Tumor Suppressor Genes
p53 &PTEN

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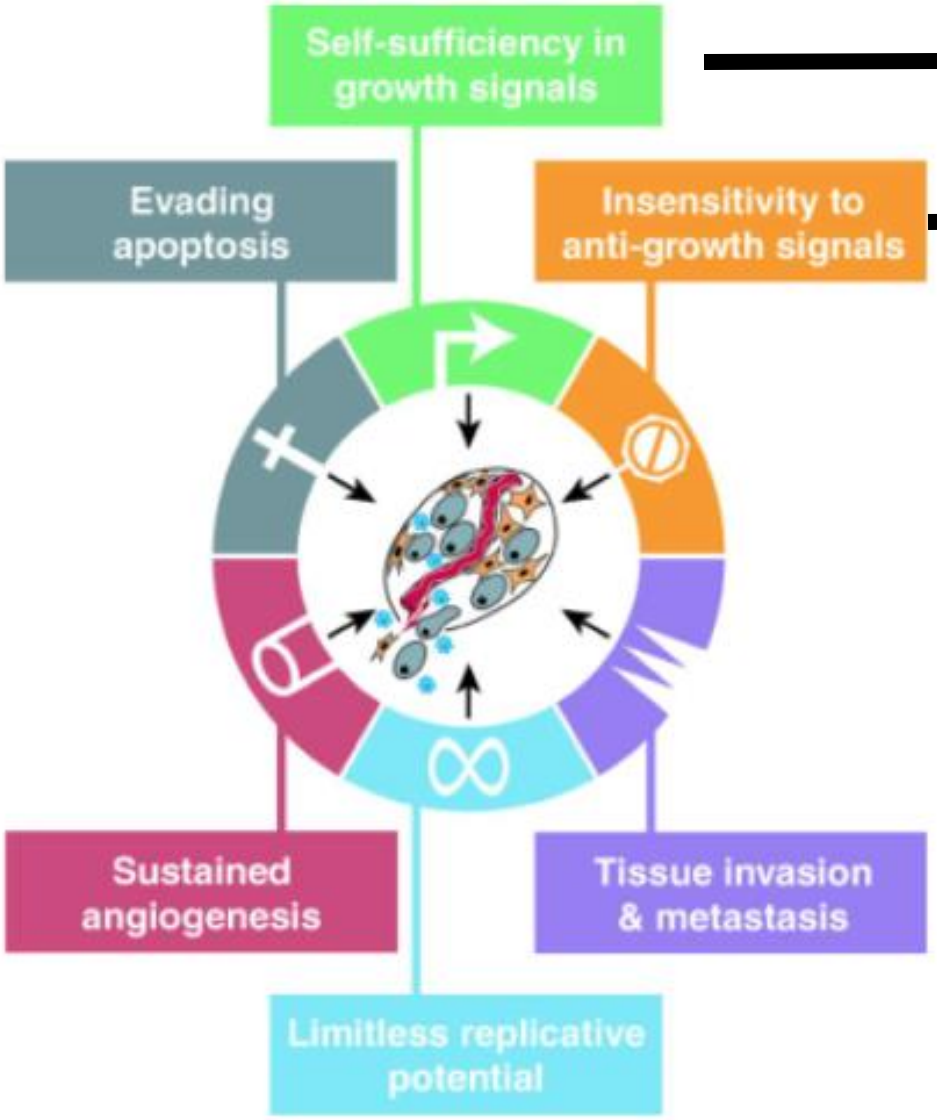
Cancer



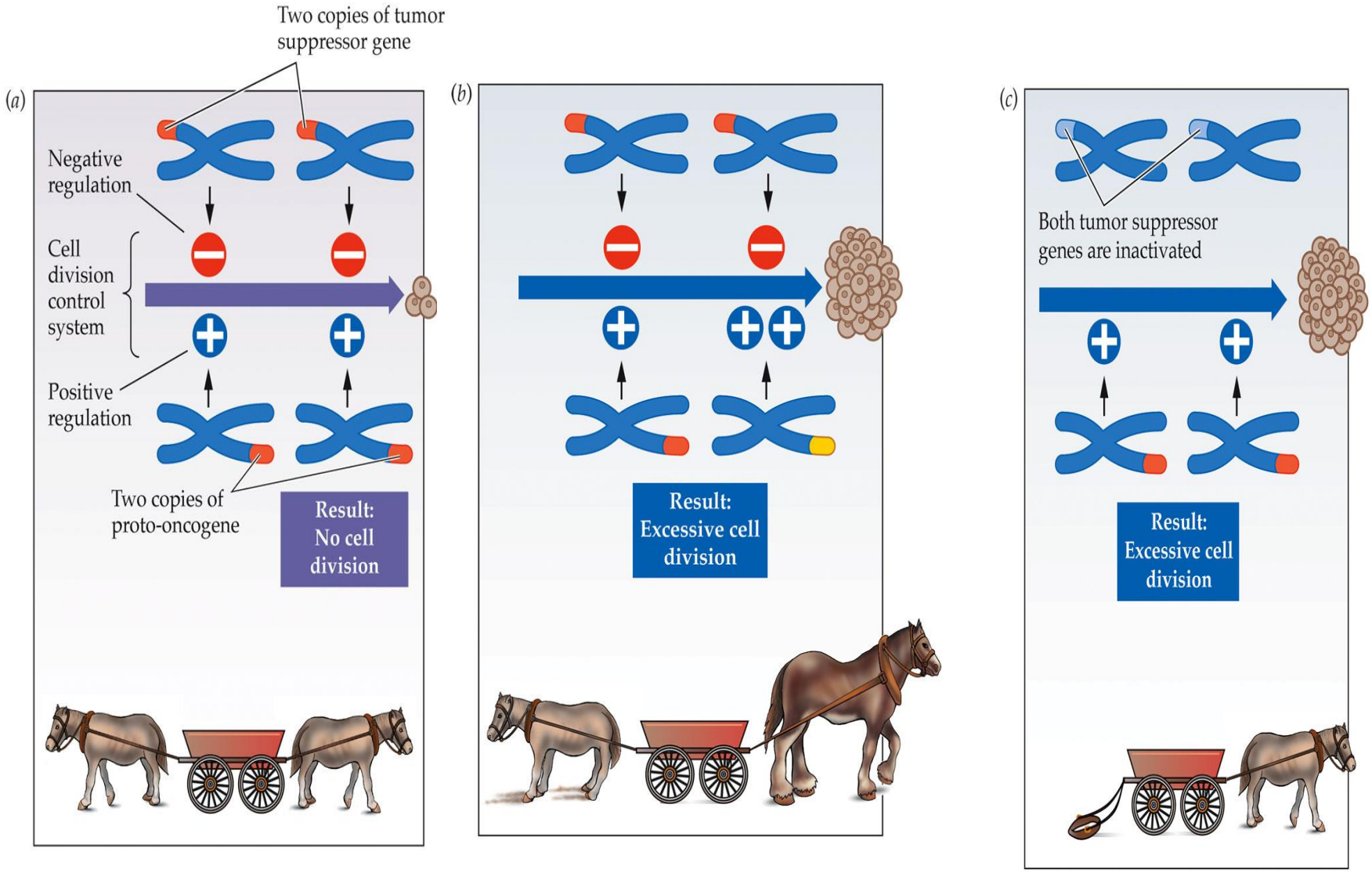
Activated proto-oncogene

Inactivated tumour suppressor gene

For cancer: two classes of cellular genes are targets for mutations

- ***PROTO-ONCOGENES***
- ***TUMOUR SUPRESSOR GENES***

A tumor suppressor gene, or antioncogene, is a gene that protects a cell from one step on the path to cancer. When this gene mutates to cause a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes.



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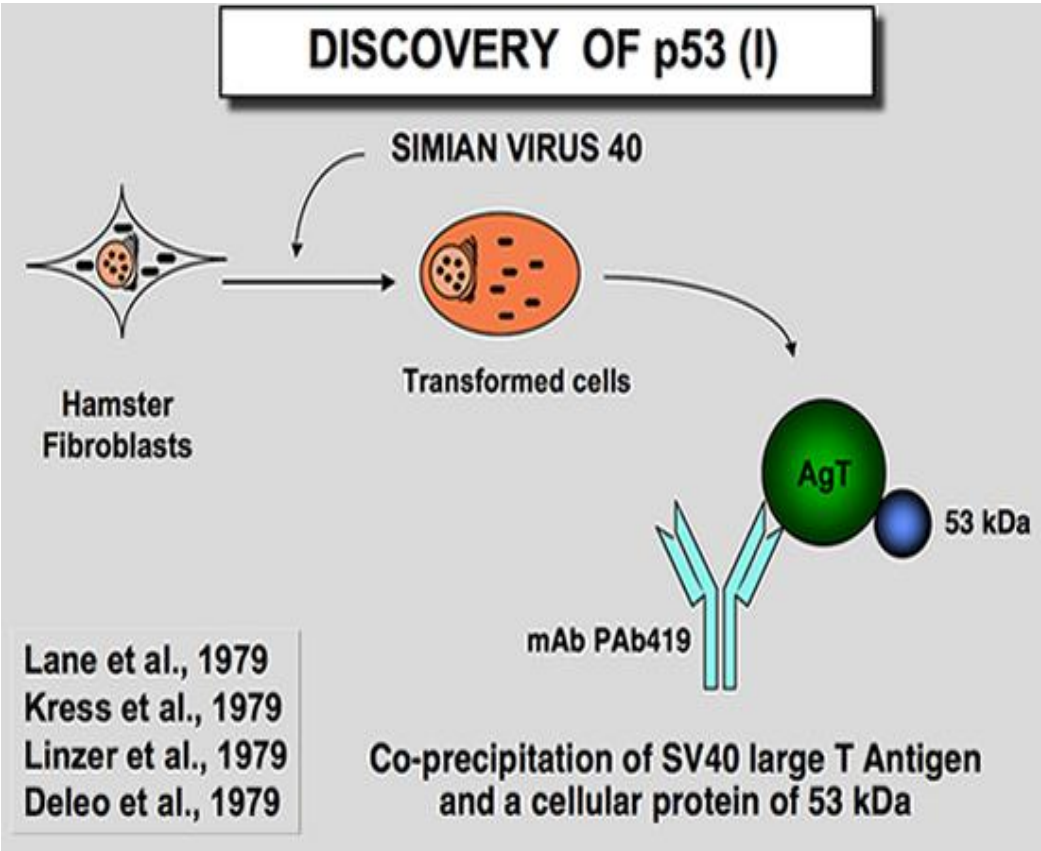
Discovery of p53

The discovery in 1979 of the p53 protein was the culmination of two types of studies involving a virologic approach and a serologic approach.

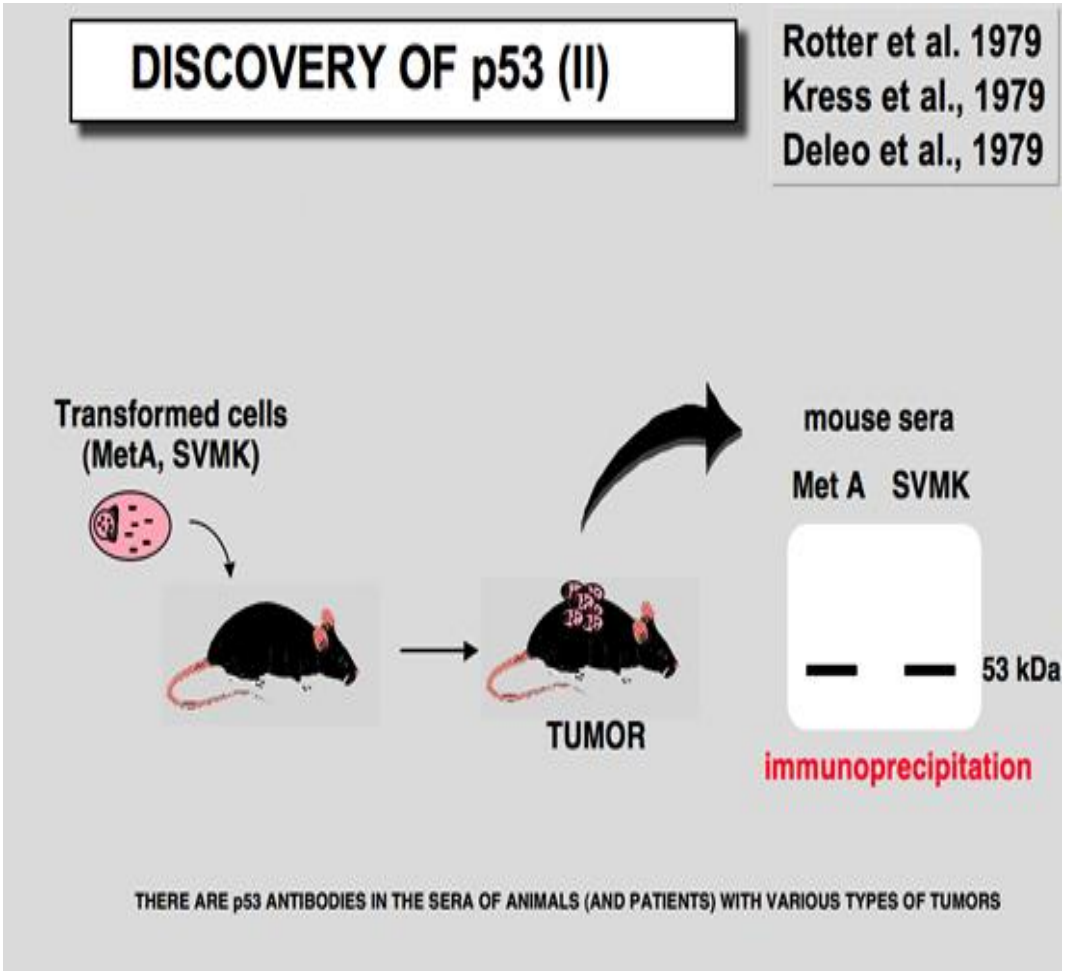


53-kDa protein was overexpressed in a wide variety of murine SV40 transformed cells, but also in uninfected embryonic carcinoma cells.

A partial peptide map from this 53-kDa protein was identical among the different cell lines, but was clearly different from the peptide map of SV40 large-T antigen (Kress et al. 1979; Linzer and Levine 1979).

It was then postulated that SV40 infection or transformation of mouse cells stimulates the synthesis or stability of a cellular 53-kDa protein.

Discovery of p53



- methylcholanthrene-induced tumor cell line such as MethA was directed toward the p53 protein.

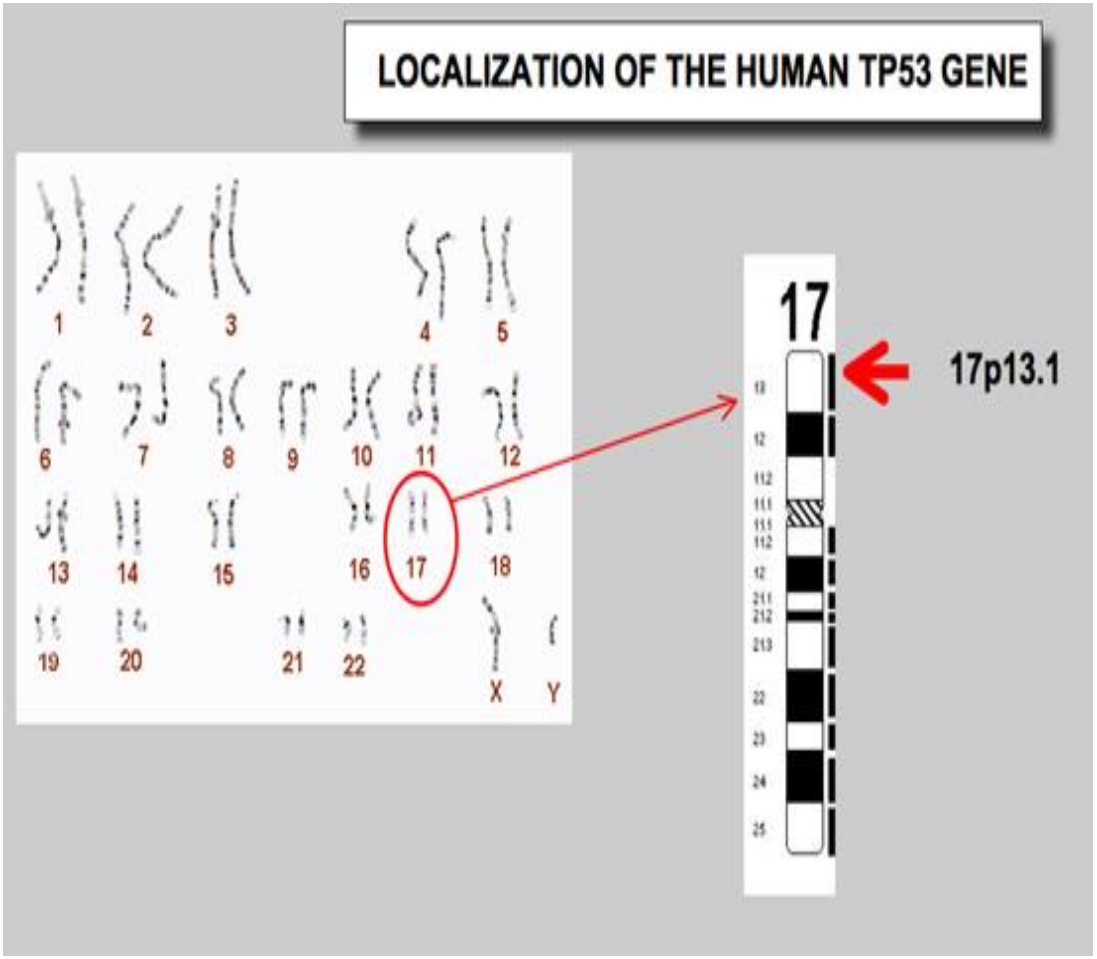
- Later, it was found that animals bearing several types of tumors elicited an immune response specific for p53 (Kress et al. 1979; Melero et al. 1979; Rotter et al. 1980).

- In 1982, Crawford et al. first described antibodies against human p53 protein in 9% of breast cancer patient sera.

No significant clinical correlation was reported, and at that time no information was available concerning mutations of the p53 gene.

p53 gene

The TP53 gene is localized on chromosome 17 (short arm, 17p13), a region that is frequently deleted in human cancer.



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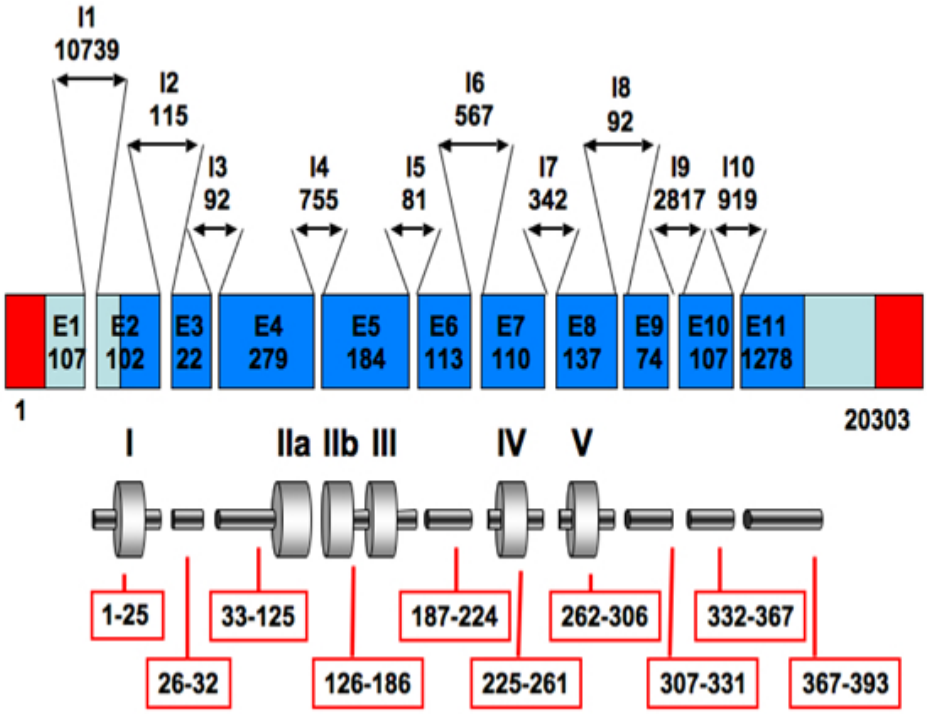
Organization of the human p53 gene



Human p53 is 393 amino acids long and has three domains:

- An N-terminal transcription-activation domain **(TAD)**, which activates transcription factors

- A central DNA-binding core domain **(DBD)**. Contains zinc molecules and arginine amino acid residues.

- C-terminal homo-oligomerisation domain **(OD)**. Tetramerization greatly increases the activity of p53 *in vivo*.

- **11 exons (blue) coding for a 2.2 Kb mRNA. Translation begin in exon 2. Sizes of exons and introns are shown in bp.**

Examples of tumour suppressor genes include:

- RB1 - retinoblastoma susceptibility gene
- WT1 - Wilm's tumour gene
- NF1 - neurofibromatosis type 1 gene
- NF2 - neurofibromatosis type 2 gene
- DCC - involved in colorectal cancer
- BRCA1, BRCA2 - involved in breast cancer

Genetic Mutations That Can Cause Cancer

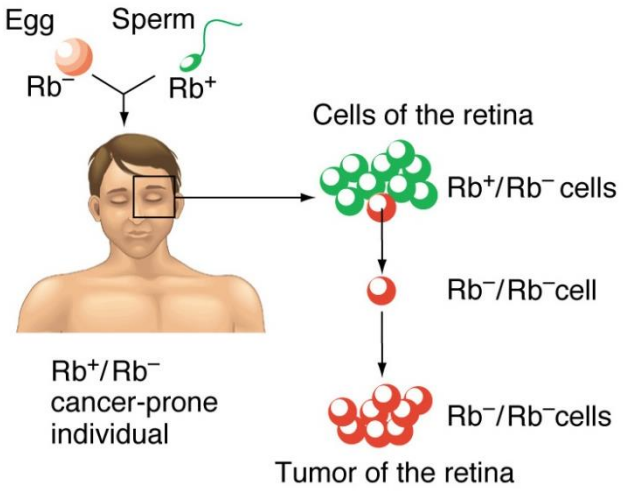
Tumor Suppressor Genes

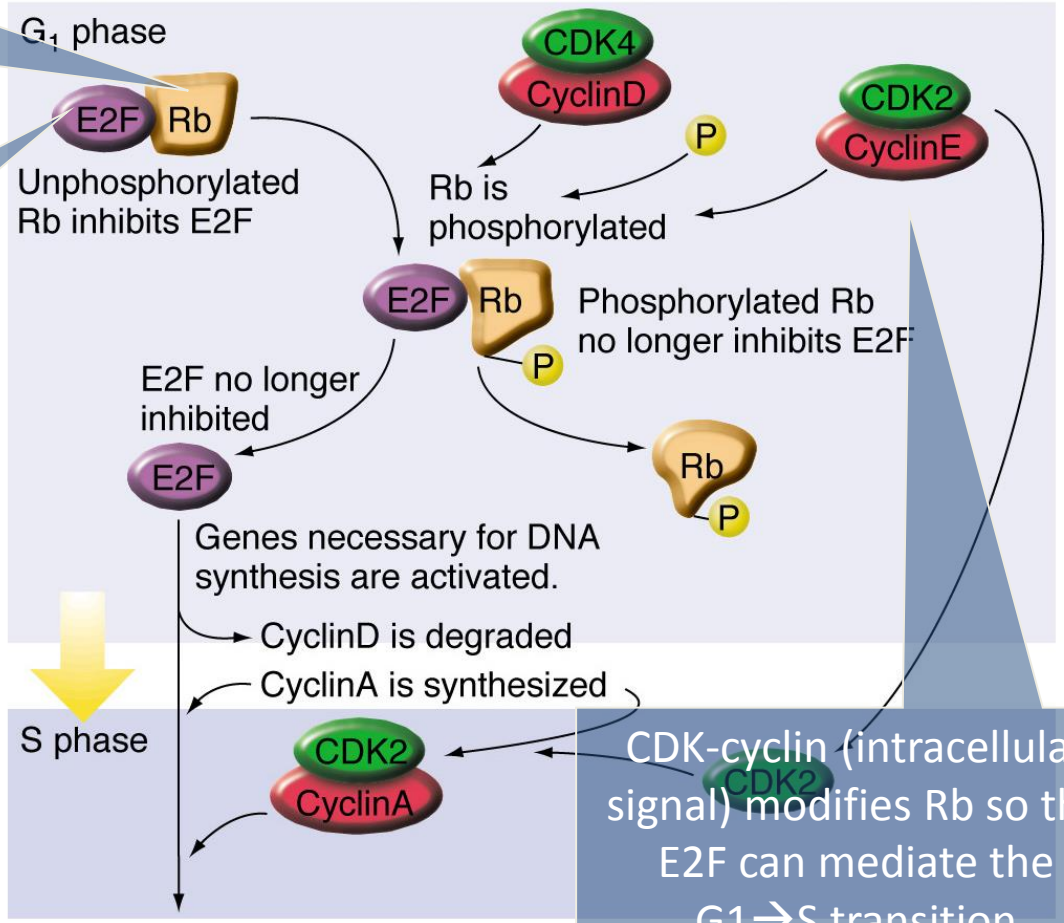
- Genes that inhibit cell division are inactivated.
  - Mutation in a gene that halts the cell cycle in G1 causes retinoblastoma.
  - Mutation in p53, a gene that promotes apoptosis if a cell has damaged DNA, leads to a variety of cancers.
  - Mutation in BRCA1, involved in tumor suppression and DNA repair, leads to inherited breast cancer.

In Normal Cells, the Rb Gene Product Controls the G1→ S Transition

Rb = product of Retinoblastoma gene, inhibits action of E2F until chemically modified

E2F = transcription factor required to activate genes for DNA synthesis





CDK-cyclin (intracellular signal) modifies Rb so the E2F can mediate the G1→S transition

People prone to retinoblastoma have one mutated copy of the Rb gene (Rb-) and one normal copy (Rb^+). Conversion of the Rb^+ copy to Rb^- by mutation leads to uncontrolled growth of retinal cells.

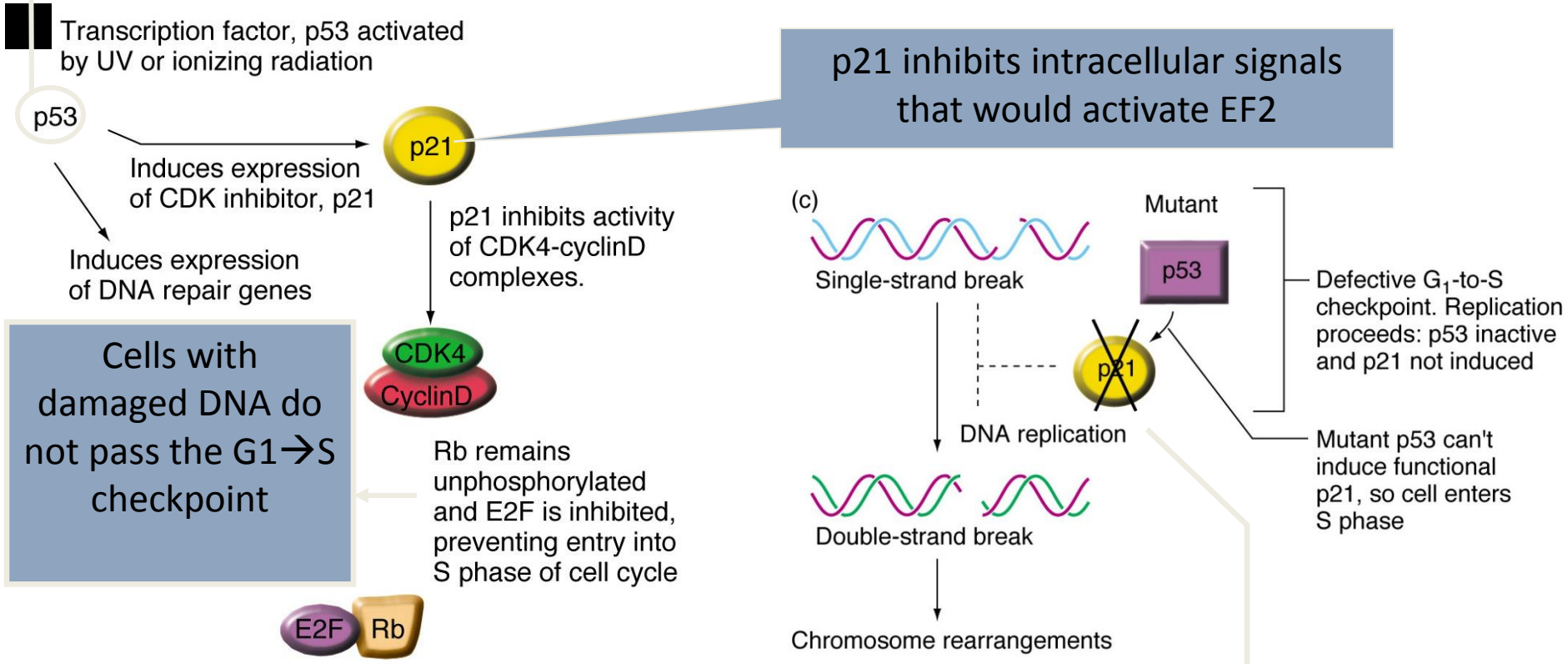
Li-Fraumeni syndrome.

- **THE p53 GENE** like the Rb gene, is a tumor suppressor gene, i.e., its activity stops the formation of tumors.

- If a person inherits only one functional copy of the p53 gene from their parents, they are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. This condition is rare, and is known as Li-Fraumeni syndrome.

p53 = transcription factor that causes p21 to be produced

In Normal Cells, the p53 Gene Product Acts at the G1→ S Checkpoint Preventing Entry Into S Phase If DNA Is Damaged

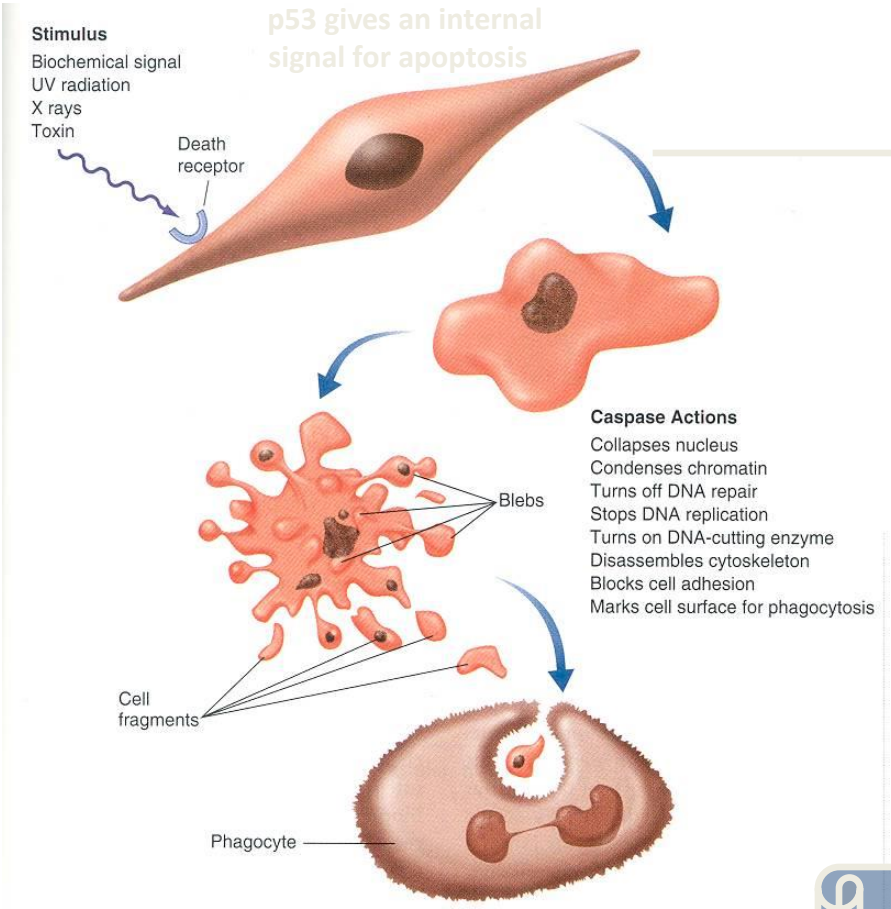


p21 inhibits intracellular signals that would activate EF2

Cells with damaged DNA do not pass the G1→S checkpoint

In cancer cells the mutated p53 gene product no longer stimulates p21 production. Cells will pass the G1→ S checkpoint even when chromosomal damage exists.

In Normal Cells, the p53 Gene Product Stimulates Apoptosis If DNA Damage Cannot Be Repaired

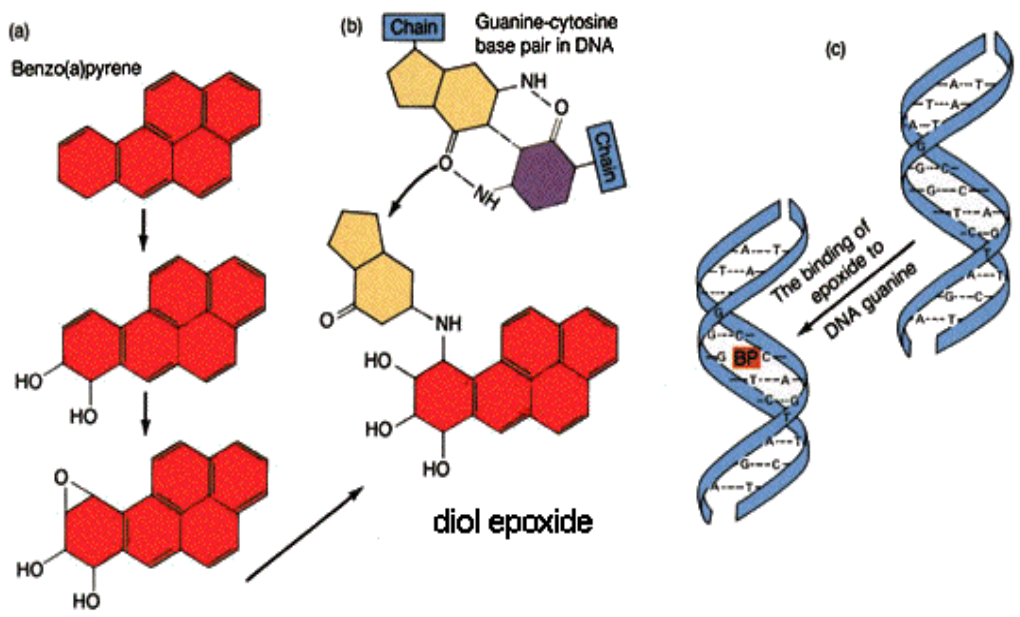


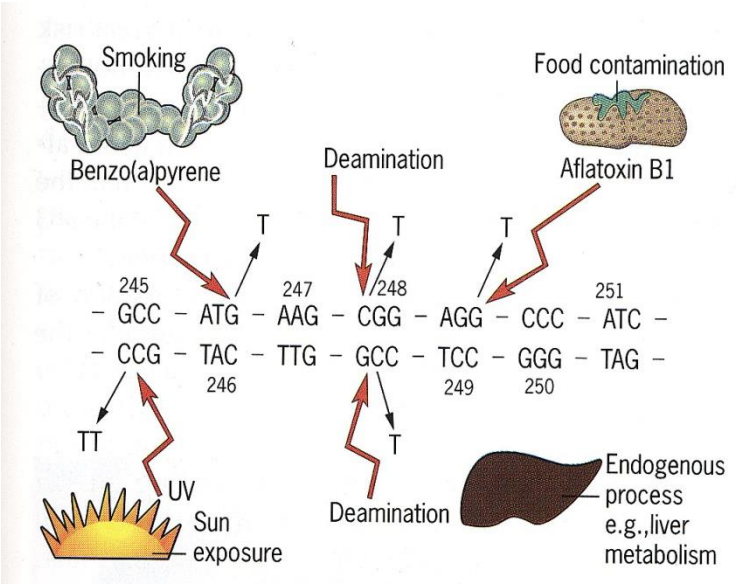
In cancer cells, a mutated p53 gene product no longer initiates self-destruction. Cells with damaged DNA can divide and more DNA damage can be accumulated.

p53 is the most frequently mutated of all known cancer-causing genes, contributing to many types of cancer.

Carcinogens can Damage the p53 Gene

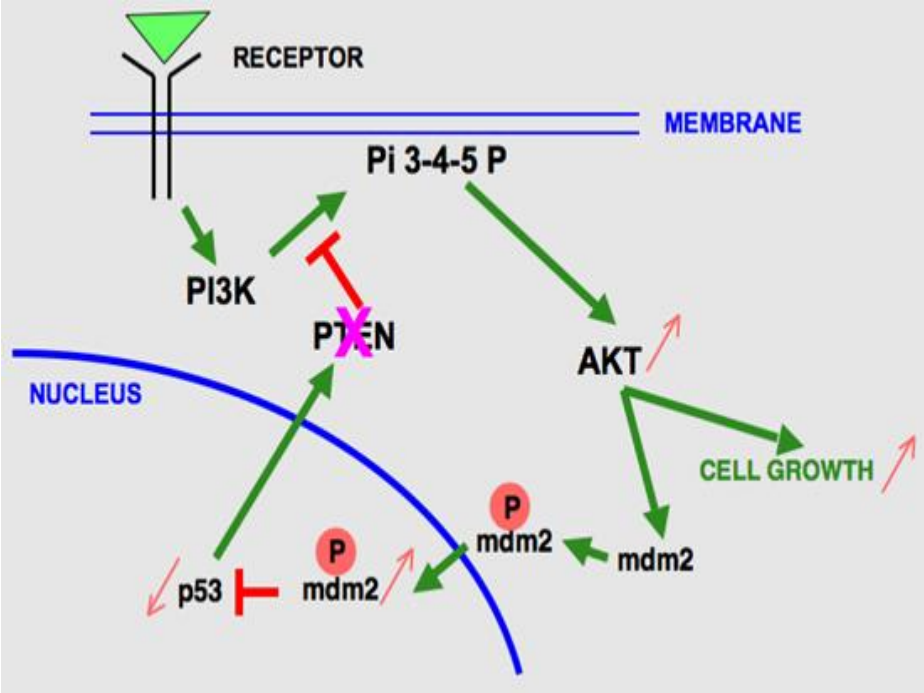
Benzo(a)pyrene, a chemical produced by internal combusion engines and thus common in the environment, is not itself mutagenic.
In the mammalian liver, benzo(a)pyrene is metabolized to **diol epoxide**, which binds covalently to guanine bases, preventing proper base pairing with cytosine bases.
Bulky Addition Products such as diol epoxide or **Aflatoxin B_1** may result in **depurination mutagenesis** and are known to be **carcinogens**.



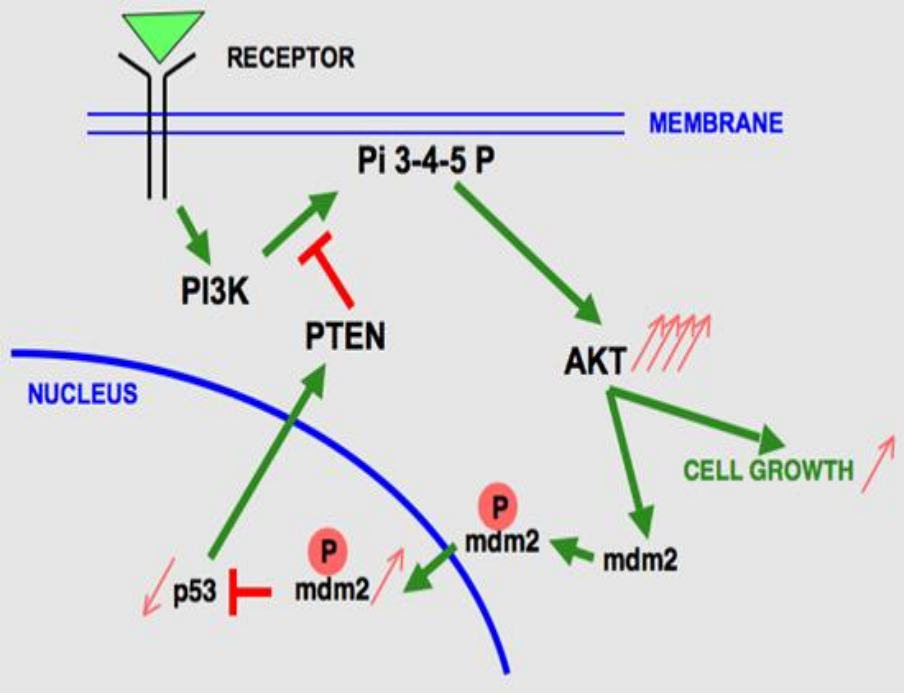


Another factor that influences p53 mutation is Caused by exposure to Ultra Violet Radiation

PTEN mutations



AKT Alterations



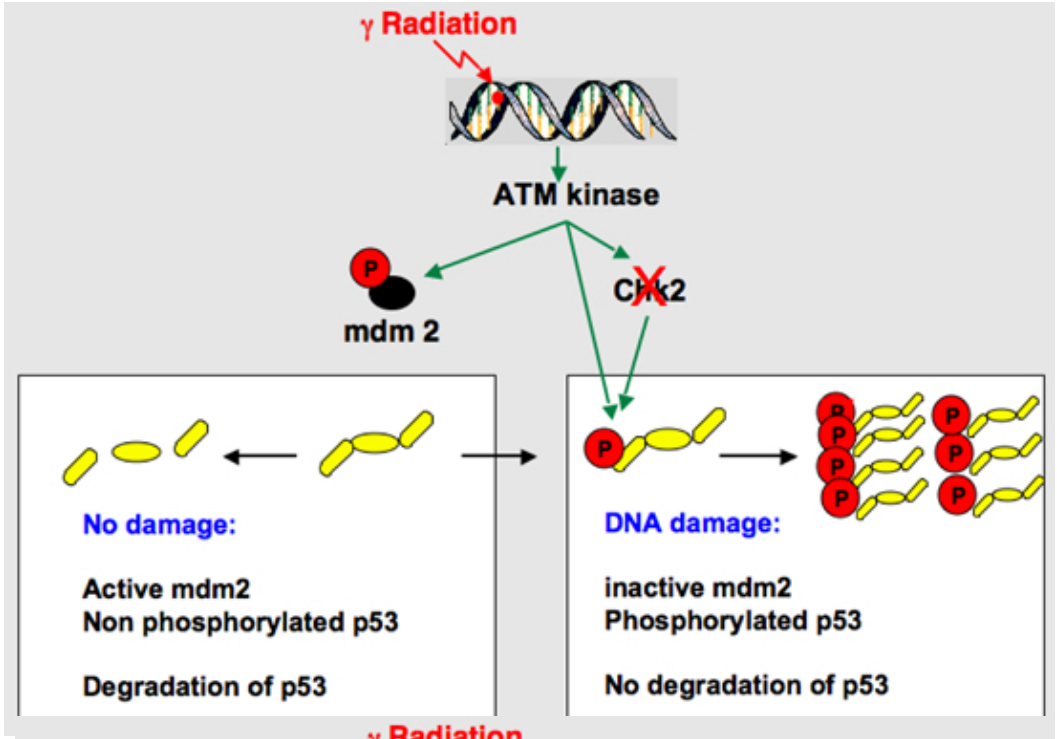
AKT kinase phosphorylates mdm2 protein and induces its migration into the nucleus where it binds and ubiquinates p53. Upon growth factor activation, mdm2 activation through AKT activation ensure proper cell growth.

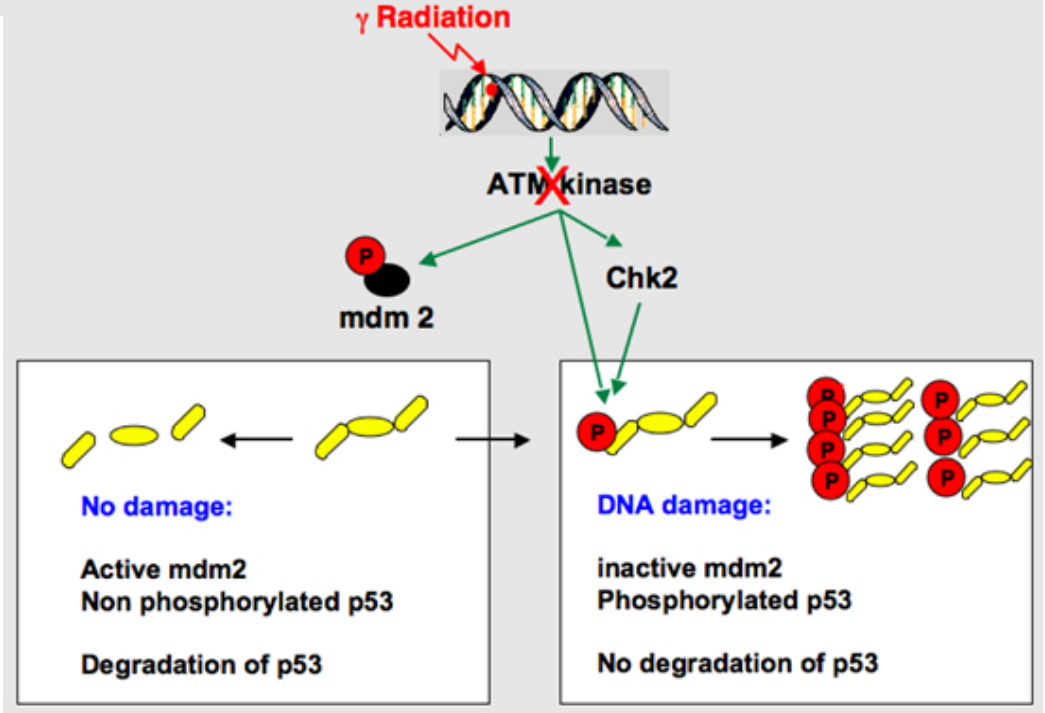
PTEN, a p53 regulated gene, down regulate the AKT pathway.

PTEN deletion leads to an increase of AKT activity, an increase of nuclear mdm2 and impairs p53 response

Although no mutation of AKT has been found in human cancer, constitutive activation of its kinase activity has been observed via deregulation of the upstream pathway

Upstream signaling





DNA damage induced by gamma radiation INDUCED activated ATM phosphorylates p53 on Ser15, CHK2 on Thr68, and murine double minute 2 (*mdm2*) on Ser395.

Activated CHK2 phosphorylates p53 on Ser20. Together, these phosphorylations interfere with p53 binding to MDM2, leading to stabilization and activation of p53.

Mutations of ATM in T-cell leukaemia impair the p53 response after gamma radiation

Mutations of CHK2 are found in Li-Fraumeni like families.

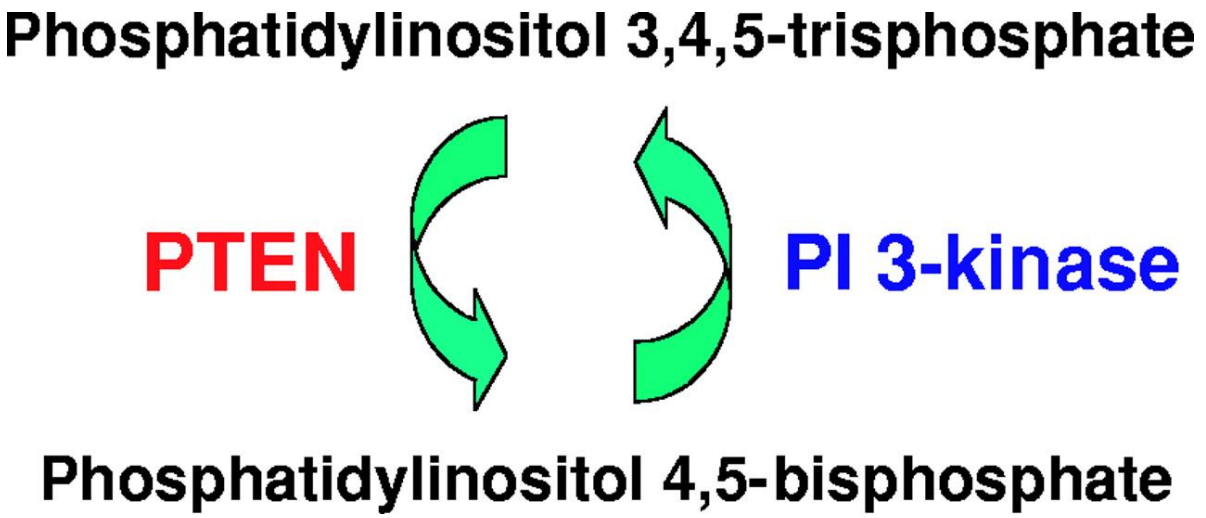
P53 mutations

- Mutations that deactivate p53 in cancer usually occur in the DBD.
- Most of these mutations destroy the ability of the protein to bind to its target DNA sequences, and prevent transcriptional activation of these genes.
- Mutations in the DBD are recessive loss-of-function mutations.
- Molecules of p53 with mutations in the homo-oligomerisation domain (OD) dimerise with wild-type p53, and prevent them from activating transcription. Therefore OD mutations have a dominant negative effect on the function of p53.

Major enzymatic function of PTEN.

PTEN is a tumor suppressor gene

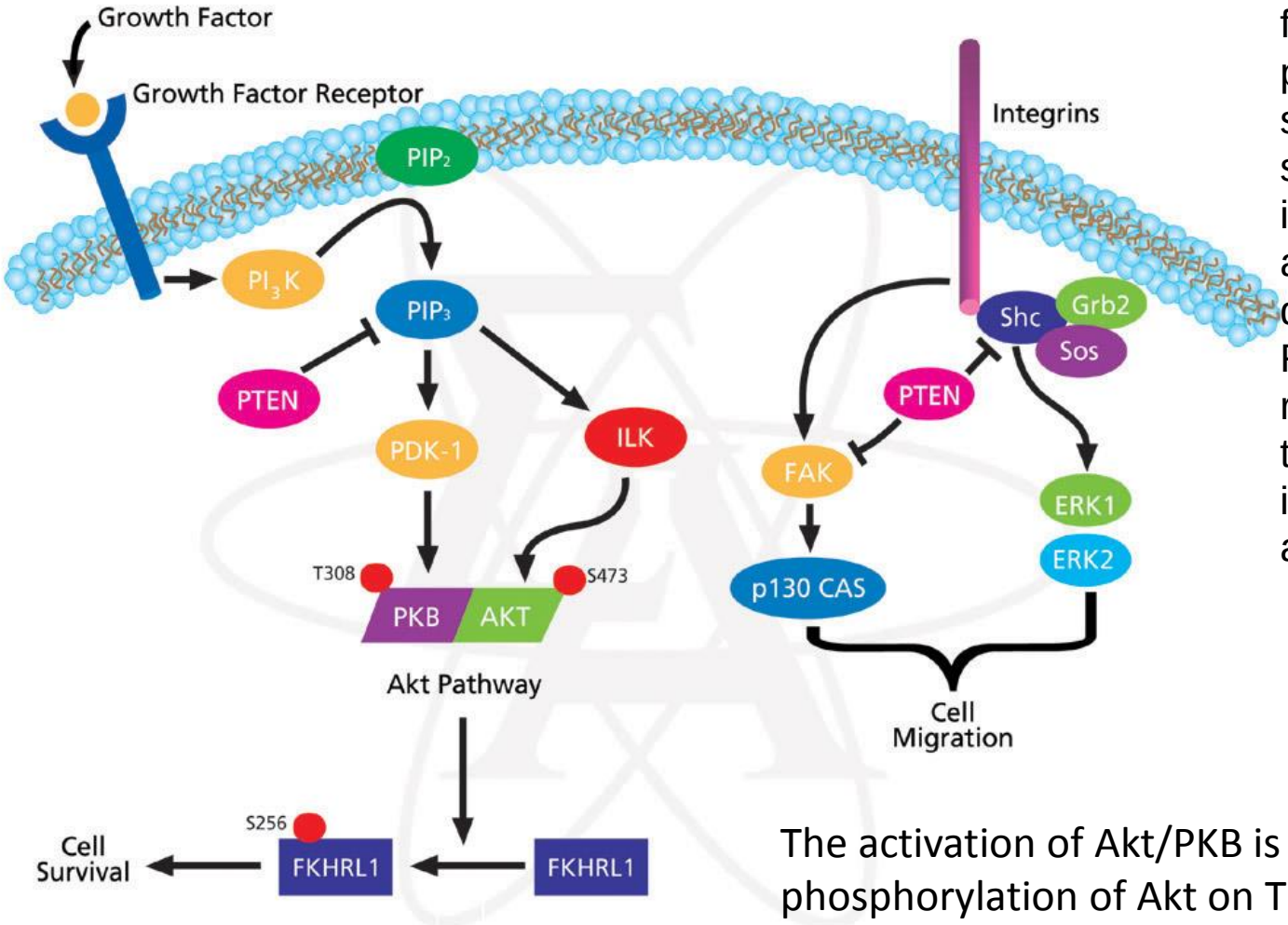
PTEN opposes action of PI3K by dephosphorylation



Yamada K M , Araki M J Cell Sci 2001;114:2375-2382

PTEN Pathway

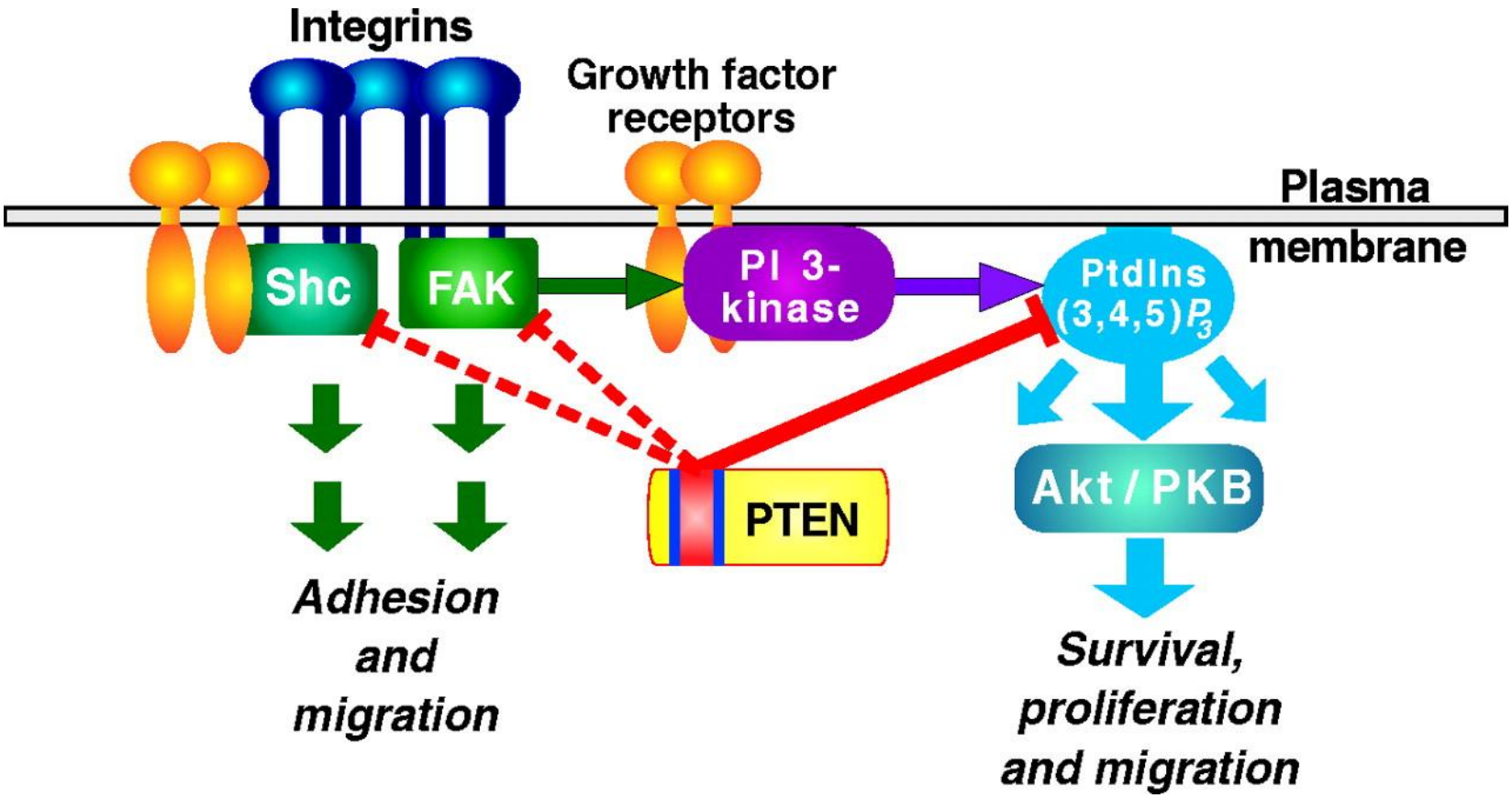
SIGMA-ALDRICH



PTEN also inhibits growth factor (GF)-induced Shc phosphorylation and suppresses the MAP kinase signaling pathway. PTEN interacts directly with FAK and is able to dephosphorylate activated FAK. PTEN-induced down-regulation of $p130^{CAS}$ through FAK results in inhibition of cell migration and spreading.

The activation of Akt/PKB is regulated by the phosphorylation of Akt on Thr^{308} and Ser^{473} by phosphoinositide-dependent kinase (PDK) and integrin-linked kinase (ILK), respectively.

Reported sites of action of PTEN.



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Thanks for your Attention

Acknowledgement

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- Thanks are due to all those original contributors and entities whose pictures used for making this presentation.