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Time courses of vascular endothelial growth factor and intercellular adhesion molecule-1 expressions in aortas of atherosclerotic rats

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Abstract

An increasing number of studies have focused on the expressions of growth factors and adhesion molecules in atherosclerotic lesions, which are confirmed to play central roles in angiogenesis and endothelial dysfunction, including vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 (ICAM-1). However, the difference of growth factor and adhesion molecule expression time courses has not been determined in vivo. This study aimed to determine the expression patterns and expression curves of ICAM-1 and VEGF in atherosclerotic rats during the time course. An experiment atherosclerotic model in rats was established by combining the high fat/cholesterol diets with injection of vitamin D_3. In situ hybridization was used to determine the expression patterns of VEGF and ICAM-1 in aortas of normal or atherosclerotic rats in 8 weeks. There was a massive increase in reactivity for both ICAM-1 and VEGF in atherosclerotic plaques. Northern blot, Western blot and ELISA analysis were used to quantify VEGF and ICAM-1 expressions in time course. In rat aorta, the expression curves in time course showed that ICAM-1, not VEGF, was up-regulated in mRNA levels significantly in 2 weeks; while VEGF expression was hysteresis than ICAM-1, which showed maximum expression level in

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8 weeks. Our results provide the evidence of VEGF and ICAM-1 expression curves in time course in atherosclerotic rats, which indicated different regulatory mechanisms of VEGF and ICAM-1 expression in atherogenesis.

Keywords: Growth factors; Cell adhesion molecules; Gene expression; Atherosclerosis; Animal model

Introduction

Atherosclerosis is not merely a disease in its own right, but a process that is the principal contributor to the pathogenesis of myocardial and cerebral infarction, gangrene, and loss of function in the extremities. Despite the universal occurrence of atherosclerosis in the world, the pathogenesis of disease remains incompletely understood. Atherosclerosis can be considered to be a modified form of chronic inflammation induced by lipids (Glass and Witztum, 2001), and many have followed in this path including evidences that numerous cell adhesion molecules and growth factors were determined in the atherosclerotic plaques (Blankenberg et al., 2003; Sihvola et al., 2003).

Among those growth factors, vascular endothelial growth factor (VEGF), also known as vascular permeability factor (Dvorak et al., 1995), is a heparin-binding, dimeric, endothelial cell-specific mitogen and angiogenic factor that promotes the proliferation and permeability in the atherogenesis, which has been confirmed to play an important role in atherosclerotic lesions (Qiu et al., 2001). Intercellular adhesion molecule-1 (ICAM-1) is considered an important mediate molecule, which is the induction of specific and reversible cell–cell adhesion, resulting in intercellular communication (Roy et al., 2001). ICAM-1 and VEGF expression have been determined within plaques in rabbit, mouse and human atherosclerotic lesions (Iiyama et al., 1999; Poston et al., 1992; Chung et al., 2003; Moulton et al., 2003; Inoue et al., 1998).

Recent studies have stressed the close interactions between the adhesion molecules and growth factors in inflammatory responses. Our laboratory has focused on the expressions of ICAM-1 and VEGF to support ongoing functional studies on the pathogenesis of atherosclerosis. The up-regulated ICAM-1 (Yang et al., 2002a) and VEGF (Yang et al., 2002b, 2003) expression kinetics have been demonstrated in the formation of the macrophage-derived foam cells, which indicated the difference of expression curves of two genes in response of oxidized lipoprotein (Yang and Rui, 2003).

The rat is considered suitable for many cardiovascular models establishment including cardiac hypertrophy (Huang et al., 2003), hypertension, heart failure, but not easy in atherosclerosis (Russell, 2003; Moghadasian, 2002) for its hyperlipidemia-resistant character. Recently, we combined the high fat/cholesterol diets containing sodium cholate and propyl-thyracil with injection of vitamin D_3, which led a new way to establishment of an experiment atherosclerotic model in rats. The different expression kinetics of growth factor and adhesion molecule led a major initiative in our laboratory to determine the expression patterns in this atherosclerotic rat model to gain further evidences in vivo. This study aimed to determine the expression patterns and expression curves of ICAM-1 and VEGF in atherosclerotic rats during the time course.