J Atheroscler Thromb, 2017; 24: 1014-1015.
http://doi.org/10.5551/jat.ED077

Editorial

Endostatin as a Biomarker of Basement Membrane Degradation

Yasufumi Sato

Department of Vascular Biology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

See article vol. 24: 1023-1030

Endostatin was originally isolated from murine hemangioendothelioma culture medium that inhibited tumor angiogenesis and growth, and biochemical analysis revealed it to be a C-terminal fragment of collagen XVIII[1]. Collagen XVIII is a non-fibrillar collagen ubiquitously expressed and accumulated in basement membrane (BM) throughout the body. There are three isoforms of collagen XVIII: long, middle, and short. These isoforms differ in their N-terminal non-collagenous 2 domain but share collagenous and C-terminal non-collagenous 1 (NC1) domain containing endostatin. These three isoforms of collagen XVIII are encoded by a single *COL18A1* gene on chromosome 21q22.3, but the expression and localization of the gene products are different. For example, the long isoform of collagen XVIII is found selectively in the liver, whereas the short isoform is present in various epithelial and endothelial BM[2]. BM is degraded proteolytically during its turnover, and that generates matricryptins including endostatin. Matricryptins are bioactive fragments originated by the proteolytic cleavage of extracellular matrices[3]. For the generation of endostatin, various proteases such as matrix metalloproteinases, elastase, and cathepsins cleave the hinge region of the NC1 domain of collagen XVIII and release a 20-kDa endostatin as well as endostatin-containing fragments with molecular weights varying from 24 to 28 kDa[2].

Because of the distinctive role of endostatin in tumor angiogenesis and growth, ELISA for endostatin was soon developed and its level was tested for the application as a biomarker. Previous studies focused on various cancers, but later on, other pathological conditions such as bronchopulmonary dysplasia, pulmonary arterial hypertension, traumatic brain injury, Alzheimer's disease, peripheral vascular disease, and chronic kidney disease were included[2].

In this issue of the journal, Kato *et al*. examined serum endostatin concentration in Japanese healthy population and revealed for the first time that a higher serum endostatin concentration reflects the presence of subclinical carotid atherosclerosis[4]. The relationship between endostatin and atherosclerosis is reported as follows: the administration of endostatin inhibited adventitial angiogenesis and intimal plaque formation in *apoE*$^{-/-}$ mice[5], whereas the absence of *col18a1* gene exacerbated atherosclerosis in *apoE*$^{-/-}$ mice[6]. Patients with Down syndrome (trisomy 21) had elevated serum endostatin concentration[7] and had a reduced prevalence of atherosclerosis[8]. Accordingly, because of the property of angiogenesis inhibitor, endostatin is anti-atherosclerotic. Therefore, the elevated serum endostatin concentration in this Japanese healthy population should not be the cause of carotid atherosclerosis but the result of basement membrane degradation probably from the vasculature during the development of atherosclerosis. Seemingly, although the elevated serum endostatin concentration is not specific to atherosclerosis, it can be a possible surrogate marker that suggests the presence of subclinical carotid atherosclerosis with basement membrane degradation.

Address for correspondence: Yasufumi Sato, Department of Vascular Biology, Institute of Development, Aging and Cancer, Tohoku University, 4-1, Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan.
E-mail: yasufumi.sato.b3@tohoku.ac.jp
Received: April 14, 2017
Accepted for publication: April 15, 2017

References

1) O'Reilly MS, Boehm T, Shing Y, Fukai N, Vasios G, Lane WS, Flynn E, Birkhead JR, Olsen BR, Folkman J: Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell, 1997; 88: 277-285
2) Walia A, Yang JF, Huang YH, Rosenblatt MI, Chang JH, Azar DT: Endostatin's emerging roles in angiogenesis, lymphangiogenesis, disease, and clinical applications. Biochim Biophys Acta, 2015; 1850: 2422-2438
3) Ricard-Blum S, Vallet SD: Proteases decode the extracellular matrix cryptome. Biochimie, 2016; 122: 300-313
4) Kato Y, Furusyo N, Tanaka Y, Ueyama T, Yamasaki S,

Murata M, Jun Hayashi: The Relation between Serum Endostatin Level and Carotid Atherosclerosis in Healthy Residents of Japan: Results from the Kyushu and Okinawa Population Study (KOPS). J Atheroscler Thromb, 2017; 24: 1023-1030
5) Moulton KS, Heller E, Konerding MA, Flynn E, Palinski W, Folkman J: Angiogenesis inhibitors endostatin or TNP-470 reduce intimal neovascularization and plaque growth in apolipoprotein E-deficient mice. Circulation, 1999; 99: 1726-1732
6) Moulton KS, Olsen BR, Sonn S, Fukai N, Zurakowski D, Zeng X: Loss of collagen XVIII enhances neovascularization and vascular permeability in atherosclerosis. Circulation, 2004; 110: 1330-1336
7) Zorick TS, Mustacchi Z, Bando SY, Zatz M, Moreira-Filho CA, Olsen B, and Passos-Bueno MR. High serum endostatin levels in Down syndrome: implications for improved treatment and prevention of solid tumours. Eur J Hum Genet, 2001; 9: 811-814
8) Parra P, Costa R, de Asúa DR, Moldenhauer F, Suárez C: Atherosclerotic Surrogate Markers in Adults With Down Syndrome: A Case-Control Study. J Clin Hypertens (Greenwich), 2017; 19: 205-211