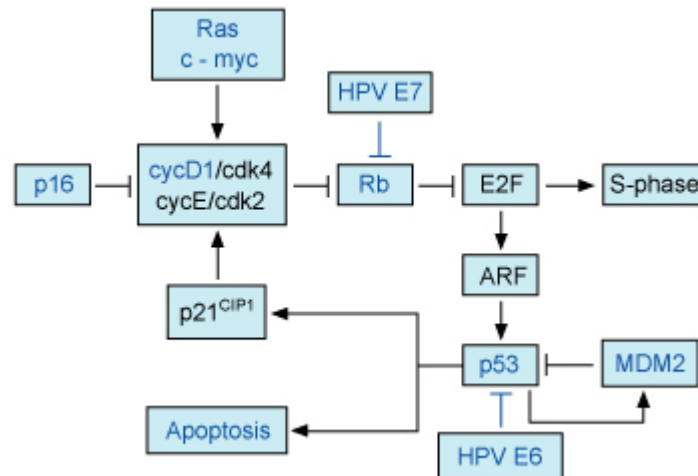


## The retinoblastoma and p53 pathways are inactivated in most, if not all, cancer cells



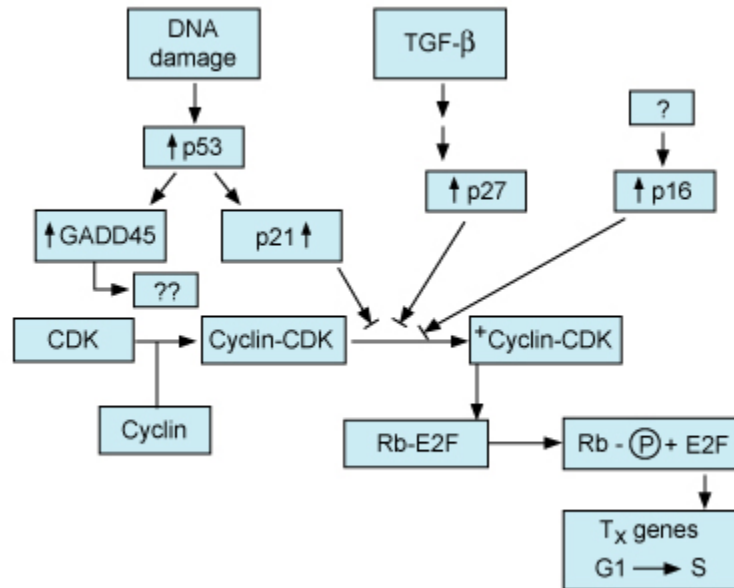
(Figure by MIT OCW.)

### ***How p53 and Rb pathway function may be disrupted in cancer cells***

Components of the pathway which are found altered in human cancers are shown in red on the diagram above.

- p53 and Rb themselves may be inactivated by gene mutation (loss of both copies or also as in familial retinoblastoma and Li-Fraumeni syndrome where there are inherited mutations in one copy of Rb or p53 gene respectively. **Alternatively, inactivation of the p53 and Rb proteins via the action of HPV oncoproteins E6 and E7 respectively.**
- Gene mutation may lead to the production of "activated Ras" which signals continuously. Gene amplification or overexpression may lead to overproduction of Myc, again promoting the cell cycle.
- Overexpression of cyclin D1 (eg by gene amplification) is found in some tumours.
- p16 loss by gene mutation (both copies) - note familial melanoma syndrome where there is an inherited mutation in one copy of p16 gene.
- Overexpression of MDM2 protein (E3 ligase controlling the levels of p53), eg by gene amplification, will lead to increased instability of p53 protein.

- A mutation in the apoptotic pathway downstream of p53 will block the induction of programmed cell death by p53.



(Figure by MIT OCW.)

# Human papilloma virus (HPV)

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**HPV (human papilloma virus)** infects epithelial cells causing warts. It is a sexually-transmitted disease and can form these lesions in the anogenital tracts (known as condyloma accuminata). There are several forms of HPV that vary on their malignancy. Some only produce the warts (as HPV-6 and -7) whereas others, such as HPV-16 and -18 are associated to malignant lesions such as **cervical cancer**. These malignant forms encode the oncoproteins E6 and E7 both able to bind cell regulatory proteins: p53 (E6) and pRB (E7).

(Image removed due to copyright considerations.)

In the case of **E6**, this oncoprotein is able to interact with a cellular E3 protein ligase (**E6-AP**) so it ubiquitinates p53. **E6 enhances p53 degradation**, preventing the infected cell from undergoing apoptosis so the virus can then ensure its own proliferation. Similarly, E7 also prevents programmed cell death by destabilization of pRB.

(Image removed due to copyright considerations.)

That's one of many reasons why it's so important to use sexual protection and to go through regular Pap smear check-ups if you are a woman. Direct contact with the warts can transmit the disease. Men can also develop anal cancer through HPV infection.

**But if E6-AP doesn't normally act on p53..what is its actual role in cells??**

## **"Angelman syndrome"**

(Image removed due to copyright considerations.)

The E3 ligase E6-AP is actually encoded by the human *UBE3A* gene. *UBE3A* is expressed biallelically in most human tissues, but is genetically imprinted in the brain of humans and mice where only the maternal allele is expressed in the hippocampal and cerebellar neurons. Loss of function mutations in the maternal gene, paternal uniparental disomy, and imprinting mutations that prevent expression of both alleles result in Angelman syndrome (AS). An overabundance of the proteins targeted by functional E6-AP is the cause of the neurological defects observed in AS patients. Angelman syndrome is a neurological disorder characterized by severe congenital mental retardation, unusual facial appearance, and muscular abnormalities. Symptoms of Angelman syndrome include unstable jerky gait, hand flapping, unusually happy demeanor, developmental delay, lack of or diminished speech, and microcephaly (small head). Epilepsy may develop in the early years of life, however it may decrease with age. Patients may also have balance problems.

Among other roles, E6-associated protein (E6-AP/*UBE3A*) directly interacts with and coactivates the transcriptional activity of the human progesterone receptor (PR) in a hormone-dependent manner. E6-AP has also been found to regulate the Src family of nonreceptor tyrosine kinases. **The Src family of nonreceptor tyrosine kinases are important regulators of a variety of cellular processes, including cytoskeletal organization, cell-cell contact, and cell-matrix adhesion. Activation of Src family kinases also can induce DNA synthesis and cellular proliferation; therefore, tight**

regulation of their kinase activities is important for the cell to maintain proliferative control.

## “Fanconi anemia”

Fanconi anemia (FA), named for Swiss pediatrician, Guido Fanconi, is one of the inherited anemias that leads to bone marrow failure (aplastic anemia). It is a recessive disorder: if both parents carry a defect (mutation) in the same FA gene, each of their children has a 25% chance of inheriting the defective gene from both parents. When this happens, the child will have FA.

There are at least seven FA genes: A, C, D2, E, F, G and BRCA2. Six of these genes have been cloned. These six account for more than 85% of the cases of Fanconi anemia. Mutations in FA-A and FA-C account for FA in 76% of patients worldwide.

FA occurs equally in males and females. It is found in all ethnic groups. Though considered primarily a blood disease, it may affect all systems of the body. Many patients eventually develop acute myelogenous leukemia (AML). Older patients are extremely likely to develop head and neck, esophageal, gastrointestinal, vulvar and anal cancers. Patients who have had a successful bone marrow transplant and, thus, are cured of the blood problem associated with FA still must have regular examinations to watch for signs of cancer. Many patients do not reach adulthood.

Fanconi anemia patients are usually smaller than average. FA usually reveals itself before children are 12 years old, but in rare cases no symptoms are present until adulthood. Patients may feel extreme fatigue and have frequent infections. Nosebleeds or easy bruising may be a first sign. Blood tests may reveal a low white cell, red cell or platelet count or other abnormalities. Sometimes myelodysplasia or AML is the first sign of FA.

FA **sometimes** is evident at birth through a variety of physical defects. These may include any of the following:

- Thumb and arm anomalies: misshapen, missing or extra thumbs or an incompletely developed or missing radius (one of the forearm bones).
- Skeletal anomalies of the hips, spine, or ribs.
- Kidney problems, including missing or horseshoe kidney.
- Skin discoloration (café-au-lait spots); portions of the body may have a suntanned look.
- Small head or eyes.
- Mental retardation or learning disabilities.
- Low birth weight
- Gastrointestinal difficulties.
- Small reproductive organs in males.
- Defects in tissues separating chambers of the heart.

The definitive test for FA at the present time is a chromosome breakage test: some of the patient's blood cells are treated, in a test tube, with a chemical that crosslinks DNA.

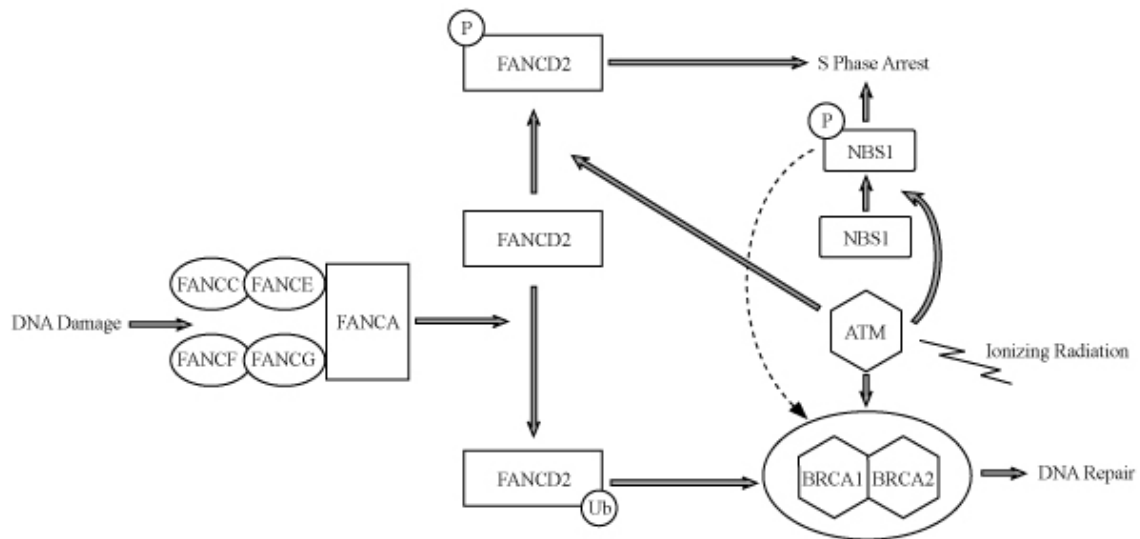
Normal cells are able to correct most of the damage and are not severely affected, whereas FA cells show marked chromosome breakage. There are two chemicals commonly used for this test, DEB (diepoxybutane) and MMC (mitomycin C). These tests can be performed prenatally on cells from chorionic villi or from the amniotic fluid.

While the total number of FA patients is not documented worldwide, scientists estimate that the carrier frequency (carriers are people carrying a defect in an FA gene, whose matching FA gene is normal) for FA is somewhere between 1 in 600 and 1 in 100. The International Fanconi Anemia Registry managed by Dr. Arleen Auerbach at The Rockefeller University maintains case data on at least 3,000 patients.

People with Fanconi anemia often develop leukemia and other cancers. In fact, Fanconi anemia patients have a much greater risk of developing acute myelogenous leukemia (AML) than people without Fanconi anemia. Leukemia is a malignancy of the blood system in which the bone marrow produces vast quantities of immature white cells called "blasts." The blasts can proliferate rapidly and suppress the development of healthy blood cells needed for effective functioning of the patient's body. If untreated, leukemia results in uncontrollable infections and bleeding, and death. The type of leukemia that FA patients are likely to develop, AML, is a particularly aggressive type, usually found in older people. AML is difficult to treat successfully, especially in FA patients, who are very sensitive to the toxic drugs used to suppress the leukemia.

Fanconi anemia patients have an extremely high risk of developing cancers in areas of the body in which cells normally reproduce rapidly, such as the mouth, esophagus, the intestinal and urinary tracts, the anus and the reproductive organs. FA patients may develop these cancers at a much earlier age than people without Fanconi anemia. Patients who have had a successful bone marrow transplant and, thus, are cured of the blood problems associated with FA, still must have regular examinations to watch for signs of cancer.

(Images removed due to copyright considerations.)



(Figure by MIT OCW.)

Fanconi Anemia has 8 identified complementation groups (A, B, C, D1, D2, E, F, and G) and genes for at least 7 of these groups have been identified. Fanconi anemia genes, FancB and FancD1, have been identified as the Early Onset Breast Cancer gene BRCA2. Five of the Fanconi Anemia genes (FancA, FancC, FancE, FancF, and FancG) form a complex which interacts with DNA and leads to the mono-ubiquitination of the FancD2 protein. Through an association with BRCA1 and BRCA2 in nuclear loci (represented by the light blue area in the diagram) this leads to activation of the processes that lead to DNA repair. The ATM kinase can be activated by ionizing radiation, which in turn activates many targets. One of these, the FancD2 protein, is phosphorylated by ATM, which then leads to S phase arrest. An additional link in this pathway includes the phosphorylation by ATM of the protein encoded by the gene of the Nijmegen Breakage Syndrome (NBS1) and BRCA1. The NBS1 protein is part of a complex which, in turn, also leads to phosphorylation of FancD2 by ATM. NBS1 appears to have two independent functions, one in inducing S-phase arrest where FancD2 is not required and the second in interacting with FancD2 in promoting DNA repair (see dashed arrow in diagram). Thus, FancD2 is at the cross roads of two pathways -- one leading to S phase arrest which functions from ATM through NBS 1 and associated proteins and the other in response to DNA damage acting through the Fanconi complex