Medical Hypotheses 73 (2009) 205–206

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Mechanism of anti-angiogenic activities of chitooligosaccharides may be through inhibiting heparanase activity

Haizhi Quan [a], Fei Zhu [a], Xinyan Han [a], Zirong Xu [a,*], Yilong Zhao [b], Zhiguo Miao [c]

[a] Ke Lab a f M ec a A a N f M f Ed ca , Feed A a Sc e ce I e, Z e a U e , Q a N R ad 164, Z e a , Ha 310029, C a
[b] Ve e a a De a e A c e C e e Ya b a U e , L 133400, C a
[c] He a I e f Sc e ce a d Tec , C e e f A a Sc e ce, X a , C a

ARTICLE INFO

A c e :
Received 25 February 2009
Accepted 28 February 2009

SUMMARY

Metastatic disease is the primary cause of death for most cancer patients. Angiogenesis is the formation of a new capillary network from pre-existing vessels and required for tumor vasculature. Heparanase, a β-endoglucuronidase, assistants tumor invasion, metastasis and angiogenesis. Chitooligosaccharides (COS) is obtained by hydrolysis of chitosan. COS has been proved to be anti-angiogenesis activity. The mechanism of COS inhibits angiogenesis is not very clear, COS is hypothesized by author to be an inhibitor of heparanase.

Introduction

Angiogenesis is the formation of a new capillary network from pre-existing vessels and is required for normal and tumor vasculature [1]. During angiogenesis upon stimulation by angiogenic growth factors and cytokines, quiescent vascular endothelial cells degrade the underlying basement membrane, migrate into the extracellular matrix, proliferate, and form capillary structures [2]. Therefore, during tumor growth and metastasis, angiogenesis is required for proper nourishment, removal of metabolic wastes from tumor sites, and creating vessels for tumor cells migration [3,4].

Heparan sulphate proteoglycans (HSPGs), a key component of basement (BM) and extracellular matrix (ECM), is prominent components of blood vessels [5]. HSPGs themselves act as a storage depot for a number of cytokines and growth factors such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF). HSPGs also bind specifically to the heparan sulphate (HS) glycosaminoglycan (GAG) chains [6]. Heparanase is a β-endoglucuronidase, which acts via a hydrolytic mechanism to cleave glycosidic bonds in HS [7]. A critical early event in the tumor angiogenic process is that heparanase degrades the HS of HSPG in BM and ECM, followed by endothelial cells migration toward the angiogenic stimulus. Moreover by releasing HS-bound angiogenic growth factors (i.e. VEGF) from the ECM, heparanase may indirectly facilitate endothelial cells migration and proliferation. The processes heparanase assistants tumor invasion and metastasis are just like those of endothelial cells migration and proliferation [8]. So heparanase plays an important role in tumor invasion, metastasis and angiogenesis.

Chitosan is the deacetylated form of chitin, and is a linear polymer of *N*-acetyl-D-glucosamine and deacetylated glucosamine. The molecular structure of chitosan makes it shares some characteristics of GAG [9]. Chitooligosaccharides (COS) can be obtained by either chemical or enzymatic hydrolysis of chitosan. COS are composed of 3–10 *N*-acetyl-glucosamine (NAGA) or glucosamine residues [10]. In biomedicine field, COS is more applicable than chitosan because of its water solubility and favorable properties of biodegradability, biocompatibility and other bioactivities [11]. COS has been proved some characteristics different from chitosan such as anti-angiogenesis [12], inhibiting vascular endothelium cells migration [13], depressing tumor invasion [14].

COS is a successful inhibitor of tumor induced angiogenesis [12]. Nevertheless the mechanism of COS anti-angiogenesis is not very clear.

Hypothesis

COS may be a competitive inhibitor for heparanase, due to its molecular structure similar to that of HS GAG, the substrate of heparanase.

Evaluation of hypothesis

Metastatic disease is the primary cause of death for most cancer patients [15]. Tumor growth and metastasis require angiogenesis when the tumor reaches 1–2 mm in diameter [16]. Heparanase activity was implicated in cellular invasion associated with tumor angiogenesis and metastasis [17]. Downregulating the expression

* Corresponding author. Tel.: +86 571 86971075.
E- a add e : zrxu@zju.edu.cn (Z. Xu).

0306-9877/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2009.02.018

of heparanase inhibits the invasion, angiogenesis and metastasis of human hepatocellular carcinoma [18]. PI-88, a heparanase inhibitor significantly reduces the expression of VEGF receptor A [19]. Excess heparanase expression is a poor prognostic indicator of breast and gastric cancer [20,21]. It can be concluded that heparanse inhibitor inhibits tumor growth, metastasisis and angiogenesis. Therefore heparanse inhibitor is a direction for drug development in cancer therapy [6].

Low molecular weight heparin has been used to control angiogenesis and heparanase activity in anti-tumor drug discovery [22,23]. However chitin, which is obtained in large quantities from crustacean shells, the material of COS, has abundant resource in nature [24]. Maybe it is a potent predominance of COS drug discovery. Besides, COS can be a safely oral administered drug because of its few side effects [25], water solubility [11] and epithelial cells permeability [26].

References

[1] Dass CR, Tran TR, Choong PFM. Angiogenesis inhibitor and the need for anti-angiogenic therapetutics. Crit Rev Oral Biol Med 2007;10:927–36.
[2] Toshikazu N, Kunio M. Angiogenesis inhibitors: from laboratory to clinical application. Biochem Biophys Res Commun 2005;333:289–91.
[3] Tiziana T, Francesca R, Pier PC. Molecular basis of angiogenesis and cancer. Oncogene 2003;22:6549–56.
[4] Douglas H, Judah F. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353–64.
[5] Rohloff J, Zinke J, Schoppmeyer K, et al. Heparanase expression is a prognostic indicator for postoperative survival in pancreatic adenocarcinoma. Br J Cancer 2002;86:1270–5.
[6] McKenzied EA. Heparanase: a target for drug discovery in cancer and inflammation. Br J Pharmacol 2007;151:1–14.
[7] Martin G, George WY. Heparanase, hyaluronan, and CD44 in cancers: a breast carcinoma perspective. Cancer Res 2006;21:10233–7.
[8] Neta I, Michael E, Israel V. Regulation, function and clinical significance of