Angiogenesis and Cancer Treatment Worksheet

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Briefly (but mention key points) describe the experiment Folkman conducted with the rat thyroid gland and what conclusion he drew from these studies.

Folkman used a rat thyroid gland to conduct his experiment in order to investigate whether or not reconstituted hemoglobin could keep body tissues alive as red blood cells do in the body. For this, he designed an imitation of the circulatory system that consisted of reconstituted hemoglobin. He managed to attach a thyroid gland with that reconstituted hemoglobin, which started circulating when the system's pump turned on. This made the thyroid gland thrive, and reconstituted hemoglobin could keep tissues of the body alive. The discovery led Folkman to draw the conclusion that cancerous tumors must rely on angiogenesis as tumors require new blood vessels to grow and spread. Moreover, Judah Folkman hypothesized that the growth and spread of tumors could be inhibited by preventing angiogenesis in cancer tumors.

Briefly (but mention key points) describe the experiments Folkman conducted with the rabbit cornea to demonstrate angiogenesis and anti-angiogenesis.

Folkman conducted an experiment using the rabbit cornea as a model system to demonstrate the processes of angiogenesis and anti-angiogenesis. He implanted various tumors in the rabbit cornea, such as melanoma cells and sarcoma cells, to observe the formation, spread, and growth of new blood vessels, during which he observed that the tumors secreted angiogenic factors in the rabbit cornea that stimulated the formation and growth of new blood vessels.

What was the unexpected result that Judah Folkman often observed when he removed a patient's primary tumor, and how did Folkman's observation help to spark the idea of anti-angiogenesis as a therapy?

Whenever Folkman operated and removed a tumor from a cancer patient, he would see the growth of new vessels of blood and wondered whether those vessels were the key to the cancer tumor's growth. That unexpected result he often observed while cutting the tumor led Folkman to develop the concept of anti-angiogenesis therapy for cancer treatment that does not target the tumors themselves but the blood vessels surrounding them. He believed that a tumor could not grow without the blood supply, and for growth, a cancer tumor has to secrete several secret chemicals that stimulate angiogenesis – the growth of new vessels of blood that nourish the cancer tumor in the affected body.

What type of substances are angiostatin and endostatin, and where are they produced? What do they do?

The substances endostatin and angiostatin are both naturally occurring protein molecules that inhibit the blood vessels' formation, growth, or angiogenesis. The former protein substance, angiostatin, is a fragment of Plasminogen that helps dissolve blood clots, whereas the second protein substance, endostatin, is a fragment of collagen XVIII that surrounds blood vessels and other tissues in the body. They can both be produced in the body as well as synthesized in the laboratory and they both are shown to be effective in the development of cancerous tumors by preventing the formation of newly formed blood vessels in the body.

Briefly (but mention key points) describe the experiments using cow bones to discover anti-angiogenic substances. Why was this used as a source of these potential proteins?

The researchers used cartilage from the hundreds of pounds of bones of cows because Folkman thought that cartilage might contain that necessary ingredient or molecule he was in search of during all his research about cancer tumor inhibitors. They used chemicals to break down cartilage gathered

from cow bones while releasing the proteins to search for angiogenesis inhibitors. The testing was meant to see what molecules could block angiogenesis which was done by putting a palette filled with vessels of the blood and a stimulator placed in the cornea. After that, the palette filled with an extract from the cartilage of cow bones was put between the nearest blood vessel and the stimulator.

Briefly (but mention key points) describe the “accidental” discovery of a novel antiangiogenic substance because of lab contamination.

Don Ingber, while offering his services to Science in Folkman’s lab, found out about the growth of fungus in the cell culture. The blood vessels popped off of the cell culture dish, rounded up, and died. To his wonder, he noticed that the cells that were nearest to the fungus in the palette were affected the most as the cells near the fungus gradually became flattened. So, Ingber presented the idea that fungus might be secreting some chemicals that controlled the shape of the blood capillaries that blocked the growth of blood vessels that were nourishing cancer tumors. The fungus as Folkman and Ingber found out that the fungus that grew in the dish inhibited the phenomenon of angiogenesis, which ultimately became an experimental medication called TNP.

What is thalidomide? Briefly explain its original use, side effects, and how it comes into play in anti-angiogenesis.

The medication, Thalidomide, was first developed as a sedative that had severe fetal side effects when taken by pregnant women, which included undeveloped limbs of the infant and birth defects such as phocomelia. The medication marketed for its anti-nausea effects was proven to have anti-angiogenic properties since it found a place in the treatment of certain types of cancer tumors. It was used to inhibit the formation of new blood vessels that were medium to provide nutrients to the tumor and affected tissues. Thus, thalidomide was and is used as an angiogenesis inhibitor that prevents the growth and formation of new blood vessels, which stimulate cancer tumors. Resultantly, the medication once prohibited is now known as anti-angiogenesis therapy as it has shown promising outcomes for improving the lives of cancer patients.

Briefly (but mention key points) describe the chick embryo experiments to isolate novel

antiangiogenic substances.

The chick embryo, before the test, was put into an incubator. When it was ready for the test then a palette that was impregnated with thalidomide was carefully put on the egg of the chick. Thalidomide did not inhibit newly formed blood vessels at all, but then Robert broke down thalidomide by the body to activate it and performed the experiment with the metabolite version of the drug. The vessels of the blood during their formation could be seen avoiding the palette and growing around it. Furthermore, the faint outline of the palette could be seen in the middle of the inhibited blood vessels because thalidomide blocked the growth of the blood vessels in the chick embryo.

Briefly (but mention key points) describe the experiments used by Michael O'Reilly to isolate endostatin.

The researcher Michael O'Reilly performed laboratory tests to search for inhibitors in the mouse tumor and found out that tumors made so many stimulators and there were also proteins that were responsible for inhibiting angiogenesis. He found many large primary tumors in the urine of rats, and he decided to design a high-speed urine collection system. The researcher strung three cages for the mice together, later, he strung six and then 12 more that had open bottoms from which urine had to run down the funnel and got collected in the collection jars through the tubes. Mice were given the solution, they urinated, and then that urine was purified to separate the protein molecules. The purification was done to find the inhibitor that stimulated the growth of new blood vessels. The experiment looking for the inhibitor lasted for two years, and O'Reilly found the ingredient he named angiostatin.

Also, briefly (but mention key points) describe the experiments and results (using a mouse model) demonstrating the effectiveness of the drug.

The molecule "Angiostatin" was used to test what these proteins kept the metastasis dormant to find a solution for the treatment of cancer tumors. Michael O'Reilly used approximately 20 mice for special cancer tumors on their back. Michael knew that those tumors would have sent many metastases to those mice's lungs, but the metastases stayed quiet when the primary tumor was in its place before its removal. Michael operated on the original tumor, removed it, and then divided the mice into two groups of 10 mice each; the first group was given an angiostatin drug every day, and the other group was left untreated with any medication. It resulted in many mice falling sick, so he ended the test and operated on a mouse that was given angiostatin, to which he found out that its lungs were clear and

no metastasis was found in the body of that mouse. He took one of the mice from the group that was not treated with any medication and found that the mouse's lungs were heavy, burnt, and bloody due to tumors. Thus, the test conducted results in proving the effectiveness of angiostatin for the treatment of cancer tumors.

Name/briefly describe three other pathologies/abnormalities associated with inappropriate angiogenesis.

1. Endometriosis is a pathology that is associated with an inappropriate form of angiogenesis in which abnormal growth of blood vessels occurs in the tissue lining the uterus. This leads to infertility, chronic pelvic pain, and several other complications, such as adhesions and the formation of scar tissues in the uterus.
2. Atherosclerosis is another abnormality that is associated with inappropriate angiogenesis. The pathology of this abnormality refers to the angiogenesis in the blood vessels that leads to the thickening of the arterial wall and plaque formation. Resultantly, angiogenesis in the blood vessels ultimately leads to heart attack and stroke.
3. Finally, the abnormality of obesity is also associated with inappropriate angiogenesis in which the excess fat tissue secretes pro-angiogenic factors in the body which promote the growth of blood vessels by stimulating angiogenesis. This contributes to the increase in adipose tissue, which results in the development of metabolic problems such as cardiovascular diseases and insulin resistance.

Name/briefly describe three potential applications of therapeutic angiogenesis.

Here are three potential applications of therapeutic angiogenesis:

Vascular Endothelial Growth Factor (VEGF)

VEGF involves the use of growth factors and other agents in case of myocardial infarction in order to stimulate the formation and growth of new blood vessels in ischemic tissue. This occurs when the blood arteries that are responsible for the blood flow to the heart become blocked, leading to shortness of breath and chest pain. To cope with this coronary artery issue, therapeutic angiogenesis can be used to improve blood flow while promoting blood vessel growth in the heart.

Fibroblast Growth Factor (FGF)

When the arteries that supply blood to the limbs of living beings become narrowed or blocked due to reduced blood supply of the heart to the affected area, alleviated pain and other symptoms can be detected. Therefore, therapeutic angiogenesis is used to stimulate blood vessel growth and improve blood flow in the affected area.

Placental Growth Factor (PGF)

PGF offers a crucial action in the process of therapeutic angiogenesis because of its potential to enhance the formation of new blood vessels. This factor can potentially be used in the treatment of other conditions, including chronic wounds, ischemic heart disease, and peripheral arterial disease, by promoting blood vessel growth and improving oxygen supply to damaged tissues.

What is VEGF, and what is its importance in angiogenesis and the development of anti-angiogenesis treatment?

Vascular Endothelial Growth Factor (VEGF) acts as a signaling protein that has a significant role in the formation of new blood vessels. It plays a role in angiogenesis from the existing vessels as it binds to specific receptors on the surface lining of endothelial cells. This binding of VEGF with endothelial cells causes the surface to divide and migrate to the places in the body where new blood vessels are required. This increases the permeability of the existing vessels and promotes the growth of newly formed vessels, allowing nutrients and oxygen to reach body tissues in need. Moreover, VEGF is a key factor and a vital target in the development of anti-angiogenesis treatment as it is inhibited to prevent or block the growth of new vessels in cancer tumor as a result of the depletion of necessary oxygen and blood supply to the affected tissues.

Explain what is meant by the “normalization window” for the treatment of cancer with antiangiogenic therapies and conventional treatments.

The term “Normalization Window” refers to a particular time period entailing the cancer tumor treatment with anti-angiogenic therapies. The normalization allows for better delivery of chemotherapy drugs in the case of conventional cancer treatment strategies, as it is believed to occur

due to the reduction of the “Vascular Endothelial Growth Factor” (VEGF). In turn, the tumor vasculature is expected to return to a normal state due to the normalization window strategy that stimulates the vasculature and makes it more functional.

Go to Science Daily.com and find two articles on angiogenesis. Give a short 1 paragraph review of major points.

The article “Researchers Explain How Protein Inhibits Angiogenesis” reflects on the new discovery led by a pool of researchers at “Beth Israel Deaconess Medical Center” (BIDMC), which states the discovery of a protein called “Tumstatin” stops angiogenesis. The study presents that the specific protein molecule halts the growth of new blood vessels in the sites nearest to the tumor or affected tissues in the body (*Researchers Explain How Protein Inhibits Angiogenesis*, n.d.). The second article sourced from ScienceDaily is entitled “Cause of Tumor Resistance to Angiogenesis Inhibitors Identified,” which shows the effectiveness of specialized medications such as angiostatin to inhibit new blood vessels and prevent blood supply to the cancer tumor. However, the article argues that these medications often do not penetrate perfectly into the tumor tissues, resulting in the inefficacy of these drugs. The researchers thus suggested developing new treatment strategies for improving the efficacy of angiogenesis inhibitors in cancer tumor tissues (*Cause of Tumor Resistance to Angiogenesis Inhibitors Identified*, n.d.).

References

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