Transcription Factors and Gene Expression

Purpose

In this lesson, students will investigate gene expression through comparison of transcription factors. They will explore gene regulation and the use of a topical cream to amplify melanin production as a means to protect against skin cancer

Audience

This lesson was designed for use in an introductory high school biology class.

Lesson Objectives

Upon completion of this lesson, students will be able to:

- to explain environmental and drug impacts on gene regulation and expression.
- to explain the role of master transcription factors.
- to defend the use of a drug, citing relevant evidence.

Key Words

melanin, model organism, tanning, transcription factor

Big Question

What does it mean to observe?

Standard Alignments

- **Science and Engineering Practices**
  - **SP 1.** Asking questions and defining problems
  - **SP 6.** Constructing explanations and designing solutions
  - **SP 8.** Obtaining, evaluating, and communicating information.
- **MA Science and Technology/Engineering Standards (2016)**

  HS-LS1-1. Construct a model of transcription and translation to explain the roles of DNA and RNA that code for proteins that regulate and carry out essential functions of life.
- **NGSS Standards (2013)**

  HS-LS-1-1. Construct an explanation based on evidence for how the structure of DNA determines the structure of proteins which carry out the essential functions of life through systems of specialized cells.

- **Common Core Math/Language Arts Standards**
  - **CCSS.ELA-LITERACY.RST.9-10.2.** Determine the central ideas or conclusions of a text; trace the text's explanation or depiction of a complex process, phenomenon, or concept; provide an accurate summary of the text.
  - **CCSS.ELA-LITERACY.RST.11-12.1.** Determine the central ideas or conclusions of a text; trace the text's explanation or depiction of a complex process, phenomenon, or concept; provide an accurate summary of the text.

Misconceptions Addressed

- This lesson addresses many common misconceptions about genes and heredity, including:
  - The actions of protein molecules do not affect an organism's physical characteristics.
  - The actions of protein molecules do not affect the basic functions of human cells.
  - Amino acids provide instructions for making proteins in an organism. (Question 1b)
  - Genes are traits. (Question 2)
- Further information about student misconceptions on this topic can be found here.

Primary Sources

- **Bite** "Self-Tanning Mice" *based on:*
  - Mujahid, Nisma, Yanke Liang, Ryo Murakami, Hwan Geun Choi, Allison Dobry, Jinhua Wang, Yusuke Suita, Qing Yu Weng, Jennifer Allouche, Lajos Kemeny, Andrea Hermann, Elisabeth Roider, Nathanael Gray, and David Fisher. 2017. "A UV-Independent Topical Small-Molecule Approach for Melanin Production in Human Skin." *Cell Reports* 19(11): 2177–84. doi: https://doi.org/10.1016/j.celrep.2017.05.042
  - Michael, Helen T., and Glenn Merlino. 2017. "A Topical Solution to the Sunless Tanning Problem." *Trends in Molecular Medicine* 23(9): 771–73.
- **Research write-ups for a general audience**
  - Cross, Ryan. "Could this New Compound Give You a Suntan—Without the Sun?." *Science.* 13 June 2017. Accessed August 06, 2018.
  - Gallagher, James. "Drug that Creates a 'Real Sun-Tan' Could Prevent Cancer." BBC News. 13 June 2017. Accessed August 06, 2018.
- **Misconceptions**
  - "AAAS Science Assessment." AAAS Project 2061. (n.d.) [Pilot and field test data collected between 2006 and 2010]. Unpublished raw data. Accessed August 06, 2018.
  - Marbach-Ad, Gili. 2001. "Attempting to break the code in student comprehension of genetic concepts." *Journal of Biological Education 35*(4): 183–189.

Materials

Copies of the Student Handout and Science Bite for each student

Time

This lesson should take approximately one to two 50-minute class periods.

Student Prior Knowledge

Students should be familiar with the structure and functions of DNA and of the general process by which genes are expressed (gene expression/protein synthesis). It would be helpful for students to have heard of transcription factors, but not necessary. Additionally, students should have a familiar understanding of the link between DNA damage and cancer.

Instructions and Teacher Tips

General Procedure

- Have students read the introduction to the Student Handout and "Natalie and Alex's Story" to themselves, or read it aloud to the class.
- Have students answer Questions 1–3 individually or with partners.
- Check for understanding and then have students read the Science Bite and answer the remainder of the analysis questions.
- Conduct a wrap-up discussion based on the next steps scientists need to take to test drugs on humans and bring drugs to market (see tips, extensions, and variations).

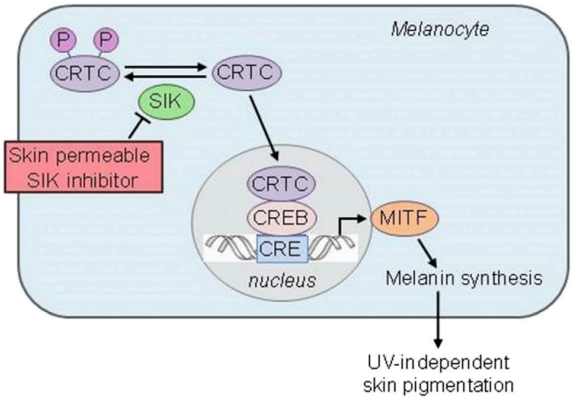
Tips, Extensions, and Variations

- To scale down the lesson, background questions (1–3) could be done as a class.
- Images in the Bite and Student Handout are most effective if printed in color. If a color printer is not available, make sure the images can be projected.
- HHMI BioInteractive has an excellent animation about human skin color. The 1-minute from 2:30 to the end would make a good introduction to the topic of skin color, tanning, and skin cancer.
- Question 5 has students consider a map showing rates of skin cancer dates from around the world. If you have time, and you think it is appropriate, consider an extension discussion. The question asks students to conclude that UV radiation affects populations in North America and Europe differently from populations in Africa and Southeast Asia because of the regions' different indigenous skin color. There are other factors at play, however, including issues of public health and even colonialism. These issues become more obvious when you look in other areas of the map. For example, skin cancer deaths are higher in Brazil than in other South American countries, perhaps these factors are relevant. Depletion of the ozone layer may also be a factor in Australia, as even though it is improving, there was a period of intense UV exposure in the 1980s and 90s. Adults in 2012 would have been exposed as children.

- As an extension, students could make an advertisement for the drug, have a debate over the market that is most in need and why, or predict how the map may change in response to the drug.
- Consider a class discussion on one of these topics upon completion of the lesson:
  - Why is it important to still use other sun protectants and avoid prolonged exposure to sun even when using this drug?
  - Should tanning beds be regulated by public health officials? Why or why not?

Background Information and Research Details

- This study involves animal testing and may be difficult to read about for some sensitive students. You can assure them, however, that the drug did not harm the mice and that they are sedated, not dead in the image shown in the Science Bite.
- There are many types of cells within the skin including melanocytes and keratinocytes. Melanocytes are the cells that are responsible for creating the pigment melanin. Melanin is then transported to the keratinocytes which are the skin cells that you see on the surface of the skin that are responsible for establishing skin tone. In general, lighter skin contains less melanin. The nuance is that the keratinocyte skin cells don't actually produce the melanin themselves.
- The paper describes a drug that can induce the natural process of tanning within the skin itself. For the purpose of student understanding, we present the drug as an agent that directly induces MITF expression. In actuality, the drug is an inhibitor of a protein called SIK which acts to decrease MITF expression. So, the drug decreases SIK which leads to the subsequent increase in MITF expression. See schematic from paper below:



- It is important to note that these drugs will induce the tanning response in humans but that tanned skin is not as strong of a protectant against skin cancer as SPF sunscreen. The drug alone will not protect against skin cancer but will only be slightly protective. This drug and possible derivative consumer product aim to decrease the usage of tanning beds and unsafe natural tanning that leads to skin cancer by providing a sunless alternative.

- Researchers spent a lot of time doing experiments in mice to determine the optimal concentration and time duration of the drug treatment to induce the tanning response. They then took this drug and created derivatives (same drug, slightly different chemical modifications) to allow it to absorb better into human skin. They then tested these drug derivatives on human skin. This human skin was extra skin leftover from surgeries, and not actually skin on living humans. (Some of the results are used as the basis for Question 12). Thus, the next steps are to take the drug, formulate it into a topical product, and conduct clinical trials on living humans. The researchers would like to do these initial experiments in fair skinned individuals who will likely benefit from increased sun protection.

Big Question Discussion

This lesson should get students thinking about the Big Question "What does it mean to observe?" In particular, how do observations in the real world and experimental settings inform what we know about skin pigmentation and sun protection. If you choose to delve into the Big Question, consider following these suggested steps:

- To open the lesson, warm students up to the idea that scientists can collect real world data such as skin pigmentation color, cancer rates, UV exposure rates, and use that information to test relationships between these factors. For example, in the lesson we see that global death rates from skin cancer are highest in regions with high levels of UV exposure (sunny areas) so this indicates that UV exposure is a possible risk factor. Observing real world data allows scientists to test hypotheses.
- Then, transitioning into sun protection, scientists determined the natural genetic pathway that our bodies use to produce melanin pigment and have observed that higher melanin pigmentation means better protection from damaging UV rays. These observations gave these scientists the idea to create a drug that increases this natural process in the skin, creating both a tan and sun protection simultaneously.

Answers

1. Transcription and translation are two important processes that occur in cells.

a. Complete the flowchart below that models the relationship between the processes.

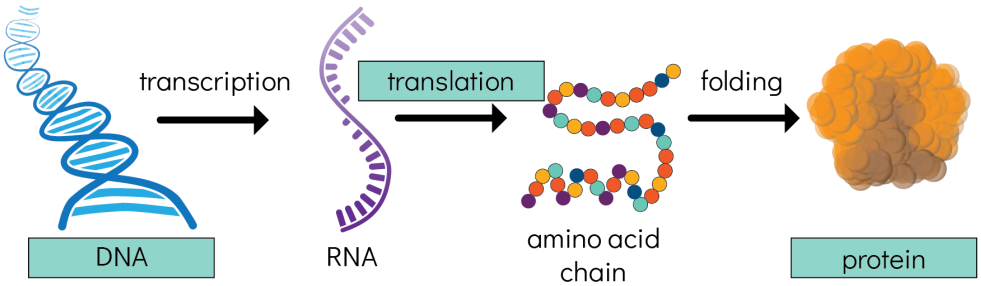


Figure 2. The Central Dogma.

b. Could translation occur without transcription? Justify your answer using the flowchart above.

No, according to the flow chart transcription must occur first to provide the "instructions" for translation to occur. Transcription must bring the protein building instructions from the DNA in the nucleus in order for translation to occur.

2. Having a copy of a particular gene does **not** guarantee that the gene will be expressed in an organism. For example, some genes require more than one copy to be present for the trait to "show up." Describe other reasons why a trait might not show up, even if the organism has a gene for the trait.

Any of the following: A gene may have a mutation in it that changes its trait or causes it not to show up; The organism may have other genes that mask the trait; You might need two copies of the gene for the trait to show up; The promoter for the gene may be missing; The enzyme to make the gene may not function properly; The transcription factor could be missing.

3. In your own words, describe the function of a transcription factor.

Sample answer: A protein that binds to a region in the DNA to promote or inhibit transcription of a protein.

4. The drug you read about causes the skin to tan without the sun.

a. What is the advantage of tanning?

Tanning increases the amount of melanin in the skin. This, in turn, creates a protective barrier around the nucleus and the DNA inside. The increased melanin acts as a shield to help prevent damage to the DNA inside.

b. If tanning has benefits, why do doctors urge people to avoid sun exposure?

Prolonged sun exposure will increase the risk of damage to DNA and may result in skin cancer.

c. Why are dermatologists (doctors that specialize in conditions related to the skin) so excited about the new drug?

The drug causes a natural response so the person is creating their own sun protection. This should reduce the rates of skin cancer from sun exposure.

Figure 3 below shows the death rates for skin cancer worldwide by country. The darker the orange, the higher the rate of death.

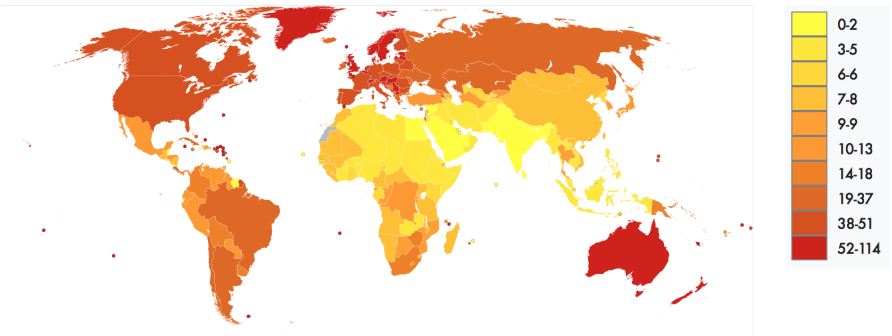


Figure 3. Global Deaths from Skin Cancer. This map, based on 2012 data from the World Health Organization, compares death rates from melanomas and other skin cancers in nations around the world. The colored scale shows deaths per one million persons. *Source:* Wikimedia Commons/Chris55.

5. Make a claim about why North American and European countries have relatively high skin cancer death rates compared to African and Southeast Asian countries. Describe evidence for your claim using information from **Figure 3**. Provide reasoning for your claim, citing information from the Bite. Provide reasoning for your claim, citing information from the Bite.

African and Southeast Asican populations tend to have naturally darker skin than North American or European populations. The Bite explains that darker skin is caused by greater amounts of melanin inside skin cells. Darker skin (or more melanin) provides greater protection against damage to the DNA inside the nucleus. This reduces the risk of skin cancer.

6. Describe the relationships among inherited genes, the pigment melanin, sun exposure, and skin cancer risk.

Genes are short segments of DNA that code for a trait and are inherited from parents via the sperm and egg. The gene for melanin production will be transcribed and then translated into the pigment melanin.

Melanin production increases in response to sun exposure. The increased melanin protects the inherited DNA from damage and skin cancer. The lighter the skin, the less melanin pigment is produced and the greater the risk of skin cancer.

Figure 4 below models how the new drug influences the production of melanin pigment.

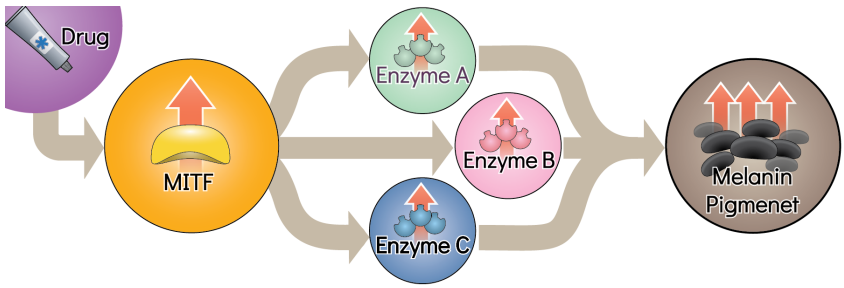


Figure 4. How the New Drug Works. The drug developed by the research team causes MITF production to increase, which in turn increases the work of many enzymes (only three modeled here to make things simpler), which in turn causes melanin production to increase.

7. Increasing the production of one molecule, MITF causes an increased response from enzymes A, B, and C because MITF is a transcription factor. In this drug pathway, the conductor is the MITF transcription factor.

Which component of the drug pathway aligns to these parts of the analogy:

a. the members of the orchestra

The enzyme pathways (A, B, C)

b. the music

The melanin pigment

8. Why would a drug that only increases the production of Enzyme A not have the same effect as the new drug, which increases the production of MITF? (*Hint:* Think about MITF's role as a conductor.)

A drug that only increases production of Enzyme A would not necessarily increase the amount of melanin pigment produced because that is only one part in the pathway. Increasing MITF, however, increases the activity of *all* the enzymes in the pathway. It'd be like if just the violins played a piece of music—it wouldn't sound right. You need the rest of the orchestra. The conductor (MITF) gets all of the instruments to play.

Use **Figure 4** below to answer Questions 9 and 10.

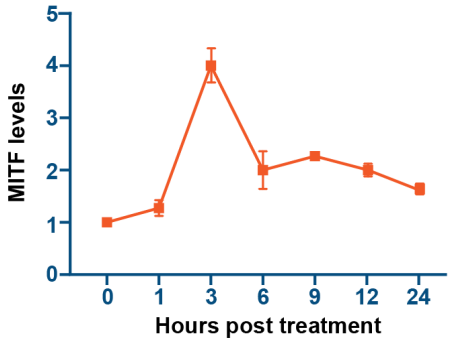


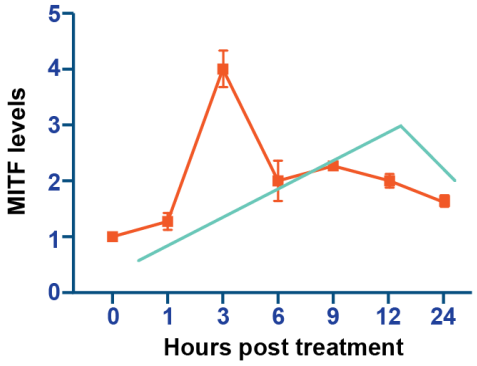
Figure 5. Experimental Levels of the MITF Transcription Factor. The drug is applied to the mice at hour 0, and levels of the MITF transcription factor are measured at different hours post-treatment. *Source:* Mujahid *et al.,* 2017.

9. Using the graph above, describe the trend in MITF production. In your answer, include information about how long it takes MITF to be expressed to its highest level and how long the MITF expression stays above normal.

MITF levels increase from level 1 at time 0 to level 4 at 3 hours post-treatment. From the graph the drug appears to continually cause expression of MITF mRNA for 24 hours, although at decreasing levels. Even at hour 24, the levels are higher than at time 0.

10. Look back at **Figure 4.** The drug first increases MITF expression, which then increases the action of the pigment producing enzymes, which then increases production of the melanin pigment itself. Thus there is likely a delay in melanin production following drug treatment.

a. Draw another line on the graph in **Figure 5** to represent the pigment production following drug exposure.



See graph, which shows the actual data. Note that any line showing a lagging increase in pigment production should be accepted.

b. Directions for applying sunscreen indicate that it should be applied twenty minutes prior to going out into the sun. How does that timeframe compare to the timeframe for effectiveness of the drug here?

Sunscreen is effective within 20 minutes. Production of melanin may not increase for nearly 3 hours.

c. How do you account for the time difference between the effectiveness of the two methods of sun protection (the new drug and traditional sun screens)?

Answers may include arguments about SPF from sunscreen being a topical shield from the outside in, while the drug is from the inside out. The drug has many steps and the process takes time while applying sunscreen is quick.

Connect to the Big Question

11. In this study, mice act as model organisms for humans. A **model organism** is a non-human animal that is studied for the purposes of understanding a biological phenomenon. In this case, mice are used to study the process of tanning and skin pigmentation in response to this drug.

a. What are some of the reasons that mice can be used as a model for humans for this study?

Answers will vary. May include reasons such as:

- The enzymatic pathway is the same.
- Mice have similar DNA.
- Mice and humans are both mammals.

b. How do scientists observe the drug's effects on the mice? How do these effects inform how the drug will be used in humans?

The researchers look for a change in skin color. They give the researchers an idea of what to expect in humans (how dark the skin might get, how long it might take for the drug to work, etc.)

c. Would you volunteer to have a new drug tested on you? For each of the following, explain whether you would you be more or less likely to volunteer for:

- a drug that has worked pretty well on mice OR a drug that has worked very well on fruit flies?
- a drug with effects you can see (like, with the skin tanning drug) OR a drug with effects you cannot see (that act on an internal organ, such as the heart or lungs)?
- a drug that could cure a disease you have OR a drug that could change the way you look (by, for example, giving you thicker hair, or stronger fingernails)?

Answers will vary.

12. After testing this drug on mice, researchers created similar drugs for humans using the same considerations that you outlined in Question 11. They tested these drugs on human skin. Results are shown in **Figure 6.**

a. Rank the three drugs shown below in terms of effectiveness in triggering the tanning response.

Drug #2, Drug #3, Drug #1

b. What other factors are important for selecting which drug to further test in humans besides the intensity of the tan it causes?

Other factors of importance are absorptivity, possible side effects and risks, environmental impacts, possibility for allergic reaction, dosage, cost, etc.

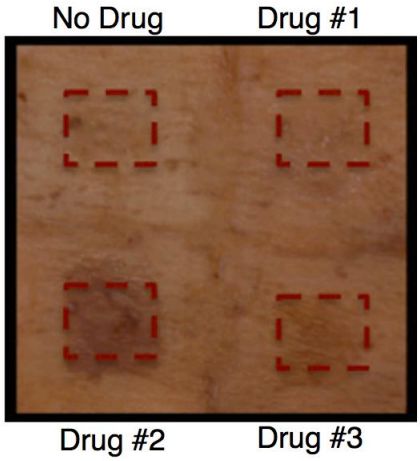


Figure 6. Drug Results. Human skin eight days after one of 4 treatments: No drug, drug #1, drug #2, or drug #3. *Source:* Mujahid *et al.,* 2017