

Cook

Open Session

May 16, 2001

*Immunological Determinants  
of the Tumorigenicity  
of Adenovirus- Transformed Cells*

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**Overview**

1. Basic premise re: tumorigenicity ~ cell substrates
  - a. Potential risk statement
  - b. Determinants of experimental tumor formation
  - t. General observations on potential risk
2. E1A -induced sensitivity to apoptotic injury and tumor rejection
3. E1A in humans

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**Potential Risk Statement**

1. Potential risk- "tumorigenic cells > nontumorigenic cells"
2. Source - Armed Forces Epidemiology Board (AFEB) - 1954  
Preference for "normal" cells over human tumor cells

3. Current Question: Concern about human tumor cells = Concern about human cells that form tumors (in nude mice)
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**Experimental Tumorigenicity**  
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**Primary Tumor Development**

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**Experimental Tumor Formation is Affected by:**

1. Host selected - immunocompetence
2. Cell dose - threshold-cell-dose effect
3. Route of inoculation - e.g., intraperitoneal vs. subcutaneous
4. Observation period
5. Experimental methodology - "wound effect", foreign bodies, addition of other cells (e.g., fibroblasts)

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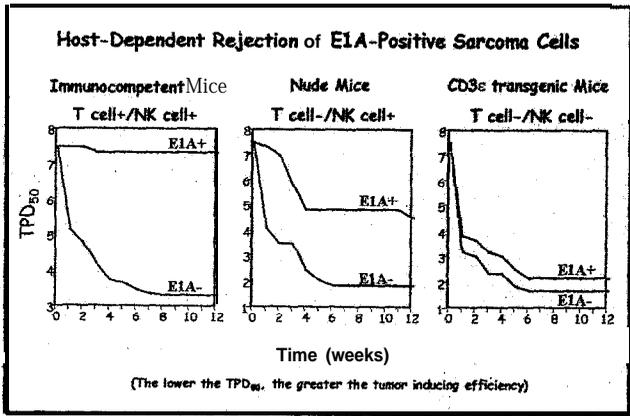
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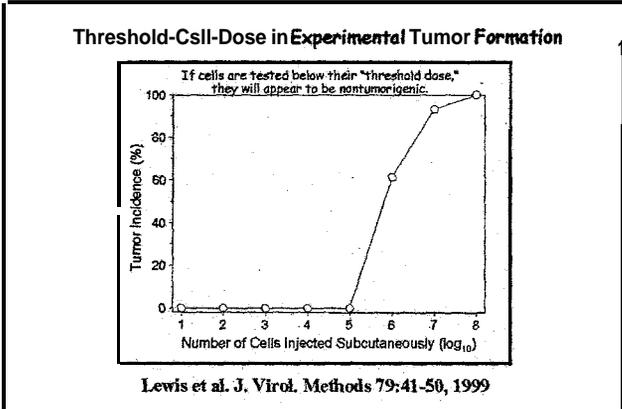
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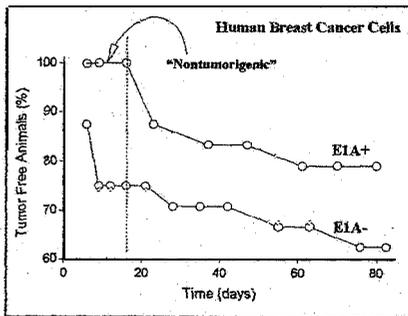
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**Importance of a "Proper" Observation Period**




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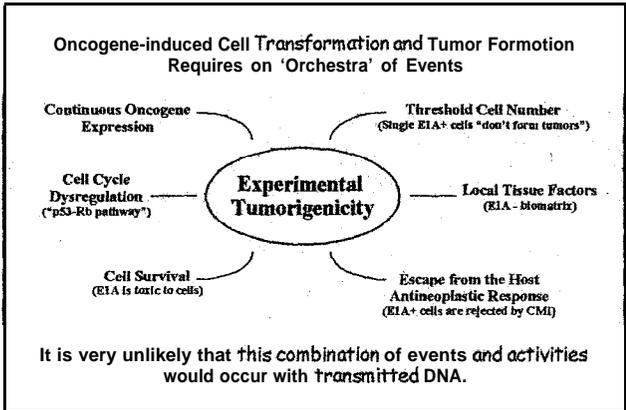
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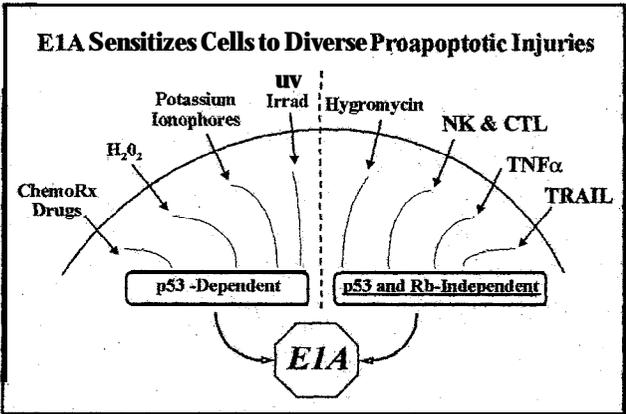
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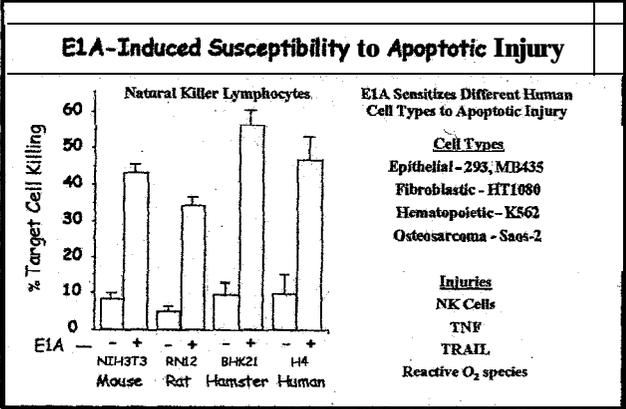
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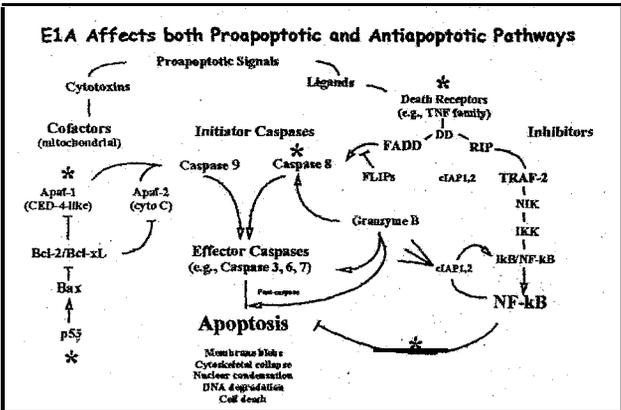
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**E1A in Humans**

1. E1A may persist in normal human tissues  
-- Matsuse et al. 146:177-84, 1992
2. E1A expressed during viral infection is being used therapeutically for p53-negative/mutant human tumor cells -- ONYX
3. E1A is being tested for gene therapy of breast and ovarian malignancies -- repression of Her-P/c-erb B-2 receptor on tumor cells

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**Conclusions**

1. Experimental tumor formation in nude mice does not predict tumorigenicity of an isolated oncogene.
2. Even if the E1A oncogene were transmitted in contaminating DNA it is very unlikely that it would become stably expressed in recipient cells -- transfection inefficiency, direct apoptosis during establishment.
3. Even if E1A became stably expressed in recipient cells, it is very unlikely that such cells would provide a tumorigenic risk because of:
  - a. Lack of a threshold-cell-dose
  - b. Reduced viability of E1A+ cells on biomatrix
  - c. Susceptibility to immune-mediated apoptosis
4. E1A expression in humans might be "normal" and, when therapeutically expressed in human tumor cells, E1A can be directly apoptotic and can reduce expression of critical growth factor receptors.

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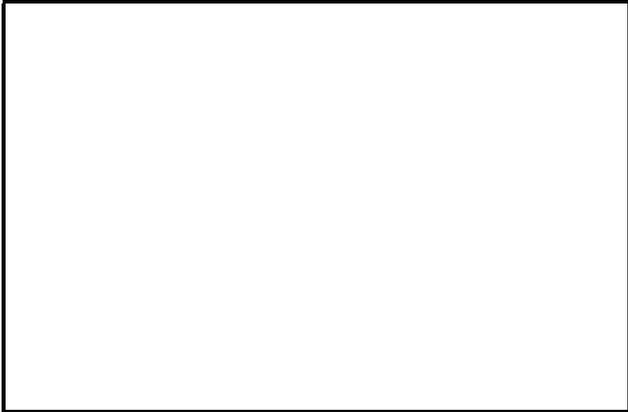
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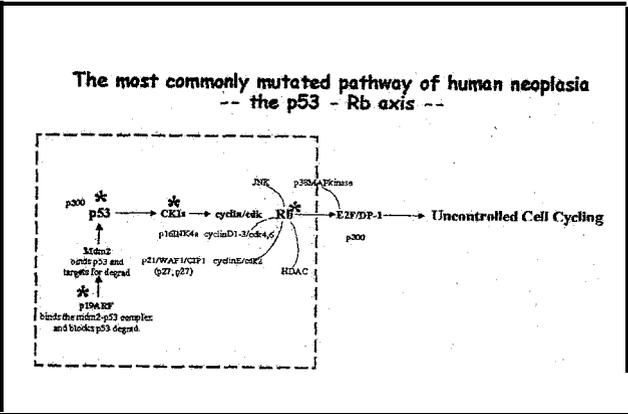
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