When a Gene Turned Off Is a Matter of Life or Death: Epigenetic Influences on Gene Regulation

by
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Part I – Jordan's Health Concerns

Jordan had just finished high school and was very excited to start a new chapter in his life. Graduation seemed like just yesterday, with all of the presents, balloons, and celebrations with friends and family. Jordan was bummed that he would not be able to go to school with his high school buddies anymore, but he could not wait to be a college student. The reality was that Jordan had wanted to go to Blake University ever since he was in 10th grade when he had visited there. The campus was amazing, and the students seemed happy. The school also had phenomenal sports teams, and Jordan was certain his chosen academic program would help him attain his career goals.

Unfortunately, a week after graduation Jordan started to feel ill and he did not seem to be getting better after several days. He was often nauseous and at times he would just throw up for what seemed like no apparent reason. Initially he thought he had a stomach virus or food poisoning, but when it persisted and he started having difficulty with his vision, he realized that it could be something more serious. One particular afternoon, Jordan was feeling extremely tired and did not want to get out of bed.

Jordan's mother entered his room: "Jordan, it's 2 o'clock in the afternoon and you're still in bed. Is something wrong?"

"I just don't feel good. My head is still hurting and I am having trouble seeing," Jordan replied.

"I'm really worried about you Jordan. This doesn't seem right."

Jordan's mother took him to the hospital that afternoon. Over the course of several days the doctors ran various tests to try to figure out what was going on, including a blood test for normal liver function as well as a CT scan.

Questions

1. Based on his symptoms, what do you hypothesize is wrong with Jordan?
2. What additional information do you need to know in order to support this hypothesis?

Part II – Jordan's Diagnosis

Jordan's blood test results came back negative, a huge relief. However, the CT scan was inconclusive as the doctors were uncertain as to whether the image showed an abnormal finding. They decided to order an MRI, which was a much more sensitive test.

Jordan had a feeling that something was not quite right when the technician performing the MRI had a concerned look on his face after the procedure. After a period of waiting, Dr. Kale called Jordan and his mother in to talk with them. Jordan would never forget that day.

"Jordan," the doctor began. "I am sorry to tell you this, but you have a brain tumor."

Jordan's heart sank. He could not believe what he was hearing. His mother gasped for breath and nearly fainted. Jordan tried to calm her and she became less agitated.

"The tumor is on your occipital lobe, a part of the brain that plays a role in vision," continued Dr. Kale as she showed them images from the MRI. "This is why you have had trouble seeing."

Dr. Kale further explained that they would need to perform surgery to remove and further characterize the tumor. At this point they were uncertain if there were additional tumors. This news made Jordan become anxious and his mind raced. What type of tumor could it be? Jordan had so many plans in life—he wanted to finish college and find a good job. He wanted to go abroad and discover the real world. Why was this happening to him? He was too young to die.

Questions

Access the following National Cancer Institute link (or another reputable source) to answer Questions 1–3: http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer

3. What type of tumor could Jordan have? Explain your reasoning.
4 What is the difference between a benign and malignant tumor?
5. How do cancers form?

Part III – Jordan's Therapy

The medical team taking care of Jordan ran further tests on the tumor by taking a biopsy of the tissue to determine whether it was cancerous. The biopsy results supported that Jordan had Stage IV glioblastoma multiforme, an aggressive cancer of the brain. Glioblastomas are cancers involving the astrocytes, a type of supporting cell in nervous tissue. They often spread quickly to other parts of the brain, and it is hard for surgeons to be able to fully remove them.

The doctors determined that they would perform surgery and attempt to remove the tumor. This was tricky as it was associated with the areas in his brain that controlled vision. With some of the top surgeons in the country performing this delicate procedure, Jordan was comforted that the surgery would have good outcomes.

The day of the surgery came and the surgeons were able to remove some of the cancer cells, but not all of them—it appeared some had spread. The doctor indicated that Jordan would need to undergo adjuvant chemotherapy as well as radiotherapy, and that they would monitor him to see how his body responded. One particular drug he would take was temozolomide. This drug damages actively dividing cells. Temozolomide works in most but not all patients with glioblastoma. An individual's epigenetic markers on a particular gene, *MGMT* (O-6-methylguanine-DNA methyltransferase), are associated with the effectiveness of temozolomide. Epigenetic tags enable genes to be turned on and off. The flow of genetic information is typically from DNA to RNA to protein. When genes are turned off, they do not express their encoded proteins. Cytosine methylation of DNA and the deacetylation of histones are two ways that genes are switched off.

All of these treatments would mean that Jordan would miss his entire first year at Blake University.

Questions

6. In general, how do cancer chemotherapies work? Use the following source of information for your answer [Informed Health Online]: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072611/
7. The promoter region of DNA is where the enzyme RNA polymerase attaches to start transcription of a gene into RNA. Figure 1 shows examples of unmethylated and methylated promoters. What effects do you hypothesize that methylation can have on the expression of a gene?
8. Examine Figure 1 and describe how methylation of the *MGMT* promoter relates to the probability of survival of patients with glioblastoma.
9. Ignoring whether or not the *MGMT* promoter is methylated or unmethylated, do these cancer patients generally have a good prognosis?

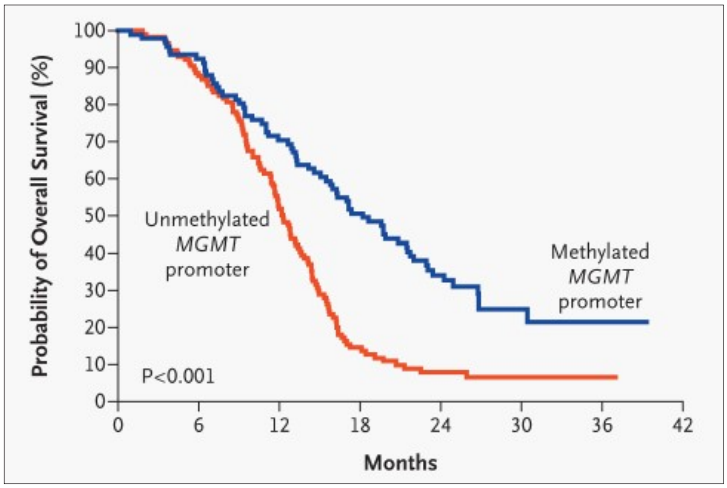

Figure 1. Probability of Overall Survival of Glioblastoma Patient. From *The New England Journal of Medicine,* Hegi, M.E. et al., *MGMT* gene silencing and benefit from temozolomide in glioblastoma, 352, 997–1003, Figure 2. Copyright © 2005 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

10. Propose at least two other ways that doctors could treat Jordan's cancer regardless of whether or not his *MGMT* promoter is methylated or unmethylated.

Part IV – Gene Regulation

Not all individuals with glioblastoma respond the same to similar treatment. This can at times be attributed to differences in their genetic backgrounds. The patients who do not respond well to temozolomide chemotherapy and have overall low survival rates are those that have unmethylated *MGMT* promoters.

Recall from the pre-class videos that chemicals and other agents such as radiation can damage DNA. Typically cells have biochemical helpers to correct such damage, including specific proteins that repair DNA.

The *MGMT* gene encodes a protein that is involved in the repair of DNA. When *MGMT* cytosines are methylated, it is turned off and does not repair the DNA in the cancer cells damaged by temozolomide. As a consequence, the cancer cells undergo apoptosis, and thus, the drug can more successfully kill the cancer cells. However, when the *MGMT* promoter is unmethylated, the gene is turned on and the protein synthesized repairs the DNA of the cancer cells damaged by temozolomide, rendering the treatment ineffective because the targeted cancer cells do not die by apoptosis.

Questions

11. What role does MGMT play in cancer cell regulation?
12. Is it more favorable for Jordan to have methylated or unmethylated *MGMT* promoters? Explain why.
13. Examine Figure 2 and describe based on the graphical results the best hypothetical treatment for Jordan if his *MGMT* promoter is unmethylated.

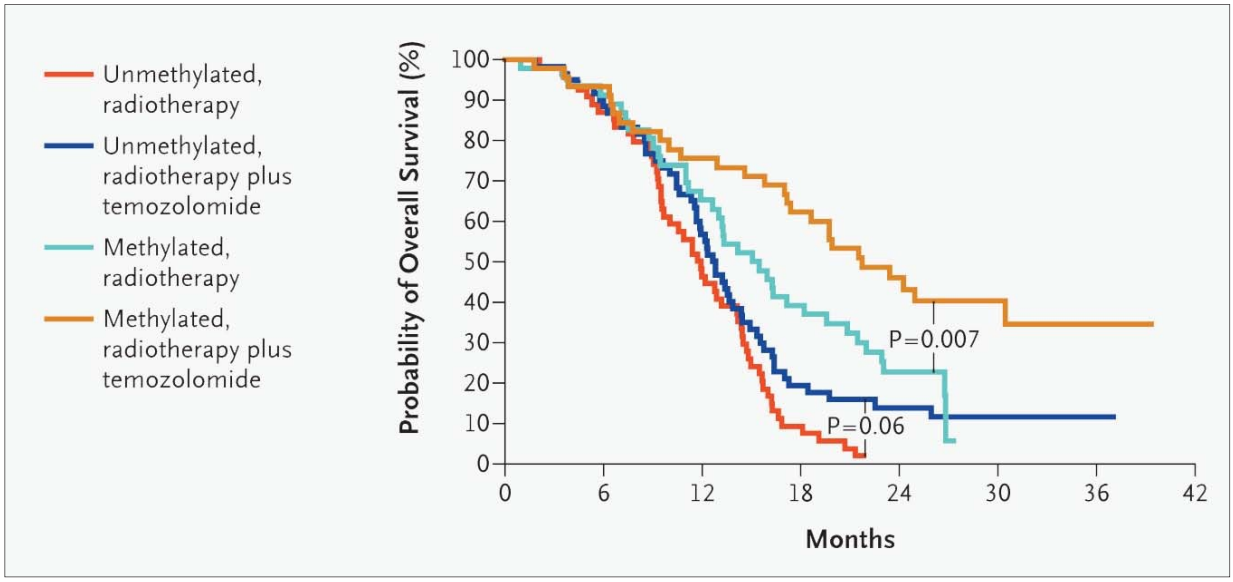

Figure 2. Treatment of Glioblastoma as Related to Overall Survival. From *The New England Journal of Medicine,* Hegi, M.E. et al., *MGMT* gene silencing and benefit from temozolomide in glioblastoma, 352, 997–1003, Figure 3A. Copyright © 2005 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

14. Relate *MGMT* methylation to what you know about the central dogma/flow of genetic information and how genes are expressed.
15. If Jordan had an identical twin, what is the likelihood that his brother would also develop this cancer?
16. Devise a therapy that could potentially circumvent resistance to temozolomide.

Part V – Jordan's Fate

Jordan was very fortunate. His *MGMT* promoter was methylated and he responded well to the combined temozolomide and radiotherapy treatment. Two years after his initial diagnosis, the doctors declared his cancer to be in remission. Soon after, Jordan was found smiling, gazing out of his dorm room window at Blake University, excited for what was to come.

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