Genetics and Cancer Activity

The cell cycle is controlled by a combination of positive and negative regulators.

**Proto-oncogenes** include positive regulator genes that produce factors that stimulate the cell cycle. Proto-oncogenes can be mutated to become oncogenes. Most proto-oncogenes found to date produce factors that stimulate the cell cycle too much. Whereas a proto-oncogene product is like a gas pedal that can be pushed or relaxed, an oncogene product is like a gas pedal that is stuck to the floor.

1. Look at the figure to the right. At the cellular level are mutations in proto-oncogenes generally dominant-acting or recessive-acting? Explain

Dominant-acting, cells that are have one mutant allele show excessive cell proliferation.

**Tumor suppressor genes** include negative regulatory genes that produce factors that inhibit cell division under normal conditions. Many tumor suppressor gene products are like the brakes for cell division. When you think of the protein products of mutant tumor suppressor genes, think of having a car brake that is defective.

2. Look at the figure on the right. At the cellular level are mutations in tumor suppressor genes dominant-acting or recessive-acting? Explain

Recessive-acting, only cells that no wild-type alleles show excessive cell proliferation.

3. The normal function of gene P is to kill cells that show signs of chromosome damage. Mutant forms of gene P are found to be involved in cancer. Is gene P likely to be a proto-oncogene or a tumor suppressor gene? Why?

**Tumor suppressor.** Cells with chromosome damage are undergoing mitosis when they would normally be prevented from doing so. Cancer arises from too little activity of the gene product.

4. The normal function of gene M is to signal for cells to divide when the body needs to heal a wound. Mutant forms of gene M have been found to be involved in cancer. Is gene M likely to be a proto-oncogene or a tumor suppressor gene? Why?

**Proto-oncogene.** The mutant M protein is encouraging cell division even when there is not a wound. Cancer arises from too much activity of the gene product.
The *breast cancer 1 (BRCA1)* gene has been implicated in breast cancer.

Below is a pedigree of a family showing the incidence of breast cancer with a particular *BRCA1* allele. *BRCA1*/*BRCA1* females who have this particular allele of *BRCA1* have a high chance of developing early onset breast cancer.

There are no *BRCA1*/*BRCA1* individuals in this family.

*BRCA1* mutations usually cause breast cancer in females but not in males; one member in generation I is heterozygous for the mutant allele; individuals II-1 and II-5 are *BRCA1*/*BRCA1*.

5. What are the possible modes of inheritance (X-linked, Autosomal, Mitochondrial, or Y-linked; dominant/recessive) in this family and why? Explain your answer.

The only possible mode of inheritance is autosomal dominant. An X-linked dominant mode of inheritance is not an option because the genotype of male II-5 is *BRCA1*/*BRCA1*. In addition, in order for male II-2 to have affected daughters with unaffected woman II-1, he would have the *BRCA1* mutation on his X-chromosome. Consequently, all of II-2’s daughters would likely be affected, but here III-1 is unaffected. X-linked recessive and autosomal recessive are also not options because there are no *BRCA1*/*BRCA1* individuals in this family. Mitochondrial inheritance also does not work because there are several examples of children who do not have the same phenotype as their mother. Finally, Y-linked will not work because women are affected.

6. Write the genotype next to each person in the pedigree above.

   answer:
7. If a man has a BRCA1 mutation (remember, there are no BRCA1+/BRCA1– individuals in this family), what is the chance he will pass the mutation on to his daughter? What about his son? In both cases it is 50%, remember the BRCA1 gene is on an autosome.

Patients with inherited forms of breast cancer inherit one normal allele and one mutant allele of a gene (ex. BRCA1+/BRCA1–). Then, subsequent somatic changes lead to a cell with no functional BRCA1 alleles. This cell then divides to make a tumor.

For example, a new somatic mutation can occur in the functional BRCA1+ allele in a population of dividing cells.

**Woman: BRCA1+/BRCA1– Heterozygote**

Or chromosomal errors (such as mitotic nondisjunction) can leave an individual with only the BRCA1– allele in a cell. A cell without any normal BRCA1 alleles can begin to divide uncontrollably, leading to cancer.

8. A woman is BRCA1+/BRCA1–. If you could analyze 10 of her non-cancerous somatic cells, how many wild-type and how many mutant copies of BRCA1 would you expect to find in each cell? Each cell will have one wild-type BRCA1 copy and one mutant BRCA1 copy.

9. If you analyzed 10 of her tumor cells, how many wild-type copies of BRCA1 would you expect to find in each cell? Each cell will have zero wild-type copies.

10. A man is BRCA1+/BRCA1– but does not have breast cancer. If you could analyze 10 of his sperm cells, how many wild-type and how many mutant copies of BRCA1 would you expect to find in each cell? Because sperm are haploid you would find either a mutant copy or a wild-type copy of BRCA1.
11. The BRCA1 gene is a tumor suppressor gene. **At the cellular level**, are mutations in tumor suppressor genes dominant acting or recessive acting (look at question 2)?

Recessive because you need a mutation in each allele before the cancer phenotype will occur.

12. Look back at the pedigree. **At the organismal level**, does the BRCA1\(^{-}\) allele behave as a dominant or recessive allele?

Dominant because BRCA1\(^{+}\)/BRCA1\(^{-}\) heterozygous females are likely to get breast cancer.

13. Explain the paradox to your answers in question 11 and question 12.

One mutation in BRCA1 is inherited. Consequently BRCA1\(^{+}\)/BRCA1\(^{-}\) women require fewer additional mutations to convert a normal somatic cell into a cell that is dividing uncontrollably. Because it is so likely that those additional mutations will occur during a person’s lifetime, the trait appears to be dominant at the organismal level. Most women who are BRCA1\(^{+}\)/BRCA1\(^{-}\) will get an additional mutation in one somatic cell and will likely get cancer.