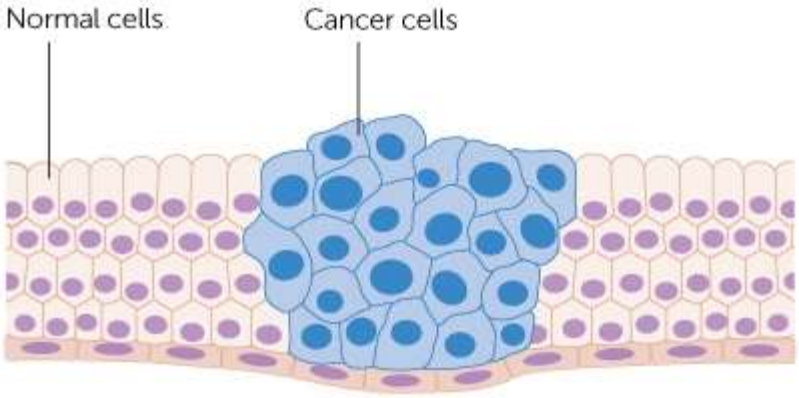
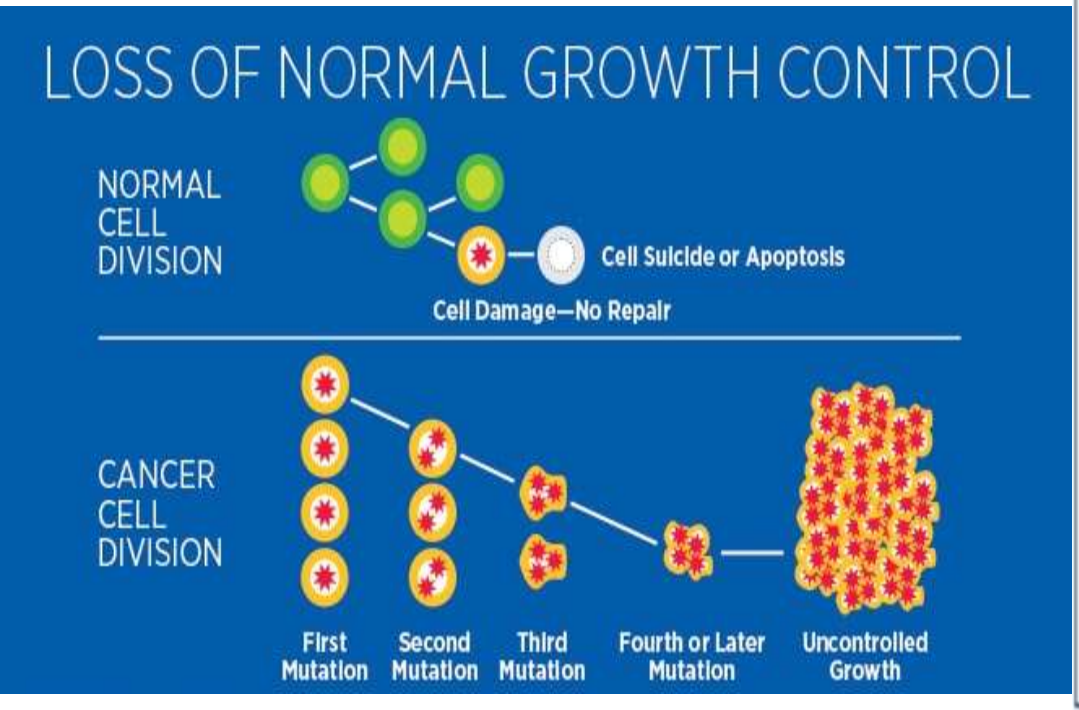
Cancer

- What is cancer?
  - uncontrolled cell growth that leads to the formation of primary tumors
  - cells that spread (metastasize) to other areas of the body and develop secondary tumors

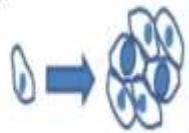




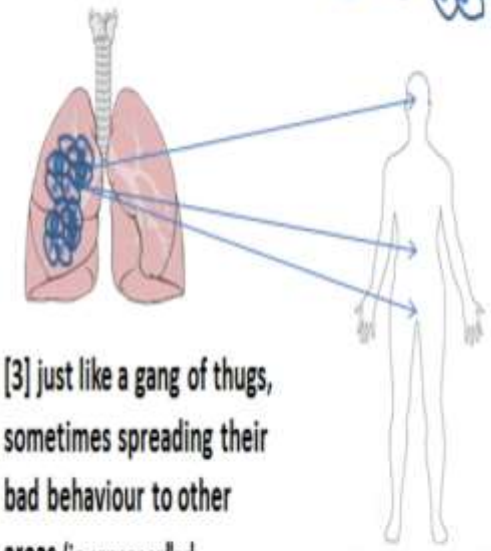
Graphic 1. What is cancer?

Very basically it is 'Cells behaving badly' by:

[1] overproducing cells which may clump together, to form lumps



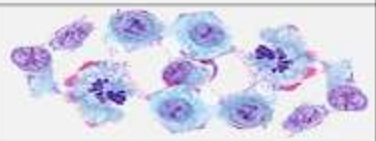
[2] 'taking over' or putting pressure on vital organs and, ...



[3] just like a gang of thugs, sometimes spreading their bad behaviour to other areas (in cancer called metastasis) or,.....

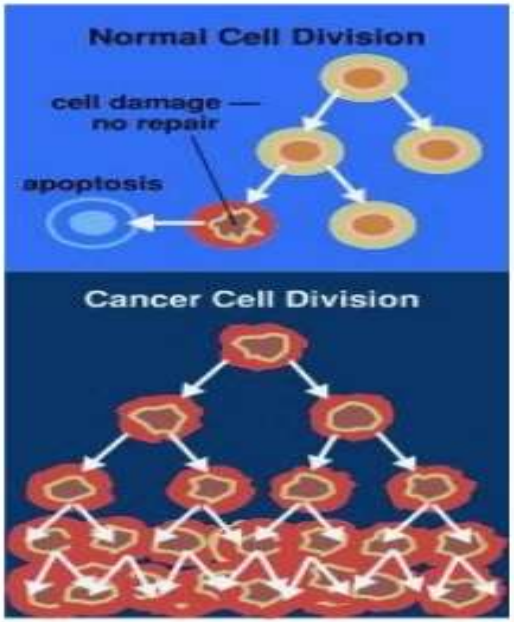
[4] producing the wrong type of blood cell (generally white blood cells)

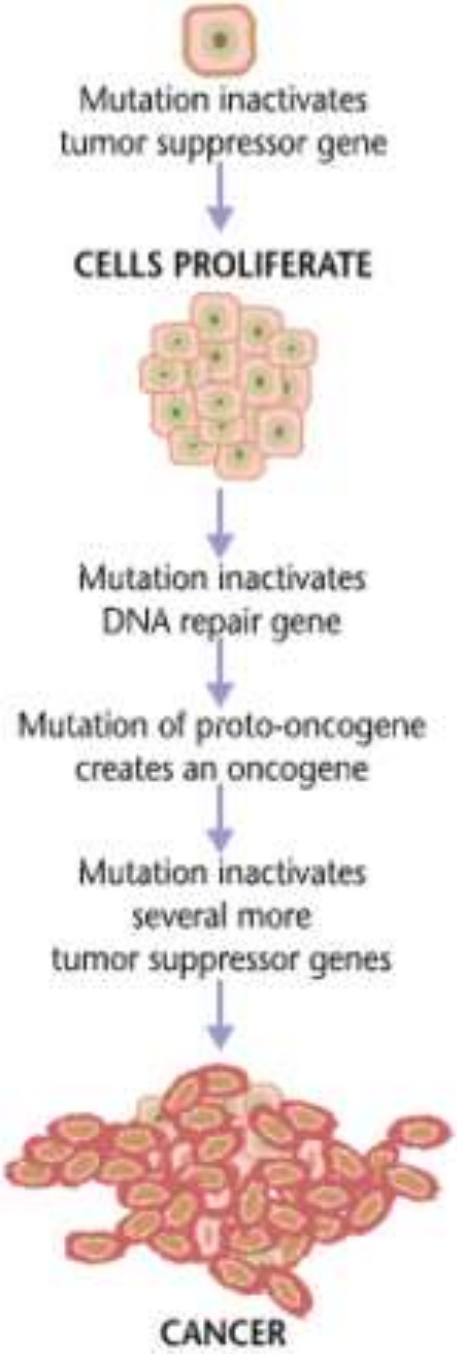
BUT cancer is NOT basic; not simple. It has a complicated undercover story.

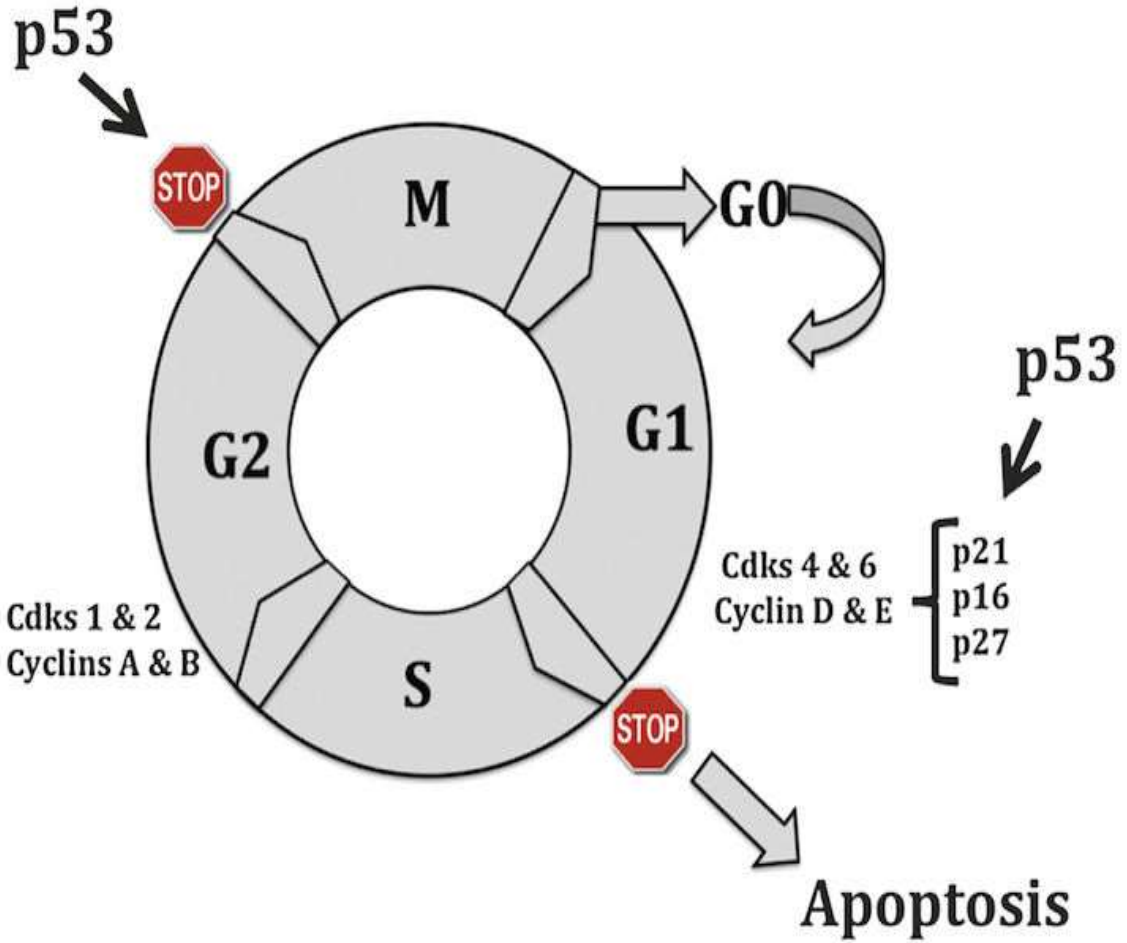
Normal	Cancer	
		Large, variably shaped nuclei
		Many dividing cells; Disorganized arrangement
		Variation in size and shape
		Loss of normal features

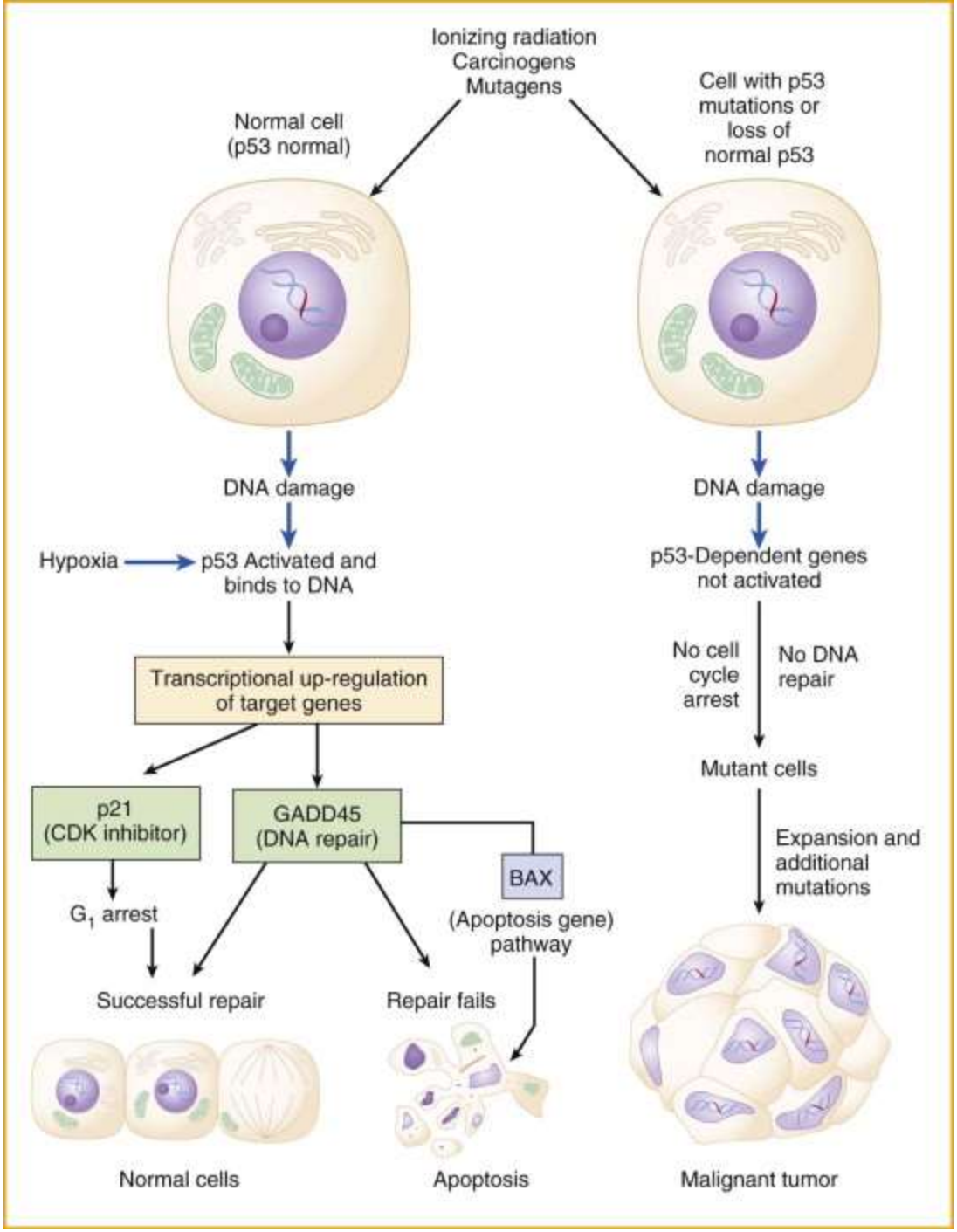
Cellular Basis of Cancer

- Cancer is characterized by abnormal and uncontrolled growth
- Cancer arises from a loss of normal growth control
- In normal tissues, the rates of new cell growth and old cell death are kept in balance
- In cancer, this balance is disrupted
- This disruption can result from
  1) uncontrolled cell growth or
  2) loss of a cell's ability to undergo apoptosis

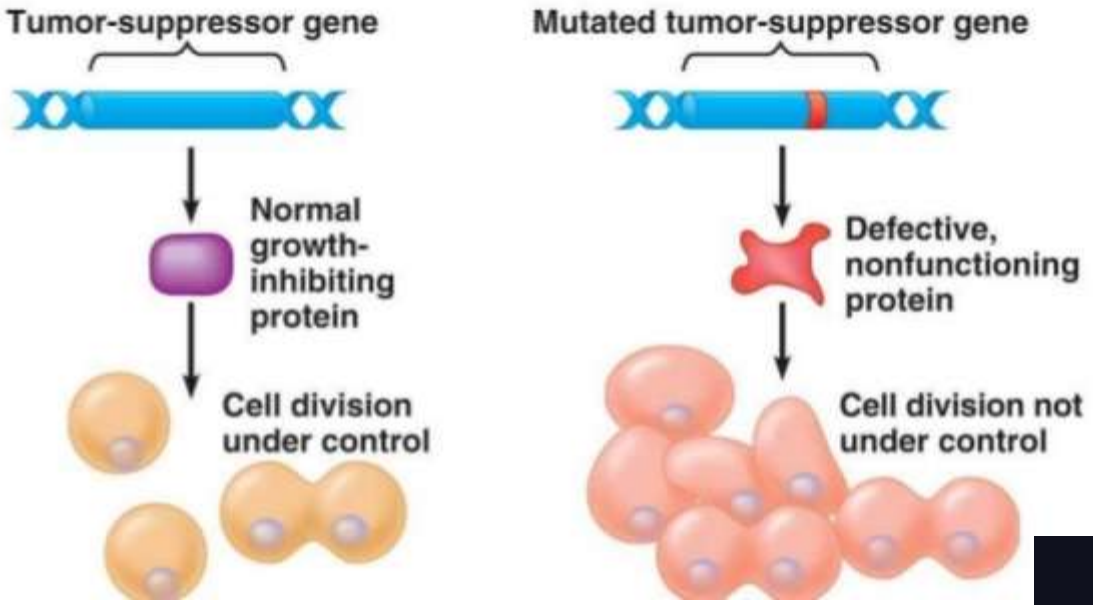


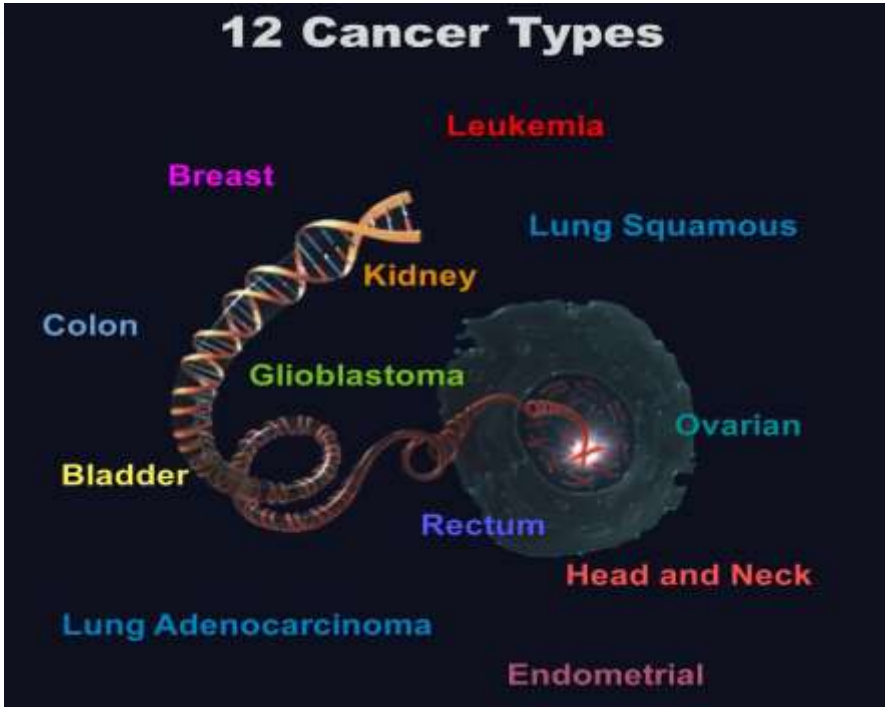

Mutation inactivates
tumor suppressor gene
CELLS PROLIFERATE
Mutation inactivates
DNA repair gene
Mutation of proto-oncogene
creates an oncogene
Mutation inactivates
several more
tumor suppressor genes
CANCER

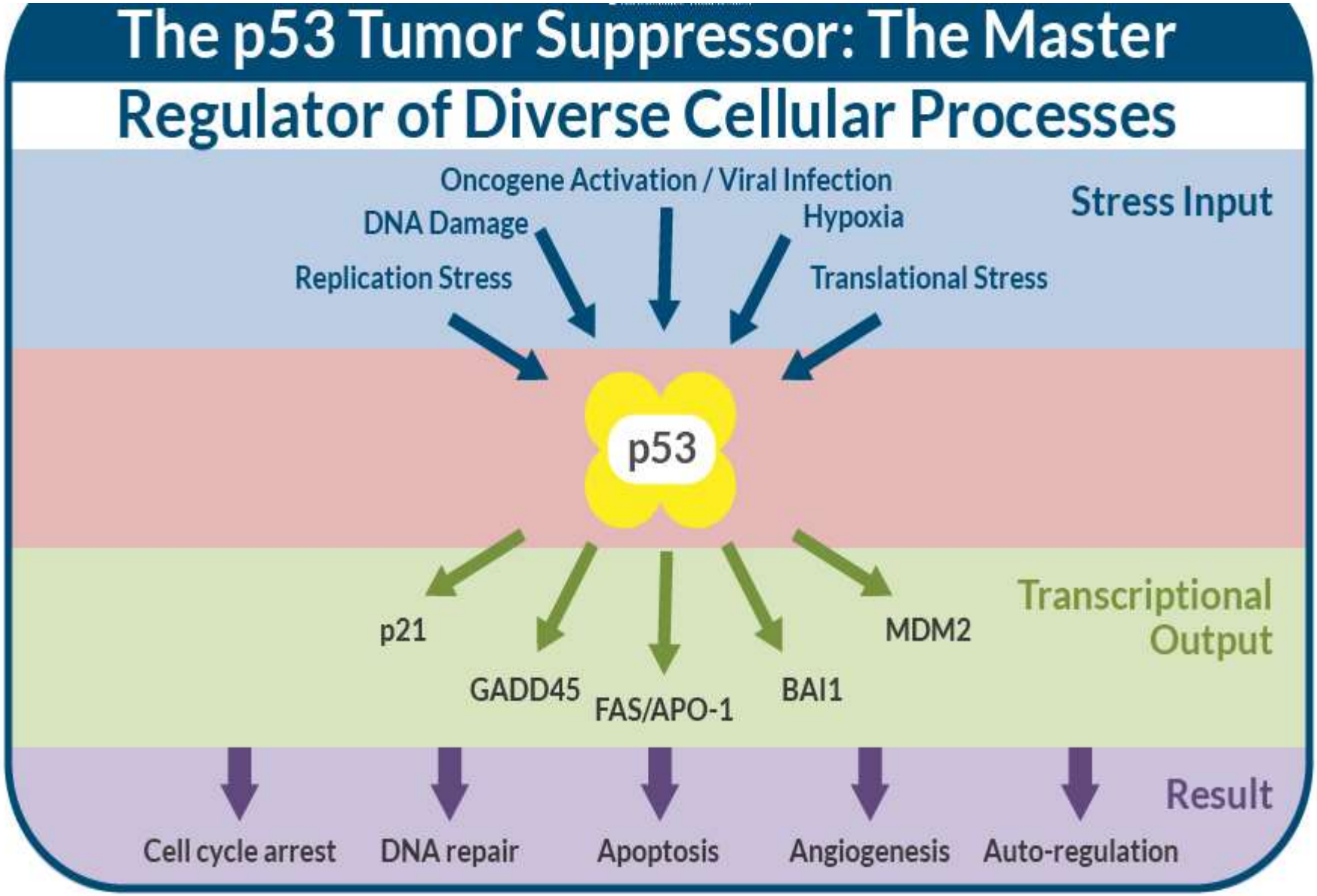

p53
STOP
M
G0
G2
G1
S
STOP
Cdks 1 & 2
Cyclins A & B
Cdks 4 & 6
Cyclin D & E
p21
p16
p27
p53
Apoptosis

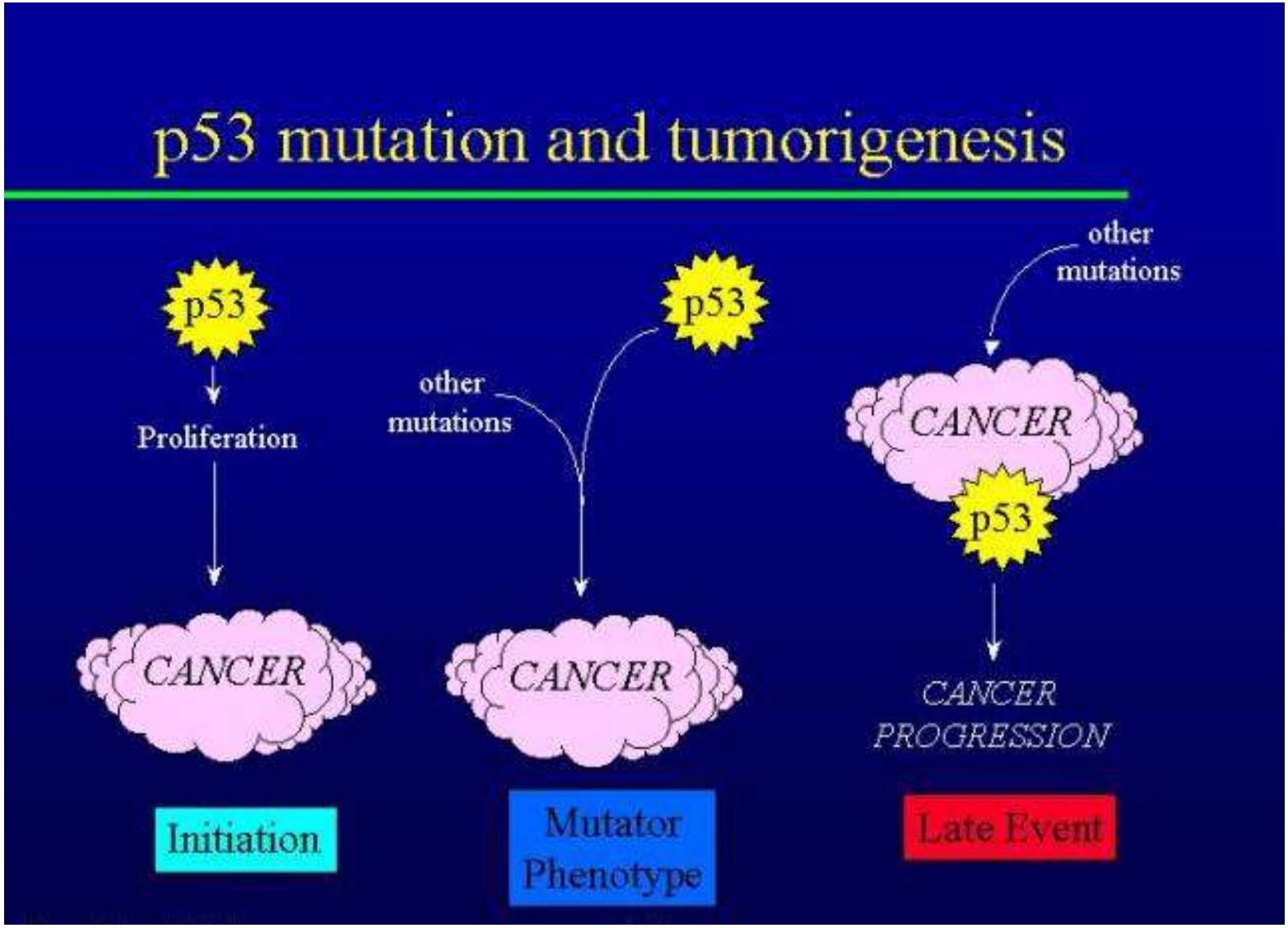

Ionizing radiation
Carcinogens
Mutagens
Normal cell
(p53 normal)
Cell with p53
mutations or
loss of
normal p53
DNA damage
DNA damage
Hypoxia
p53 Activated and
binds to DNA
p53-Dependent genes
not activated
No cell
cycle
arrest
No DNA
repair
Transcriptional up-regulation
of target genes
Mutant cells
p21
(CDK inhibitor)
GADD45
(DNA repair)
BAX
Expansion and
additional
mutations
G1 arrest
(Apoptosis gene)
pathway
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor

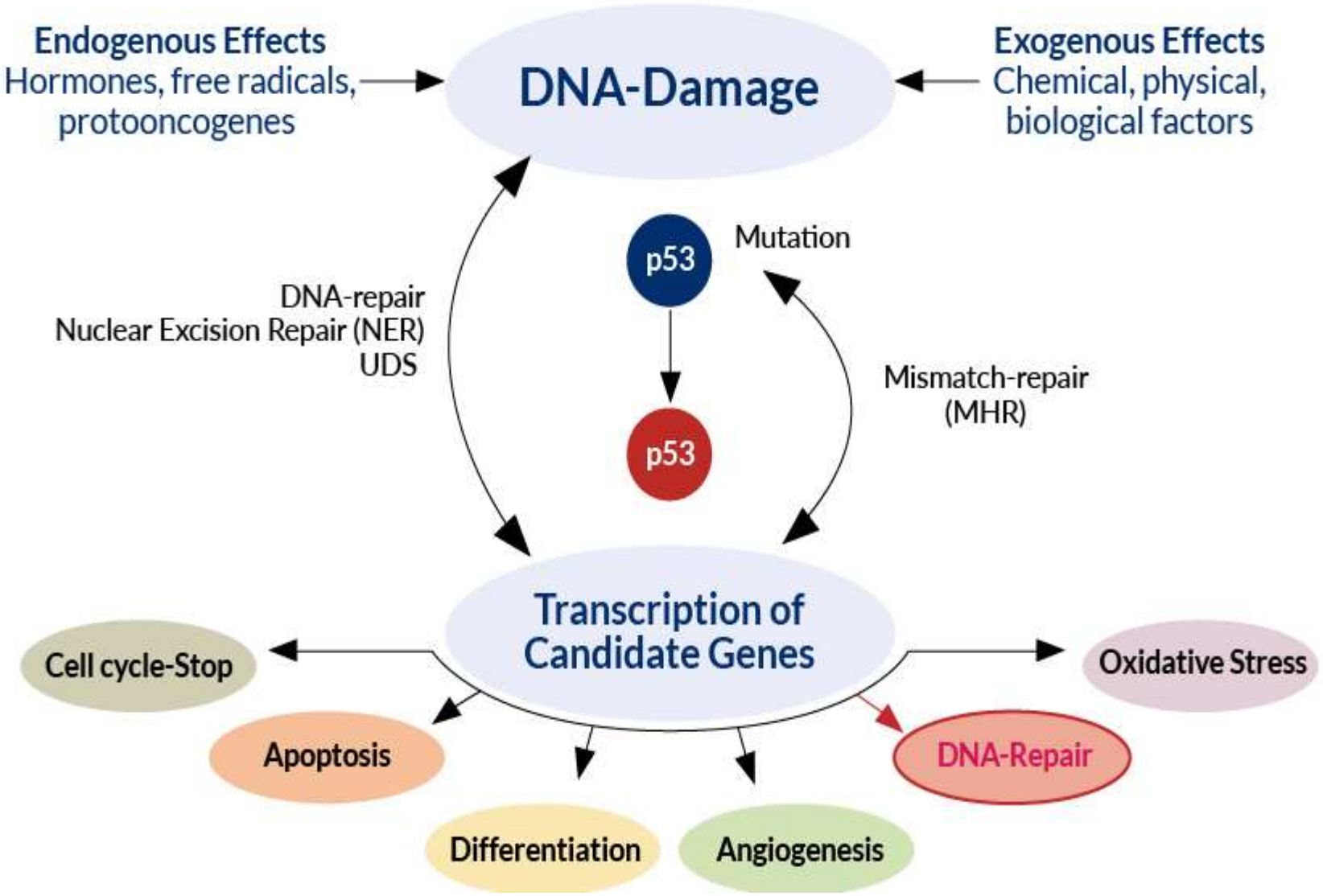
Tumor-Suppressor Genes

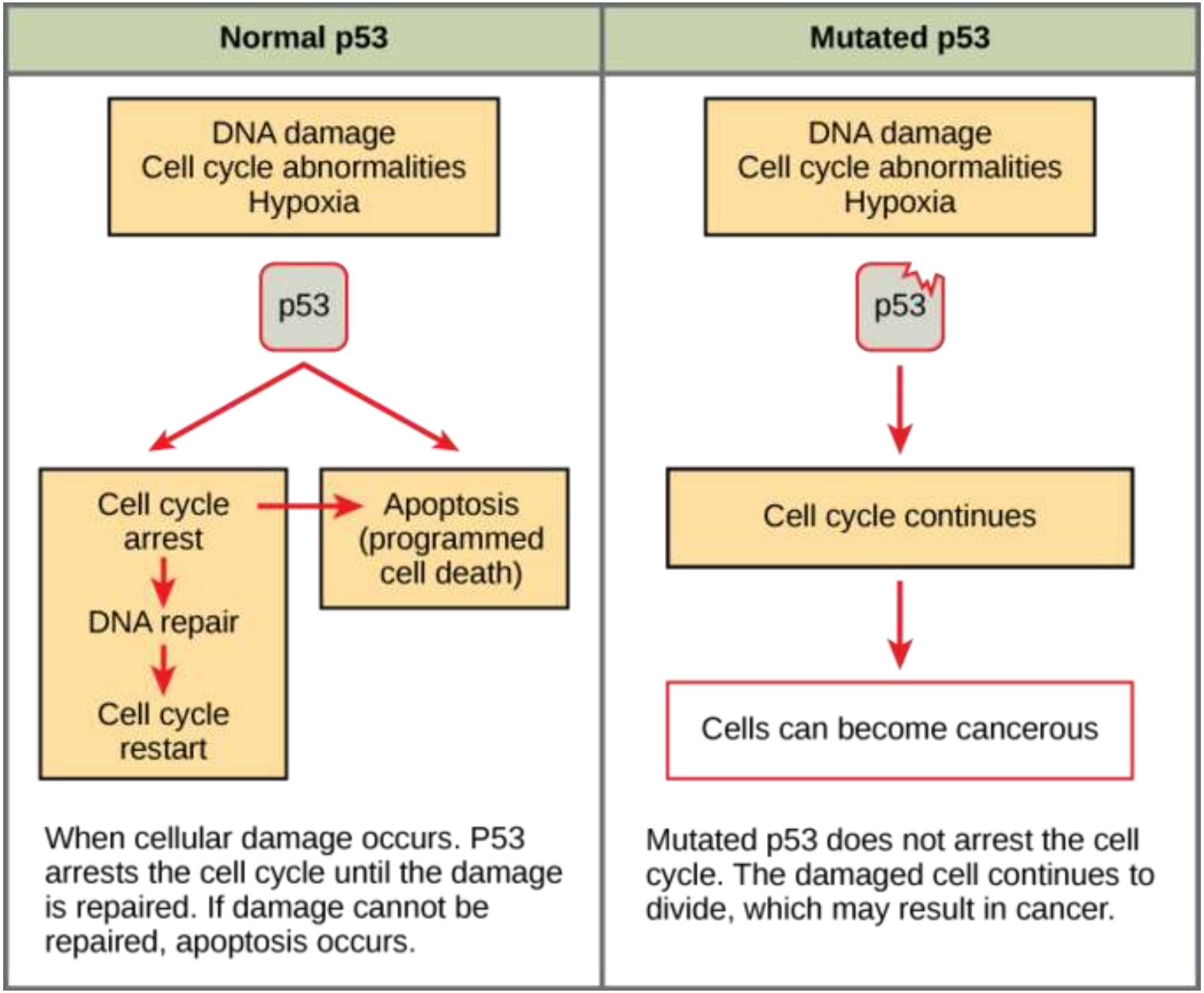





The p53 Tumor Suppressor: The Master Regulator of Diverse Cellular Processes
Stress Input
Oncogene Activation / Viral Infection
DNA Damage
Hypoxia
Replication Stress
Translational Stress
p53
Transcriptional Output
p21
GADD45
FAS/APO-1
BAI1
MDM2
Result
Cell cycle arrest
DNA repair
Apoptosis
Angiogenesis
Auto-regulation


p53 mutation and tumorigenesis
p53
Proliferation
CANCER
Initiation
other
mutations
p53
CANCER
Mutator
Phenotype
other
mutations
CANCER
p53
CANCER
PROGRESSION
Late Event


Endogenous Effects
Hormones, free radicals, protooncogenes
DNA-Damage
Exogenous Effects
Chemical, physical, biological factors
p53
Mutation
DNA-repair
Nuclear Excision Repair (NER)
UDS
Mismatch-repair
(MHR)
p53
Transcription of Candidate Genes
Cell cycle-Stop
Oxidative Stress
Apoptosis
DNA-Repair
Differentiation
Angiogenesis


Normal p53
DNA damage
Cell cycle abnormalities
Hypoxia
p53
Cell cycle arrest
DNA repair
Cell cycle restart
Apoptosis (programmed cell death)
When cellular damage occurs. P53 arrests the cell cycle until the damage is repaired. If damage cannot be repaired, apoptosis occurs.
Mutated p53
DNA damage
Cell cycle abnormalities
Hypoxia
p53
Cell cycle continues
Cells can become cancerous
Mutated p53 does not arrest the cell cycle. The damaged cell continues to divide, which may result in cancer.