



p53 and Cancer

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Biochemistry 118Q



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 → degradation of p53



Today's focus: stressor DNA damage

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

p53 = 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)

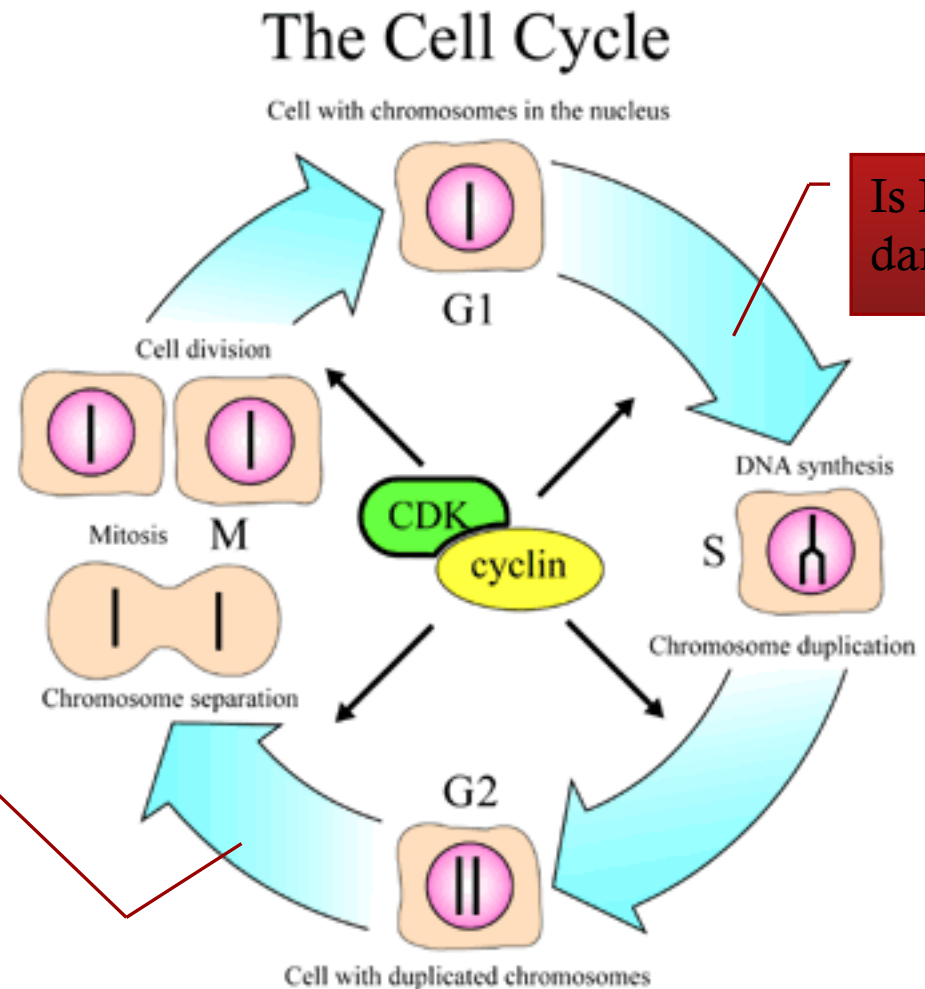
What does p53 do?

p53 has 2 main functions

1. Cell cycle arrest

= p53 STOPS cell cycle
-until DNA is repaired

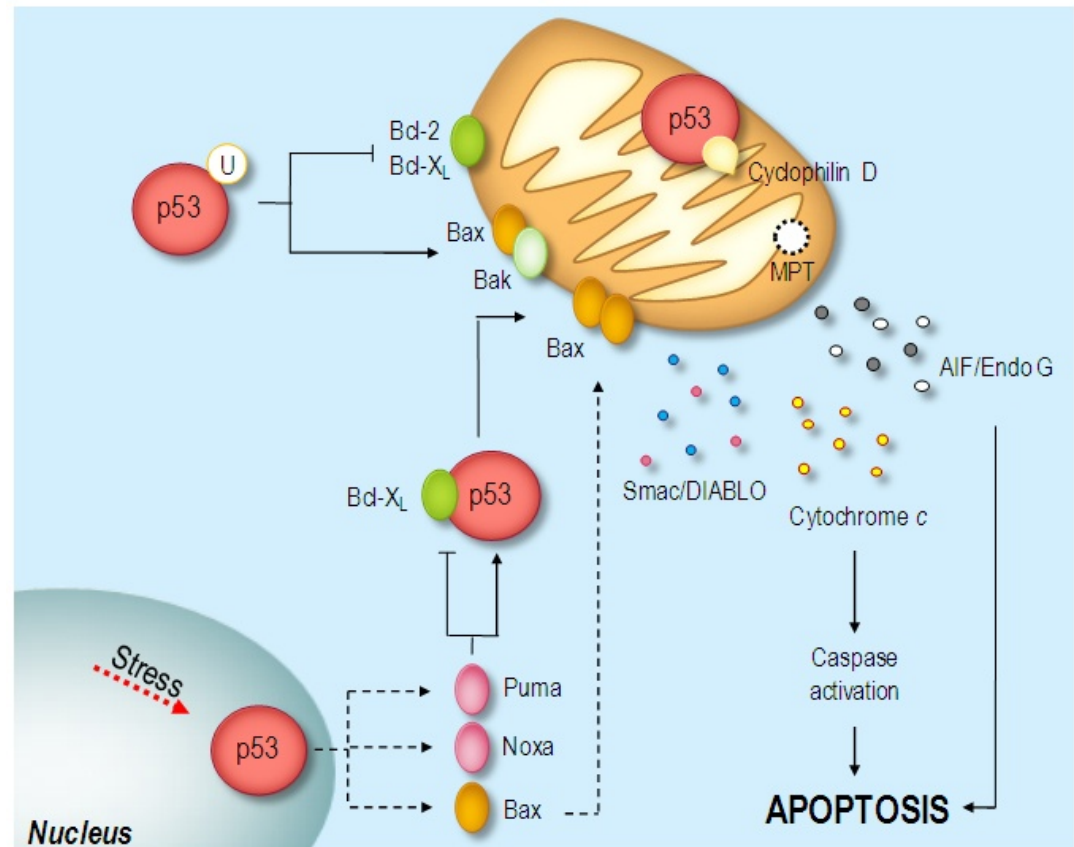
Is DNA
damaged?



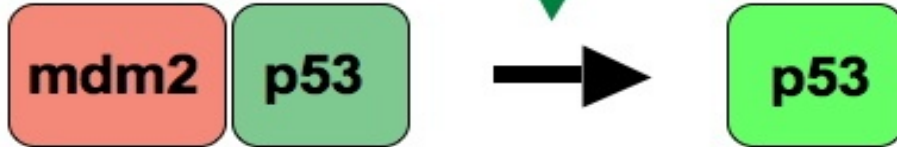
Is DNA
damaged?

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



DNA damage
Cell cycle abnormalities
Hypoxia



Cell cycle arrest

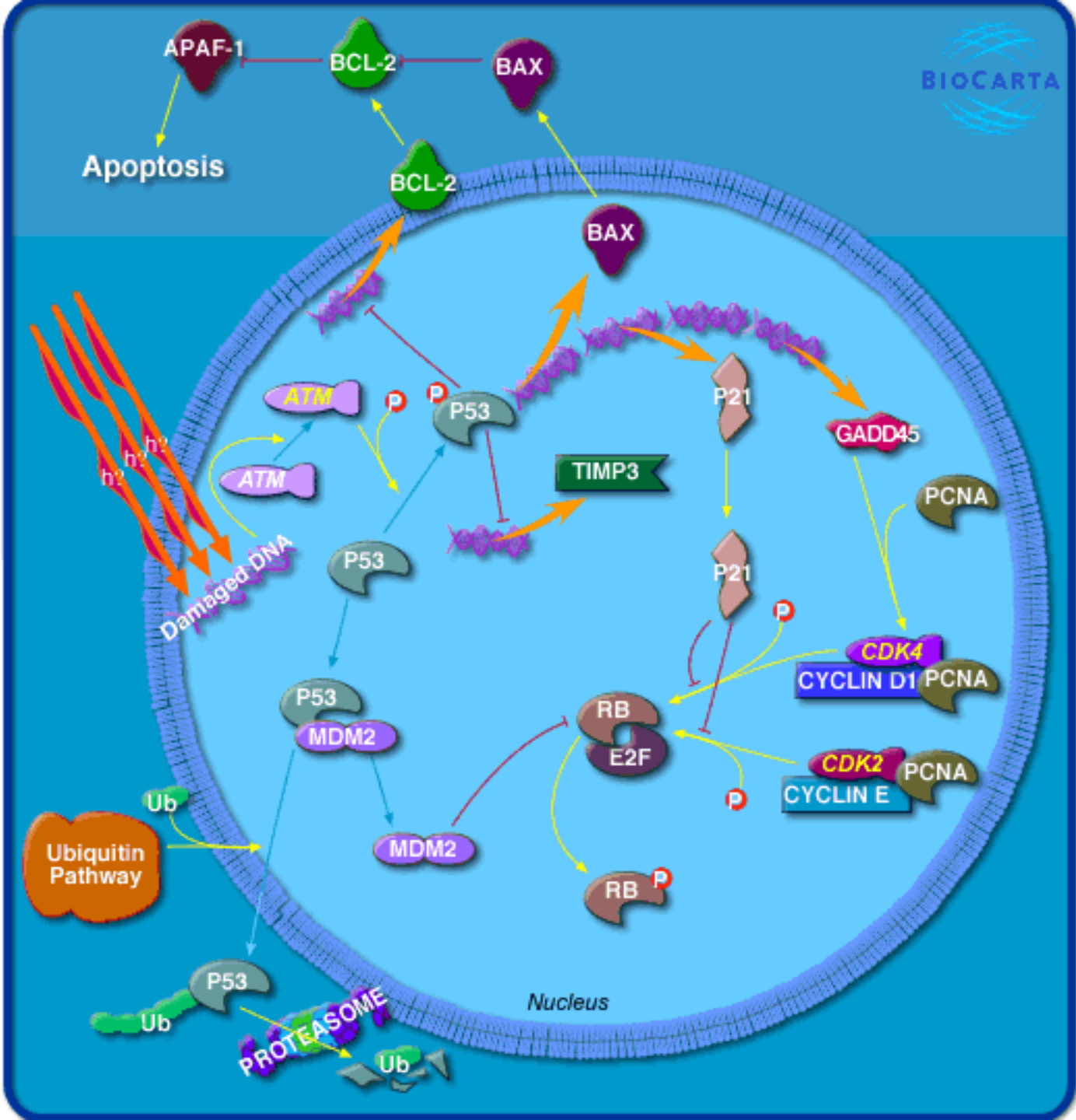
DNA repair

Cell cycle restart

Apoptosis

**Death and elimination of
damaged cells**

CELLULAR AND GENETIC STABILITY



Cancer and p53

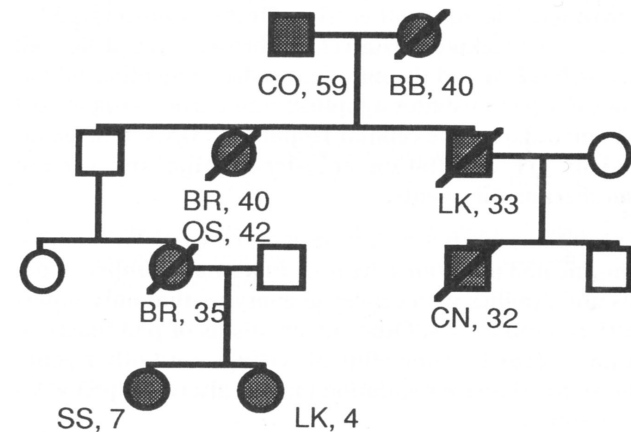
- p53 prevents cancer (evidence: knockout mice)
- Inheriting only 1 copy of functional p53 gene
= predisposition to cancer (many kinds)



- *“Li-Fraumeni syndrome”*
- Patients have a 50% chance of developing cancer by 30 yrs old
- rare condition

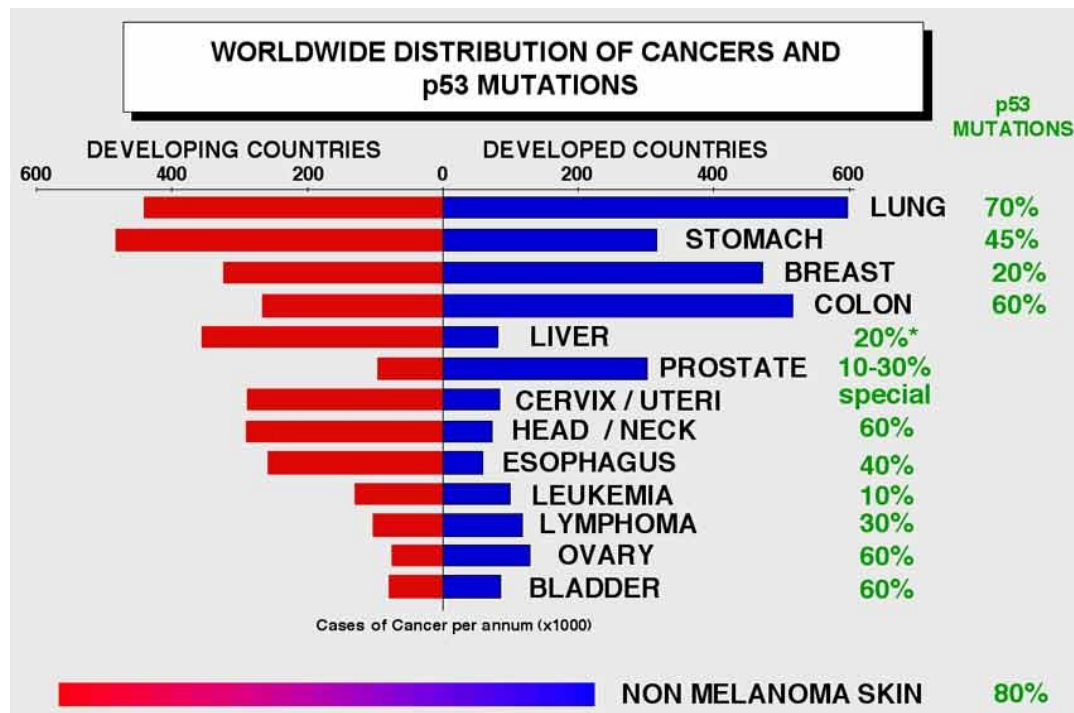
-Is this the only way that p53 relates to cancer?

Li-Fraumeni Syndrome "Classic" Pedigree



p53 is the most commonly mutated gene in cancer

→ P53 has been found to be mutated in more than 52 kinds of cancers

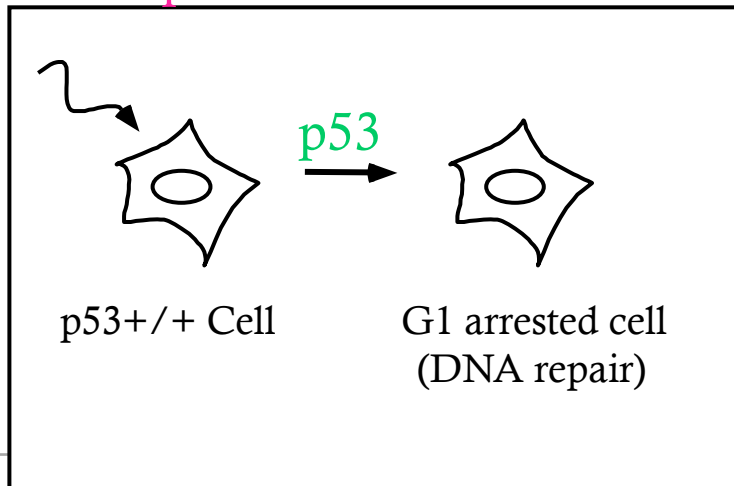


How does a mutation in p53 → cancer?

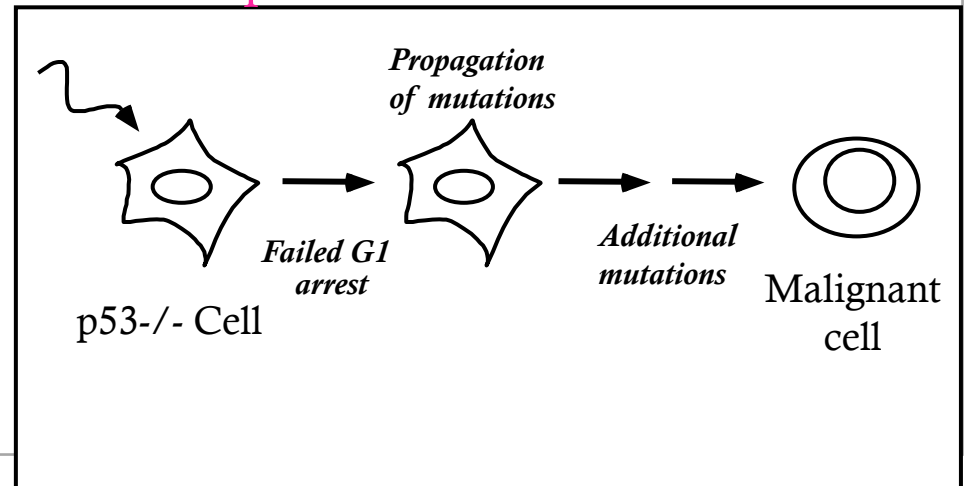
**What is Cancer? Uncontrolled growth/proliferation of cells*

- **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



Without p53



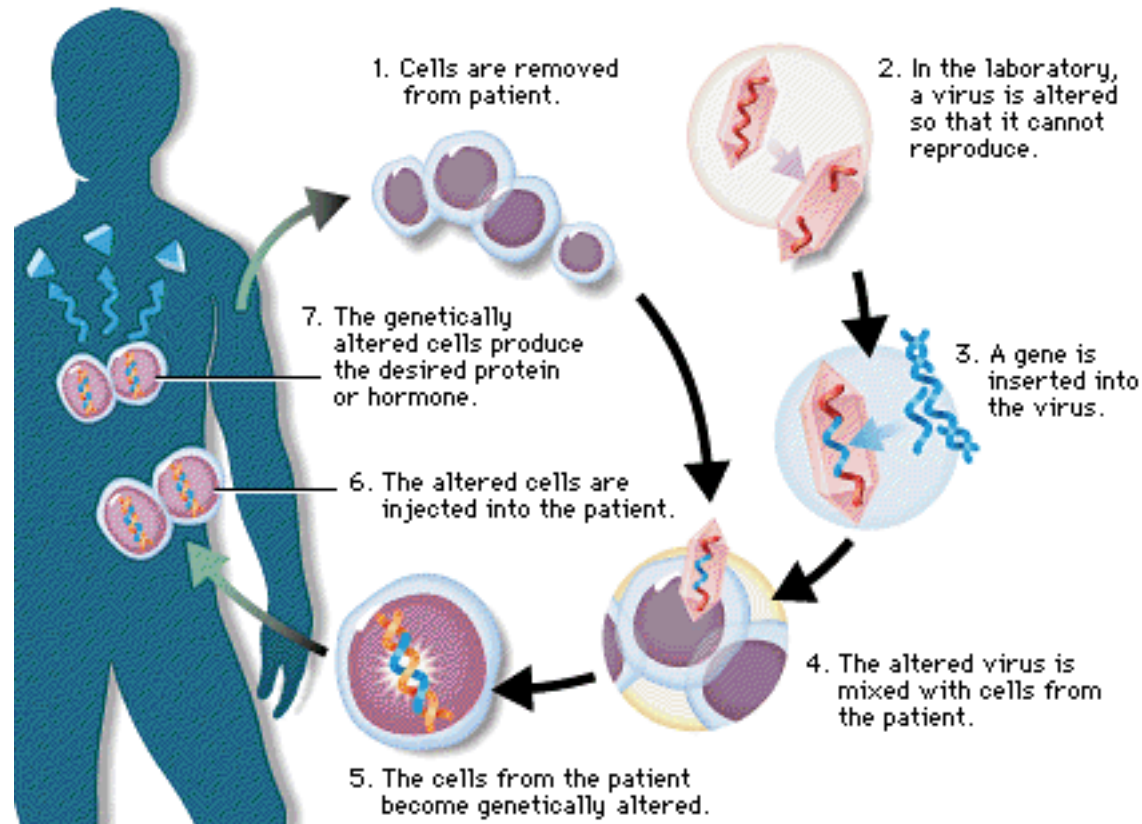
Using what we know about p53 → cancer therapy

- 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

Alternative Treatments: Gene Therapy



Introducing genetic material into cells to compensate for abnormal genes or to make beneficial protein

Gene Therapy: Gendicine China, 2003

*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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