p53 and Cancer

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What is p53?

- A protein found inside cells
- A **stress** sensor of signals:
  - DNA damage
  - hypoxia
  - oncogene expression
  - nutrient deprivation
  - ribosome dysfunction
- In *unstressed* cells = p53 is inactive
  - MDM2 ubiquitin ligase $\rightarrow$ degradation of p53
Today’s focus: stressor DNA damage

- p53 *senses* damaged DNA
  → aids in regulation of DNA repair

\[ \textit{p53} = \textit{tumor suppressor protein} \]

prevents cancer

*What is a tumor?*

-a mass of tissues that result from excessive & uncontrolled cell division (can be benign or malignant)
What does p53 do?

p53 has 2 main functions

1. **Cell cycle arrest**
   
   = p53 STOPs cell cycle
   - until DNA is repaired

*Is DNA damaged?*
2. Apoptosis (cell suicide)

- p53 = transcription factor for 3 pro-apoptotic genes
- Cytochrome c release
- Caspase activation:
  - cleavage of key cell proteins that cause cell death
Cancer and p53

- p53 prevents cancer (evidence: knockout mice)
- Inheriting only 1 copy of functional p53 gene
  = predisposition to cancer (many kinds)
    - "Li-Fraumeni syndrome"
    - Patients have a 50% chance of developing cancer by 30 yrs old
    - rare condition

-Is this the only way that p53 relates to cancer?
p53 is the most commonly mutated gene in cancer

→ P53 has been found to be mutated in more than 52 kinds of cancers
How does a mutation in \( p53 \) → cancer?

*What is Cancer? Uncontrolled growth/proliferation of cells

- **Mutant** \( p53 \) can NO longer bind to DNA in an effective way = p21 protein is not made = no stop signal for cell division (no apoptosis/arrest)
- Even if DNA is damaged cell proliferates!
- = mutations propagate = malignant tumors are formed = cancer

**With \( p53 \)**
- \( p53^{++} \) Cell
- G1 arrested cell (DNA repair)

**Without \( p53 \)**
- \( p53^{-/-} \) Cell
- Failed G1 arrest
- Additional mutations
- Propagation of mutations
- Malignant cell
Using what we know about p53 → cancer therapy

- Cancers that have a p53 mutation= poor prognosis
  Why?
  - Tumor cells not likely to undergo apoptosis/cell cycle arrest when damaged by therapy
  - Radiation and chemotherapy may → secondary cancers
Gene Therapy

Introducing genetic material into cells to compensate for abnormal genes or to make beneficial protein.
**Gene Therapy: Gendicine**

*What is Gendicine?*  
Recombinant Human Ad-p53 Injection

- Target cells: cancer cells (has been FDA approved for neck and head sarcomas)

- Vector: replication-defective adenovirus
  - *Viruses can infect specific cells and deliver their DNA*
  - Genetically engineered virus to have p53 gene
  - p53 will be expressed via the host’s transcription and translation processes

- Results: cancer cured (apoptosis of damaged cells)
References

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