



## DAWNING OF THE AGE OF ANGIOGENESIS

Angiogenesis is the development of new, from pre-existing blood vessels. Vascular endothelial cells line our blood vessels, like our capillaries, for example. These cells manufacture some of the most potent cancer growth factors that can promote or inhibit the growth of cancer cells. These vascular endothelial cells control angiogenesis.

Some of the proangiogenic factors that can promote the growth and/or spread of cancer cells include:

VEGF	Vascular Endothelial Growth Factors
FGF	Fibroblast Growth Factors
TGF- $\beta$	Transforming Growth Factor - Beta
TNF	Tumor Necrosis Factor
Platelet Derived Growth Factor	
Interleukin-8	
Miscellaneous	

The antiangiogenic factors inhibit cancer growth:

- Angiostatin
- Endostatin
- Interferons
- Interleukin
- Platelet factor 4

All of these factors are made by our vascular endothelial cells.

A tumor or cancer is unable to grow beyond 1-2 mm in size without the development of a new blood supply. Tumor endothelial cells divide much more rapidly than normal endothelial cells; up to 50 times as fast, as in breast cancer.

The balance between proangiogenic and antiangiogenic factors determines whether cancer cells remain dormant and under control, or whether cancer cells will grow and multiply and spread.

Antiangiogenic drugs may not necessarily cause cancer regression, but at times can produce disease stabilization. In my opinion, the two most exciting antiangiogenesis drugs are angiostatin and endostatin.

## ANGIOGENESIS

### Page 2

I have previously written about angiostatin and endostatin in two papers, "Angiostatin and Why Local Therapy Fails to Cure So Many Men" and "The Capitulation of Radiation Therapy Has Begun." I spent one month working with Dr. Judah Folkman in 1974. What follows is a summary from those papers:

**"Angiostatin and Why Local Therapy Fails to Cure So Many Men,"**  
9/97:

... "There is now considerable direct evidence that tumor growth is angiogenesis dependent. Angiostatin inhibits angiogenesis and can induce dormancy (hibernation) of metastases. If you remove angiostatin, the metastases begin growing again within a few weeks. Angiostatin inhibits the growth of human prostate cancer cells by almost 100% (in animal model systems)." (*Nature Medicine*, Volume 2, Number 6, June 1996.)

"By potentially inhibiting angiogenesis, angiostatin can cause human carcinomas to regress to a dormant state," where there is balanced cell growth (proliferation) and cell death (apoptosis). The mechanism by which angiostatin leads to an increase in tumor cell apoptosis is unknown, although some reasonable possibilities are mentioned (loss of paracrine growth factors, for example). This is fascinating new information. Most of us thought that tumor metastases were dormant and not growing. Dr. Folkman shows us that these cells grow three times faster than normal cells, but because of mechanisms like apoptosis (programmed cell death), they are being killed three times faster. The state of dormancy exists because of this delicate balance. If you remove the factors that kill these cancer cells, you are left with cells growing three times faster than the normal cells in your body.

Another Dr. Folkman article (*Nature Medicine*, Volume 1, Number 2, February 1995) points out that:

"In cancer patients, dormant micrometastases are often asymptomatic and clinically undetectable, for months or years, until relapse...However, tumor cells of dormant metastases exhibited a more than threefold higher incidence of apoptosis."

These data show that, in my opinion, there is balanced tumor cell proliferation and an equivalent rate of cell death, and I suggest that angiostatin controls metastatic growth by increasing apoptosis in cancer cells. Angiostatin inhibits cancer cell growth by suppressing tumor angiogenesis.

## ANGIOGENESIS

Page 3

In *Cancer Research*, Volume 56, pages 4887-4890, November 1, 1996, Dr. Stephan Gately reported that human prostate cancer cells express an enzyme that converts human plasminogen into ...angiostatin. This helps to show us that angiostatin isn't just important to laboratory mice experiments, but to human prostate cancer cells, as well.

I am simply using the above three references to illustrate my point that if you fail to cure a patient with any form of local treatment, you could end up doing far more harm because your local therapy might remove the only source of angiostatin and/or endostatin. If the patient already has metastases (dormant or otherwise), you could cause an exponential increase in growth rate of those metastases by removing (or radiating and implanting or freezing) his prostate. This could also help explain why I believe debulking local treatments have the potential to shorten a man's life. If you cannot cure a patient with local treatment, don't think you are helping him by getting rid of almost all of his cancer. You may be doing far more harm than is currently understood.

And, an excerpt from another paper:

### **"The Capitulation of Radiation Therapy Has Begun," 9/97:**

... Recently, Judah Folkman and others reported that prostate cancer cells make angiostatin, a potent inhibitor of angiogenesis. When you remove a primary cancer (like prostate cancer or lung cancer in animal models), angiostatin is no longer made. Angiostatin inhibits distant metastases from growing. If you remove or radiate the prostate (or other primary cancers like lung cancer), you stop angiostatin production. The result is an exponential increase in the growth rate of metastases. Removing the inhibitor frees the metastases and they grow exponentially. This is another reason why I never recommend any radical local treatment for prostate cancer. If you don't cure the patient, then you can cause the unsuspected metastases to grow much faster.

References: O'Reilly, *Nature Medicine*, Volume 6,  
June 96, pages 689-692  
Holmgren, *Nature Medicine*, Volume 2,  
February 95, pages 149-153  
Gately, *Cancer Research*, Volume 56,  
November 96, pages 4887-4890

## ANGIOGENESIS

Page 4

In the August 1997 issue of the *Journal of Urology*, Connolly, et al., pages 515-518, show that the cells in locally recurrent prostate cancer patients have a much higher growth (proliferation) rate compared to the original prostate cancer cells. Could it be the lack of the inhibitor, angiostatin, that causes the accelerated growth of these cells?

I believe this is one good explanation for the rapid increase in PSA we often see in so many men following the failure of radiation therapy, or other local forms of treatment.

- - - End of Prior Papers - - -

In the *Journal, Cell*, Volume 88, pages 277-285, January 24, 1997, Dr. Michael O'Reilly, working with Dr. Judah Folkman (the Father of Angiogenesis), describes endostatin. What follows is sensational, and gives us hope and optimism.

He writes that to stimulate angiogenesis, tumors produce a variety of stimulatory growth factors, like FGF and VEGF. Many malignant tumors also generate inhibitors of angiogenesis (like angiostatin and endostatin).

The net balance between these positive and negative regulators of new blood vessel formation determines which cancers remain dormant and which cancers grow and spread.

What follows in this paragraph is **my** speculation. The primary tumor (like the prostate) can inhibit the growth of its latent micrometastases (like prostate cancer cells in the bones and/or lymph nodes) by producing angiostatin and/or endostatin. Systemic therapy with angiostatin can lead to the maintenance of metastases in a microscopic DORMANT state. It is as if angiostatin and/or endostatin causes cancer cell death, like through the process of apoptosis (programmed cell death).

Now back to the article. The article clearly reports that they have not found **any** tumors that became resistant to angiostatin and have not observed any toxicity of angiostatin, even in very high doses. The subject of this particular article is the discovery of an even more miraculous substance -- endostatin. "All of the tumors tested rapidly regressed and there was no evidence of any toxicity in any of the treated mice. Continued endostatin therapy maintained the tumors in a state of dormancy for as long as it was administered."

## ANGIOGENESIS

Page 5

"While it appears counter-intuitive that tumors should be a source of angiogenesis inhibitors, the results shown here" show exactly this.

Folkman and colleagues administered repeated cycles of endostatin to mice, resulting in regression of lumps and islands of cancer cells from lung cancer, malignant melanoma, or sarcoma cells. (Sarcoma is cancer of connective tissue like muscle or bone, etc.)

Initially, tumor regrowth was noted when you stopped endostatin treatment, but when you retreated, all of the tumors once again regressed.

Finally, all of the tumors stopped regrowing even after you stopped endostatin. This means that in these experiments, endostatin cured 100% of the mice from these three, different malignancies, even though treatment with endostatin was stopped. And no toxicity. Now if only every successful animal experiment would prove successful in humans, we would call this miraculous.

None of these cancer cells became resistant to endostatin, whereas these types of cells eventually **always** become resistant to any and all types of chemotherapy, when tested in animal experiments.

However, remember the first polio vaccines fully protected monkeys. But when given to children, many children got polio from the vaccine and ended up on iron lungs. It took two decades after this disaster before Dr. Jonas Salk would succeed with his polio vaccine.

The National Cancer Institute will hopefully begin human trials with angiostatin and/or endostatin in 1999.

Until one of these potentially miraculous substances becomes available, what other antiangiogenesis drug can be tried? Thalidomide!!