ACTIVITY 2: EXAMINING CANCER PATIENT DATA

OVERVIEW

Refer to the "Overview of Cancer Discovery Activities" for Key Concepts and Learning Objectives, Curriculum Connections, and Prior Knowledge, as well as background information, references, and additional related resources.

MATERIALS

- *Cancer as a Genetic Disease* video clip (http://www.hhmi.org/biointeractive/cancer-genetic-disease-video-highlights)
- *Activity 2: Examining Cancer Patient Data* student document, which includes the *Video Worksheet*, (one per student)
- Set of 32 *Cancer Patient Cards*, to be distributed one per student. Cut out the cards before class. You may wish to laminate the cards for future use.

PROCEDURE

This activity consists of the following:

- A before-class assignment in which students watch a video clip (8:30 minutes) and complete the accompanying *Video Worksheet* (included in the *Activity 2: Examining Cancer Patient Data* student document) to learn about the genetic basis of cancer
- An in-class activity using the *Cancer Patient Cards,* which involves small-group discussions about the genes involved in different cancers
- A 3-2-1 analysis assignment, which can be done in class or as homework
- An optional research project (in the *Overview of Cancer Discovery Activities* document).

Before Class

Distribute the *Activity2: Examining Cancer Patient Data* document to students. Ask them to watch the *Cancer as a Genetic Disease* video clip and complete the *Video Worksheet* before class.

- Note: Some students find the gas pedal and brake analogy confusing (around 2:30 in the film). A mutated oncogene is like putting the foot on the gas pedal, and a mutated tumor suppressor gene is like taking the foot off the brake. Tumor suppressor genes normally act as brakes in the cell cycle.

ANSWERS TO VIDEO WORKSHEET

1. *What was the main purpose of the large-scale cancer study that Dr. Sawyers describes in the video?* **The study's aim was to identify the genetic causes of cancer.**
2. *As of spring 2013, about _____ genes associated with cancer had been identified. What is the approximate breakdown of oncogenes versus tumor suppressor genes?* **140 cancer genes; 60 oncogenes and 80 tumor suppressor genes**
3. *Using Dr. Sawyers' analogy (the gas pedal and brake), a mutated oncogene is like _____ and a mutated tumor suppressor gene is like _____. What does this mean in terms of how the cell grows and divides?* **A mutated oncogene is like putting the foot on the gas pedal, and a mutated tumor suppressor gene is like taking the foot off the brake**.
4. *Distinguish between a proto-oncogene and an oncogene.* **Proto-oncogenes normally stimulate cell growth and division in a carefully controlled way; oncogenes are mutated genes whose protein products cause cells to divide faster.**
5. *The mutated allele* (oncogene) *is dominant/recessive compared to the normal, non-mutated allele (proto-oncogene) on the other chromosome. (Circle a choice.)* **The mutated allele is dominant**.
6. *The mutated allele of a tumor suppressor gene is dominant/recessive compared to the normal, non-mutated allele on the other chromosome. (Circle a choice.)* **The mutated allele of a tumor suppressor gene is recessive.**
7. *Does Dr. Sawyers think many more cancer genes will be identified? Will the number grow exponentially?* **More will be identified, but not exponentially more.**
8. *List the three "buckets" in which scientists categorize cancer genes. Approximately how many genes are in each bucket?* **The three buckets are cell growth and survival (~70 genes), cell fate (~60 genes), and gene maintenance (~10 genes).**
9. *Is p53 a tumor suppressor gene/oncogene? Is cyclin D1 a tumor suppressor gene/oncogene? (Circle a choice.)* ***p53*** **is a tumor suppressor gene and** ***cyclin D1*** **is an oncogene. Students may point out that** ***cyclin D1*** **is actually a proto-oncogene and the mutated form of the gene is an oncogene.**
10. *How do p53 and cyclin D1 differ in how they affect the cell cycle?* **p53 limits cell growth and division (brakes), and cyclin D1 stimulates the cell cycle, causing cells to divide.**
11. *Consider genome maintenance genes:*
    a. *Does DNA polymerase make mistakes during DNA replication*? **Yes**
    b. *How often?* **DNA polymerase makes a mistake about once every billion bases.**
    c. *Explain the proofreading system.* **Enzymes in the cell correct errors in DNA sequence made during DNA replication.**
    d. *Explain what happens if a mutation occurs in the genes that encode proofreading enzymes.* **Without proofreading enzymes, errors would not be corrected and there would be many more mutations in the DNA of cells.**
12. *Why is it that the longer we live, the more likely we are to develop cancer*? **Over time, more errors and mutations occur.**

In Class: Discussion and Cancer Patient Cards

Video Discussion

As a class, discuss the video clip and address students' questions or points of confusion. Suggested discussion questions include the following:

- What does Dr. Sawyers mean when he says that cancer is a genetic disease?
- What is the difference between oncogenes and tumor suppressor genes?
- How do mutations in genes involved in cell growth and survival, cell fate (differentiation), and genome maintenance (or the repair of mistakes in DNA replication) cause cancer?

Cancer Patient Cards Activity

This activity uses a set of 32 *Cancer Patient Cards*, each listing the genes mutated in an actual patient's cancer. The data displayed on the cards were obtained from the Catalogue of Somatic Mutations in Cancer (COSMIC) database and information provided in a study by Vogelstein *et al.* (see references in the overview document). The cancers fall into **eight types** defined by the organ or tissue they affect—lung cancer, breast cancer, colorectal cancer, glioma (brain), melanoma (skin), hepatic cancer (liver), pancreatic cancer, and leukemia (blood)—with **four different patients** per cancer type.

The DNA from each patient's tumor was sequenced to identify all the mutations present. Only mutations known to *drive* the development of cancer, according to Vogelstein *et al.*, are listed on the cancer cards. Each card (**Figure 3**) contains the cancer type, the patient number, the genes mutated in that particular patient, the chromosome location of each gene, the gene classification (oncogene or tumor suppressor), and the cellular process that gene affects (cell survival, cell fate, or genome maintenance). Altogether the cards list 51 different genes (**Table 1**).

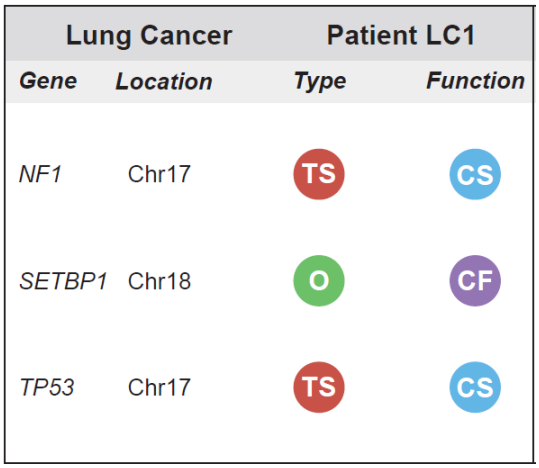

Figure 3. Example of a *Cancer Patient Card*. Abbreviations: TS, tumor suppressor; O, oncogene; CS, cell survival; and CF, cell fate.

Table 1. List of *Cancer Patient Cards.* There are four cards per cancer type, each card representing a different patient sample. In total, 51 genes are associated with the cancers listed on the 32 cards.

Cancer Type	Sample	Genes					
Lung cancer	1	*NF1*	*SETBP1*	*TP53*			
	2	*EGFR*	*MLL2*				
	3	*CTNNB1*	*KRAS*	*NF2*	*TP53*		
	4	*KT*	*MEN1*	*MLL3*	*TP53*		
Breast cancer	1	*BRCA1*	*TP53*				
	2	*CDH1*	*PIK3CA*				
	3	*ARID1B*	*TP53*				
	4	*FGFR2*	*GATA3*				
Colorectal cancer	1	*APC*	*TP53*				
	2	*KDM6A*	*KRAS*	*PIK3CA*	*SMAD4*		
	3	*APC*	*ATM*				
	4	*BRAF*	*CARD11*	*GNAS*	*PIK3CA*	*SMAD4*	*TP53*
Glioma	1	*CIC*	*IDH1*	*PIK3C5*			
	2	*CBL*	*TP53*				
	3	*ALK*	*ATM*	*BRCA1*	*TP53*		
	4	*HNF1A*	*PTEN*				
Melanoma	1	*BRAF*	*CREBBP*	*EP300*			
	2	*FGFR2*	*MLL3*	*NRAS*	*PTCH1*		
	3	*BRAF*	*APC*	*BCOR*	*JAK3*	*MLL2*	
	4	*BRAF*	*CDKN2A*	*MLL3*	*ATM*	*PAX5*	
Hepatic cancer	1	*ARID1A*	*ARID2*	*BRCA1*	*RB1*	*TP53*	
	2	*CTNNB1*	*MED12*				
	3	*HNF1A*	*TP53*				
	4	*ARID2*	*AXIN1*	*JAK2*	*TP53*		
Pancreatic cancer	1	*APC*	*GNAS*	*KRAS*	*RNF43*		
	2	*KRAS*	*TRAF7*	*TP53*			
	3	*CDKN2A*	*KRAS*	*MPL*	*TP53*		
	4	*KRAS*	*SMAD4*	*TP53*			
Leukemia	1	*MYD88*	*SETD2*				
	2	*BCOR*	*NOTCH1*				
	3	*BRAF*	*FAM123B*	*KRAS*			
	4	*NOTCH1*	*PIK3CA*	*TP53*			

Note: *TP53* is the gene that encodes the tumor suppressor p53. *BRCA1* is a gene involved in familial cases of breast cancer. Some of these genes have multiple names. For example, *FAM123B* is also called *AMER1*; *MLL2* is also called *KMT2D*, and *MLL3* is also called *KMT2C*.

1. Distribute the cards.

There are 32 *Cancer Patient Cards*; distribute one card to each student in the class. Briefly explain the information found on each card. Note that each card describes the driver genetic mutations found in a cancer from one person. The 32 cards reflect 32 different patients' cancers. You may wish to write the cancer card legend on the board to remind students of the definitions of the acronyms TS, O, CF, CS, and GM.

2. Form small groups based on cancer type.

Ask the students to form small groups based on their cancer types. Students should locate other students in the class with the same cancer type on their cards. All the lung cancers should be together, all the breast cancers, and so on. Allow students 15 minutes to compare cards and to identify and record patterns or trends they observe as they study the information on the cards. They should record their observations in their notebooks. Students may make the following observations:

- The genes are located on many different chromosomes.
- Different combinations of the mutated genes can cause tumors of the same cancer type.
- A different number of genes can be involved in the same type of cancer.
- Some genes are more common than others in the same type of cancer (i.e., *TP53* is on three of the four lung cancer cards; *BRAF* is on three of four skin cancer cards).

3. Form small groups based on patient number.

After 15 minutes, ask students to form groups based on their sample numbers. Students should locate other students in the class who have the same patient number (i.e., all the cards with a "1" together; for example, LC1, BC1, CC1, L1, etc.). This time each group consists of different cancer types. Students will have 10 minutes to identify and record any *new* patterns or trends that they did not identify when they were in their cancer-type groups. Remind students that each card represents a different patient. Students may make the following observations:

- Mutations in the same genes (i.e., *TP53*, *KRAS*, *BRAF*) have been identified in different types of cancer.
- Different driver mutations affect genes that are on the same chromosome but are involved in different types of cancer.
- Few driver mutations are in genes involved in genome maintenance.

Whole Class Activity and Discussion

1. Construct a cancer genes table.

Construct a cancer genes table as a class either on the board or using the template provided in **Table 2**. Ask each student to read aloud the names of the genes on his or her card and keep a tally on the table of how many times a gene name is called out. You may also note the type of cancer each gene is associated with or whether the gene is a tumor suppressor gene or an oncogene. By creating this table, students will see an overall picture of the genes mutated in different cancer types, which will be different from what they observed in their small groups.

Table 2. Cancer Gene Table Template. Use this template to build a cancer gene table by asking each student to read aloud the mutations on their *Cancer Patient Cards* and record the number of times a particular gene is called out. Note the type of cancer associated with a mutation. The 51 cancer genes are listed alphabetically in the sample table below.

Gene	Cancer Type(s)	Tally
ALK		
APC		
ARID1A		
ARID1B		
ARID2		
ATM		
AXIN1		
BCOR		
BRAF		
BRCA1		
CARD11		
CBL		
CDH1		
CDKN2A		
CIC		
CREBBP		
CTNNB1		
EGFR		
EP300		
FAM123B		
FGFR2		
GATA3		
GNAS		
HNF1A		
IDH1		
JAK2		
JAK3		
KDM6A		
KIT		
KRAS		
MED12		
MEN1		
MLL2		
MLL3		
MPL		
MYD88		
NF1		
NF2		
NOTCH1		
NRAS		
PAX5		
PIK3CA		
PTCH1		
PTEN		

RB1		
RNF43		
SETBP1		
SETD2		
SMAD4		
TP53		
TRAF7		

2. Lead a class discussion.

Ask students to make observations from the table and from their own small-group discussions.

Students may make the following observations:

- Fifty-one different genes are mutated in these cancers.
- Cancers of the same type don't have the same combinations of mutated genes.
- Certain genes are involved in multiple types of cancer.
- Some genes are mutated more frequently than other genes.
- There are 19 oncogenes and 32 tumor suppressor genes.
- Twenty-four of the genes influence cell fate, 23 influence cell survival, two influence both cell fate and cell survival, and two influence genome maintenance.

Assign a 3-2-1 analysis.

Assign students a 3-2-1 analysis for the activity either individually or in small groups. The analysis should include three things the student learned from the activity, two things that surprised or particularly interested them, and one question they still have. If students are assigned to do the analysis individually, they can complete it either in class or as homework. A grading rubric for this analysis can be found in the "Overview" document.

TEACHING TIPS

- If students need a refresher on the cell cycle, consider using "The Eukaryotic Cell Cycle and Cancer" Click and Learn before doing this activity. "The p53 Gene and Cancer" Click and Learn can also be helpful.
- Depending on the number of students in the class, you can adjust the number of cancer cards distributed. For example, if you have 21 students, you could use seven of the eight cancer types and three of the four patient groups (i.e., $7 \times 3 = 21$ cards). Try to make sure that you distribute an equal number of patient-number cards for each cancer type.
- Rotate among the groups as students work and, if necessary, ask them to consider the following questions: Are any genes in common among your patients? Are all the genes on the same or different chromosomes? How many oncogenes versus tumor suppressor genes are there? You might prompt them to make a list of the genes mutated in multiple cancers versus genes that were only mutated in a single type of cancer.
- Point out to students that these genes represent only a subset of all genes known to be involved in cancer. Researchers have so far identified about 140 genes involved in cancer. About 80 are tumor

suppressor genes and about 60 are oncogenes. For an activity that illustrates all of the cancer-causing genes, see *Activity 1: Classifying Cancer Genes*.

SOCIAL MEDIA SUGGESTIONS

- The cancer gene table could be assembled using a pre-prepared Google Docs spreadsheet. Students add their data to the spreadsheet, and the whole class can see it build collectively. If the tally column is built as a formula, it will grow as the students enter their data. You could draw an analogy between the collaborative, online building of a data set accomplished by the students and the genome analysis done by the researchers (on a larger scale).
- Students could post their 3-2-1 analyses as blog posts (on a class blog or individual student blogs). Once posted, the comments feature could be used to facilitate peer review. With the suggested rubric, students could be assigned to review their own blog post plus those of two other students.
- As an alternative optional extension project, students could create a "genetics of cancer" infographic, intended for patient education at an oncologist's office. Free, online infographic creation tools (such as Easel.ly or Picktochart) are available.

AUTHORS

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