Transglutaminase type 2 in human abdominal aortic aneurysm is a potential factor in the stabilization of extracellular matrix

Sung Shin, MD¹; Yong-Pil Cho, MD, PhD¹; Heungman Jun, MD¹; Hojong Park, MD¹; Hea Nam Hong, PhD²; Tae-Won Kwon, MD, PhD¹

¹Division of Vascular Surgery, Department of Surgery, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea
²Department of Anatomy and Cell Biology, University of Ulsan College of Medicine, Seoul, Korea

Corresponding author
Name: Tae-Won Kwon
Address: Division of Vascular Surgery, Department of Surgery, University of Ulsan College of Medicine and Asan Medical Center, 388-1 Pungnap-2dong, Songpa-gu, Seoul, Korea 138-736
E-mail: twkwon2@amc.seoul.kr,
Telephone: 82-2-3010-3492
Fax: 82-2-3010-697
Abstract

Objective The aim of this study is to evaluate transglutaminase type 2 (TG2) expression in a human abdominal aortic aneurysm (AAA) tissue, and to elucidate a potential role of TG2 for AAA formation. TG2 which is a Ca\textsuperscript{2+}-dependent cross-linking enzyme, has been proven the importance for stabilizing the extracellular matrix. However, there is no evidence of the effect of TG2 on AAA formation in a human model.

Methods Aortic wall tissues were obtained during surgery in AAA patients (n=38) and patients with aortoiliac occlusive disease (Control) (n=4) in Asan Medical Center from March 2011 to February 2012. In each AAA patient, aortic neck (Neck) and maximally dilated portion (Max) of the aneurysm were sampled for analysis. TG2 expression was evaluated using immunohistochemistry and western blotting. In addition, ex vivo experiments of isolated AAA tissue culture with TG2 inhibitor cystamine and recombinant human TG2 were performed.

Results Among 38 AAA patients, 11 had ruptured (contained or free) AAA. Mean maximal diameter of AAA was 6.09±1.46 cm. TG2 expressions of Max were significantly increased as compared with those of Control (1.7-fold increase of the control, P = .00). Compared with Control, the intensities of tissue necrosis factor (TNF)-α, MMP-2, MMP-9 and TIMP-2 were significantly upregulated in Max (1.7-fold, 1.5-fold, 1.3-fold and 1.6-fold increases of the control, P = .00, P = .004, P = .046 and P = .007, respectively). Furthermore, double immunofluorescent staining showed that the colocalization of TG2/transforming growth factor (TGF)-β or TG2/fibronectin was prominent in Max as compared with those of the Neck or the Control. In addition, MMP-2 intensity was upregulated in ruptured AAA compared with unruptured AAA with marginal significance (P = .078). Ex vivo experiments showed that protein expressions of TNF-α, MMP-2, and MMP-9 in the cultured AAA tissue were decreased by recombinant human TG2, while were increased by exogenous cystamine.

Conclusions TG2 expression in maximally dilated portion of AAA was enhanced as compared with that of non-dilated aorta. It is suggested that TG2 has a potential effect in the stabilization of extracellular matrix by the inhibition of proinflammatory cytokines and MMPs or by interaction with fibronectin and TGF-β.