US009409963B2

(12) **United States Patent**
Soo et al.

(10) **Patent No.: US 9,409,963 B2**
(45) **Date of Patent: Aug. 9, 2016**

(54) **FIBROMODULIN PEPTIDE**

(75) Inventors: **B. Chia Soo**, Beverly Hills, CA (US); **Kang Ting**, Beverly Hills, CA (US); **Zhong Zheng**, Van Nuys, CA (US)

(73) Assignee: **The Regents of the University of California**, Oakland, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/322,124**

(22) PCT Filed: **May 26, 2010**

(86) PCT No.: **PCT/US2010/036262**

§ 371 (c)(1), (2), (4) Date: **Mar. 14, 2012**

(87) PCT Pub. No.: **WO2010/138637**

PCT Pub. Date: **Dec. 2, 2010**

(65) **Prior Publication Data**

US 2012/0171253 A1 Jul. 5, 2012

Related U.S. Application Data

(60) Provisional application No. 61/181,226, filed on May 26, 2009.

(51) **Int. Cl.**

A61K 38/16	(2006.01)
C07K 14/47	(2006.01)
A61K 38/18	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 14/4725*** (2013.01); ***A61K 38/1841*** (2013.01); *C07K 2319/02* (2013.01); *C07K 2319/21* (2013.01)

(58) **Field of Classification Search**

CPC A61K 38/00; A61K 38/1841

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,654,270 A 8/1997 Longaker et al.

FOREIGN PATENT DOCUMENTS

WO WO 96-25178 8/1996
WO WO 2004/099784 11/2004

OTHER PUBLICATIONS

Hildebrand et al., "Interaction of the small interstitial proteoglycans biglycan, decorin and fibromodulin with transforming growth factor β", Biochem. J. vol. 302, pp. 527-534 (1994).

Honardoust et al., "Localization of small leucine-rich proteoglycans and transforming growth factor-beta in human oral mucosal wound healing", Wound Rep. Reg. vol. 16, pp. 814-823 (2008).

Soo et al. "Differential expression of fibromodulin, a transforming growth factor-β modulator, in fetal skin development and scarless repair", Am J. of Pathol. vol. 157, No. 2, pp. 423-433 (2000).

Supplemental European Search Report mailed Oct. 2, 2012, 2 pages.

Ebner, R., Chen, R.H., Lawler, S., Zioncheck, T. & Derynck, R. Determination of Type-I Receptor Specificity by the Type-II Receptors for TGF-Beta or Activin. *Science* 262, 900-902 (1993).

Brandes, M.E., Mai, U.E., Ohura, K. & Wahl, S.M. Type I transforming growth factor-beta receptors on neutrophils mediate chemotaxis to transforming growth factor-beta. *J Immunol* 147, 1600-6 (1991).

De Crescenzo, G., Pham, P.L., Durocher, Y. & O'Connor-McCourt, M.D. Transforming growth factor-beta (TGF-beta) binding to the extracellular domain of the type II TGF-beta receptor: receptor capture on a biosensor surface using a new coiled-coil capture system demonstrates that avidity contributes significantly to high affinity binding. *J Mol Biol* 328, 1173-83 (2003).

Cui, W. et al. Concerted action of TGF-beta 1 and its type II receptor in control of epidermal homeostasis in transgenic mice. *Genes Dev* 9, 945-55 (1995).

Lopez-Casillas, F. et al. Structure and expression of the membrane proteoglycan betaglycan, a component of the TGF-beta receptor system. Cell 67, 785-795 (1991).

Lopez-Casillas, F., Payne, H.M., Andres, J.L. & Massague, J. Betaglycan Can Act as a Dual Modulator of TGF-Beta Access to Signaling Receptors—Mapping of Ligand-Binding and Gag Attachment Sites. *Journal of Cell Biology* 124, 557-568 (1994).

Boucher, P. et al. LRP1 Functions as an Atheroprotective Integrator of TGF beta and PDGF Signals in the Vascular Wall: Implications for Marfan Syndrome. *Plos One* 2(2007).

Baghy, K., Iozzo, R.V. & Kovalszky, I. Decorin-TGF beta Axis in Hepatic Fibrosis and Cirrhosis. *Journal of Histochemistry & Cytochemistry* 60, 262-268 (2012).

Hildebrand, A. et al. Interaction of the small interstitial proteoglycans biglycan, decorin and fibromodulin with transforming growth factor β. *Biochem J* 302, 527-534 (1994).

Annes, J.P., Chen, Y., Munger, J.S. & Rifkin, D.B. Integrin alpha(v)beta(6)-mediated activation of latent TGF-beta requires the latent TGF-beta binding protein-1. *Journal of Cell Biology* 165, 723-734 (2004).

Hyytiainen, M., Penttinen, C. & Keski-Oja, J. Latent TGF-beta binding proteins: Extracellular matrix association and roles in TGF-beta activation. *Critical Reviews in Clinical Laboratory Sciences* 41, 233-264 (2004).

Keski-Oja, J. et al. Latent Tgf-Beta Binding Proteins (Ltbps) in Targeting TGF-Beta Action. *Anticancer Research* 28, 3345-3346 (2008).

Todorovic, V. et al. Latent TGF-beta binding proteins. *International Journal of Biochemistry & Cell Biology* 37, 38-41 (2005).

Vehvilainen, P. et al. Latent TGF-beta binding proteins (LTBPs) 1 and 3 differentially regulate transforming growth factor-beta activity in malignant mesothelioma. *Human Pathology* 42, 269-278 (2011).

Philip, A., Bostedt, L., Stigbrand, T. & Oconnormccourt, M.D. Binding of Transforming Growth-Factor-Beta (Tgf-Beta) to Pregnancy Zone Protein (Pzp)—Comparison to the Tgf-Beta-Alpha(2)-Macroglobulin Interaction. *European Journal of Biochemistry* 221, 687-693 (1994).

Lastres, P. et al. Endoglin modulates cellular responses to TGF-beta 1. *Journal of Cell Biology* 133, 1109-1121 (1996).

Mooradian, D.L., Lucas, R.C., Weatherbee, J.A. & Furcht, L.T. Transforming Growth Factor-Beta-1 Binds to Immobilized Fibronectin. *Journal of Cellular Biochemistry* 41, 189-200 (1989).

Primary Examiner — Prema Mertz

(74) *Attorney, Agent, or Firm* — Duane Morris LLP

(57) **ABSTRACT**

Embodiments of the present invention provide a fibromodulin (FMOD) peptide (FMOD-P), a composition and a formulation comprising a FMOD-P, option-ally with a TGF-β isoform, or comprising FMOD with a TGF-β isoform. The present invention also provides methods of making and using the FMOD-P, composition, or formulation.

8 Claims, 23 Drawing Sheets