

鯊魚軟骨能治癌嗎？

編輯部

過去三十多年來，鯊魚的軟骨被用來治療各種疾病，例如癌症、乾癬、關節炎、骨質疏鬆症、潰瘍性大腸炎、局部性腸炎、青春痘、硬皮症、痔瘡、過敏性皮膚炎¹⁻¹⁹。其中令人注意的是癌症治療，原因之一是很多人以為鯊魚不會得癌症。由於在鯊魚的骨骼中軟骨約佔6%^{16,18,20}，而牛的骨骼中軟骨佔不到1%¹⁸，所以鯊魚骨骼自然就引人注意。

由於軟骨裡面沒有血管，因此有假說認為，軟骨細胞可以產生某種成份來抑制血管的形成²¹⁻²⁷。新血管的形成，又謂之「血管新生（angiogenesis）」，被認為是腫瘤要成長超過幾毫米直徑所必要的步驟。也就是說，腫瘤要超過十萬到一百萬個細胞的時候，它需要有血管帶來氧氣和營養²⁸⁻³⁴。因此，除非腫瘤接上宿主的循環系統，否則它是無法繼續成長的。

血管新生需要至少四個步驟。首先，腫瘤必須讓血管的內皮細胞分泌血管新生因子，例如血管內皮生長因子（vascular endothelial growth factor; VEGF）³¹⁻³⁵。接著，活化的內皮細胞必須複製分裂產生新的內皮細胞^{32,34-37}；再來，複製分裂中的內皮細胞必須朝向腫瘤移動³²⁻³⁷；最後，新的內皮細胞必須形成一個中空的管子來變成新的血管^{34,35}。有研究發現，腫瘤細胞達到一百個的時候，就啟動

血管新生了³³。如果能在這麼早期時就抑制血管新生，那麼就有可能讓腫瘤完全退化³³。因此，有許多的動物研究，觀察軟骨製品對雞胚胎、絨毛尿囊膜（chorioallantonic membrane）、兔子角膜或老鼠結膜之血管的形成^{21,22,25,27,38-44}。在動物研究中，軟骨產品以各種方式來給予動物，有些研究是口服液體或粉末狀的軟骨產品^{15,19,41,43,45-48}，也有些研究是以注射、外敷或植入的方式給予軟骨產品^{21,22,25,27,28,38-44}。

軟骨的主要結構成份是膠原纖維蛋白和幾種的醣胺聚多醣（glycosaminoglycan），而硫酸軟骨素（chondroitin sulfate）是軟骨中主要的醣胺聚多醣^{34,45}。目前有證據指出，鯊魚軟骨含有至少一種血管新生抑制劑，它是一種醣胺聚多醣成份⁴⁴。其他資料指出，軟骨中大部分抗血管新生的活性並非來自軟骨的主要結構成份^{24,27,38}。

除了抑制血管新生，軟骨還有一些醣胺聚多醣具有抗發炎和刺激免疫的能力^{1,2,14,16,49,50}，有人認為這些物質或是其分解產物對腫瘤細胞有毒性^{2,3,51}。此外，正常軟骨對於外來腫瘤細胞的侵犯具有相當的抵抗力^{23-25,27,29,44,52,53}，所以，腫瘤細胞需使用基質金屬蛋白酶（matrix metalloproteinase）從利其轉移^{47,52,54,55}。顯然，軟骨裡面確實有幾種成份具有抗腫瘤的活性^{2-4,7,15-19,21-23,38,51,54}。因此，軟骨

的抗腫瘤能力機轉可能不只一種。如果軟骨中血管新生的抑制因子也能夠抑制基質金屬蛋白酶的話，那麼同一個分子就能同時抑制血管新生和抑制腫瘤轉移了。

有研究指出，就同等重量而言，鯊魚軟骨的抗血管新生活性比牛的軟骨還要強一千倍⁴⁰。由於有可能從鯊魚軟骨萃取血管新生的抑制子，這個想法自然引起了治療癌症的研究。從1970年起，已有十幾個臨床實驗以軟骨來治療癌症病人^{2-4,6-9,15-18,56,57}。近年來，美國國立癌症研究所也用軟骨萃取物對非小細胞肺癌（MDA-ID-99303）、多發性骨髓瘤（AETERNA-AE-MM-00-02）、大腸癌和乳癌（NCCTG-971151）進行臨床試驗。將379名使用化療和電療之非小細胞肺癌的病人，以隨機分布雙盲的第三期臨床試驗來比較鯊魚軟骨（n=188）和安慰劑（n=191）的療效，結果發現兩處的整體存活率並沒有統計學上的差別⁵⁸。對於83名無法治癒的乳癌和大腸直腸癌病人，以隨機分布的方法接受鯊魚軟骨或安慰劑加上標準療法，試驗結果發現，這兩組病人的存活率或生活品質並沒有差異⁵⁹。

目前各國衛生主管機關並未核准使用軟骨來治療癌症或其他疾病。所以軟骨產品在市面上都是以健康食品販售。由於健康食品不是藥品，因此食藥署不會要求作上市前評估，除非該產品宣稱能夠預防或治療某種疾病。也因如此，軟骨產品的製造商不作此宣稱，以避免被要求提出證據顯示其產品具有抗癌和其它生物的效能。在此灰色地帶，百家爭鳴，以致目前美國在市面上竟有四十多種品牌的鯊魚軟骨¹⁷。

目前看來，我們還不知道可否用鯊魚軟骨治療，不過我們倒是知道，鯊魚自己的確可罹患各種癌症^{20,60-62}。

引用文獻

1. Prudden JF, Balassa LL. The biological activity of bovine cartilage preparations. Clinical demonstration of their potent anti-inflammatory capacity with supplementary notes on certain relevant fundamental supportive studies. *Semin Arthritis Rheum* 1974 Summer;3:287-321.
2. Prudden JF. The treatment of human cancer with agents prepared from bovine cartilage. *J Biol Response Mod* 1985;4:551-584.
3. Romano CF, Lipton A, Harvey HA, et al. A phase II study of Catrx-S in solid tumors. *J Biol Response Mod* 1985;4:585-589.
4. Puccio C, Mittelman A, Chun P, et al. Treatment of metastatic renal cell carcinoma with Catrx. [Abstract] *Proceedings of the American Society of Clinical Oncology* 1994;13:A-769,246.
5. Dupont E, Savard PE, Jourdain C, et al. Antiangiogenic properties of a novel shark cartilage extract: potential role in the treatment of psoriasis. *J Cutan Med Surg* 1998;2:146-152.
6. Falardeau P, Champagne P, Poyet P, et al. Neovastat, a naturally occurring multifunctional antiangiogenic drug, in phase III clinical trials. *Semin Oncol* 2001;28:620-625.
7. Miller DR, Anderson GT, Stark JJ, et al. Phase I/II trial of the safety and efficacy of shark cartilage in the treatment of advanced cancer. *J Clin Oncol* 1998;16:3649-3655.
8. Leitner SP, Rothkopf MM, Haverstick L, et al. Two phase II studies of oral dry shark cartilage powder (SCP) with either metastatic breast or prostate cancer refractory to standard treatment. [Abstract] *Proceedings of the American Society of Clinical Oncology* 1998;17:A-240.
9. Rosenbluth RJ, Jennis AA, Cantwell S, et al. Oral shark cartilage in the treatment of patients with advanced primary brain tumors. [Abstract] *Proceedings of the American Society of Clinical Oncology* 1999;18:A-554.
10. Iandoli R. Shark cartilage in the treatment of psoriasis. *Dermatologia Clinica* 2001;21:39-42.
11. Milner M. A guide to the use of shark cartilage in the treatment of arthritis and other inflammatory joint diseases. *American Chiropractor* 1999;21:40-42.

12. Himmel PB, Seligman TM. Treatment of systemic sclerosis with shark cartilage extract. *Journal of Orthomolecular Medicine* 1999;14:73-77.
13. Sorbera LA, Castañer RM, Leeson PA. AE-941. Oncolytic, antipsoriatic, treatment of age-related macular degeneration, angiogenesis inhibitor. *Drugs Future* 2000;25:551-557.
14. Prudden JF, Migel P, Hanson P, et al. The discovery of a potent pure chemical wound-healing accelerator. *Am J Surg* 1970;119:560-564.
15. AE 941--Neovastat. *Drugs R D* 1999;1:135-136.
16. Cassileth BR. Shark and bovine cartilage therapies. In: Cassileth BR, editors. *The Alternative Medicine Handbook: The Complete Reference Guide to Alternative and Complementary Therapies*. New York, NY: WW Norton & Company 1998;197-200.
17. Holt S. Shark cartilage and nutraceutical update. *Altern Complement Ther* 1995;1:414-416.
18. Hunt TJ, Connelly JF. Shark cartilage for cancer treatment. *Am J Health Syst Pharm* 1995;52:1756,1760.
19. Fontenele JB, Araújo GB, de Alencar JW, et al. The analgesic and anti-inflammatory effects of shark cartilage are due to a peptide molecule and are nitric oxide (NO) system dependent. *Biol Pharm Bull* 1997;20:1151-1154.
20. Finkelstein JB. Sharks do get cancer. few surprises in cartilage research. *J Natl Cancer Inst* 2005;97:1562-1563.
21. Moses MA, Sudhalter J, Langer R. Isolation and characterization of an inhibitor of neovascularization from scapular chondrocytes. *J Cell Biol* 1992;119:475-482.
22. Moses MA. A cartilage-derived inhibitor of neovascularization and metalloproteinases. *Clin Exp Rheumatol* 1993 Mar-Apr;11:S67-69.
23. Takigawa M, Pan HO, Enomoto M, et al. A clonal human chondrosarcoma cell line produces an anti-angiogenic antitumor factor. *Anticancer Res* 1990;10:311-315.
24. Ohba Y, Goto Y, Kimura Y, et al. Purification of an angiogenesis inhibitor from culture medium conditioned by a human chondrosarcoma-derived chondrocytic cell line, HCS-2/8. *Biochim Biophys Acta* 1995;1245:1-8.
25. Takigawa M, Shirai E, Enomoto M, et al. A factor in conditioned medium of rabbit costal chondrocytes inhibits the proliferation of cultured endothelial cells and angiogenesis induced by B16 melanoma: its relation with cartilage-derived anti-tumor factor (CATF). *Biochem Int* 1987;14: 357-363.
26. Hiraki Y, Inoue H, Iyama K, et al. Identification of chondromodulin I as a novel endothelial cell growth inhibitor. Purification and its localization in the avascular zone of epiphyseal cartilage. *J Biol Chem* 1997;272:32419-32426.
27. Suzuki F. Cartilage-derived growth factor and antitumor factor: past, present, and future studies. *Biochem Biophys Res Commun* 1999;259:1-7.
28. Langer R, Conn H, Vacanti J, et al. Control of tumor growth in animals by infusion of an angiogenesis inhibitor. *Proc Natl Acad Sci U S A* 1980;77:4331-4335.
29. Takigawa M, Shirai E, Enomoto M, et al. Cartilage-derived anti-tumor factor (CATF) inhibits the proliferation of endothelial cells in culture. *Cell Biol Int Rep* 1985;9:619-925.
30. McGuire TR, Kazakoff PW, Hoie EB, et al. Antiproliferative activity of shark cartilage with and without tumor necrosis factor-alpha in human umbilical vein endothelium. *Pharmacotherapy* 1996 Mar-Apr;16:237-244.
31. Folkman J. The role of angiogenesis in tumor growth. *Semin Cancer Biol* 1992;3:65-71.
32. Sipos EP, Tamargo RJ, Weingart JD, et al. Inhibition of tumor angiogenesis. *Ann N Y Acad Sci* 1994;732:263-72.
33. Li CY, Shan S, Huang Q, et al. Initial stages of tumor cell-induced angiogenesis: evaluation via skin window chambers in rodent models. *J Natl Cancer Inst* 2000;92:143-147.
34. Alberts B, Bray D, Lewis J, et al. *Molecular Biology of the Cell*. 3rd ed. New York, NY: Garland Publishing, 1994.
35. Moses MA. The regulation of neovascularization of matrix metalloproteinases and their inhibitors. *Stem Cells* 1997;15:180-189.
36. Stetler-Stevenson WG. Matrix metalloproteinases in angiogenesis: a moving target for therapeutic intervention. *J Clin Invest* 1999;103:1237-1241.
37. Haas TL, Madri JA. Extracellular matrix-driven matrix metalloproteinase production in endothelial cells: implications for angiogenesis. *Trends Cardiovasc Med* 1999 Apr-May;9:70-77.
38. Moses MA, Sudhalter J, Langer R. Identification of an inhibitor of neovascularization from cartilage. *Science* 1990;248:1408-1410.
39. Langer R, Brem H, Falterman K, et al. Isolations of a cartilage factor that inhibits tumor neovascularization. *Science* 1976;193:70-72.
40. Lee A, Langer R. Shark cartilage contains inhibitors of tumor angiogenesis. *Science* 1983;221:1185-1187.
41. Sheu JR, Fu CC, Tsai ML, et al. Effect of U-995, a potent shark cartilage-derived angiogenesis inhibitor, on anti-angiogenesis and anti-tumor activities. *Anticancer Res* 1998 Nov-Dec;18:4435-4441.
42. Oikawa T, Ashino-Fuse H, Shimamura M, et al. A novel angiogenic inhibitor derived from Japanese shark cartilage

- (I). Extraction and estimation of inhibitory activities toward tumor and embryonic angiogenesis. *Cancer Lett* 1990;51:181-186.
43. Dupont E, Falardeau P, Mousa SA, et al. Antiangiogenic and antimetastatic properties of Neovastat (AE-941), an orally active extract derived from cartilage tissue. *Clin Exp Metastasis* 2002;19:145-153.
44. Liang JH, Wong KP. The characterization of angiogenesis inhibitor from shark cartilage. *Adv Exp Med Biol* 2000;476:209-223.
45. Davis PF, He Y, Furneaux RH, et al. Inhibition of angiogenesis by oral ingestion of powdered shark cartilage in a rat model. *Microvasc Res* 1997;54:178-182.
46. Morris GM, Coderre JA, Micca PL, et al. Boron neutron capture therapy of the rat 9L gliosarcoma: evaluation of the effects of shark cartilage. *Br J Radiol* 2000;73:429-434.
47. Wojtowicz-Praga S. Clinical potential of matrix metalloprotease inhibitors. *Drugs R D* 1999;1:117-129.
48. Horsman MR, Alsner J, Overgaard J. The effect of shark cartilage extracts on the growth and metastatic spread of the SCCVII carcinoma. *Acta Oncol* 1998;37:441-445.
49. Rosen J, Sherman WT, Prudden JF, et al. Immunoregulatory effects of catrinx. *J Biol Response Mod* 1988;7:498-512.
50. Houck JC, Jacob RA, Deangelo L, et al. The inhibition of inflammation and the acceleration of tissue repair by cartilage powder. *Surgery* 1962;51:632-638.
51. Durie BG, Soehnen B, Prudden JF. Antitumor activity of bovine cartilage extract (Catrinx-S) in the human tumor stem cell assay. *J Biol Response Mod* 1985;4:590-595.
52. Sadove AM, Kuettner KE. Inhibition of mammary carcinoma invasiveness with cartilage-derived inhibitor. *Surg Forum* 1977;28:499-501.
53. Pauli BU, Memoli VA, Kuettner KE. Regulation of tumor invasion by cartilage-derived anti-invasion factor in vitro. *J Natl Cancer Inst* 1981;67:65-73.
54. Murray JB, Allison K, Sudhalter J, et al. Purification and partial amino acid sequence of a bovine cartilage-derived collagenase inhibitor. *J Biol Chem* 1986;261:4154-4159.
55. McCawley LJ, Matrisian LM. Matrix metalloproteinases: multifunctional contributors to tumor progression. *Mol Med Today* 2000;6:149-156.
56. Batist G, Champagne P, Hariton C, et al. Dose-survival relationship in a phase II study of Neovastat in refractory renal cell carcinoma patients. [Abstract] *Proceedings of the American Society of Clinical Oncology* 2002;21:A-1907.
57. Loprinzi CL, Levitt R, Barton DL, et al. Evaluation of shark cartilage in patients with advanced cancer: a North Central Cancer Treatment Group trial. *Cancer* 2005;104:176-182.
58. Lu C, Lee JJ, Komaki R, et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. *J Natl Cancer Inst* 2010;102:859-865.
59. Loprinzi CL, Levitt R, Barton DL, et al. Evaluation of shark cartilage in patients with advanced cancer: a North Central Cancer Treatment Group trial. *Cancer* 2005;104:176-182.
60. Ostrander GK, Cheng KC, Wolf JC, et al. Shark cartilage, cancer and the growing threat of pseudoscience. *Cancer Res* 2004;64:8485-8491.
61. Schlumberger HG, Lucke B. Tumors of fishes, amphibians, and reptiles. *Cancer Res* 1948;8:657-754.
62. Wellings SR. Neoplasia and primitive vertebrate phylogeny: echinoderms, prevertebrates, and fishes--A review. *Natl Cancer Inst Monogr* 1969;31:59-128.