NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Metabolism Out of Control: Does Dysfunctional Regulation Lead to Cancer?

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Julia sat lost in thought in the library. "Julia! Snap out of it! We have to get back to studying this metabolism stuff for our biochemistry exam!" came a sharp voice. It was Sam, her best friend and biochemistry study partner.

"I'm sorry, Sam. It's just that my mom called earlier. My grandmother has breast cancer. I just can't stop thinking about it, but at least they caught the cancer early. The doctors are hopeful that she can make a full recovery. It's weird though; in addition to chemotherapy or radiation, the doctor suggested that she try a low carbohydrate diet. She isn't overweight or diabetic, so what's the point of that?"

Sam thought for a moment. "I actually remember Professor Smith mentioning that there might be a link between abnormal metabolism and some cancers. Maybe we can find something in our metabolism information!"

"That's a great idea," Julia said and she was visibly more relaxed. "This might help both my grandmother and our biochemistry grades."

A few minutes later, Sam and Julia found some useful information. Julia read that it has been known for a long time that many cancer cells use a larger amount of glucose, have much higher rates of glycolysis, and produce more lactic acid (even when oxygen is present) than normal healthy cells (Koppenol, 2011; Warburg, 1956). Cancer cells preferentially produce the majority of their ATP from glycolysis instead of mitochondrial oxidative phosphorylation. Julia looked up from her computer. "So there really might be a link between metabolism and cancer. Do you think that cancer disrupts the patient's ability to perform normal oxidative phosphorylation?"

Sam thought for a moment. "No, this says that for a long time, researchers believed that a cancer cell's increased reliance on glycolysis was due to an impairment of the oxidative phosphorylation mechanisms in cancer cells. A number of recent studies, however, have shown that the oxidative phosphorylation machinery in most cancer cells is functional (Chen, 2012). It must be something else."

Just then Julia's cell phone rang. It was her mother. "Hi, Julia. I got some more information from your grandmother's lab tests about her cancer, but I don't understand it. You're in biochemistry, what does this mean? It says that her tumor has a high level of c-Myc/HIF-1α/GLUT-1."

"GLUT-1 is a glucose transporter. I think I remember something about that from our biochemistry notes. I'll get back to you," replied Julia.

Questions

1. The expression of the GLUT-1 glucose transporter usually correlates with the rate of anaerobic glycolysis. A number of cancer cells show increased synthesis of the GLUT-1 transporter due to c-Myc and HIF-1α. Why would cancer cells need to increase the synthesis of the glucose transporter?

"That makes some sense, but there must be more to it than that. Even if there are more glucose transporters, that doesn't explain why cancer cells need to use glycolysis instead of the citric acid cycle for energy production," Julia noted.

2. Given what you know about the rates of ATP production by glycolysis and the citric acid cycle, propose two reasons why many cancer cells preferentially use glycolysis for ATP production.

"Ok. I get that," commented Sam, "but cancer cells are rapidly dividing and they need cellular components, amino acids, and other things to make new cells. Would relying on glycolysis be useful for that as well?"

3. In addition to energy needs, cancer cells also need metabolic intermediates for biosynthesis. Explain how increased reliance on glycolysis would be beneficial in this respect.

Julia was getting excited. Maybe there really was something to this low carbohydrate diet stuff—and it was helping her study for the metabolism exam. She went back to studying, but a few minutes later another question occurred to her. "Wait a minute, didn't we learn that many parts of tumor cells grow in low oxygen environments since angiogenesis can't always keep up? What did Professor Smith tell us about metabolism under anaerobic conditions?"

4. Glycolysis offers a growth advantage to cancers growing under hypoxic conditions. Why might this be the case? (*Hint:* what is the product of anaerobic glycolysis?)

5. A decrease in oxidative phosphorylation also leads to a decrease in reactive oxygen species (ROS). Why might this be an advantage for cancer cells?

Meanwhile, Sam looked up information about c-Myc and HIF-1α. Sam learned that a complex of the transcription factors c-Myc and HIF-1α (hypoxia inducible factor 1, alpha subunit) enhances the synthesis of the majority of the glycolytic enzymes and two major glucose transporters (Chen, 2012). In addition, this complex inhibits pyruvate dehydrogenase kinase (PDK). "Let's look more at glycolysis to see if we can see why this complex is important," said Julia.

6. What are the three major metabolic control points in glycolysis? What generic reaction do these enzymes perform? Why are these enzymes the ones most regulated?

7. Hexokinase II (the isoform usually discussed in biochemistry classes as part of glycolysis) catalyzes the first step in glycolysis. The isoform of hexokinase that is expressed in most tumor cells is bound to the mitochondrial outer membrane facing the cytosol. Propose two reasons why this would be beneficial to the tumor cell.

8. Another highly regulated enzyme in glycolysis is phosphofructokinase (PFK1). There is evidence from some tumors that PFK1 undergoes a posttranslational proteolysis that yields a truncated functional enzyme (47 kD vs 85 kD) that is insensitive to citrate and ATP. How might this work and why would it be beneficial for a tumor cell?

9. Several isoforms of pyruvate kinase (PK) exist, including PK-M2 which exists mainly in embryonic and adult stem cells. PK-M2 has also been found in many tumor cells, but is in an inactive state. Explain why this seemingly counter-intuitive discovery is actually a benefit for tumor cells.

"It's all starting to come together now!" Julia exclaimed. "What about post-glycolysis? Do you think pyruvate dehydrogenase or the citric acid cycle is affected?"

"I don't know, but let's find out!" said Sam.

10. What is the normal function of pyruvate dehydrogenase kinase (PDK)?

11. PDK is more active in cancer cells than regular cells due to the presence of the HIF-1α transcription factor. Why is increased activity of PDK beneficial to cancer cells?

Julia and Sam learned that a class of enzymes known as prolyl-4-hydroxylases (PHDs) performs oxygen-dependent hydroxylation reactions. Under normal cellular oxygen conditions, PHDs hydroxylate two proline residues in HIF-1α, which allows it to be tagged for proteasome degradation. High concentrations of succinate and fumarate inhibit PHDs.

12. Succinate and fumarate have been shown to accumulate in some cancer cells. Dysregulation of which two CAC cycle enzymes are most likely implicated in this accumulation?

13. How does the accumulation of succinate and fumarate affect the interplay of glycolysis and the CAC?

"This is all so interesting, but I can't find very much information about low carbohydrate diets in cancer patients. All the studies seem to be in mice or other animals," sighed Julia. "What should I tell my mom and grandmother?"

14. Should Julia tell her grandmother to follow the low carbohydrate diet? Why or why not?

References

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