Teacher Resource for:
BRCA1 Tumor Suppression Depends on BRCT Phosphoprotein Binding, But Not Its E3 Ligase Activity.

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GENERAL USE OF Science in the Classroom

Student Learning Goals:
“One fundamental goal for K-12 science education is a scientifically literate person who can understand the nature of scientific knowledge.”

The U.S. National Academy of Sciences defines science as: “Any new finding requires independent testing before it is accepted as scientific knowledge; a scientist is therefore required to honestly and openly report results so that they can readily be repeated, challenged, and built upon by other scientists. Proceeding in this way over centuries, the community effort that we call science has developed an increasingly accurate understanding of how the world works. To do so, it has had to reject all dogmatic claims based on authority, insisting instead that there be reproducible evidence for any scientific claim.”

An important student learning goal, central to any understanding of “the nature of scientific knowledge,” is to give each student an appreciation of how science is done.

This includes knowing why:
- Scientists must be independent thinkers, who are free to dissent from what the majority believes.
- Science can deal only with issues for which testable evidence can be obtained.
- All scientific understandings are built on previous work.
- It is to be expected that one scientist’s conclusions will sometimes contradict the conclusions of other scientists.
- Science is a never-ending venture, as the results from one study always lead to more questions to investigate.

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1 A Framework for K-12 Science Education, National Research Council, 2012
Using This Resource

**Learning Lens:**

The Learning Lens tool can be found on the right sidebar of each resource and is the source of annotations. Click on the headings to highlight portions of the text of the corresponding research article. A subsequent click on the highlighted text will produce a text box containing more information about that particular piece of text. Below is an example of the Glossary function of the Learning Lens.

**ABSTRACT**

*White-Nose Syndrome (WNS)* is an emerging disease affecting hibernating bats in the eastern United States. It is spreading rapidly across eastern North America and currently affects seven states, resulting in a regional population collapse and is predicted to lead to regional extinction of the little brown myotis (Myotis lucifugus), previously one of the most common bat species in North America. Novel diseases can have serious impacts on native wildlife populations, which in turn can have substantial impacts on ecosystem integrity.

**REPORT**

Emerging infectious diseases are increasingly recognized as direct and indirect agents of extinction of free-ranging wildlife (1–4). Introductions of disease into native wildlife populations have led to serious declines or local extinctions of different species in the past few decades, including amphibians from chytridiomycosis (5, 6), rabbits from myxomatosis in the United Kingdom (7), Tasmanian devils from infectious cancer (8), and birds in North America from West Nile virus (9). Here we demonstrate that White-Nose Syndrome (WNS), an emerging infectious disease, is causing unprecedented mortality among hibernating bats in eastern North America and has caused a population collapse that is threatening regional extinction of the little brown myotis (Myotis lucifugus), a once widespread and common bat species.

WNS is associated with a newly described psychrotrophic fungus, *Geomyces destructans*, that grows on exposed tissues of hibernating bats, apparently causing premature arousals, aberrant behavior, and premature loss of critical fat reserves (9, 10) (Fig. 1). The origin of WNS and its putative pathogen, *G. destructans*, is uncertain (5). A plausible hypothesis for the origin of this disease in North America is introduction via human trade or travel from Europe, based on recent evidence that *G. destructans* has been observed in at least one hibernating bat species in Europe (11). Anthropogenic spread of invasive pathogens in wildlife and domestic animal populations, so-called pathogen pollution, poses substantial threats to biodiversity and ecosystem integrity and is of major concern in conservation efforts (1, 2).

An example of the resource with the Glossary, Previous Work, Author’s Experiments, News and Policy Links, and References and Notes tools turned on. The Glossary tool is in use.
**Learning Notes:**

Learning Notes accompany each figure and are designed to help students deconstruct the methods and data analysis contained within each figure.

Fig. 1. Spatial distribution of head scales. (A) Head scales in most snakes (here, a corn snake) are polygons (two upper panels) with stereotyped spatial distribution (two lower panels): left (yellow) and right (red) scale edges overlap when reflected across the sagittal plane (blue). (B) Polygonal head scales in crocodiles have a largely random spatial distribution without symmetrical correspondence between left and right. (C) Head scales from different individuals have different distributions of scales’ sizes and localizations (blue and red edges from top and bottom crocodiles, respectively).

The authors took 120 color pictures of each animal to create detailed, three-dimensional models of reptile heads. Watch this video in which the authors further explain their modeling methods:

http://www.sciencemag.org/content/suppl/2012/11/29/science.1226265.DC1/1...
References:

The Reference section of each resource is annotated with a short statement about how or why each reference relates to the current research study.

17. Lewejohann et al., Environmental bias: Effects of housing conditions, laboratory environment and experimenter on behavioral tests. Genes Brain Behav. 5, 64 (2006).
28. L. Jang, R. R. McGee, A. Angletta, R. Riemann, W. J. Liverais, Heritability of face-level traits in a cross-cultural twin
**Thought Questions**

Thought Questions are located above the Learning Lens in the right sidebar of each resource. These questions were written to be universal and applicable to any primary research paper. Thought questions do not have a single answer, or a correct answer for that matter, and can be used to stimulate discussion among students.
Suggestions for Classroom Use:

In addition to the thought questions discussed above, other resources are provided for use in the classroom. These can be found toward the end of the teacher guides associated with each specific article and include:

1. Discussion questions specific to the article, related to the standards, and/or associated with the figures.

2. Activities tied to the articles.

Some ways to use the *Science* in the Classroom articles:

1. Assign to student groups to read and discuss during class.

2. Assign small sections of the article to student groups to read and discuss during class, with the expectation that they will present or use jigsaw to teach the entire class what is in their part of the article.

3. Assign to individual students to complete during class or as homework.

4. Assign reading as an extra credit project.

Some ideas for interactive student engagement after reading the article:

1. Students write answers to discussion questions (for example, those linked to the standards or those linked to the diagrams).

2. Go over the abstract, as well as information about the purpose and structure of an abstract, and have students write their own abstracts for the articles in language that could be understood by their peers.

3. Have students edit the article, or parts of the article, to a simpler reading level.

4. Have students, alone or in small groups, use the annotated list of references to explain how the scientists who wrote this article built on the published work of at least one independent group of scientists in making their discoveries. In the process, did they produce data that supports the findings of the earlier publication that they have cited in the text? In what way does this article support the statement that scientific knowledge is built up as a “community effort”?
5. Use the article and discussion questions linked to the standards and the diagrams for a teacher-led classroom discussion. The discussion can focus on the nature of science and scientific research, as well as on the science in the article itself.

6. Have students give a classroom presentation about the article, parts of the article, or their answers to discussion questions.
**ARTICLE-SPECIFIC MATERIALS**

**Student Learning Goals:**

**Connections to the nature of science from the article**

How can this information help us diagnose, prevent, or treat cancer?

What else can mouse models of cancer teach us?

**The importance of this scientific research**

This research helps scientists and physicians better understand the functions of the BRCA1 protein.

A better understanding of the protein’s different functions may lead to better therapeutics for cancers with BRCA1 mutations.

**The actual science involved**

- Ubiquitination
- Phosphorylation
- DNA repair
- point mutations
Connect to Learning Standards:


- Connects to AP Biology Essential knowledge 3.C.1:

  Changes in genotype can result in changes in phenotype. (Alterations in a DNA sequence can lead to changes in the type or amount of the protein produced and the consequent phenotype. [See also 3.A.1])

- Connects to AP Biology Essential knowledge 3.B.1:

  Gene regulation results in differential gene expression, leading to cell specialization. (In eukaryotes, gene expression is complex and control involves regulatory genes, regulatory elements, and transcription factors that act in concert.)

- Connects to AP Biology Essential knowledge 2.E.1:

  Timing and coordination of specific events are necessary for the normal development of an organism, and these events are regulated by a variety of mechanisms. (Genetic mutations can result in abnormal development.)
**Summary of the Article for the Teacher:**

*It is recommended that this not be used by students in place of reading the article.*

**General Overview:**

Inherited mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 are associated with a markedly increased risk of breast and ovarian cancer. Exactly how these mutations cause this increased risk has been the subject of much research over the last 20 years. Learning more about the functions of these genes could help us develop prophylactic strategies to reduce this risk in BRCA mutation carriers—as well as better chemotherapeutics to treat tumors that harbor BRCA mutations.

**Topics Covered:**

- cancer biology
- cancer predisposition
- animal models

**Why this Research is Important:**

It furthers our understanding of a protein that is important in preventing cancer development

**Methods used in the Research:**

- Immunoprecipitation
- site-directed mutagenesis
- mouse models of cancer
- mammalian cell culture

**Conclusions:**

Surprisingly, the enzymatic (E3 ligase) function of BRCA1 is not required for its tumor suppressive activity. Rather, BRCA1 tumor suppression is dependent on the phospho-recognition property of its BRCT domains and formation of the BRCA1/BARD1 heterodimer.

**Areas of Further Study:**

Targeting the interaction between BRCA1 and its BRCT phospho-ligands for therapeutic intervention
**Resources for Interactive Engagement:**

**Discussion Questions**

1. **What makes mice good models for studying cancer?**

   Mice and humans are both mammals, and thus share significant genetic and biological similarities. With the advent of targeted mutagenesis in mice, we can now design mouse models of human cancer by introducing the same gene mutations observed in human tumors. The resulting mouse cancer models can then be used 1) to elucidate the genetic and biological mechanisms of cancer development and 2) to develop and test new therapeutic strategies for prevention and treatment of cancer.

2. **Why would mutations in BRCA1 result in increased cancer predisposition?**

   Your DNA is continuously damaged by radiation, chemicals and spontaneous errors of replication. If this damage isn’t repaired, or is repaired inaccurately, there may be serious consequences, such as mutations or breaks in the DNA. BRCA1 functions in a highly accurate (“homology-directed”) pathway of DNA repair. If BRCA1 is mutated and cannot function in this repair pathway, the resulting DNA damage can yield lethal or mutagenic consequences. While most cells with severe DNA damage will die, some may survive and become cancerous. So, by reducing accurate repair of DNA damage, mutations in BRCA1 can promote tumor development.

3. **In Figure 2B, the authors compare the sensitivity of different BRCA1-mutant cells to mitomycin C (MMC), a DNA-damaging drug that is also used to treat certain kinds of cancer. Why would doctors prescribe a drug that causes DNA damage to treat cancer patients?**

   Some mutations that result in increased cancer predisposition (like those in BRCA1) also make cancer cells susceptible to DNA damaging agents. While treating a patient with DNA damaging agents (like MMC) is harmful to all of their cells, if the dose is just right, it will selectively kill the cancer cells. However, this perfect dose is difficult to achieve, and if any cancerous cells are resistant to the drug, they won’t be killed. What’s worse, those resistant cells produce more resistant cells, and the drug becomes ineffective. So, it’s important to continue researching more effective treatments for different types of cancers.

4. **What is the advantage of using the enzyme cre to induce a particular mutation?**
Cre is a recombinase, a type of enzyme that can cut and rejoin DNA at specific sequences, called “loxP” sites. The Cre/loxP system is a widely used genetic method to control gene function in a tissue-specific manner. For example, in this paper, cre is linked to the transcriptional promoter of WAP, a gene that is only active in certain mammary epithelial cells. As a result, expression of Cre and recombination of loxP-containing genes (such as the Brca1 and p53 alleles used in this paper) will be restricted to the breast. This strategy can afford researchers both spatial and temporal control over gene function in mice.