J. Biochem. 2011;149(3):229–230 doi:10.1093/jb/mvq152

JB THE JOURNAL OF BIOCHEMISTRY

JB Commentary

# Is vasohibin-1 for more than angiogenesis inhibition?

*Received December 14, 2010; accepted December 22, 2010; published online January 8, 2011*

**Yasufumi Sato***

Department of Vascular Biology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan

*Yasufumi Sato, Department of Vascular Biology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan. Tel: +81-22-717-8528, Fax: +81-22-717-8533, email: y-sato@idac.tohoku.ac.jp

**Angiogenesis, a formation of neo-vessels from pre-existing ones, is regulated by the local balance between its stimulators and inhibitors. Vasohibin-1 (VASH1) was originally identified as an endothelium-derived vascular endothelial growth factor (VEGF)-inducible angiogenesis inhibitor that acts in a negative feedback manner. The expression of VASH1 has been shown in endothelial cells (ECs) in both physiological and pathological conditions associated with angiogenesis. However, recent reports indicate that VASH1 is expressed not only in ECs but also in other cell types including haematopoietic cells. The function of VASH1 may not be restricted to angiogenesis inhibition.**

*Keywords*: Angiogenesis/Bone Marrow/Endothelium/FeedbackHematopoiesis.

*Abbreviations*: AMD, age-dependent macular degeneration; EZH2, the enhancer of Zeste homologue 2; HCs, hematopoietic cells; HPs, hematopoietic progenitors; HSCs, hematopoietic stem cells; PcG, polycomb group.

Angiogenesis is defined as a formation of neo-vessels from pre-existing ones. The body contains a number of angiogenesis stimulators and inhibitors, and the local balance between those factors regulates this process of neo-vessel formation (*1*). The majority of angiogenesis inhibitors are extrinsic to the vasculature. However, endothelial cells (ECs) themselves have been found to produce intrinsic angiogenesis inhibitors.

Vasohibin-1 (VASH1) has been isolated from vascular endothelial growth factor (VEGF)-inducible genes in ECs that inhibits migration and proliferation of ECs in culture, and exhibits anti-angiogenic activity *in vivo* (*2*) (Fig. 1). The expression of VASH1 in ECs is induced not only by VEGF but also by fibroblast growth factor 2 (FGF-2), another potent angiogenic factor (*2*, *3*). Thus, VASH1 is thought to be a negative-feedback regulator of angiogenesis. One alternative splicing form of VASH1 lacking exons 5–8 is present in humans (*3*, *4*). Immunohistochemical analysis revealed that VASH1 protein is shown selectively in ECs in the developing human or mouse embryo, reduced expression in the post-neonate, but appears in ECs at the site of angiogenesis (*5*). Analysis of the spatiotemporal expression and function of VASH1 during angiogenesis revealed that VASH1 is expressed not in ECs at the sprouting front but in ECs of newly formed blood vessels behind the sprouting front where angiogenesis terminates (*6*). In addition, *VASH1 (−/−)* mice contain numerous immature microvessels in the area where angiogenesis should be terminated (*6*). Thus, the principal function of endogenous VASH1 is thought to terminate angiogenesis.

The expression of VASH1 is evident in various pathological conditions including cancers (*7–10*), atherosclerosis (*11*), age-dependent macular degeneration (AMD) (*12*), diabetic retinopathy (*13*) and so forth. Patients with active AMD tend to have a lower VASH1-to-VEGF mRNA ratio, whereas those with the inactive disease have a higher VASH1-to-VEGF mRNA ratio (*12*). Lu *et al*. (*14*) recently reported the relationship between VASH1 and the enhancer of Zeste homologue 2 (EZH2), a member of the polycomb group (PcG) proteins. When EZH2 is expressed in ovarian cancers, EZH2 downregulates VASH1 expression by the methylation of VASH1 promoter, and that enhances tumour angiogenesis. These observations suggest that the level of VASH1 expression influences the clinical course of diseases with pathological angiogenesis.

Vascular development and haematopoiesis are closely related, as ECs and haematopoietic cells (HCs) arise from a common progenitor in embryo. Moreover, several molecules such as VEGF and erythropoietin are commonly utilized both in vascular development and haematopoiesis. Recently, Naito *et al*. found that the expression of VASH1 mRNA in adult bone marrow (BM) was evident in the steady-state haematopoietic stem cells (HSCs), a minor fraction in BM, but not in other fractions including haematopoietic progenitors (HPs) or mature HCs (*15*). However, interestingly, VASH1 expression was induced in HPs but not in HSCs during the recovery from BM ablation (*15*). In addition, knockdown of the *VASH1* gene enhanced proliferation of $VASH1^{+}$ cells from leukaemic cell lines (*15*). During the recovery from BM ablation, HPs need to proliferate, but their cell division needs to be halted when sufficient mature HCs are generated. The mechanism responsible for this negative regulation has thus far

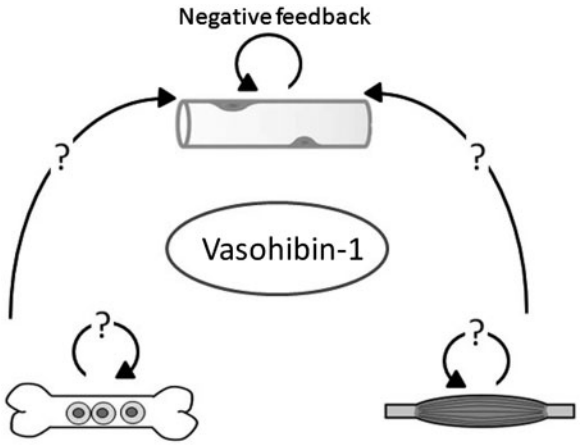


**Fig. 1 VASH1 is originally identified as an endothelium-derived angiogenesis inhibitor that acts in a negative feedback manner.** However, recent reports indicate that VASH1 is expressed in other cell types including BM cells and striated muscles. The entire function of VASH1 needs to be determined.

eluded identification. Observations by Naito *et al.* raise the possibility that VASH1 might be one of the negative regulators acting at the final stage of acute recovery following BM ablation (Fig. 1).

The accumulating information indicates that the range of VASH1 expression is more extensive than the original concept. Nimmagadda *et al.* (*16*) reported that VASH1 is expressed in a wide range of tissues and organs in the chicken embryo. Kishlyansky *et al.* (*17*) reported that VASH1 is expressed in striated muscles in the adult rat (Fig. 1). Apparently, the entire role of VASH1 needs to be determined in the future analysis.

**Conflict of interest**
None declared.

## References


1. Sato, Y. (2006) Update on endogenous inhibitors of angiogenesis. *Endothelium* **13**, 147–155
2. Watanabe, K., Hasegawa, Y., Yamashita, H., Shimizu, K., Ding, Y., Abe, M., Ohta, H., Imagawa, K., Hojo, K., Maki, H., Sonoda, H., and Sato, Y. (2004) Vasohibin as an endothelium-derived negative feedback regulator of angiogenesis. *J. Clin. Invest.* **114**, 898–907
3. Shimizu, K., Watanabe, K., Yamashita, H., Abe, M., Yoshimatsu, H., Ohta, H., Sonoda, H., and Sato, Y. (2005) Gene regulation of a novel angiogenesis inhibitor, vasohibin, in endothelial cells. *Biochem. Biophys. Res. Commun.* **327**, 700–706
4. Kern, J., Bauer, M., Rychli, K., Wojta, J., Ritsch, A., Gastl, G., Gunsilius, E., and Untergasser, G. (2008) Alternative splicing of vasohibin-1 generates an inhibitor of endothelial cell proliferation, migration, and capillary tube formation. *Arterioscler. Thromb. Vasc. Biol.* **28**, 478–484
5. Shibuya, T., Watanabe, K., Yamashita, H., Shimizu, K., Miyashita, H., Abe, M., Moriya, T., Ohta, H., Sonoda, H., Shimosegawa, T., Tabayashi, K., and Sato, Y. (2006) Isolation and characterization of vasohibin-2 as a homologue of VEGF-inducible endothelium-derived angiogenesis inhibitor vasohibin. *Arterioscler. Thromb. Vasc. Biol.* **26**, 1051–1057
6. Kimura, H., Miyashita, H., Suzuki, Y., Kobayashi, M., Watanabe, K., Sonoda, H., Ohta, H., Fujiwara, T., Shimosegawa, T., and Sato, Y. (2009) Distinctive localization and opposed roles of vasohibin-1 and vasohibin-2 in the regulation of angiogenesis. *Blood* **113**, 4810–4818
7. Hosaka, T., Kimura, H., Heishi, T., Suzuki, Y., Miyashita, H., Ohta, H., Sonoda, H., Moriya, T., Suzuki, S., Kondo, T., and Sato, Y. (2009) Vasohibin-1 expressed in endothelium of tumor vessels regulates angiogenesis. *Am. J. Pathol.* **175**, 430–439
8. Yoshinaga, K., Ito, K., Moriya, T., Nagase, S., Takano, T., Niikura, H., Yaegashi, N., and Sato, Y. (2008) Expression of vasohibin as a novel endothelium-derived angiogenesis inhibitor in endometrial cancer. *Cancer Sci.* **99**, 914–919
9. Tamaki, K., Moriya, T., Sato, Y., Ishida, T., Maruo, Y., Yoshinaga, K., Ohuchi, N., and Sasano, H. (2008) Vasohibin-1 in human breast carcinoma: a potential negative feedback regulator of angiogenesis. *Cancer Sci.* **100**, 88–94
10. Tamaki, K., Sasano, H., Maruo, Y., Takahashi, Y., Miyashita, M., Moriya, T., Sato, Y., Hirakawa, H., Tamaki, N., Watanabe, M., Ishida, T., and Ohuchi, N. (2010) Vasohibin-1 as a potential predictor of aggressive behavior of ductal carcinoma in situ of the breast. *Cancer Sci.* **101**, 1051–1058
11. Yamashita, H., Abe, M., Watanabe, K., Shimizu, K., Moriya, T., Sato, A., Satomi, S., Ohta, H., Sonoda, H., and Sato, Y. (2006) Vasohibin prevents arterial neointimal formation through angiogenesis inhibition. *Biochem. Biophys. Res. Commun.* **345**, 919–925
12. Wakusawa, R., Abe, T., Sato, H., Yoshida, M., Kunikata, H., Sato, Y., and Nishida, K. (2008) Expression of vasohibin, an antiangiogenic factor, in human choroidal neovascular membranes. *Am. J. Ophthalmol.* **146**, 235–243
13. Sato, H., Abe, T., Wakusawa, R., Asai, N., Kunikata, H., Ohta, H., Sonoda, H., Sato, Y., and Nishida, K. (2009) Vitreous levels of vasohibin-1 and vascular endothelial growth factor in patients with proliferative diabetic retinopathy. *Diabetologia* **52**, 359–361
14. Lu, C., Han, H.D., Mangala, L.S., Ali-Fehmi, R., Newton, C.S., Ozbun, L., Armaiz-Pena, G.N., Hu, W., Stone, R.L., Munkarah, A., Ravoori, M.K., Shahzad, M.M., Lee, J.W., Mora, E., Langley, R.R., Carroll, A.R., Matsuo, K., Spannuth, W.A., Schmandt, R., Jennings, N.B., Goodman, B.W., Jaffe, R.B., Nick, A.M., Kim, H.S., Guven, E.O., Chen, Y.H., Li, L.Y., Hsu, M.C., Coleman, R.L., Calin, G.A., Denkbas, E.B., Lim, J.Y., Lee, J.S., Kundra, V., Birrer, M.J., Hung, M.C., Lopez-Berestein, G., and Sood, A.K. (2010) Regulation of tumor angiogenesis by EZH2. *Cancer Cell* **18**, 185–197
15. Naito, H., Kidoya, H., Sato, Y., and Takakura, N. (2009) Induction and expression of anti-angiogenic vasohibins in the hematopoietic stem/progenitor cell population. *J. Biochem.* **145**, 653–659
16. Nimmagadda, S., Geetha-Loganathan, P., Pröls, F., Scaal, M., Christ, B., and Huang, R. (2007) Expression pattern of vasohibin during chick development. *Dev. Dyn.* **236**, 1358–1362
17. Kishlyansky, M., Vojnovic, J., Roudier, E., Gineste, C., Decary, S., Forn, P., Bergeron, R., Desplanches, D., and Birot, O. (2010) Striated muscle angio-adaptation requires changes in Vasohibin-1 expression pattern. *Biochem. Biophys. Res. Commun.* **399**, 359–364