16.5: Tumor Suppressor Genes

Tumor suppressor genes normally do what would be expected from their name. Whereas the oncogenes mostly drive the cell cycle forward, the tumor suppressor genes' primary functions are to temporarily stall the cell cycle so that DNA repair mechanisms can have time to work. However, if repair is unsuccessful after a few attempts, the tumor suppressor gene product may then trigger apoptosis rather than allow a damaged cell to replicate and potentially create another genetically damaged cell. Thus, the presence of an oncogene in a cell will not necessarily lead to development of cancer because a functioning tumor suppressor gene might prevent the cell from replicating. Equally, if a tumor suppressor gene is knocked out but there is no oncogene present, then the cell is unlikely to be immediately cancerous because although a cellular “emergency brake” is nonfunctional, if there is nothing to drive the cell through its cycle any faster or more frequently than usual, then the “brake” is never needed anyway.
Figure \(\PageIndex{14}\). Tumor suppressor gene mutations can lead to cancer.

Like oncogenes, tumor suppressor genes can work (or not work, as would be the case in cancer) in several ways. Here is an example with the breast cancer-associated genes, BRCA1 and BRCA2. These gene products are involved in DNA repair (chapter 7). When BRCA1 or BRCA2 is knocked out, the cell loses its ability to use that DNA repair pathway. There are other repair pathways, and even if there weren’t there may not be any serious lesions to the DNA, so the cell could behave normally for the time being. What is important from a cancer standpoint, is that each safety/repair mechanism that is lost increases the likelihood that an additional mutation may cause the cell to become cancerous.

Figure \(\PageIndex{15}\). Cell cycle arrest due to DNA damage. ATM detects the double strand break, and activates Chk2 and BRCA1. Chk2 also activates BRCA1, which with BRCA2 forms a repair complex. However, if BRCA1 is not immediately available, the cell needs to go into a holding pattern until one becomes available. Therefore, Chk2 activates p53, which induces transcription of p21, which binds to cdk, preventing association with cyclin, and thus preventing cell cycle progress. If this continues for long, some of the p53 activates transcription of Bax, which will induce apoptosis to
kill off a cell with damaged DNA. When p53 is hit with a loss of function mutation, the cell does not die, and it attempts to replicate even with damaged DNA, which may lead to more mutations in the subsequent generation, if it is successful in reproduction. Without p53, the accumulation of errors in successive generations increases. The mechanism of buying time for the cell to make repairs is not limited to the ATM-BRCA situation. The left side of the Figure shows another response to DNA damage that leads to cell cycle arrest.

It should be clear now how recessive loss-of-function mutations in a tumor suppressor gene can lead to an inherited predisposition to cancer. As diploid organisms, we have two copies of each gene in our cells, so losing one to mutation does not wipe out the protective function. Thus, if nothing happens to the other one, then the cell is fine. It is just a question of probability. Losing the function of one is a very low probability event, but the probability of losing both copies is extremely small. Thus, even though it is “only 1 step” on the way to losing the protection of this particular tumor suppressing function, it is a very large difference in probabilities. Of course, keep in mind that even complete loss of a single tumor suppressor gene is usually not enough to lead immediately to cancer, and still other mutations must occur to take advantage of the weakened cell defenses and push it towards a cancerous state.