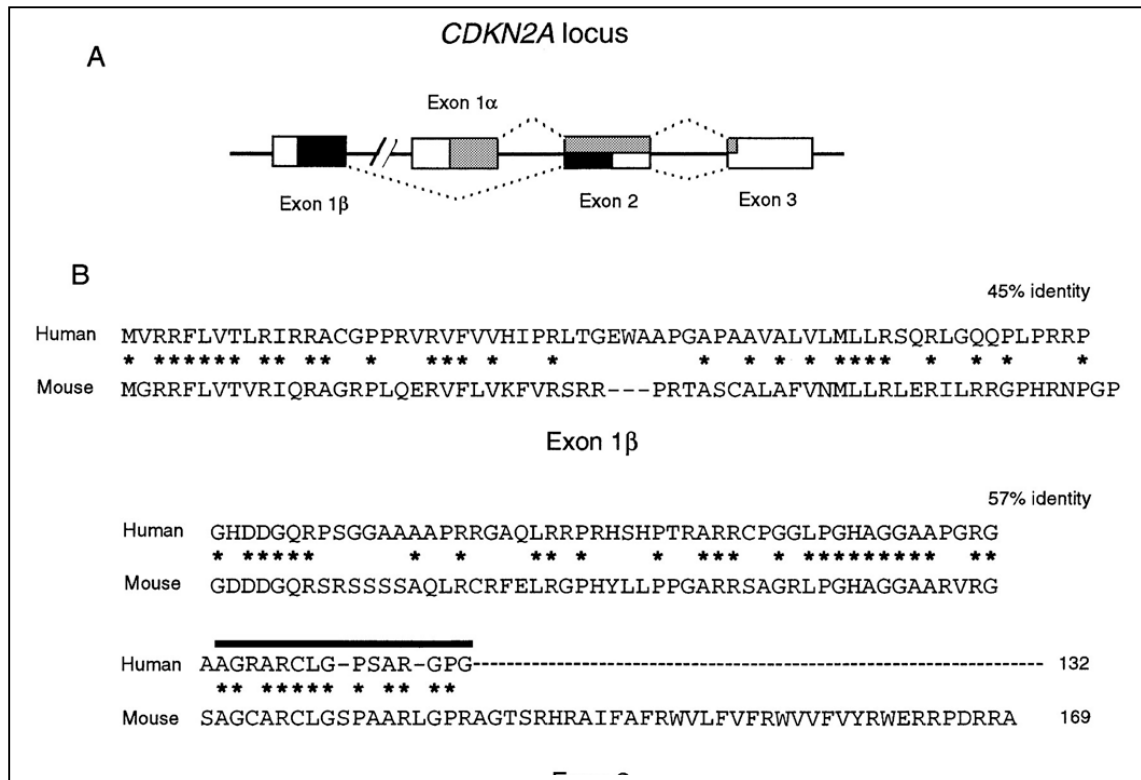
I. Multi-step model of carcinogenesis

A. Colorectal cancer



- APC interacts with beta-catenin facilitating degradation; loss of APC leads to upregulation of myc via TCF and altered cell adhesion due to interaction with cadherins
- DCC is extracellular matrix protein, located at 18q: few second hits seen in colon tumors, DCC knock-out in APC mouse model shows no increase in adenoma progression, relevant suppressor may be smad4, find second hits, smad4 knock-out in APC model increases progression, targets include p15 cdk inhibitor
- MMR deficiency: loss of mismatch repair genes, increase in genomic instability

B. ARF



- loss of Rb leads to apoptosis, subsequent loss of p53 leads to tumors
myc triggers p53-dependent apoptosis
E1a triggers p53-dependent apoptosis
- structure of INK4A locus: identification of ARF [ARF growth arrest is p53-dependent]
- myc, E2F, E1a activates ARF transcription, ARF blocks mdm2-mediated p53 degradation

C. Myc and ras

- ras triggers senescence which is p53 and p16 dependent
- myc triggers apoptosis which is p53 dependent
- cooperation between two leads to transformation

II. Epithelial-Mesenchymal Transition

Madin-Darby canine kidney cells (MDCK cells)

- treat with conditioned medium from fibroblast
- behave like migratory fibroblasts
- role of scatter factor (Hepatocyte growth factor, HGF)

loss of polarity

loss of cell-cell junctions (loss of E-cadherin expression)

migratory behavior

III. Tumor growth and metastasis

- cancer death caused largely by metastasis
- dependent on properties of tumor (invasiveness) and properties of host (immune response and host and tumor vasculature)
- steps

- 1. Angiogenesis

mass reaches 1-2 mm angiogenesis factors are produced that induce blood vessel formation

activators: acidic FGF, basic FGF, VEGF

inhibitors: thrombospondin, fragments of larger proteins
[angiostatin=plasminogen fragment]

- 2. Invasion

tumor cell attachment to subendothelial extracellular matrices by cell surface receptors

protease-mediated degradation of the matrix [collagenase and urokinase-type plasminogen activator, uPa, cleaving to make plasmin]

migration via chemotaxis using degradation products or tumor-associated autocrine motility factors

- 3. Intravasation

invade through vascular endothelial cells and their subendothelial basement membranes and enter vasculature

- 3. Metastasis

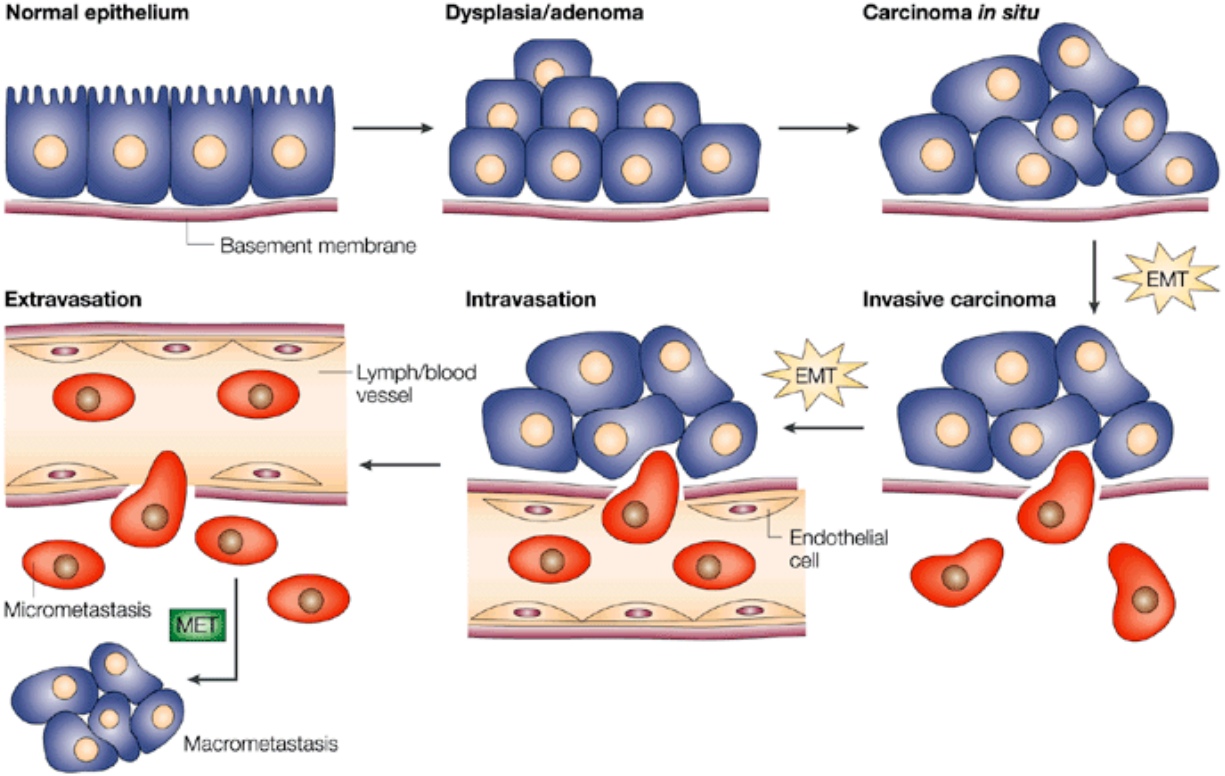
tumor cells must survive shear of blood flow and attack by immune system, then adhere to endothelial cells of target organ or exposed subendothelial extracellular matrix basement membranes

- 4. Extravasation

extravasate out of vasculature into perivascular stroma (reverse of invasion)

- 5. Secondary growth

formation and growth of secondary tumor metastasis



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From Thierry, J.P. (2002) Epithelial-mesenchymal transitions in tumour progression. Nature Reviews Cancer 2, 442-454