Teacher Notes for "What causes melanoma and other types of cancer?"[1]

This minds-on, analysis and discussion activity introduces students to basic cancer biology and regulation of the cell cycle. Students view an introductory video about a teen with melanoma and then complete six sections: "What is melanoma?", "How does a melanoma develop?", "Why do melanoma cells divide too much?", "Environment and inherited genes influence your risk of melanoma.", "Different Types of Cancer", and "Research Challenge". Concepts covered include cell cycle checkpoints, somatic mutations, and DNA repair enzymes.

Before beginning this activity, students should have a basic understanding of DNA, mutations, and the cell cycle. To provide this background, you may want to use:

- "DNA Function, Structure and Replication" (https://serendipstudio.org/exchange/bioactivities/DNA)
- "Mitosis and the Cell Cycle" (at least the first two pages of https://serendipstudio.org/exchange/bioactivities/MitosisRR or https://serendipstudio.org/sci_edu/waldron/#mitosis).

Learning Goals Related to National Standards

In accord with the Next Generation Science Standards[2]:

- Students will gain understanding of the Disciplinary Core Ideas:
  - LS1.A: Structure and Function –"All cells contain genetic information in the form of DNA molecules. Genes are regions in the DNA that contain the instructions that code for the formation of proteins."
  - LS1.B: Growth and Development of Organisms – "In multicellular organisms individual cells grow and then divide via a process called mitosis, thereby allowing the organism to grow…"
- Students will engage in the Scientific Practices:
  - Constructing Explanations: "Apply scientific ideas, principles, and or evidence to provide an explanation of phenomena…."
  - Obtaining, Evaluating and Communicating Information: "Critically read scientific literature adapted for classroom use to determine the central ideas or conclusions…" and "Communicate scientific and/or technical information or ideas (e.g. about phenomena and/or the process of development…) …"
- This activity provides the opportunity to discuss the Crosscutting Concepts:
  - Cause and Effect: Mechanism and Prediction: "Cause and effect relationships can be suggested and predicted for complex natural… systems by examining what is known about smaller scale mechanisms within the system."
  - Stability and Change: "Much of science deals with constructing explanations of how things change and how they remain stable."
- This activity helps to prepare students for the Performance Expectations:
  - HS-LS1-1, "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."
  - HS-LS1-4, "Use a model to illustrate the role of cellular division (mitosis) and differentiation in producing and maintaining complex organisms."

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[1] By Dr. Ingrid Waldron, Department of Biology, University of Pennsylvania, © 2024. The Student Handout and these Teacher Notes are available at https://serendipstudio.org/exchange/bioactivities/melanoma .

[2] Quotations are from https://www.nextgenscience.org/ and NGSS "High School Life Sciences" (http://www.nextgenscience.org/sites/default/files/HS%20LS%20topics%20combined%206.13.13.pdf)

General Instructional Suggestions

To maximize student learning, I recommend that you have your students work in pairs to complete groups of related questions. Student learning is increased when students discuss scientific concepts to develop answers to challenging questions. After students have worked together to answer each group of related questions, I recommend having a class discussion that probes student thinking and helps students to develop a sound understanding of the concepts and information covered.

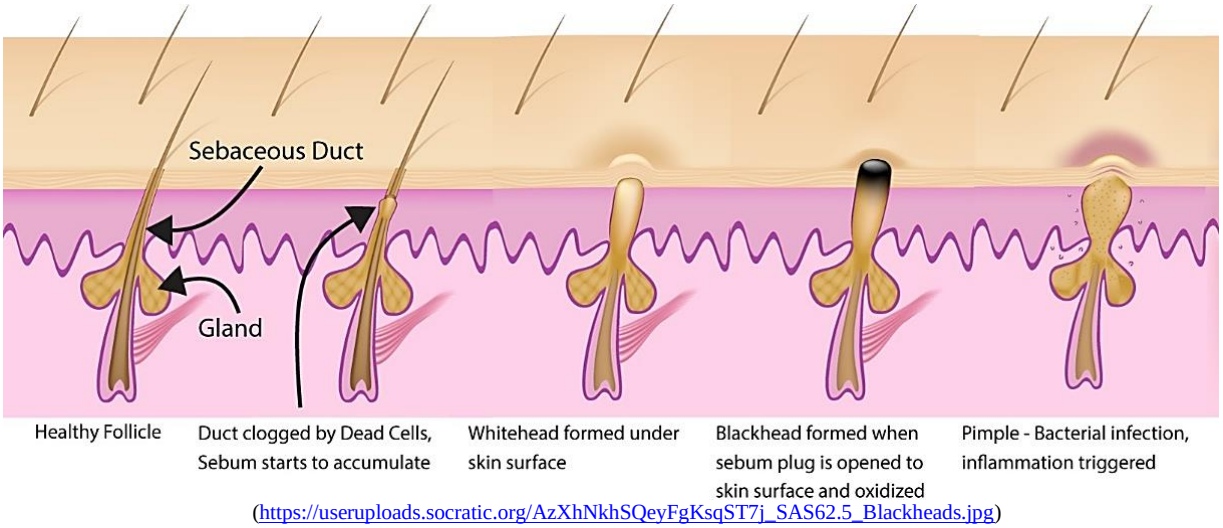
If your students are learning online, I recommend that they use the Google Doc version of the Student Handout available at https://serendipstudio.org/exchange/bioactivities/melanoma. To answer questions 3 and 12, students can either print the relevant pages, draw on them and send pictures to you, or they will need to know how to modify a drawing online. To answer online, they can double-click on the relevant drawing in the Google Doc to open a drawing window. Then, they can use the editing tools to answer the question.

You may want to revise the Word document or Google Doc to prepare a version of the Student Handout that will be more suitable for your students. If you use the Word document, please check the format by viewing the PDF.

If you want a key with the answers to the questions in the Student Handout, please send a message to iwaldron@upenn.edu. The following paragraphs provide additional instructional suggestions and background information – some for inclusion in your class discussions and some to provide you with relevant background that may be useful for your understanding and/or for responding to student questions.

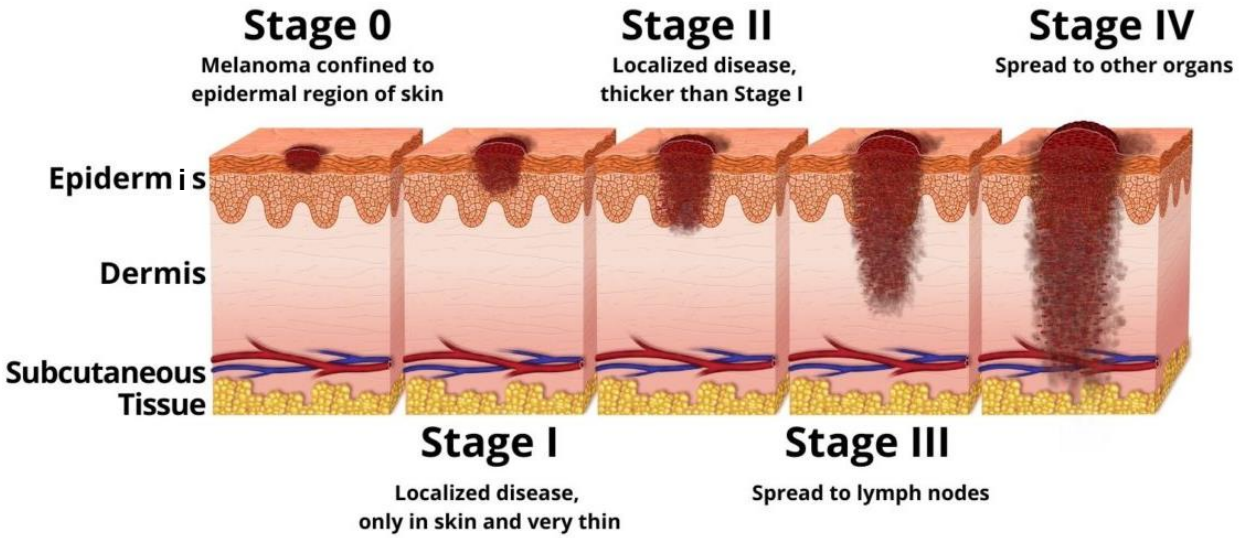
Biology Background and Suggestions for Implementation

The anchoring phenomenon is presented in the 2-minute video, Teen Survives Deadly Melanoma (https://www.youtube.com/watch?v=Zj4Bbu0xwRY). She mentions that initially she thought the mole was a blackhead, which is the accumulation of dead skin cells and sebum inside a hair follicle (https://www.mayoclinic.org/diseases-conditions/acne/symptoms-causes/syc-20368047; https://www.medicinenet.com/difference_between_blackheads_and_whiteheads/article.htm).



(https://useruploads.socratic.org/AzXhNkhSQeyFgKsqST7j_SAS62.5_Blackheads.jpg)

Early in the video the narrator says that the teen was diagnosed with stage III melanoma. Stage III melanoma is melanoma that has spread beyond the primary tumor to the closest lymph nodes, but not to any distant sites. More information about the stages of melanoma is available in the figure below and at https://www.aimatmelanoma.org/stages-of-melanoma/.



(https://www.aimatmelanoma.org/stages-of-melanoma/)

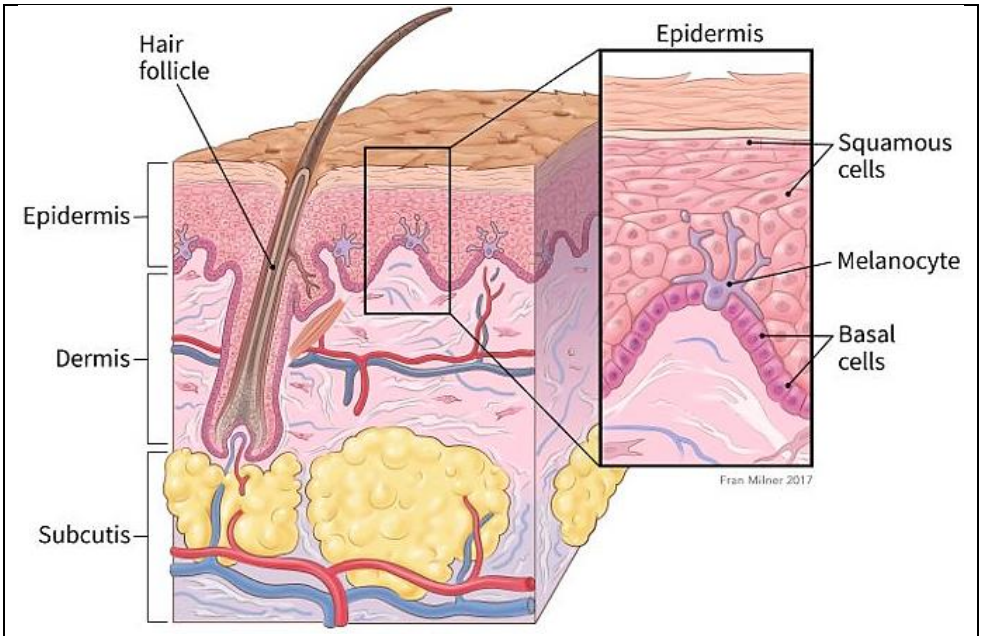
Question 1 asks students to ask questions inspired by the video. Some of these questions will be answered by the Student Handout, including the final Research Challenge section. These Teacher Notes provide answers to other likely student questions. The Student Handout focuses on answering these questions.

- What is melanoma?
- How does a melanoma develop?
- Why do melanoma cells divide more than normal melanocytes?
- What is the role of somatic mutations vs. inherited mutations (alleles)?
- Which major points about melanoma generalize to other types of cancer?

What is melanoma?

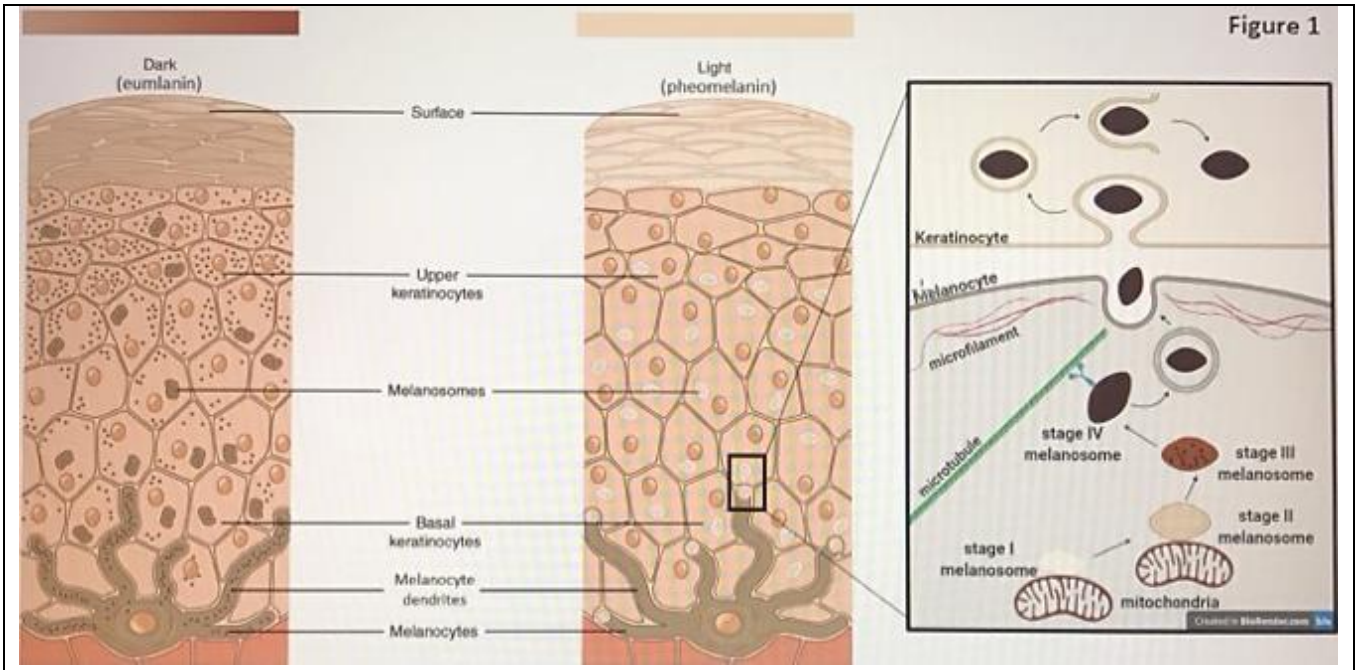
Melanoma is one type of skin cancer. Cancer is a disease in which cells divide excessively and move out of their normal location (https://www.cancer.gov/about-cancer/understanding/what-is-cancer). There are many types of cancer, including two other types of skin cancer. The right-hand part of the figure below shows the basal cells, which constantly divide to replace the squamous cells that wear off the skin's surface. Basal cell carcinoma is the most common type of skin cancer, and squamous cell carcinoma is also more common than melanoma. Fortunately, basal cell carcinoma and squamous cell carcinoma are much less likely to be fatal than melanoma. Repeated, unprotected exposure to the ultraviolet (UV) rays in sunlight or from tanning beds substantially increases the risk of basal cell carcinoma and squamous cell carcinoma.[3] (https://www.cancer.org/cancer/basal-and-squamous-cell-skin-cancer/about/what-is-basal-and-squamous-cell.html#:~:text=Basal%20and%20squamous%20cell%20skin%20cancers%20are%20the%20most%20common,body%20can%20become%20cancer%20cells.)

[3] The risk of basal cell and squamous cell carcinoma is associated with cumulative UV exposure, whereas the risk of melanoma is associated with severe blistering sunburns, usually before age 18 (https://my.clevelandclinic.org/health/diseases/10985-sun-exposure-and-skin-cancer). One hypothesis to explain this difference is that melanocytes have a limited capacity for mitosis and correspondingly melanocytes are less prone to apoptosis (cell suicide) when mutations occur; therefore, after a severe sunburn, mutated melanocytes are much more likely to survive than mutated basal cells or squamous cells which generally die by apoptosis and thus do not result in cancer (https://www.nejm.org/doi/full/10.1056/NEJM199904293401707).



The pink cells between the basal layer and the surface of the epidermis are called keratinocytes. Keratinocytes produce keratin which provides structural strength for the skin and helps to make the skin waterproof.
(https://www.cancer.org/content/dam/cancer-org/images/illustrations/medical-illustrations/en/skin-cells-epidermis.jpg/jcr:content/renditions/cq5dam.thumbnail.980.980.jpeg)

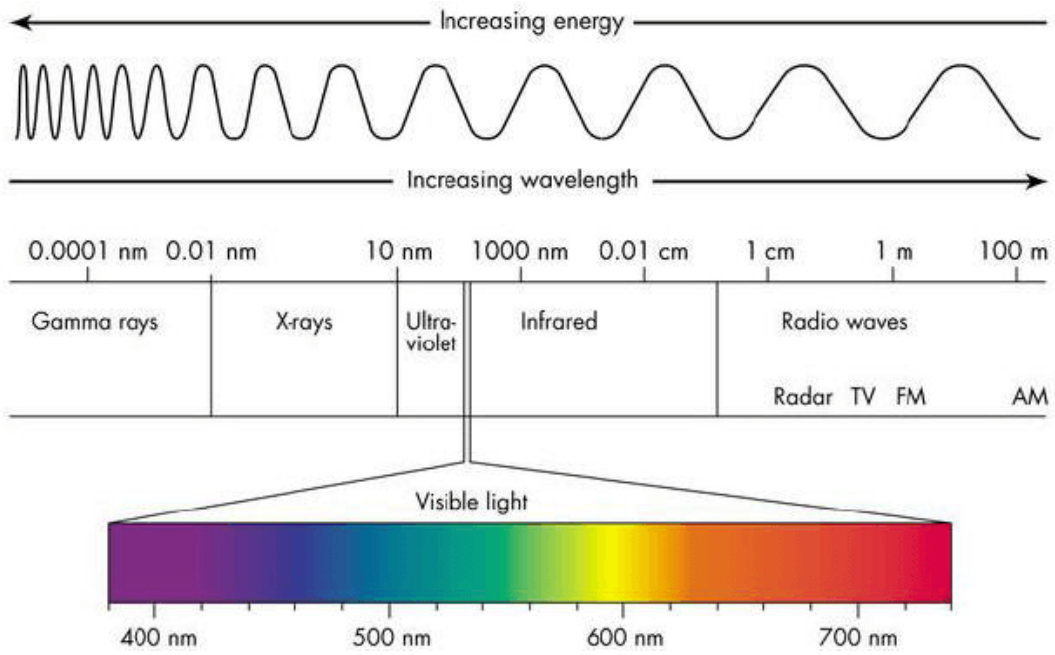
You may want to show your students the color version of the second figure on page 1 of the Student Handout, since the shape of the melanocyte is much clearer in color than in black and white. The figure below shows how melanocytes pass melanin to other skin cells (keratinocytes).



(https://www.chegg.com/homework-help/questions-and-answers/melanocytes-specialized-cell-type-gives-rise-colour-skin-hair-eyes-many-organisms-includin-q48124019)

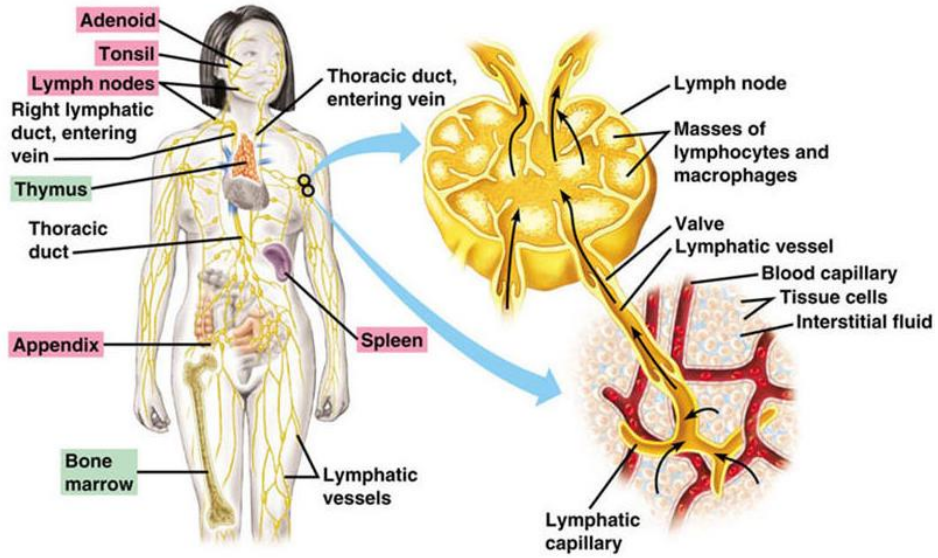
How does a melanoma develop?

The figure below shows the spectrum of electromagnetic radiation, including ultraviolet (UV) light. Additional information about UV light is available at https://blog.lightbulbs-direct.com/choosing-ultraviolet-bulbs-the-difference-between-uva-uvb-and-uvc/.



(https://www.globalspec.com/ImageRepository/LearnMore/20122/em_spectrumfa75ed256b85499ab6069256a073796c.png)

The figure below shows additional information about the lymphatic system. (See also https://www.macmillan.org.uk/cancer-information-and-support/worried-about-cancer/the-lymphatic-system.) The lymph nodes contain phagocytic and immune cells (e.g., macrophages and lymphocytes), which attack and kill some cancer cells, bacteria and viruses.



Interstitial fluid (which baths the cells) is formed continuously as some blood plasma leaks from the blood capillaries that carry the blood from the arterioles to the venules. The lymph system collects excess interstitial fluid and returns it via lymphatic vessels (including lymphatic capillaries and the thoracic duct) to the blood. (https://en.wikipedia.org/wiki/Lymph)

(figure from https://www.back2health4you.com/wp-content/uploads/2014/09/lymph-system.jpg)

The figure on page 2 of the Student Handout shows how melanoma can develop. Prognosis is often measured as the 5-year relative survival rate, which compares survival for people with a specific type and stage of cancer relative to people in the overall population. The 5-year relative survival rate for localized melanoma is 99.6%, but for melanoma that has spread to regional lymph nodes the relative survival rate is about 74%, and for metastatic melanoma the relative survival rate is only about 35% (https://seer.cancer.gov/statfacts/html/melan.html). Prognosis

also depends on the effectiveness of treatment. To improve the teen's prognosis, her second doctor removed additional lymph nodes and prescribed medicines to help her immune system recognize and destroy melanoma cells more effectively (https://www.cancer.org/cancer/melanoma-skin-cancer/treating/immunotherapy.html[4]).

Why do melanoma cells divide too much?
The 2-minute animation in the video, "Cancer: Unregulated Cell Division" (https://www.youtube.com/watch?v=IeUANxFVXKc) will give students an intuitive feel for the increased cell division that is a key characteristic of cancer cells.

Growth factors are molecular signals that influence whether a cell divides or differentiates. These molecular signals are secreted by other cells and help to coordinate the amount of cell division so the right amount of each type of cell is produced (https://www.ncbi.nlm.nih.gov/books/NBK442024/). In the absence of growth factor, the cell differentiates to carry out its normal functions.

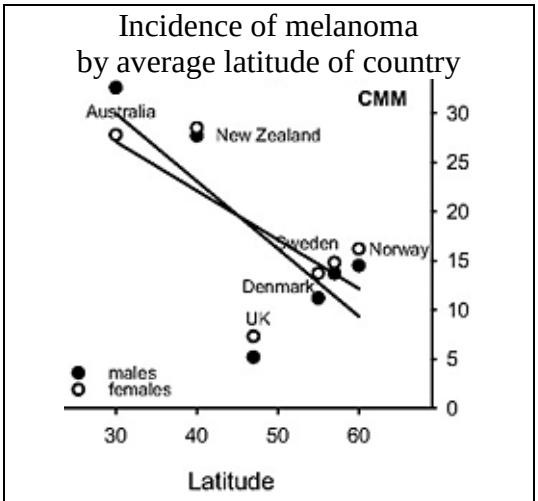
The Student Handout refers to the dividing cells as melanocytes, but they are more accurately called "melanoblasts". Melanoblasts differentiate into melanocytes by acquiring the ability to produce melanin and developing the characteristic melanocyte shape with multiple long narrow extensions that carry the melanin to multiple keratinocytes.

Normal versions of the genes that code for proteins that move the cell cycle forward are called proto-oncogenes. Mutated versions of proto-oncogenes that result in excessive cell division are called oncogenes because they contribute to the development of cancer. Genes that code for proteins that inhibit movement through the cell cycle are called tumor suppressor genes.[5] For example, if DNA is damaged, the normal p53 protein inhibits progression through the first checkpoint and recruits enzymes to repair the DNA; if the cell cannot repair the DNA damage, the normal p53 protein can trigger the cell to kill itself.[6] If both copies of this tumor suppressor gene are mutated so they code for nonfunctional proteins, this allows cells with damaged DNA to divide, which can contribute to the development of tumors. The gene for p53 is mutated in roughly one-quarter of melanomas.

Regulation of the cell cycle is more complex than the description in the Student Handout. If you want to include more information about cell cycle checkpoints, you can insert Appendix 1 after question 6. The figure in the Appendix describes the requirements to pass each major checkpoint. Growth factors are required to pass the G_1 checkpoint in order to begin cell division. The other checkpoint requirements ensure that cell division is only completed if two healthy cells can be produced. The three major cell cycle checkpoints are described further in https://www.biointeractive.org/classroom-resources/eukaryotic-cell-cycle-and-cancer?playlist=181755 and https://courses.lumenlearning.com/suny-wmopen-biology1/chapter/cell-cycle-checkpoints/.

[4] If you read this reference, you should be aware that immune system checkpoints are different from the checkpoints in the cell cycle that are discussed in the Student Handout.
[5] These categories of genes were first discovered in cancer research, which accounts for their names. Our cells need proto-oncogenes and tumor suppressor genes for normal regulation of cell division.
[6] Cell suicide is called programmed cell death or apoptosis. In order to focus on basic concepts and prevent student overload, the Student Handout does not mention technical terms such as apoptosis. Obviously, you can modify the Word or Google Doc version of the Student Handout to include any technical terms you want your students to learn.

Environment and inherited genes influence your risk of melanoma.



(https://mpkb.org/home/pathogenesis/vitamind/latitude)

This figure shows that, for predominantly white populations, the risk of melanoma is greater for geographic areas closer to the equator where UV rays are more intense. (The incidence data are age-adjusted rates for number of cases per hundred thousand population per year. CMM = cutaneous malignant melanoma.)

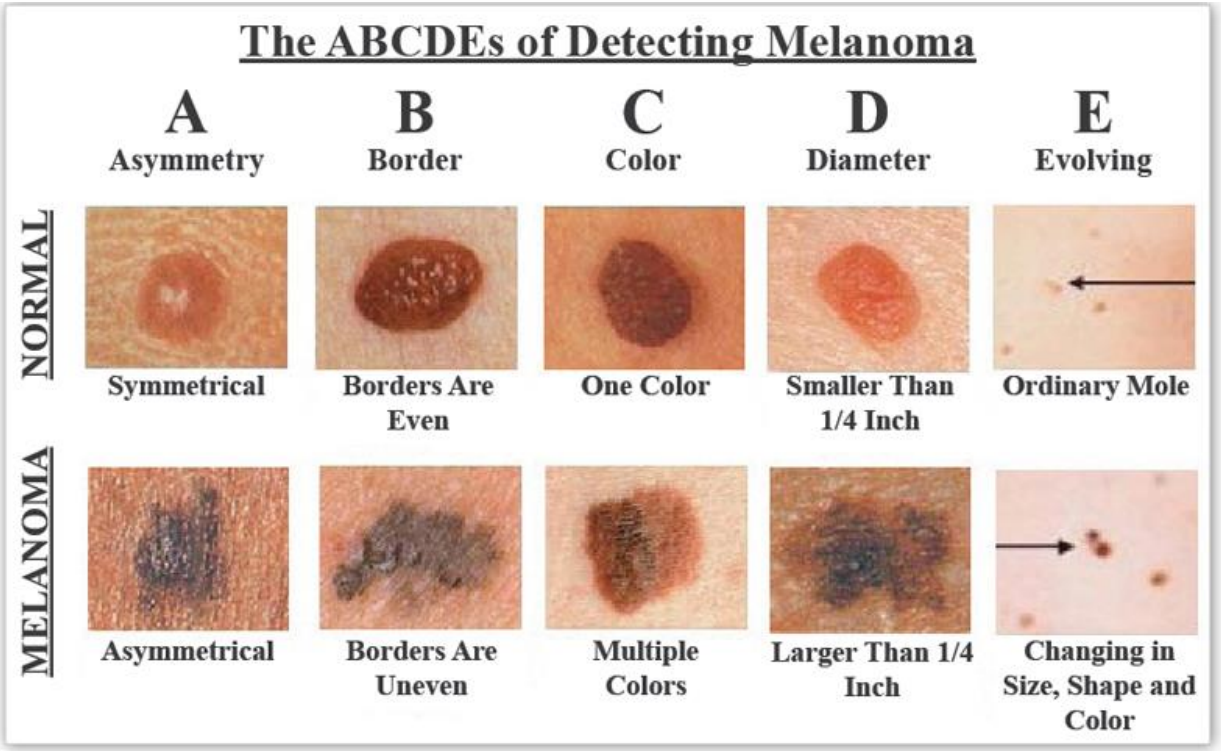
In some people, melanoma diagnosis comes decades after sunburns in childhood or as a teen. This lag is explained by the need to accumulate multiple mutations in the same cell line. The need to accumulate multiple mutations over several decades also helps to explain why the rates of being diagnosed with melanoma are higher for older people. (In addition, older people have less effective immune defenses against melanoma.)

The most effective ways to prevent melanoma are to limit your exposure to UV rays by applying enough of a broad-spectrum sunscreen with an SPF of at least 30, wearing clothing that blocks UV rays, avoiding exposure to intense mid-day sun, avoiding tanning booths, and wearing sunglasses[7] (https://www.cancer.org/cancer/melanoma-skin-cancer/causes-risks-prevention/prevention.html; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7759112/).

To prevent metastatic melanoma, it is also important to watch for new darkly pigmented spots and changing or abnormal moles.[8] If any new dark spots or abnormal moles are found, the person should seek prompt medical evaluation. The "ABCDE" criteria help doctors to diagnose melanoma in adults. These criteria include asymmetry, border irregularity, color variation, diameter > 6 mm, and evolution (change) of the spot (see figure below). It should be noted that pediatric melanomas tend to lack pigment, bleed, make raised bumps, appear uniform in color (pink or red), form from new skin spots, and have varying sizes." (https://kids.frontiersin.org/articles/10.3389/frym.2021.570445#:~:text=Melanoma%20is%20abnormal%20growth%20of,the%20diagnosis%20challenging%20for%20doctors.) You may want to show your students the 5-minute video, "Dear 16-year-old me" (https://www.youtube.com/watch?v=_4jgUcxMezM).

[7] Most melanomas arise in the skin, but rarely melanomas occur in the eye (https://www.nature.com/articles/s41572-020-0158-0); these uveal melanomas are not discussed in this activity.

[8] Only about 30% of melanomas arise from pre-existing moles. Roughly 70% of melanomas arise from individual melanocytes or a microscopic cluster of melanocytes, so it is important to look for new dark spots, as well as abnormal moles (https://www.medicalnewstoday.com/articles/319173#Broad-spectrum-confuses-consumers). It should be noted that most moles do not become cancerous.

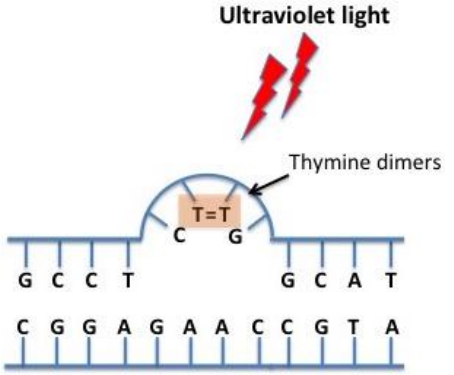


(https://pbs.twimg.com/media/EKOvPANXsAMxll_.png)

Students are introduced to the distinction between somatic mutations vs. inherited mutations (alleles). A somatic mutation is only present in the cells that are descended from the specific cell where the somatic mutation occurred. In contrast, inherited alleles are present in all the cells in the body.

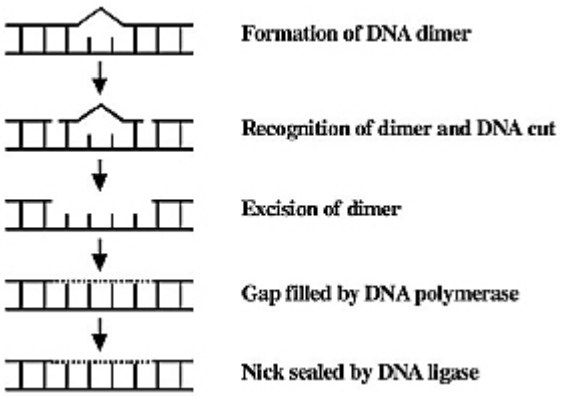
DNA damage is common, so it is crucial for a cell to be able to repair DNA damage.[9] The figures below show the type of DNA damage caused by UV light and the process of repairing this DNA damage. DNA damage can be caused not only by external factors (e.g., UV radiation), but also by molecules produced by cellular metabolism, and errors in DNA replication.

UV rays typically causes the formation of a dimer.



(https://serendipstudio.org/sci_edu/waldron/#uvmutations)

Repair of a Dimer



(http://www.nature.com/scitable/content/18125/10.1039_b201230h-f3_full.jpg)

Question 10 describes xeroderma pigmentosum (XP). XP is an inherited condition that affects about one in a million people in the US (https://medlineplus.gov/genetics/condition/xeroderma-

[9] It has been estimated that an individual cell can suffer up to 1 million DNA changes per day (https://www.nature.com/scitable/topicpage/dna-damage-repair-mechanisms-for-maintaining-dna-344/).

pigmentosum/). An individual with XP has two recessive alleles for inactive versions of one of the proteins involved in repairing the type of DNA damage caused by UV rays (see above figures). The risk of melanoma is about 2000 times greater for people with XP; this illustrates the importance of DNA repair for our health. For a person with XP, stringent measures to avoid any UV exposure can reduce the risk of skin cancers (https://rarediseases.org/rare-diseases/xeroderma-pigmentosum/).

Inherited or somatic mutations in the genes for DNA repair enzymes can result in inactive DNA repair enzymes and thus increase the rate of mutations that contribute to the development of melanoma. Nine different genes that code for DNA repair enzymes are each mutated in approximately 4-7% of melanomas.

To summarize information about mutations from this and previous sections, the development of a metastatic melanoma typically requires the accumulation of multiple mutations in the same cell line, including:

- mutations of proto-oncogenes to oncogenes
- mutations of tumor suppressor genes so they code for inactive proteins
- mutations of genes for DNA repair enzymes so they code for inactive repair enzymes
- other types of mutations that contribute to the varied abnormal characteristics of cancer cells (e.g., the ability to spread beyond the normal location of melanocytes and invade blood or lymph vessels).

A person's risk of melanoma is also influenced by inherited alleles that affect skin color. For example, in the US, melanoma is more than twenty times more common in whites than in African-Americans. Overall, the lifetime risk of getting melanoma is about 1 in 38 for whites, compared to 1 in 1000 for African-Americans (https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html). The amount and type of melanin determine skin color.[10] More melanoma in skin cells provides better protection against DNA damage due to UV rays in sunshine. You may want to show your students the 3.5-minute video, "How We Get Our Skin Color" (https://www.youtube.com/watch?v=VC0TL_lYLm8), which provides an introduction to the normal function of melanocytes and can serve as helpful background for question 11.

This section of the activity illustrates how the risk of melanoma is influenced by environmental exposures and inherited alleles. Families with multiple cases of melanoma usually have inherited alleles that increase their risk. However, 90% of melanomas occur in families that do not have another case of melanoma; this indicates the importance of environmental factors and also random, unpredictable events. An example that illustrates the importance of random events comes from breast cancer. Most women who have breast cancer in one breast do not have another cancer in the other breast, even though the cells in both breasts have the same inherited alleles and have had the same hormonal exposures and usually the same environmental exposures.

After your discussion of student answers to questions 7-11, you can ask your students how the phenomena described in this activity illustrate the Crosscutting Concept, "Cause and effect relationships can be suggested and predicted for complex natural… systems by examining what is known about smaller scale mechanisms within the system."

[10] The genetics of skin color are analyzed in "Soap Opera Genetics" (https://serendipstudio.org/exchange/bioactivities/SoapOperaGenetics) and "Were the babies switched?" (https://serendipstudio.org/sci_edu/waldron/#blood).

Different Types of Cancer

Question 12 asks students to identify important points about melanoma that they think will also apply to other types of cancer. Processes that apply to cancers generally include the following.

- Mutations in genes for checkpoint proteins can cause cells to divides excessively or allow a cell with damaged DNA to survive and divide.
- Mutations that result in inactive DNA repair enzymes increase the risk of cancer.
- Additional mutations can allow cancer cells to spread via the lymphatic or circulatory systems to cause metastases in distant locations.
- Metastatic cancer can kill a person by interfering with the function of the organ where the metastases are growing and/or by using so much nutrition that healthy cells in the rest of the body do not get adequate nutrition.
- Environmental exposures that damage DNA can increase the risk of cancer. Inherited alleles also influence a person's risk of cancer.

Cigarette smoke contains chemicals that can damage DNA and cause cancer. A pack-a-day smoker has about 10 times greater risk of lung cancer than a person who has never smoked.

Research Challenge

Concerning question 15a, if your students are having trouble thinking of a question they would like the answers to, you can suggest that they look at their answers to question 1 and/or look through the references listed in question 15b for inspiration.

With regard to question 15b, you can decide:

- whether students will work on their own or in pairs or small groups
- the format for student answers
- whether and how students will share their answers.

One suggested approach would be to have students work in pairs or small groups to prepare an answer to their question and then prepare to present their findings, using a poster or PowerPoint. Their classmates should be encouraged to ask (thoughtful) questions. Class reports with discussion are useful for (1) sharing information, reinforcing learning, and adding and clarifying important points, and (2) motivating students to develop a good understanding of the topic they are researching since they will need to be prepared to answer questions from their classmates and teacher.

I recommend that you encourage your students to use online dictionaries to find the meaning of any unfamiliar technical terms. One problem that I have encountered is that some students tend to copy information from their sources without understanding the material and putting it in their own words. Helpful guidance on this issue and the appropriate use of quotations is available at https://owl.purdue.edu/owl/avoiding_plagiarism/best_practices.html. For example, this source previously recommended these steps to help students put information in their own words:

1. Reread the original passage until you understand its full meaning.
2. Set the original aside, and write the main points you remember on a note card or in a document in a word processing program.
3. Check your version with the original to make sure that your version accurately expresses all the essential information in your own words.
4. Use quotation marks to identify any unique term or phraseology you have borrowed exactly from the source.

The recommended sources are reliable. If your students use other sources, you may want to have them first read "Evaluating Internet Research Sources" (http://www.virtualsalt.com/evaluating-internet-research-sources/).

Related Learning Activities

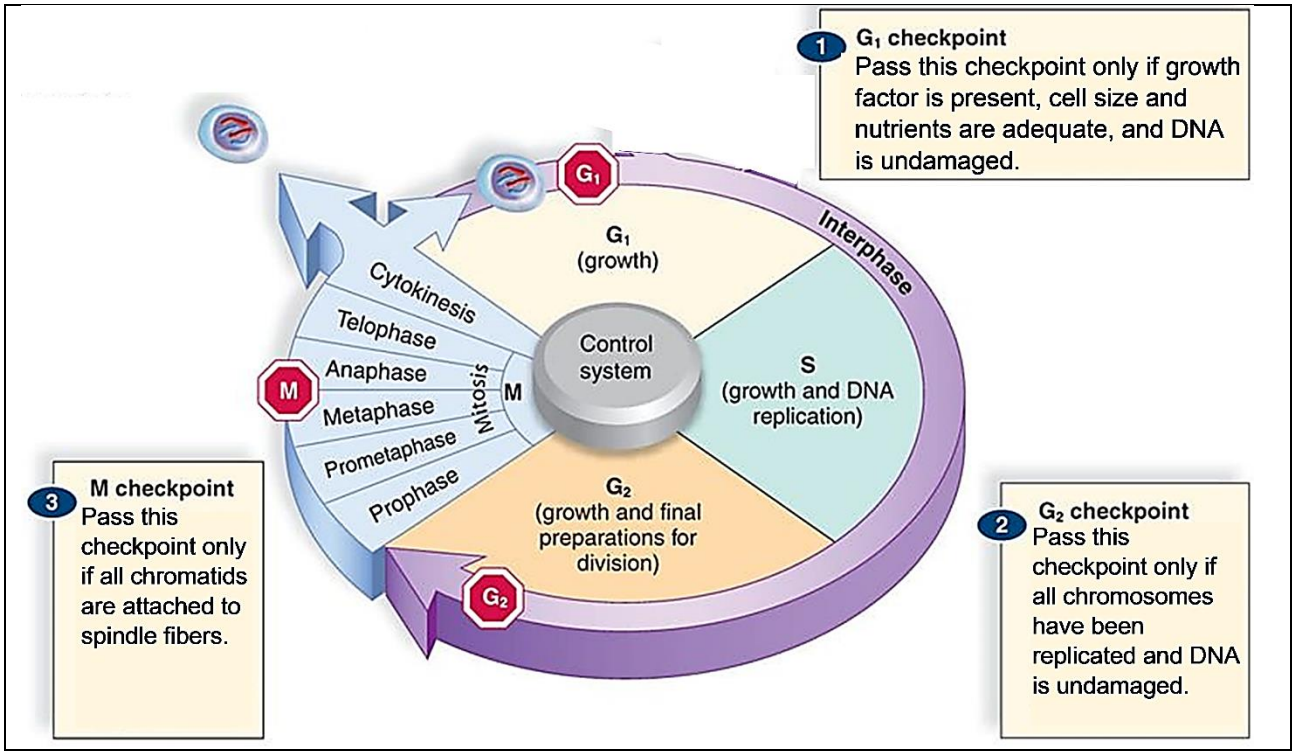
- "UV, Mutations, and DNA Repair" (https://serendipstudio.org/sci_edu/waldron/#uvmutations)
- Suggested learning activities related to cancer are described in "Resources for Teaching Cancer Biology" (https://serendipstudio.org/exchange/bioactivities/cancer).

Sources for Student Handout Figures

- on page 1, melanoma, adapted from https://www.aimatmelanoma.org/melanoma-101/understanding-melanoma/ and melanocyte, adapted from https://obgynkey.com/wp-content/uploads/2016/06/B9781455743339000719_f071-002-9781455743339.jpg
- on page 2, development of melanoma, adapted from https://www.frontiersin.org/articles/10.3389/fonc.2020.626129/full#f1
- on page 3, molecular action of growth factor, adapted from https://slideplayer.com/slide/12142459/71/images/13/Cell+cycle+control+system.jpg

Appendix 1 – Possible Student Handout insert after question 6
(figure adapted from https://images.slideplayer.com/32/10102335/slides/slide_9.jpg)

For each checkpoint, this figure shows the criteria that must be satisfied before a cell is allowed to progress to the next phase in the cell cycle. If the criteria for a checkpoint are not satisfied, the cell tries to fix the problem(s). If the cell can fix the problem(s), then the cell cycle progresses. If the cell cannot fix the problem(s), then the cell kills itself. If growth factor is absent, then a normal melanocyte exits the cell cycle and differentiates to produce and distribute melanin.



7. Complete the second column of this table to explain why the checkpoints are useful.

Checkpoints	What could go wrong if this checkpoint doesn't function correctly?
G_2	
M	