

Due Date: Friday Nov 18 at the beginning of lecture (*you may turn it in earlier*).

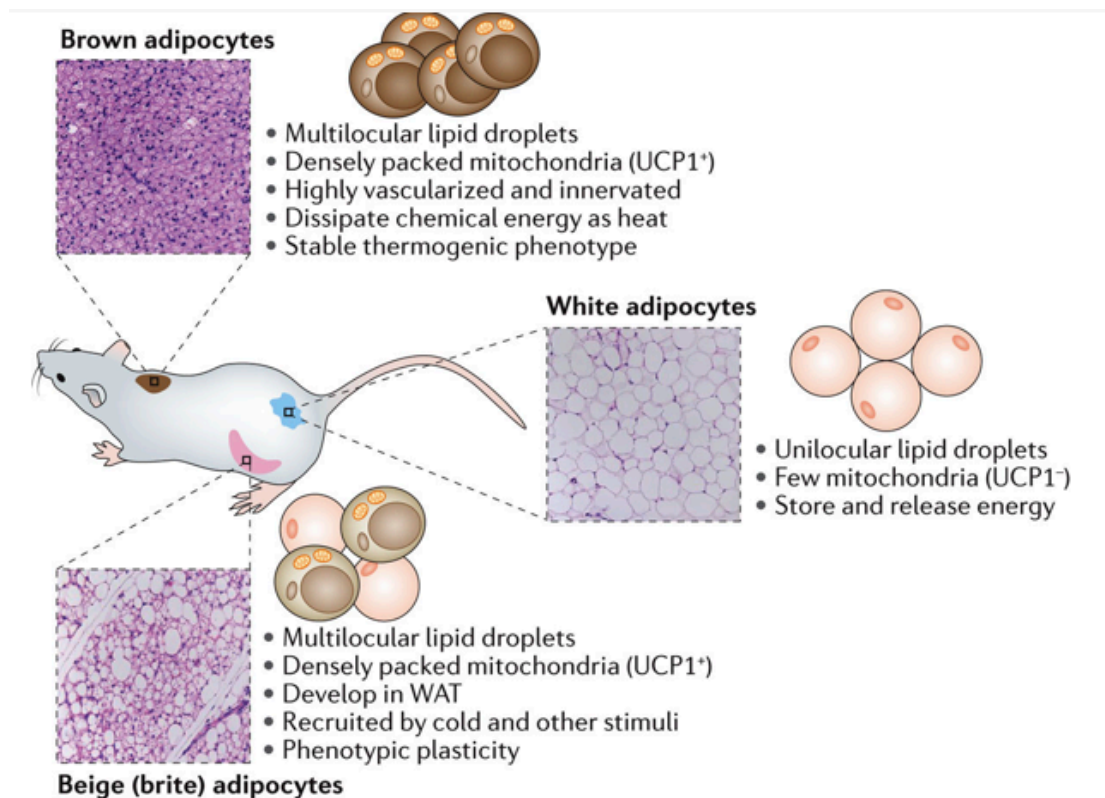
Honor Code: My signature below confirms that I did not plagiarize other students or sources while completing this worksheet.

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Learning Goal: The overall purpose of this assignment is to learn more about brown fat and the role that exercise may play in the “browning of white fat by examining a variety of current references.

Part I: Background Information

1. (2 pts) Adipose Cell Types: Mammals, including humans, have three major types of fat. The figure below is from a recent article in Nature Reviews¹. Examine the figure and read the legend carefully.



Brown, white and beige adipocytes. There are three types of adipocyte: brown, white and beige. Mice have a major interscapular brown adipose tissue (BAT) depot, as indicated. Brown adipocytes in BAT are characterized by the presence of multilocular lipid droplets and densely packed mitochondria containing uncoupling protein 1 (UCP1). BAT is highly innervated and vascularized so that it can efficiently dissipate chemical energy as heat. White adipose tissue (WAT) is dispersed in various subcutaneous and intra-abdominal depots, and contains mostly white adipocytes. White adipocytes are characterized by the presence of unilocular lipid droplets and few mitochondria that are devoid of UCP1. WAT is a major organ for the storage and release of energy. Beige adipocytes are found in various WAT depots and are especially prominent in the subcutaneous inguinal WAT. Beige fat cells develop in response to cold and certain

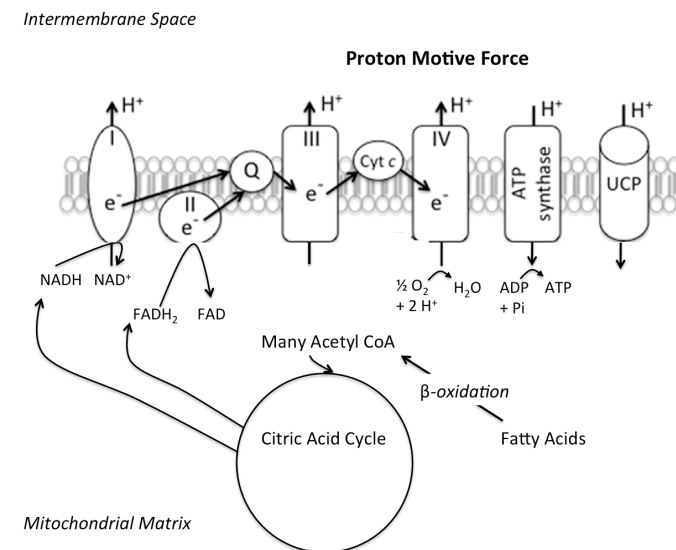
other stimuli. Like brown adipocytes, beige cells have multilocular lipid droplets and densely packed UCP1-positive mitochondria. Compared with brown adipocytes, beige adipocytes have more phenotypic flexibility, and can acquire a thermogenic or storage phenotype, depending on environmental cues

Glossary: **Interscapular:** situated between the shoulder blades; **Multilocular:** many; **Unilocula:** one; **Inguinal:** groin region

Use the table below to summarize this figure and legend.

	Type of Adipocyte		
	Brown	White	Beige
Number of lipid droplet(s)?			
Number of mitochondria?			
Presence of UCP1 in inner mitochondrial membrane?			
Within mice, what is the primary location of tissue containing this type of cell?			
What is the primary function of the adipocyte (energy dissipation, energy storage, or both)?			
Is the cell phenotype stable or can it be regulated by environmental or hormonal cues?			

2. (1 pt) Oxidative Phosphorylation in Brown/Beige Fat Cells: In brown/beige fat cells, fatty acids undergo oxidation to generate many acetyl CoA molecules. These enter the citric acid cycle to produce many NADH and FADH₂ molecules. These electron carriers donate electrons that flow down the electron transport chain to ½ O₂. The presence of the uncoupling protein (UCP1) within the inner mitochondrial membrane indicates that an adipose cells has thermogenic capabilities.



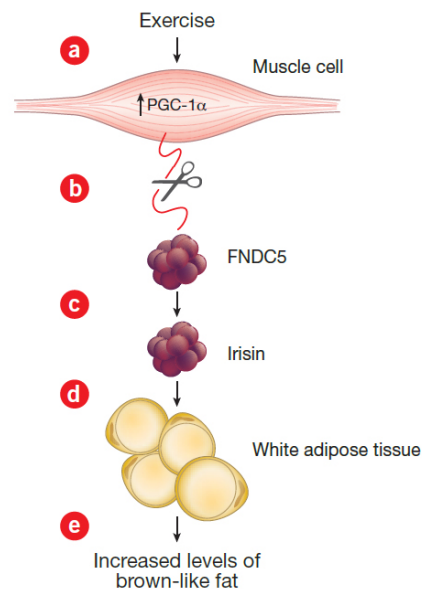
2a. (0.2 pt) Why is the exergonic flow of electrons important for ATP production?

2b. (0.4 pt) What are the four chemical products of oxidation phosphorylation?

2c. (0.4 pt) How does the presence of the uncoupling protein (UCP) in the inner mitochondrial membrane affect ATP and heat production in brown/beige fat cells?

3: (1 pt) **Irisin, Exercise, and White Fat Browning in Mice:** Below is a figure from another review article².

Exercise messenger. Dana-Farber Cancer Institute researchers have identified a new hormone, irisin, which mediates some of the benefits exercise has on metabolism. Exercise induces increased expression of peroxisome proliferation-activated receptor-g coactivator 1a (PGC-1 α) [a], which boosts expression of the membrane protein fibronectin type iii domain containing 5 (FNDC5) [b]. FNDC5 is proteolytically cleaved, resulting in the release of irisin [c], which is carried in the blood to white adipose tissue [d], where it stimulates the browning of white fat [e]. In mice fed a high-fat diet, greater expression of irisin decreased weight gain and increased glucose tolerance compared with normal irisin expression.



3a. (0.2 pt) What signaling molecule is stimulated by exercise within muscle cells?

3b. (0.2 pt) This signaling molecule stimulates the production of FNDC5, an integral protein that is the precursor of irisin. What action must occur within muscle cells before irisin is released into the blood?

3c. (0.2 pt) Irisin functions as a hormone. What is its target cell and what is its action within this cell?

3d. (0.2 pt) Scientists engineered mice to express high levels of irisin. Usually when non-engineered mice are fed a high fat diet, they become obese and show decreased glucose tolerance. What happened when the engineered mice were fed the same high-fat diet as the non-engineered mice?

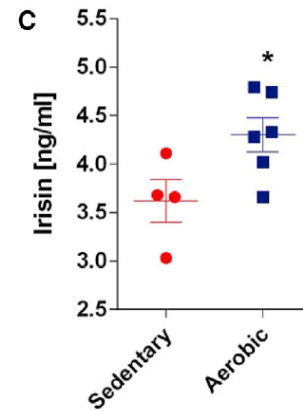
3e. (0.2 pt) Why are scientists excited about this result?

4. (1.5 pts) **Does Exercise Stimulate Irisin in humans?** Recently, a few scientists questioned the validity of previously published data that showed that exercise also stimulated irisin production in humans. This is mostly because they found fault with antibodies used to measure human irisin levels within the blood³. To

overcome experimental pitfalls related to the commercially available hormone assays, irisin levels in the blood were recently measured using the gold standard of chemical monitoring, quantitative mass spectrometry³. Below is a description from part of the Material and Methods section of this paper describing the aerobic interval training that some of the study subjects received.

Plasma samples were collected from young healthy participants (n = 6 males, 25 ± 5 years, BMI = 24.3 ± 2.5 kg/m²) following 12 weeks of high-intensity aerobic training. Training consisted of 3 days/week of intervals on a cycle ergometer (4 3 4 min > 90% peak aerobic capacity + 3 min rest) separated by 2 days/week of walking on a treadmill (45 min at 70% peak aerobic capacity).

All training was supervised at the Dan Abraham Healthy Living Center at the Mayo Clinic, Rochester. A separate sedentary group served as no-treatment control (n = 4 males, 26 ± 3 years, BMI = 26.1 ± 3.4 kg/m²).



Irisin levels in plasma from sedentary subjects (Sedentary) or subjects undergoing aerobic interval training (Aerobic). Values are shown as mean ± SEM; n = 4 (Sedentary) and n = 6 (Aerobic). *p = 0.0411 compared to sedentary subject group as determined by unpaired t test, two-tailed.

4a. (0.5 pt) In this study, what was the sex, average age, and average body mass index (BMI) of the subjects in the treatment and control groups?

4b. (0.5 pt) What type of aerobic training did the treatment group receive?

How long was the aerobic training?

4c. (0.5 pt) Statistically, the plasma irisin levels were higher in the aerobic treatment group than the control group.

What statistical test was conducted to determine this finding?

What value is used to determine if two means are statistically different?

What p values indicate that two mean are significantly different?

Part II: New research findings

5. (2.5 pts) **How Exercise May Turn White Fat into Brown**⁴. This recent NYT article discusses findings from a paper published in the American Journal of Physiology – Endocrine and Metabolism. In this study, scientists obtained mature white fat cells, fat stem cells, and brown fat cells from human tissue and cultured each cell type with irisin for four days.

a. (2 pts) Use the table on the follow page to help you summarize the findings from this investigation.

Human Cell Type	Mature White Fat Cells	Fat Stem Cells	Brown Fat Cells
What is the source of fat tissue?			
Did irisin treatment increase or have no effect on UCP1 expression in fat cells?			
Did irisin cause the cells to change function?			

b. (0.5 pt) Who is Dr. Li-Jun Yang, where does she work, and why does she suggest you “exercise as much as you can”?

6. (2 pts) Locating the primary paper discussed in *How exercise may turn white fat into brown*.

6a. (0.5 pt) Identify several key words or dates from the NYT article that will help you locate the primary paper.

6b. (1 pt) Locate the primary paper using Google Scholars. Remember to access Google Scholars through IU libraries and click on the IU-link to download free copy of the **PDF version** of the paper. Carefully examine the first page of the **PDF**, and answer the following questions.

6b1. (0.25 pt) What is the title of the paper?

6b2. (0.25 pt) How many authors contributed to the paper?

6b3. (0.5 pt) Read the first paragraph of the introduction to answer the following questions.

If an individual has a high BMI, would he/she most likely have high or low amounts of brown adipose tissue (BAT)?

Why might individuals lose weight if the amount and/or activity of their brown fat deposits increased?

6c. (0.5 pt) Use the CSE **citation-sequence** format⁵ as you did in DG4 worksheet to provide a citation for this primary reference (see class website/Scientific inquiry for a link to information about the CSE citation-sequence format and follow the link for **End References** and **Reference List/ Journals**).

References:

- ¹Wang W, Seale P. Control of Brown and Beige Fat development. *Nat Rev Mol Cell Biol.* 2016;17:691-702
- ²Kotz J. Browning fat. *SciBX.* 2012;5(5):114
- ³Jedrychowski MP, D. Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP, Spiegelman BM. Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. *Cell Metab.* 2015;22:734–740
- ⁴Reynolds G. How exercise may turn white fat into brown. *The New York Times* [Internet]. 2016 Oct 12 [access 2016 Oct 16]. Available from: <http://www.nytimes.com/2016/10/12/well/move/how-exercise-may-fight-obesity-by-turning-white-fat-into-brown.html>
- ⁵The Writer’s Handbook CSE Citation-Sequence and Citation-Name Documentation [Internet]. Madison (WI): The University of Wisconsin-Madison; c2014 [cited 2016 Feb 14]. Available from https://writing.wisc.edu/Handbook/DocCSE_CitationSystems.html#internet