

Angiogenesis:

An Examination of both Tumorigenic and Rehabilitative Properties

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The study of angiogenesis is making a profound impact on the biological and medical world. Angiogenesis has been found to play such a vital role in tumor progression that has long been the focus of study by microbiologists. Further, it has recently been gaining attention in clinical research as well, as a possible therapeutic agent in the assistance of cardiac deficiencies and recoveries. But what is angiogenesis, and, more importantly, how does it have the ability to both be a source of cancer sustenance and cardiac rehabilitation?

Angiogenesis is a term that refers to the “recruitment” of blood vessels. These blood vessels are recruited to masses of cells, as they provide the cells with a source of oxygen and a waste reservoir. Without a readily available, nearby source of blood, the proliferating cells would not have the chance to grow and survive. Angiogenesis is a natural phenomenon that allows for cell growth (both for numbers and size). However, angiogenesis is an extremely intricate process, regulated by several different pro- and anti-angiogenic factors. Further, it is triggered by different physiological conditions as well. In this review, the role of angiogenesis both in tumors and in cardiac rehabilitation, will be examined more closely.

History

Much of the foundation of angiogenesis research was laid down by Professor Judah Folkman. In 1971 Folkman published an article in the *New England Journal of Medicine* discussing this new theory of angiogenesis based on several years of work. In his research, Folkman noted that tumors would never grow past a certain critical size unless increased vasculature was introduced. In his paper, he also discussed the theory that tumors contain new blood vessels, which were somehow recruit a diffusible factor he referred to as TAF- tumor angiogenesis factor. Finally, he wrote that, in theory, if this angiogenesis could be turned off, the tumors would remain small in size, and ultimately not as harmful. Of course, as in many cases of theoretical innovation, he was met with *extreme* pessimism from the scientific community. It took almost 10 years for the academic public to acquiesce to the notion that there was, indeed, new vasculature in tumors. Finally, more than 30 years after his publication, tumor angiogenesis is a focal point in cancer research. In 1984, Folkman and his crew published another paper in *Science*, exposing the world to the first found angiogenic factor. This paper caused an impetus of research: There are over 15 known angiogenic factors.¹

Molecular Basis of Angiogenesis

The diffusion limit for oxygen in vivo is approximately 100-200 μ m. Beyond this distance, oxygen cannot reach cells, and they will suffer from hypoxia, or a lack of oxygen pressure. How the cells call on new vessel formation is of extreme interest to scientists, and much work has been dedicated to mapping the path taken. Small vessels are composed of endothelial cells (ECs), and it was thought that, while an embryo, vessels developed from endothelial progenitor cells, and as an adult, vessel formation stemmed from ECs. However, it is currently believed that endothelial progenitors contribute to vessel formation both in the embryo and in the ischemic tissues.² Many factors are responsible for this ultimate formation.

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Research has pointed to several angiogenic factors, both pro-angiogenic and anti-angiogenic. Angiogenesis is regulated by these two determinants, and errors in either of the two sets could cause an imbalance in the regulation of angiogenesis. One of the main pro-angiogenic factors is the vascular endothelial growth factor (VEGF). It is thought that VEGF is the "critical rate-limiting step in physiological angiogenesis."³ In vitro it has been shown to promote the survival of ECs from such blood vessels as arteries, veins, and lymph. Further, in vivo, VEGF stimulates angiogenesis as well, mainly targeting endothelial cells. Ferrara et. al. also refer to VEGF as a "survival factor," preventing apoptosis in ECs in tissue culture by upregulating anti-apoptotic proteins (i.e. Bcl-2). And so, VEGF remains the key focal point in the study of angiogenesis onset.³ Along with VEGF, several other factors have been found to promote angiogenesis, such as TGF- β and α (transforming growth factor), and IGF (insulin growth factor).³

On the other hand, there are also prominent anti-angiogenic factors. I am currently working on a project that deals with the major anti-angiogenic factor, Thrombospondin-1 (Tsp-1). There are several different factors that are involved in the Tsp-1 pathway, which seems to be overall regulated positively by p38. Like VEGF, the pathway is tied to the infamous oncogenic Ras pathway.

The "Angiogenic Switch"

The sheer complexity of cancer has been illustrated over and over again with each new experiment in the field. There are so many different pathways and factors that can be mutated or altered to bring about tumors that it is impossible to explicitly determine when angiogenesis kicks in and turns on itself. The "angiogenic switch" is a term that refers to the balance between pro- and anti-angiogenic factors. When the balance is in favor of the pro-angiogenic factors, angiogenesis results, and it is this "tipping of the balance" that is being studied to determine how tumorigenic cells are able to promote angiogenesis.

To more closely study the turning on of the switch, one may examine the physiological factors that trigger angiogenesis, such as hypoxia. As stated by Ferrara et. al., an increase in tissue mass will cause hypoxia, which will in turn cause an upregulation of gene expression of pro-angiogenic factors. Further, mutations can also stimulate angiogenesis. A mutation in the Ras pathway will cause an overstimulation of VEGF, which will ultimately promote angiogenesis as well. A mutation in tumor suppressor genes can additionally cause a similar effect.³

There are many ways that tumor angiogenesis occurs, physiologically. In a review in *Nature*, Carmeliet and Jain postulated several different ways in which tumor angiogenesis may be instigated. One possibility is that the host vessel system expands by either budding or sprouting. Another option is that vessels are formed by the insertion of interstitial tissue into preexisting vessel

lumen. Finally, a third possibility is that EC precursors (angioblasts) aid in vasculogenesis. In other words, they contribute to the addition of endothelial lining in these vessels.⁴

Upon even closer study, one may observe that tumor angiogenesis brings about a very different vasculature than normal angiogenesis. In a review article by Bergers and Benjamin, it was stated that tumor blood vessels may be "irregularly shaped, dilated, tortuous and can have dead ends."⁵ They go on to state that some of the leakiness and hemorrhagic properties of these vessels may be due to the overproduction of VEGF, with cancer cells even "integrated into the vessel wall."⁵

All the studies, however, make clear that the angiogenic switch is turned on at different stages in tumor development. Hence, it is difficult to attempt to create a magic drug that could eliminate this extra angiogenesis (among other complications). However, experiments have shown that inhibiting VEGF does downregulate angiogenesis, and so research is being conducted to investigate this further.

Rehabilitating Effects

Just as angiogenesis may assist tumor growth and development, it also helps to repair normal vasculature, as in the aftermath of a heart attack, also known as a myocardial infarction (MI). The narrowing or blocking of blood vessels leads to blocks in the ischemic system which ultimately cause tissue damage. Without sufficient blood flow through these vessels, nutrients are not properly exchanged with the cells of the tissues; oxygen is not delivered, nor are wastes disposed of. Further, one of the leading causes of MIs is such a blocking in coronary arteries. One way of alleviating these blocks is to perform bypass surgeries, in which blood vessels from other parts of the body are used to provide an alternate route of blood around blocked regions; however this approach is not feasible for many patients. Angiogenesis is being studied as a possible means of increased vasculature and vessel rehabilitation for these patients.⁶

Several experiments have been performed investigating the therapeutic effects of angiogenesis. Many experiments have yielded promising results, lending even more credence to the possibility of therapy via angiogenesis. One way to induce therapy is via gene therapy.

Gene therapy is ideal for a patient suffering from an MI or even a peripheral infarction, and who cannot receive traditional "revascularization therapies."⁷ As defined by Hertzuala and Alitalo, gene therapy is a transfer of nucleic acids to somatic cells, conferring a therapeutic effect. There are several benefits to gene therapy, such as the ability to act locally within a patient. Further, gene therapy offers the possibility for prolonged recovery, along with possibly avoiding a procedure that could cause harmful side effects.⁷

Gene therapy was used as a method of cardiac repair in an experiment by Li, Takemura, and Kosai et. al. Adenovirus was used as a genetic carrier, and was

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expected, HGF levels rose in these mice, compared to HGF levels in control mice (in which LacZ was used). Further, in these experimental, HGF-upregulated mice, there was improved left ventricular remodeling, and overall increased recovery efficiency. The researchers concluded this type of gene therapy to be effective in providing a possible approach against subsequent problems with heart failure.⁸

Research is also being directed toward approaches other than gene therapy. In a similar experiment by Nishida, Li, and Hirata et. al., bone marrow cell infusion was studied as a remedial factor in cardiac repair. Bone marrow cells (which normally help induce angiogenesis) were injected into the left ventricular anterior wall of damaged hearts in experimental rats. Following the injection, cardiac function was evaluated at regular intervals. It was found that the bone marrow cell injection caused an increase in levels of angiopoietin-1 (a pro-angiogenic factor) and in VEGF in the anterior wall, which induced angiogenesis. These influences helped retrieve increased cardiac functioning in the heart.⁹

Conclusion

Angiogenesis is a potent phenomenon in natural physiology. Beginning with Folkman's visions back in the late 1960s, modern science has come a long way in its evaluation of the biology of angiogenesis. Even though it has proven to be a sustaining element for tumors, insight into the several known anti-angiogenic factors may provide clues for controlling tumor angiogenesis. And, insight into pro-angiogenic factors is being used for angiogenesis' possible remedying effects on vasculature damage. 

injected into the muscles of the hind limb of mice following an MI. This adenoviral vector expressed hepatocyte growth factor (HGF), a pro-angiogenic molecule. As

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