Nutriceuticals and Angiogenesis

New Therapeutic Horizons

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The phenomenon of antiangiogenesis has attracted considerable interest in the scientific community. Angiogenesis plays a major role as a determining factor in a variety of diseases, including: cancer, arthritis, skin conditions, eye disorders, and inflammatory disease. The application of methods to manipulate angiogenesis has created fascinating therapeutic options, including the potential of natural-based compounds that may modify new blood vessel growth.

Modulating Angiogenesis

The process of forming new blood vessels is essential to tissue repair, ulcer healing, ovulation, and menstruation. Vascularization plays a major role in the propagation of several disease States. Judah Folkman, M.D., of Children's Hospital, Boston, and Harvard Medical School is credited with the discovery of the importance of angiogenesis in tumor development. [1] His research has offered a unique and promising basis for the application of antiangiogenic and proangiogenic compounds. Some natural natural compounds, such as shark cartilage and isflavones, may modulate angiogensis *in vivo*.

The importance of angiogenesis in the promotion of cancer growth has fueled a considerable amount of research into the control and mechanism of angiogenesis. The growth of most solid tumors depends on the development of a tumor circulation. So it seems logical to inhibit this vascularization, thereby causing the death of neoplasia or limitation of tumor expansion. Many substances are not recognized as exerting a modulating effect on angiogenesis. The initial crude extracts of angiogenic factors isolated from neoplasia by Dr. Folkman were referred to as tumor angiogenesis factors (TAFs). A flurry of research has identified inhibitors of TAF and assisted in the characterization of many agents and cofactors that are required for the modulation of angiogenesis.

The simplest way to explain angiogenesis is to consider a four-step process; (1) the localized erosion of the basement membrane in tissues; (2) the migration of activated endothelial cells promoted by angiogenic factors; (3) endothelial cell proliferation; (4) a complex combination of sustaining influences on the angiogenic process. Angiogenic factors and antiangiogenic compounds may play a role in one or more of these four steps.

The complex steps in the process of angiogenesis and its control provide a multitude of Sites for the potential application of antiangiogenic or proangiogenic therapy. The large, ever increasing number of identified angiogenic factors makes it unlikely that one discrete, antiangiogenic molecule can be used as a successful treatment. This reinforces the use of potentially more versatile antiangiogenic agents that may have multiple sites of activity. These agents may be used either alone or in combination with other antiangiogenic compounds of natural Origin. Shark cartilage, bovine cartilage, and isoflavones of soyabean origin are candidates for investigation as antiangiogenic agents in humans.

Cartilage Controversy

Shark cartilage has become the most popular unconventional cancer treatment since the Laetrile controversy of the l970s. This enthusiasm has been manifested by premature reports of the beneficial effects of shark cartilage in cancer therapy (I. William Lane. Ph.D., and Linda Comac, R.N., Sharks Don’t Get Cancer, Avery Publishing Group, 1992). However, scientifically appropriate studies are under wav to investigate the potential safety and efficacy of cartilage for the treatment of cancer and other chronic diseases that depend on angiogenesis.

Illogical projections, scientific naiveté, and commercial interests have led to an antagonistic division between basic scientists pursuing the mechanisms of angiogenesis and individuals who are enthusiastic about the clinical uses of natural products with angiogenic properties. The danger is that the potential benefit of cartilage and other natural based antiangiogenic compounds in certain diseases may he either minimized or overemphasized. For example, soyabased products, which contain isoflavones, have not been marketed with correct instructions for use, and the medical importance of isoflavones has been significantly underestimated. In the author's opinion, research on the use of natural-based antiangiogenic compounds is long overdue, poorly funded, and probably forgotten because of the difficulties in protecting nonproprietary treatments. The manufacturers of nutriceuticals have an obligation to fund such research, especially if products are going to be promoted or used for assumed antiangiogenic properties.

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Modulation of angiogenesis is potentially important in the following common diseases:

Cancer:
Prostate, breast, colon, and central nervous system cancers

Arthritis:
Rheumatoid disease, progressive systemic sclerosis, osteoarthritis, and mixed connective tissue disease.

Skin Conditions:
Burns, wound healing, psoriasis, eczema, meangiomas, angiofibroma, Kaposi's sarcoma

Eye Diseases:
Diabetic retinopathy, retrolental fibrophasia, macular degeneration, corneal vascularization, neovascular glaucoma

Inflammatory:
Bowel disease

Historical Perspective

To understand the development of the prevailing theory of cartilage therapy, one needs to put angiogenesis into historical perspective. The term angiogenesis was coined approximately 60 year ago. In the 1960s and 1970s, models were designed to study tumor growth and the importance of neovascularization as a rate-limiting step in tumor growth was identified.

A recent newspaper report traces the history of the early rejection of Dr. Folkman's theories of angiogenesis by the scientific community and their current acceptance, together with an account of his "vindication." The writer states: "Dr. Judah Folkman's work illustrates the slow pace of progress in cancer research. But his visionary ideas have led to new ways of understanding this pernicious disease and to renewed hope that it can be vanquished. [1,2]

The emergence of interest in shark cartilage a source of angiogenic inhibitors came out of the observations of Drs. Lee and Langer. [3] **T**hey discovered a substance in bovine cartilage with potent angiogenic properties, but rocognized that cartilage is present in only small quantities in mammals. Drs. Lee and Langer noted that the shark's skeleton was composed entirely of cartilage and that cartilage does not have a network of blood vessels because it contains a protein fraction or fractions that prevent angiogenesis. Crude extracts of shark cartilage strongly inhibited tumor-induced neovascularization, and bovine cartilage had to be highly purified by chromatography before angiogenic activity became apparent. Drs. Lee and Langer (1983) estimated that sharks may contain about 100,000 times more potential antiangiogenic activity per animal than cattle. These observations are some of the compelling reasons to favor shark over bovine cartilage a potential natural source of inhibitors of vascularization.

In addition, shark cartilage appears to be nontoxic. Over many years of research and thousands of human doses, no significant metabolic toxicity has been reported from using shark cartilage, that can be ascribed to administering the cormpound. When administered orally or rectally, it has shown no evidence of local or systemic reactions in several clinical trials. The author does not believe that cartilage compounds should be administered rectally as a route to access the systemic circulation. Injection of crude cartilage in humans presents an antigenic load and is not to be recommended.

Use of Antiangiogenic Therapy in Cancer

The rationale for antiangiogenice therapy in neoplastic disease rests upon the hypothesis that tumor growth and metastatic dispersion of malignant disease are angiogenic-dependent processes. Considerable indirect and direct evidence has accumulated during the past two decades to support this hypothesis and confirm the angiogenic dependence of neoplasia. The onset of angiogenic activity appears to occur as a definable event in tumor formulation, and most tumors progress from a prevascular to a vascular stage.[4]

A promising level of antitumor activity of shark carti1age that been demonstrated in two small clinical trials, one conducted in Mexico on eight patients[5] and another in Cuba involving 29 patients (Jose Menendez, M.D., and J, Fernandez-Britto, M.D., personal communication, 1994). The Cuban study demonstrated that shark cartilage induced histologic changes in tumors, and these changes were not explicable by chance. The author had the opportunity to review the histologic slides of tumors that were obtained from shark cartilage-treated patients in the Cuban trial. The author feels strongly that the observations of fibrous encapsulation of the tumors and evidence of cell death within the tumors are extremely interesting. These observations are significant and need further study.

James Lott, Ph.D., Professor of Physiology and Biophysics at North Texas State University, Denton, has performed experiments in immunocompetent mice bearing transplanted tumors (data presented at the First international Congress on Alternative and Complementary Medicine, May 1995). After administering shark cartilage, the tumor-bearing mice lived longer and Dr. Lott found definite histologic changes in transplanted tumors that resemble some of the histologic changes observed in tumor specimens examined in the Cuban clinical trial.[6]

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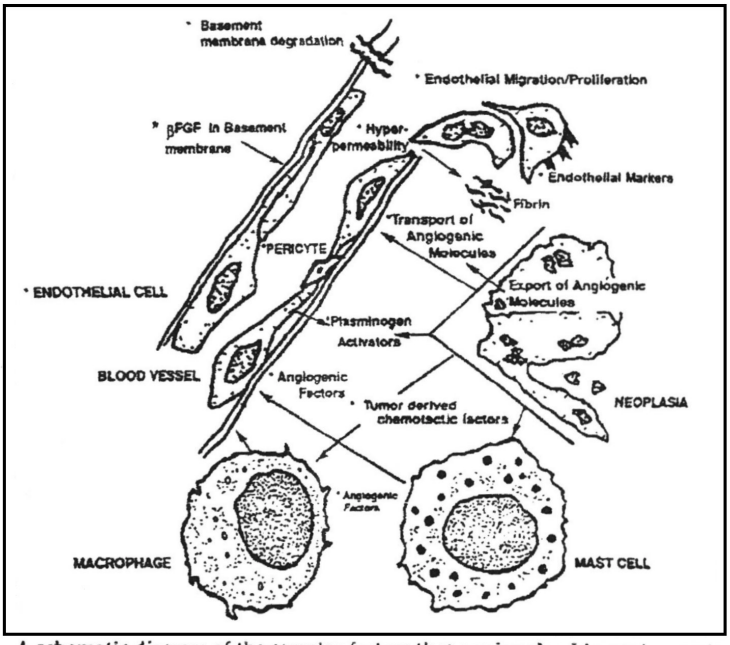
However, the author has been unable to substantiate any conclusive clinical outcome concerning the benefit of shark cartilage therapy in the Cuban or Mexican studies. Any contemporary claims about the benefit of shark cartilage in the treatment of cancer must be considered purely speculative.

The data from these studies, although subject to contention, had provided the rationale for further human testing in patients with advanced malignancies. Charles Simone, M.D., of the Simone Protective Cancer Institute in New Jersey, received a recommendation from the Office of Alternative Medicine of the National Institutes of Health to conduct clinical trials using shark cartilage in advanced cancer, but these studies were recently placed on hold. Unfortunately, Dr. Simone's studies may confuse the assessment of shark cartilage further because his protocol adds in a ten-point Lifestyle Program that could confound the results. One of the alleged benefits of shark cartilage therapy has been the suggestion that therapy improves quality of life measures in cancer patients. Therefore, clinical outcomes in studies of shark cartilage need to be clearly identified in clinical protocols. Protocols should not be constructed that confuse clinical outcome variables. This is one of the most important limitations of research in the field of alternative and complementary medicine.



A schematic diagram of the complex factors that are involved in angiogenesis associated with neoplasia. Sites where agents may act to modulate angiogenesis are shown by asterisks.

Clinical Trials of Other Antiangiogenic Modalities

Increasing knowledge of the factors that "switch on" angiogenesis and the upregulation of positive stimulators has led to several phase I and phase II clinical trials of a variety of antiangiogenic therapies besides cartilage. Georgetown University researchers have begun phase II trials of the potent antiangiogenic compound pentosan polysulfate. This is one of a group of polysaccharides that are capable of interfering with the function of heparin-binding growth factors that promote angiogenesis. Other antiangiogenic compound in clinical trials include alpha interferon, platelet factor IV, and AGM 1470. At least eight angiogenic agents are in early clinical trials, with some impressions of benefit emerging from these pilot studies.[7]

Not enough attention has been focused on the modulators of angiogenesis from natural sources. Several such compounds have been discovered in addition to those in cartilage. The potential angiogenesis inhibitor isolated from cartilage is collagenase inhibitor. Other natural antiangiogenics include vitamin D3-analogues, fumigallin, herbimycin A, and isoflavones. Isoflavones found in soya beans are very exciting compounds. They have direct tumoricidal properties against several tumor types and regulate key enzyme expression, that is, a process involved in tumor growth. Isoflavones are also antioxidants.

Arthritis and Angiogenesis

Various types of arthritis may be amenable to therapy with antiangiogenic compounds. Shark cartilage has been well recognized and it has been characterized as having a major potential application in the treatment of pain and inflammation associated *with* arthritis in animal studies. John Prudden, M.D., and colleagues at the Columbian Presbyterian Medical Center administered bovine cartilage to humans by both mouth and injection to treat osteoarthritis, rheumatoid arthritis, psoriasis, and regional enteritis with alleged stignificant therapeutic benefit. [8] However, the group did not subscribe to the notion that the observed beneficial effects were caused by antiangiogenic activity. Several other researchers have reported a clear association between neovascularization and osteoarthritis, adding weight to the rationale to use cartilage and other antiangiogenic compounds to treat arthritis. Shark cartilage is also a rich source of calcium, which is beneficial for patients with osteoporosis who may require calcium supplementation.

Skin Disorders

Angiogenesis plays a major role in several types of skin disease, such as psoriasis and eczema, and it is one of the pivotal steps in

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wound healing. Bovine cartilage preparations have been shown to have beneficial effects on wound healing, and topical application of cartilage has accelerated healing of wounds in some circumstances. The tensile strength of wounds has also been significantly enhanced by administering cartilage. However, no controlled studies have been conducted as a follow up to this promising research.

Several clinicians have suggested the use of topical or systemic administration of cartilage, especially shark cartilage, as a potential treatment for such skin diseases as psoriasis, contact dermatitis,
eczema, pruritis, angiofibrroma, hemangioma, Kaposi's sarcoma, and even burns. Because angiogenesis may play an important role in the pathogenesis of these diseases, they may be amenable to antiangiogenic treatment. However, without controlled studies, the results of such treatments become susceptible to illogical projection amid misrepresentation of the potential benefits of antiangiogenic compounds.

Eye Diseases

Many eye diseases are associated with angiogenesis, including neovascular glaucoma, diabetic retinopathy, retrolental fibroplasias, and subtypes of macular degeneration. Considerable basic scientific research, as well as anecdotal use of shark cartilage in patients with eye disease, seem to support the need for further human clinical trials. Researchers in Israel and the United States have begun pilot studies using shark cartilage in the treatment of diabetic retinopathy and neovascular glaucoma.

Angiogenesis: A Double-Edged Sword

There are circumstances where angiogenesis is necessary, including pregnancy, ovulation, and the need to develop a collateral circulation, such as in coronary artery disease. These circumstances are examples of conditions where antiangiogenic therapy is best avoided.

Several pathologic states result directly from reduced vascularity. Tissue necrosis or ulceration, fistulae, and avascular atrophic changes cause organ damage. The question that remains unanswered is:
Is there a circumstance in neoplastic proliferation where angiogenesis is a beneficial phenomenon? This question arises from observations where avascularity of neoplasia can be associated with resistance to treatment by chemotherapy and radiation.

Attempts to induce angiogenesis have helped to identify many potentially applicable proangiogenic cytokines, including acidic fibroblast growth factor, epidermal growth factor, transforming growth factors alpha and beta-1, tumor necrosis factor alpha, vascular endothelial growth factor, p1atelet derived endothelial ce1l-growth factor, angiogenin, and angiotensin.

Angiogenic cytokines show promise in plastic and reconstructive surgery. Pretreatment of donor and receptor skin graft sites with angiotropin has prevented tissue necrosis in skin f1aps. Cytokines have also been used to promote angiogenesis during surgical procedures. Administering agents that promote angiogenesis may even be a means of overcoming radiation-induced effects in tissues that result from impaired angiogenesis.

The intriguing role that angiogenesis may play in the amelioration of disease has led to speculation that anigiogenic promoters may be useful in treating such disorders as peptic ulcers, fistulac, and hypoxia-induced resistance of neoplasia to repeated irradiation treatments and chemotherapy. In addition, other patients with disorders may benefit from inducing neovascularization, including those with aseptic bone necrosis and vascular occlusion of organs, notably peripheral vascular disease and ischemic heart disease. Inflammatory bowel disease, in which blood-flow abnormalities and neovascularization may occur, has been reported to show some favorable response to bovine cartilage treatments. Several clinical trials of angiogenic compounds in the treatment of peptic ulcer are under way. Antiangiogenic agents should be avoided in peptic ulcer disease.

Angiogenesis has been associated with life-threatening pathologies, such as cancer, and contributes to the pathology of diseases, such as atherosclerosis, psoriasis, and arthritis. New drugs and compounds that inhibit angiogenesis are under intense research and development. Once proper clinical trials are completed, antiangiogenic compounds, especially shark cartilage and isoflavones, may well become the first new class of anticancer compounds and afford great promise for the treatment of arthritis and many other diseases. □

EDITOR'S NOTE: The author makes no recommendations concerning the use of nonapproved substances for the treatment of any illnesses or disorders.

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