Tumor Suppressor Genes

Like proto-oncogenes, **tumor suppressor genes** are involved in various processes, including cell cycle regulation and the stimulation of apoptosis. As previously discussed, retinoblastoma protein (pRb), p53, and p21 are involved in regulating cell cycle checkpoints. Mutations in the gene that encodes for the p53 protein are found in half of all cancers. Tumor suppressor genes undergo loss-of-function mutations, and this leads to a loss of cell cycle regulation. This results in the cell rapidly progressing through the cell cycle, with the possibility for mutations to occur in the absence of DNA repair.

Cells that would normally pause their cell cycle under the influence of tumor suppressor genes are now no longer stopped from moving forward with mitosis. For example, the anaphase promoting complex (APC) regulates the progression from metaphase of mitosis, where the chromosomes are aligned, into anaphase, where they are separated. If proteins making up this complex lose function due to mutations in the genes encoding these proteins, a cell may not properly attach the mitotic spindle (microtubules) to the centromeres of the chromosomes during metaphase of mitosis. And, when the cell transitions to anaphase, the chromosomes may not be appropriately distributed. There are multiple other ways that chromosomes may be altered—such as nondisjunction and chromosomal translocations that can also lead to mutations; however, we will not discuss these other types of mutations here.[74]

Previously, it was thought that for cancer to develop, both copies of a tumor suppressor gene had to be mutated. This two-hit hypothesis was originally studied in the retinoblastoma tumor suppressor gene in the retina of the eye, which results in retinoblastoma, a pediatric eye cancer. Sometimes the first hit in the two-hit hypothesis is a genetic mutation that was inherited. The second hit can be caused by environmental factors. For example, a person who has an inherited mutation and then gets a second mutation due to UV light (sun) exposure may then develop cancer. It is now generally believed that the development of cancer requires an accumulation of mutations that typically include mutations in tumor suppressor genes and oncogenes and possibly even DNA repair genes.[75]

As with mutated proto-oncogenes, a car can offer us a good analogy to understand mutations in tumor suppressor genes. Tumor suppressor genes are like the brakes on your car. If your brakes are not working, the car will not stop. Similarly, if the tumor suppressor genes are mutated, the cell cycle does not stop.

DNA Repair Genes

Although the process of DNA replication is very accurate, mistakes will be made, and they must be corrected. Additionally, DNA may become damaged due to exposure to UV light or X-ray radiation, for example. Damage may involve incorrect **nucleotide** sequences in the DNA or may involve single-stranded or double-stranded breaks in the DNA. Single-stranded breaks happen most often, with as many as 55,000 breaks a day. In a single day, there are as many as 70,000 total incidences of damage that occur to our DNA—this leads to a lot of needed repair![76]

If an error is made while copying the DNA, a method known as proofreading in used. This is like when you are typing, and you realize immediately that you pressed the wrong key. You just backspace and fix it right away. In paper writing, sometimes you miss a mistake and must go back and fix it later in your writing and editing process. Similarly, DNA replication also involves identifying and fixing errors later in the process. Mismatch repair is used in fixing errors in replication where the wrong nucleotide was added. Mismatch repair occurs immediately after replication.

When DNA is being copied during DNA replication, each strand is used as a template to make a new strand that is anti-parallel and complementary to the template strand. For example, adenine on the template strand forms two hydrogen bonds with thymine on the complementary strand, and cytosine on one strand forms three hydrogen bonds with guanine on the complementary strand. This makes the DNA replication semiconservative. If an error is made and the wrong pairing is formed, mismatch repair will help to correct this error.[77] Some of