Biology of Cancer Writing Assignment

Based on the information below, you will write a research proposal 3-5 pages in length (double-spaced, not including references). Draw upon information that you have learned in this course (and others) to guide you.

Due Dates:

- Outline – Friday, 3/21/2014 @11:59 pm
- Rough draft – Friday, 4/4/2014 @ 11:59 pm
- Final draft – Thursday, 4/10/2014 @ 11:59 pm

Background Information

During DNA replication, sometimes the DNA polymerase can make an error and incorporate DNA bases that don't match up (a T with a G, for example). Cells have a system to check for these kinds of mistakes called **mismatch repair**. A complex of proteins (creatively named the **mismatch repair complex**) scans the DNA for areas where the nucleotides look irregular and don't follow the typical base pairing rules. Once they find a mismatched pair of nucleotides, they recruit an exonuclease to remove the mutated bases, and DNA polymerase fills in the gap. For a video of this process, see http://www.hhmi.org/biointeractive/mismatch-repair.

In eukaryotes, the mismatch repair complex is composed of many different genes, including *MSH2*, *MSH3*, *MSH6*, *MLH1*, *MLH3*, and *PMS2*. In mouse studies, homozygous deletion of these mismatch repair proteins causes an increase in somatic mutation frequency (see Figure 1). Homozygous mutation of *Pms2*, *Mlh1*, or *Msh2* cause moderate increases in somatic mutation frequency. Mutation of *Msh3* or *Msh6* cause smaller increases in somatic mutation. Knockout of two genes together (either *Msh2* and *Msh3* or *Msh3* and *Msh6*) causes a large increase in somatic mutation, showing some synergistic effects of these combinations of genes.

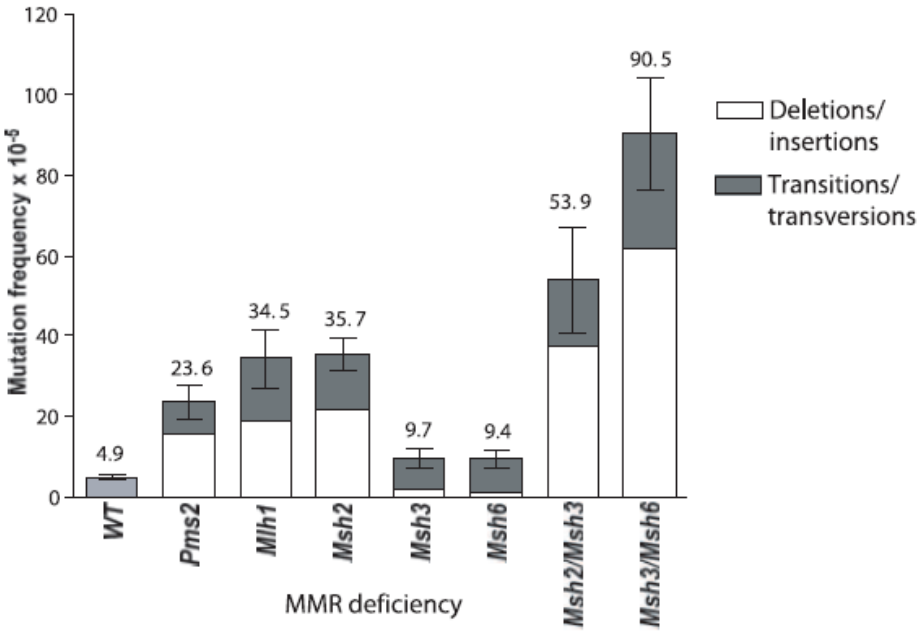

Figure 1. Mutation frequencies in wild-type and mismatch repair-deficient mouse lines. (Hegan DC Narayanan L, Jirik FR, Edelmann W, Liskay RM, Glazer PM. Differing patterns of genetic stability in mice deficient in the mismatch repair genes Pms2, Mlh1, Msh2, Msh3 and Msh6. Carcinogenesis 2006; 27: 2402-2408.).

In this manner, the mismatch repair complex has a function similar to the DNA damage response genes and p53 (Weinberg, pg. 320). These pathways attempt to maintain genetic integrity and avoid mutations. Either repair mechanisms can fix the DNA damage, or the cells will undergo apoptosis (Weinberg, pg. 329). Mutations in these genes can mean that DNA damage will not be repaired and instead will be passed on to daughter cells during cell division, a notable source of mutation in human cancers (Weinberg, pg. 311).

Germline mutations in the mismatch repair genes can be passed down through families from parent to child. Section 9.12 and Figure 9.20 in Weinberg (pg. 332-333) illustrate that germline mutations in tumor suppressor genes can lead to a variety of different cancer phenotypes. Patients who are heterozygous for one of the mismatch repair genes (one wild-type allele and one mutated allele) are prone to Lynch syndrome (hereditary nonpolyposis colorectal cancer as well as cancers of the ovaries, uterus, stomach, small intestine, urinary tract, brain, and skin).

There is evidence that these diseases follow a Knudson two-hit mutation mechanism (Weinberg, pg. 214). As you may recall, diseases such as retinoblastoma follow a two-hit mechanism where both alleles of a particular gene must be mutated to cause disease. In the case of people with heterozygous mutations in a mismatch repair gene, a single somatic mutation in the wild-type copy of the gene would be sufficient to cause tumor formation.

Given that people who are heterozygous for mismatch repair gene mutations are prone to higher rates of cancer, and that the incidence of cancer depends on how frequently somatic mutations

occur, then it would be prudent to study environmental factors that can predispose this at-risk population to somatic mutations and cancer.

Research Proposal

Question to be answered: What environmental factors or behaviors cause an increase in somatic mutation and cancer in patients heterozygous for a mismatch repair gene?

Introduction

First, you should investigate what sorts of environmental factors or behaviors can cause an increase in somatic mutations. Search the literature (PubMed, Google Scholar, etc.) for studies on your environmental factor or behavior of choice. You can also look for cancer experiments that you would want to apply to your research question. Keep track of these papers in the References section.

From these papers, introduce the question to be answered. Discuss why this question is important and who would be affected by this problem. Direct your writing to someone who has never heard of this problem, so include background information that the reader would need to understand your proposed experiments.

Hypothesis and Variables

Use your background research from your introduction to propose a hypothesis. Identify the independent and dependent variables in your experiment. Remember that the independent variable is either what you are changing or the group that you are studying, whereas the dependent variable is what you will be measuring. Lastly, what variables are you going to hold constant between the groups (name at least 2).

Experimental Design

As in a real research project, you will have to choose a model system or organism for your experiments. You can work in cell culture (animal cells grown in Petri dishes). Another possibility is to work in a model organism such as yeast (*Saccharomyces cerevisiae*), flies (*Drosophila melanogaster*), zebrafish (*Danio rerio*), mice (*Mus musculus*), rats (*Rattus norvegicus*), or another animal of your choice. Keep in mind that the smaller the organism, the faster/shorter its lifespan. For example, flies can breed more flies in about 10 days whereas a mouse would require 2 months. Lastly, you can conduct a clinical trial on people. State which species or system that you will use and explain why you made that choice.

In designing your experiment(s), be sure to include control and experimental groups. Clearly explain what you will do to these groups in the experiment and what you will be measuring. Based on your hypothesis, what results are you expecting to find? This section is the heart of the assignment, so make sure you include lots of details and descriptions of your experiments.

Conclusions

Based on your predicted results, what conclusions could you draw about your experiments? What recommendations would you make to patients who are heterozygous for mutations in one of the mismatch repair genes? Do you recommend that they take precautions for their diet, behavior, medical treatment, etc.?

References

You are required to use at least 5 scholarly references, meaning they have appeared in professional science journals. In addition, you can reference your textbook, but it will not count as 1 of your 5 required references. References should be formatted in this manner:

Author 1, Author 2, Author 3,…, Last Author. Title of article. Journal name. Year published; Volume: Page numbers. Paste URL.

For example:

Hegan DC Narayanan L, Jirik FR, Edelmann W, Liskay RM, Glazer PM. Differing patterns of genetic stability in mice deficient in the mismatch repair genes Pms2, Mlh1, Msh2, Msh3 and Msh6. Carcinogenesis 2006; 27: 2402-2408. http://carcin.oxfordjournals.org/content/27/12/2402.short.

Outline – Due Friday, 3/21/2014 @ 11:59pm **(25pts)**

The outline for this assignment should state:

- Question to be answered – **1pt**
- Your hypothesis – **4pt**
- Independent variable – **2pt**
- Dependent variable – **2pt**
- Constant variables – **1pt**
- System or organism to be used (cell culture, mouse, zebrafish, human, etc.) – **2pt**
    - State why you chose that system or organism – **2pt**
- A brief overview of your experiment
    - Identify the control and experimental groups – **2pt**
    - State what you will do to these groups and what you will measure – **8pt**
- At least 3 scholarly references you will use in your proposal – **1pt**

Rough Draft – Due Friday, 4/4/2014 @ 11:59pm

Turn in a complete rough draft of your proposal along with the scholarly references (at least 5) you used. This draft will be read and you will receive feedback to help make your proposal (and grade) better. While this draft will be examined for content and style, the grade for the rough draft is based on completion. You will earn **25pts** for submitting a completed rough draft by the due date. Drafts submitted after the deadline will receive **0pts**, but we will still read the drafts and give feedback.

Final Draft – Due Thursday, 4/10/2014 @ 11:59pm

After incorporating the feedback from the rough draft, turn in the completed final draft of your proposal along with the scholarly references (at least 5). This is the version of the final draft that will be assessed for a final grade on this assignment.

Grading Rubric – Rough & Final Drafts

Proposal Section	**Criteria**	**Points Possible**	**Points Earned**
Introduction	-Background information -State central question	4 1	
Variables	-Independent variable -Dependent variable -At least two constant variables	2 2 1	
Hypothesis	-Answers central question -Contains indep. & dep. variables	5 5	
Experimental Design	-System/organism identified and justified -Control & experimental groups described -Detailed description of experiments -How is the independent variable changed in groups studied? -How is the dependent variable measured? -Predicted results if hypothesis true	10 10 10 5 5 5	
Conclusions	-Conclusions based on predicted results -Recommendations for patients	5 5	
References	-At least 5 scholarly references -Formatted correctly	2.5 2.5	
Writing	-Organization – topic sentences, transitions, flow of ideas -Content & support – effective points, good use of references -Audience – vocabulary appropriate for target audience -Grammar & spelling – very few errors	5 5 5 5	