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REGULAR ARTICLE

Expression of annexin II in human atherosclerotic abdominal aortic aneurysms

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Abstract

Background: Annexin II is a receptor for tissue-type plasminogen activator (t-PA) that converts plasminogen to plasmin. Although the fibrinolytic system is known to play an important role in the pathogenesis of abdominal aortic aneurysms (AAAs), the relationship between annexin II and AAA development is unknown. Therefore, we examined annexin II localization in the wall of human atherosclerotic AAAs.
Methods and Results: Specimens from 13 patients undergoing elective repair of an AAA were taken. Annexin II expression was evaluated by immunohistochemical analysis. Immunostaining results were semiquantitatively analyzed using histology scores and WinROOF software based on staining intensity. The expression of annexin II was increased and the histology score was higher in the shoulder region of the atheromatous plaque than in the atheroma and fibrous plaque regions. Annexin II appeared to have greater expression and the histology score was higher in regions where the media was preserved. Furthermore, there was a significant inverse correlation between AAA size and histology score in the fibrous plaque region.
Conclusions: The present work demonstrates various levels of annexin II expression within the aneurysm wall. Therefore, we suggest that alteration of annexin II

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expression within the aortic wall may be associated with the development of an aneurysm.

Introduction

Abdominal aortic aneurysm (AAA) is a common and highly lethal disease. The destruction of elastin is considered to be one of the major factors responsible for the pathogenesis of AAA. As elastic fibers normally maintain the structure of the vascular wall against hemodynamic stress, proteolytic degradation induces disorganized extracellular remodeling, leading to progressive aortic enlargement and ultimate rupture [1].

The fibrinolytic system also plays an important role in the process of extracellular-matrix (ECM) remodeling [2], and there have been many reports on its expression in the vessel wall [3,4]. In this system, two plasminogen activators (PAs), tissue-type (t-PA) and urokinase-type (u-PA), generate plasmin from the inactive proenzyme plasminogen. Plasmin is a trypsin-like proteolytic enzyme capable of directly degrading some components of the ECM, as well as activating matrix metalloproteinases (MMPs) [5]. MMPs are known to degrade the ECM, including collagen and elastin, impairing the structural integrity of the vascular wall [6–8]. Previous studies demonstrated increased fibrinolytic activity and t-PA and u-PA gene expression in atherosclerotic human aortic aneurysms compared with nondilated atherosclerotic aortic wall and normal aorta [9,10]. In addition, other reports showed that t-PA and u-PA mRNA as well as their immunoreactivities were increased within the aneurysmal wall [11]. These data suggest that the fibrinolytic balance in the aneurysmal wall is disturbed, and this imbalance may lead to increased plasmin generation, activation of MMPs, and structural degeneration of the vessel wall.

Annexin II has been described as a receptor for fibrinolytic proteins and belongs to a family of calcium-regulated, phospholipid-binding, membrane proteins [12,13]. Annexin II is mainly expressed on the surface of vascular endothelial cells and is also found in some epithelial cells [13,14], promyelocytic leukemia cells [15], and cells of several monocyte-like lines [16]. According to kinetic studies, annexin II binds plasminogen and t-PA independently, thereby enhancing the catalytic efficiency of plasminogen activation by 60-fold [13]. As annexin II has a variety of biological activities, it was recently shown that annexin II plays an important role in the pathophysiological action of macrophages during the inflammatory process, and facilitates plasminogen-mediated matrix invasion and degradation by macrophages [17].

In this study, we used immunohistochemical analysis to detect the expression of annexin II in atherosclerotic AAAs. In addition to identifying specific areas of annexin II expression, we also described various levels of annexin II expression according to the magnitude of destruction of elastic fibers in the tunica media. These results suggest a linkage between atherosclerosis, enhanced fibrinolysis, and the potential breakdown of the vessel wall.

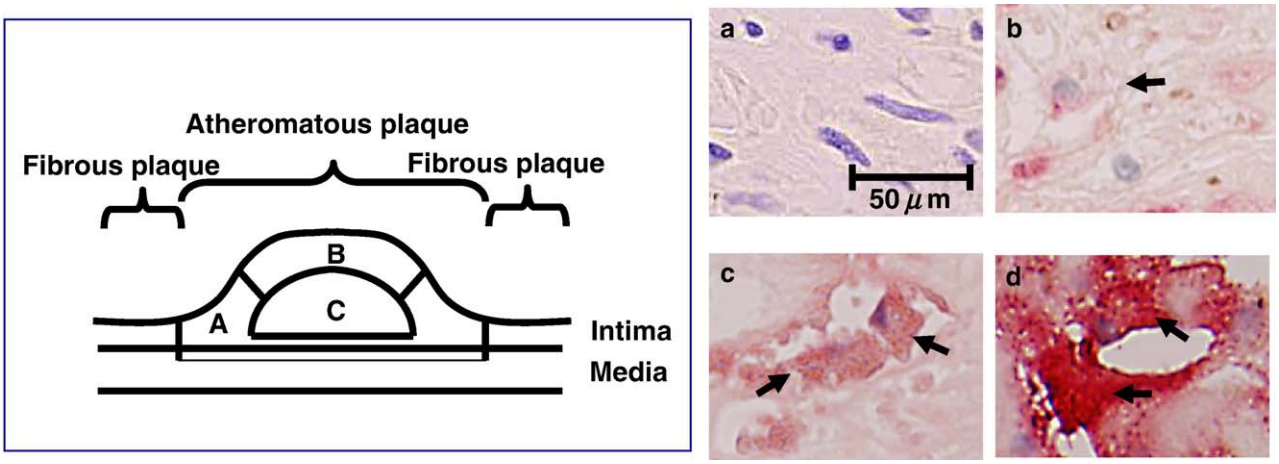

Figure 1 Schematic showing a portion of the atheromatous plaque, as described in Materials and Methods. (A): shoulder region, (B): fibrous cap, (C): atheroma. Histological classification of the cells according to their immunointensity. Representative immunohistochemical images for Annexin II (red stain) are shown in each panel. a: 0, negative, b: 1+, weekly positive, c: 2+, moderately positive, d: 3+, strongly positive.