

Epigenetics

Activity Summary

Students make a model of chromatin and use it to show how chemical tags that bond to the chromatin can influence its uncoiling.

Materials (per group)

- copy of “Epigenetics” student handout (2 pages)
- colored, fine-tipped permanent marker
- ballpoint pen
- 3 lengths of thin (i.e., small-diameter) rubber surgical tubing, each 24 inches long ($\frac{1}{8}$ -inch rubber bungee cord can be used as a substitute)
- 2 small binder clips ($\frac{3}{4}$ -inch size)
- packaging tape or duct tape, 2 inches in width

Background

For students to grasp the basics of epigenetics, they will need an understanding of DNA and its structural chemistry in the chromosome. Consequently, this lesson is appropriate for a high school biology class in which students have had some exposure to the fundamentals of DNA and RNA. However, as the lesson’s theme is epigenetics rather than DNA, the lesson’s goal is for students to be able to explain the difference between genetics and epigenetics and to describe the role epigenetic factors play in enabling DNA to be “read” by enzymes and transcribed by messenger RNA.

In the field of epigenetics, scientists study how chemical tags attach themselves to DNA or to the structures surrounding the DNA. These chemical tags can control gene expression, silencing or activating genes. Because these chemical tags are independent of the DNA sequence itself, they are considered to be epigenetic factors. Epigenetic researchers examine the role this silencing or activation of genes might play in cell differentiation, cell development, disease, and heredity.

Epigenetics is a highly relevant area, offering scientists new ways to investigate many fundamental questions about life, health, and disease. For example, how does a single fertilized egg cell differentiate into over 200 cell types? How do exposures to nutrients, toxins, pollutants, and other environmental agents affect gene expression? These questions are at the core of much of today’s cutting-edge research and technology in such fields as health care, medicine, pharmacology, fertility, and the management of environmental pollutants.

LEARNING OBJECTIVES

Students will be able to:

- explain the difference between genetics and epigenetics.
- state that the structure of chromatin includes DNA and histones coiled together.
- demonstrate how chemical tags that attach to the chromatin help the chromatin uncoil.
- describe how chemical tags (i.e., an epigenetic factor) play an important role in enabling DNA to be “read” by enzymes and transcribed into messenger RNA.

STANDARDS CONNECTION

The “Epigenetics” activity aligns with the following National Science Education Standards (see books.nap.edu/html/nses).

GRADES 9–12

Life Science

- The cell
- The molecular basis of heredity

Science and Technology

- Understandings about science and technology

Science in Personal and Social Perspectives

- Personal and community health

EXPLORE MORE ONLINE

Epigenetics research

Learn about cutting-edge research where scientists investigate mechanisms controlling gene expression that are independent of the DNA sequence itself. Visit hhmi.org/research/investigators/zhang_bio.html.

CLASSROOM ACTIVITY (CONT.)

In this activity, students build a model showing that DNA is enclosed in a histone cushion to form chromatin, the basic component of a chromosome. They use the model to demonstrate one way that methyl groups can bind to the chromatin, enabling it to uncoil to expose the DNA. The activity should clarify the meaning of the term *epigenetics* and suggest why researchers from many fields are so keenly interested in learning more about the interaction between genetics and epigenetics.

Depending on how familiar your students are with DNA and RNA, you might want to review DNA's structure and the processes of transcription and translation. For example, have students list three facts they can recall about DNA and RNA. Then ask students to share their facts and develop a class list on the board or on a flip chart. Also, discuss how the coiling of DNA around the histone proteins enables nearly two meters-worth of DNA to fit into a microscopic cell nucleus!

Procedure

- 1 Demonstrate how DNA is coiled into a double helix. Before class, prepare a set of two tubes representing DNA. Mark these tubes as described in Steps 1a and 1b on the Student Handout. Tape the ends. Invite two students to help you in a demonstration. Have each helper take a taped end of the tubing and face one another. Ask them to twist the tubes into a spiral. Point out that, after just a few twists, the tubing forms into a "double helix."
- 2 Demonstrate that DNA's double helix is itself arranged into a secondary spiral. Have the students continue to twist. The tubing will begin to knot up. Have the helpers pull lightly, maintaining gentle outward pressure while still slowly twisting the tubing. The knots should begin to organize into a thick spiral. The structure you are aiming for is a neat, tight, thick spiral. Make sure the class understands what the model shows: (1) the DNA double helix; and (2) the double helix itself is twisted into a secondary spiral.
- 3 Add a histone strand and twist the three tubes into a secondary spiral. Uncoil the DNA model and add the third piece of tubing. (It does not matter where the third tube is in relation to the others, as long as it is neatly alongside the other two.) Tape the three tubes together at the ends. Tell students that chromosomes are made of more than just DNA—the DNA is coiled around proteins called histones. Together, the histone proteins and DNA form the chromatin. Chromatin, in turn, forms the chromosome. Once taped together, the three lengths of tubing represent a section of chromatin. Have the helpers repeat the twisting. Invite observations from the class about the appearance of the three tubes.

KEY TERMS

base pairs: The pairs of nucleotides adenine-thymine and cytosine-guanine that join by hydrogen bonding to form DNA's double helix.

chromatin: Chromatin is a molecule consisting of DNA and histones. It is the primary constituent of a chromosome. When a chromosome is uncoiled, it is referred to as chromatin.

chromosome: A tightly coiled macromolecule of DNA and its associated proteins.

deoxyribonucleic acid (DNA): A double-stranded chain of nucleotides. It carries a cell's genetic information and is found in the cells of all living organisms. It is capable of self-replication and the synthesis of RNA.

epigenetics: The study of inherited characteristics that lie outside of the genome in organisms (from the word *epi*, meaning "outside" or "above," originally from the Greek).

gene: The basic unit of inheritance. Genes usually consist of two parts. The first is a sequence of nucleotides that transcribe onto RNA. The second is sequences of DNA that control the transcription process.

genetics: Genetics is the study of DNA-based inherited characteristics in organisms.

histone: A protein that is found in six different forms. Four of these types of histones form a core around which the double-helix DNA strand winds to form chromatin. This spooling enables the DNA to be compacted to 1/50,000 of its length, enabling it to fit inside the nucleus of a cell.

nucleosome: The fundamental unit of chromatin. It is composed of two copies of each of the four core histones, around which 146 base pairs of DNA are wrapped.

CLASSROOM ACTIVITY (CONT.)

Make sure the class understands what the model shows: (1) chromatin is made of DNA and histones; and (2) the chromatin is twisted into a secondary spiral. *(Tell students that in this model, the third surgical tube [i.e., the one with dots or stripes] represents chromatin's histone proteins. As with the two tubes, the three tubes will also twist into the second spiral of knots. Point out how the inclusion of the third tube as well as the twisting makes the sequence of letters [i.e., the DNA's sequence of nucleotides] hard to read.)*

- 4 Discuss how coiling makes it hard to read the DNA but offers other advantages. Explain that the secondary level of coiling permits the chromatin to be densely packed, enabling two meters-worth of DNA to fit into a cell's nucleus. See if students can identify a major problem with this arrangement. Ask: When your body needs to make a protein, how can the genetic instruction hidden in this coil of chromatin get "read"? Record the ideas on the board. *(When coiled, the DNA's sequence of nucleotides cannot easily be read. Consequently, the instructions for protein synthesis are unavailable, and enzymes cannot read the DNA to begin the process of transcription. When the chromatin is in its tightly coiled state, the chromosomes are inactive—no transcription [or protein synthesis] can take place.)*
- 5 Have students make their own models. Divide your class into groups of three or four students and distribute the materials. Have each group follow the steps on the Student Handout, in which they make their own chromatin model and use it to show how chemical tags (i.e., epigenetic factors) can uncoil segments of the chromatin. Then have them answer the questions at the end of the Student Handout.
- 6 Review how epigenetic factors uncoil the chromatin. After students have finished, discuss the Handout questions and students' answers.

KEY TERMS (CONT.)

nucleotide: A chemical compound consisting of a sugar, one phosphate group, and one of four nitrogenous bases: adenine, cytosine, guanine, and thymine.

ribonucleic acid (RNA): A single-stranded chain of nucleotides. One form (messenger RNA) acts as a messenger between DNA and the cell's protein synthesis machinery.

transcription: The enzymatic copying process by which DNA produces a complementary copy of RNA.

translation: The process by which a complete messenger RNA molecule serves as a template for the biosynthesis of a specific protein.

Video is not required
for this activity.

Classroom Activity Author

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ACTIVITY ANSWER

Student Handout Questions

- 1 Why can it be difficult for enzymes to “read” DNA base pairs in a coiled nucleosome? *In the nucleosome the DNA strand is wound onto the histone proteins the way a thread is wound onto a spool. Furthermore, the nucleosomes are themselves coiled. All the winding, twisting, and coiling make it essentially impossible for the transcription enzymes to read a complete sequence of base pairs (i.e., a gene).*
- 2 In your own words, explain the process of how methyl tags (represented by the binder clips) help chromatin uncoil to reveal the base pairs in a nucleosome. *When methyl groups attach to particular sites on the tightly coiled chromatin, specific parts of the chromatin (i.e., the nucleosomes) uncoil, revealing segments of base pairs (i.e., the genes). Once the genes are revealed, it is possible for messenger RNA to be transcribed.*
- 3 How are methyl groups examples of an epigenetic factor? *Methyl groups originate outside the nucleus. They pass through the nuclear membrane and attach at activation sites on the histones in the chromatin. The chromatin affected by these methylated activation sites unravels, enabling transcription of the genes in this section of the chromatin.*
- 4 What would happen if methyl groups stayed attached to the nucleosome forever and kept it continuously open? *There could be overproduction of a particular compound synthesized by that stretch of DNA. Such an overproduction might be related to cancer-like processes.*
- 5 List some ways that a nucleosome stuck in “continuous reading” mode might become unstuck. *Remove the methyl groups. If the groups cannot be removed, remove the segment containing the groups (i.e., the strip with the two clips attached).*

LINKS AND BOOKS

Links

NOVA scienceNOW

www.pbs.org/wgbh/nova/sciencenow/3411/02.html

Offers epigenetics-related resources, including a streamed version of the show, an audio slide show about how the epigenome produces differences, and an Ask the Expert area where site visitors can ask researcher Randy Jirtle questions about epigenetics.

Environmental Health Perspectives

ehponline.org/members/2006/114-3/focus.html

Provides a well-written overview, with a clear diagram, of the connection between epigenetic factors and disease in humans.

Epigenome Network of Excellence

epigenome-noe.net/aboutus/epigenetics.php

Offers a brief yet informative overview of the field of epigenetics.

Epigenome Network of Excellence

epigenome.eu/en/1,1,0

Presents a brief, clear overview of epigenetics, with quotes from various researchers, followed by a series of accessible descriptions of different topics in epigenetics.

The Functions of Chromatin

Modifications

hhmi.org/research/investigators/zhang.html

Explains how epigenetic-mediated dynamic changes in chromatin structure affect gene expression, cell lineage commitment, and cancer development.

Johns Hopkins Epigenetics Center in the Institute for Basic Biomedical Sciences

hopkinsmedicine.org/press/2002/November/epigenetics.htm

Provides a basic introduction with an overview of epigenetics presented in lay terms.

ACTIVITY ANSWER

- 6 List some strengths and weaknesses of this activity's model of the DNA–chromatin complex. *Weaknesses:* 1) *The relative sizes of the molecules are not accurately represented by the rubber tubing. Specifically, the DNA strand is very fine and narrow compared to the much larger histone protein core molecules.* 2) *In real life, the substances coil in patterns different from those of the model tubing—the DNA is almost like a fine double thread wound around the much more bulky histone proteins. These histone proteins, in turn, resemble spools that are connected to each other.*

Strengths: 1) *Rubber tubing provides a usable representation of the components of chromatin and their respective three-dimensional relationship with each other.* 2) *The secondary coiling pattern creates a reasonable representation of the nucleosome.* 3) *Both of these characteristics help to show how more than two meters of DNA can fit into the nucleus of a microscopic cell.*

7. Why might high-level exposures in early life to factors that lead to the accumulation of methyl groups have health consequences much later in life? *The accumulation of chemical tags, such as methyl groups, that can stick to the histones or DNA might affect cellular repair mechanisms, causing them to break down or become less effective.*

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LINKS AND BOOKS (CONT.)

Books

Biology: Concepts and Connections
by Neil Campbell, Jane Reece, Martha Taylor, and Eric Simon.
Pearson/Benjamin Cummings, 2006.
Provides overview of genetics, DNA, RNA, and other related basic information; written at level appropriate for high school.

Epigenetics

by C. David Allis, Thomas Jenuwein, Danny Reinberg, and Marie-Laure Caparros.

Cold Spring Harbor Press. 2007.
Compiles an up-to-date technical scientific collection of papers with useful overviews.

Articles

A Cell's Second Act

by Richard Saltus
HHMI Bulletin, 19 (1), February, 2006. (Available at: hhmi.org/bulletin/feb2006/features/cell2.html)

Describes researchers' efforts to understand nuclear reprogramming to revert adult cells to medically useful embryonic stem cells.

DNA Is Not Destiny

by Ethan Watters
discovermagazine.com/2006/nov/
The new science of epigenetics rewrites the rules of disease, heredity, and identity.

Epigenetics: A historical overview

by Robin Holliday
Epigenetics, 1:2, 76–80, 2006.
(Available at: cnru.pbrc.edu/pdf/history_of_epigenetics.pdf)

Offers a brief history of the field of epigenetics.

Nurture Takes the Spotlight: Decoding the environment's role in development and disease

by Christen Brownlee.
Science News, 169 (25), June 2006.
(Available at: www.sciencenews.org/articles/20060624/bob8ref.asp)

Reviews current research and gives an accessible overview of epigenetics.

Epigenetics

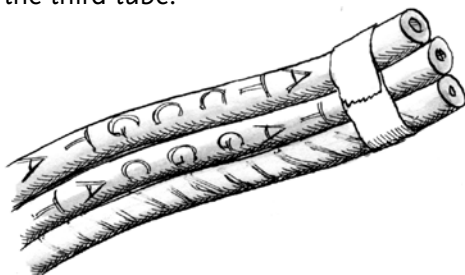
Epigenetics is a field of research that investigates heritable information carried in the cell that is not directly coded by DNA. The prefix *epi*, which comes from both Latin and Greek, means “above” or “outside.” The term epigenetics refers to mechanisms controlling gene expression that are independent of the DNA sequence itself.

Methyl groups are one kind of chemical known to have an epigenetic effect. Methyl groups occur

naturally, and the body obtains them through food and as natural products of metabolism. They enable the nucleus’s very tightly wound chromatin to uncoil. Since they originate outside the DNA, methyl groups are considered epigenetic factors. Today, you will build a model of chromatin and explore how chromatin can be chemically influenced by factors originating from “outside” the DNA.

Procedure

- 1 Build a model of chromatin. Gather the materials you need to make a model similar to the one your teacher demonstrated. Mark and assemble the three tubes as follows:
 - a Make the first “DNA” tube: Using a ballpoint pen, mark the length of the tube using combinations of the letters A, C, T, G. The letters should be large and in random order. You can use a letter more than once, and you can have two of the same letter in a row. These letters represent the amino acids of the nucleotides (A for Adenine, C for Cytosine, T for Thymine, and G for Guanine).
 - b Make the second “DNA” tube: Lay a second tube beside the first one. Where you’ve written an A on the first tube, mark a T on the second; where there’s a T on the first, write an A on the second. Similarly, where you’ve written a C on the first, mark a G on the second; where there’s a G on the first, mark a C on the second.
 - c Make the “histone” tube: Using a colored marker, put dots or stripes along the length of the third tube.



- d Hold the ends of the three tubes together, keeping them parallel (i.e., no twists, overlaps, or kinks). It does not matter which tube is next to which. Wrap tape around the ends, securing the tubes together. Repeat with the other end to make a single 24-inch, three-strand unit.
- 2 Twist the tubes. With one person holding each end of the triple bundle, begin twisting it into a spiral. When it begins to form knots, continue to twist slowly while pulling gently outward. Maintain tension so that the first spiral of knots forms into a secondary spiral of knots.



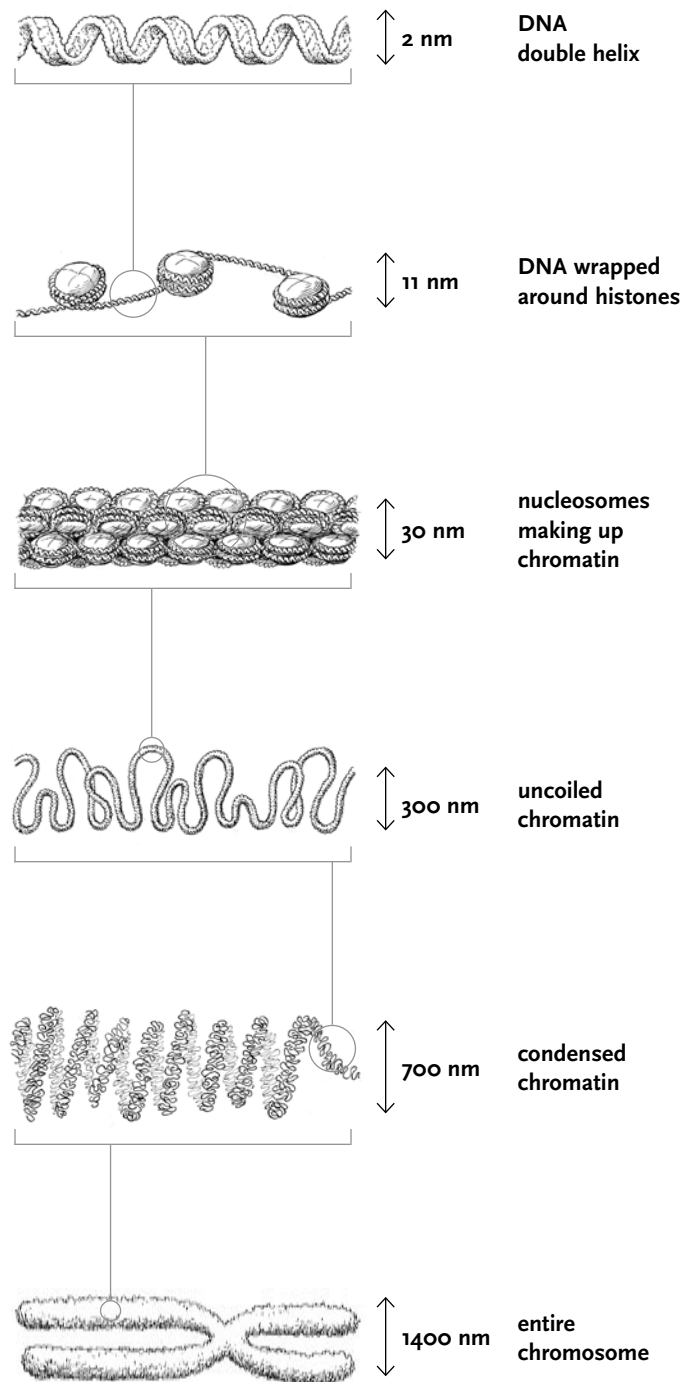
Epigenetics (cont.)

- 3 Show how epigenetic factors control the behavior of chromatin. Use your model to show how chromatin uncoils to reveal the sequence of the nucleotides so they can be “read” by enzymes and then transcribed by messenger RNA.
- Select a zone about six inches long near the middle of the twisted tubes. Mark this zone by attaching a binder clip to the “histone” tube at each end of the zone. The clips represent chemicals called methyl groups that are able to attach to the histone complex.
 - Have a third person from your group work to carefully uncoil the three tubes in the six-inch zone marked off by the clips.
 - Once this zone is uncoiled, read the sequence of base pair letters on the DNA tubes. This models the way that enzymes would “read” DNA base pairs to transcribe messenger RNA.
 - After reading the base pair sequence, carefully recoil the three tubes and remove the clips.

Questions

Write your answers on a separate sheet of paper.

- Why can it be difficult for enzymes to “read” DNA base pairs in a coiled nucleosome?
- In your own words, explain the process of how methyl tags (represented by the binder clips) help chromatin uncoil to reveal the base pairs in a nucleosome.
- How are methyl groups examples of an epigenetic factor?
- What would happen if methyl groups stayed attached to the nucleosome forever and kept it continuously open?
- List some ways that a nucleosome stuck in “continuous reading” mode might become unstuck.
- List some strengths and weaknesses of this activity’s model of the DNA-chromatin complex.
- Why might high-level exposures in early life to factors that lead to the accumulation of methyl groups have health consequences much later in life?



Strings of nucleosomes make up the chromatin. In the model, the secondary spiral of knots in the twisted tubing represents nucleosomes.