Atherosclerosis 229 (2013) 304–309

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Pharmaceutical stabilization of mast cells attenuates experimental atherogenesis in low-density lipoprotein receptor-deficient mice

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ARTICLE INFO

Article history:
Received 24 January 2013
Received in revised form
19 April 2013
Accepted 22 May 2013
Available online 7 June 2013

Keywords:
Mast cell
Atherosclerosis
Cromolyn
C48/80
LDL receptor-deficient mice

ABSTRACT

Mast cells (MCs) contribute to atherogenesis by releasing pro-inflammatory mediators to activate vascular cells and other inflammatory cells. This study examined whether MC activation or stabilization affects diet-induced atherosclerosis in low-density lipoprotein receptor-deficient ($Ldlr^{-/-}$) mice. When $Ldlr^{-/-}$ mice consumed an atherogenic diet for 3 or 6 months, MC activation with compound 48/80 (C48/80) increased aortic arch intima and total lesion areas, and plasma total cholesterol, LDL, and triglyceride levels, whereas MC stabilization with cromolyn reduced these parameters. There were significant differences in arch intima and total lesion areas, and plasma total cholesterol, LDL, and triglyceride levels between C48/80-treated and cromolyn-treated mice. To examine a therapeutic application of cromolyn in atherosclerosis, we fed $Ldlr^{-/-}$ mice an atherogenic diet for 3 months followed by giving mice cromolyn for additional 3 months. Cromolyn did not affect aortic arch intima area, but significantly reduced lipid deposition in the thoracic-abdominal aortas. In aortic arches, however, cromolyn treatment significantly reduced lesion contents of Mac-3^{+} macrophages, CD4^{+} T cells, activated MCs, and lesion cell proliferation. While plasma total cholesterol and LDL levels increased and high-density lipoprotein (HDL) levels decreased from 3 months to 6 months of an atherogenic diet, cromolyn treatment decreased significantly plasma total cholesterol, LDL, and triglyceride levels and increased HDL levels above those of 3-month time point. These observations demonstrate that MC stabilization reduces lesion inflammation, ameliorates plasma lipid profiles, and may serve as a potential therapy for this cardiovascular disease.

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1. Introduction

Accumulating evidences suggest an essential role of mast cells (MCs) in the initiation and progression of atherosclerosis. Since the original detection of MCs in human atherosclerotic lesions [1,2], possible mechanisms of MC participation in atherosclerosis have been postulated from in vitro cell cultures and experimental models. After activation, MCs release pro-inflammatory mediators, including cytokines, proteases, histamine, proteoglycans, and chemokines, all which participate directly or indirectly in atherogenesis [3–6]. By releasing cytokines, MCs induce endothelial cell (EC) expression of adhesion molecules to recruit blood-borne leukocytes [7], or induce EC and vascular smooth muscle cell (VSMC) expression of cathepsins [8] that consequently mediate arterial wall extracellular matrix protein degradation [9,10]. By releasing MC-specific chymases and tryptases, MCs promote VSMC apoptosis [11–13] and EC apoptosis and desquamation [14] that enhance intima formation and plaque vulnerability or rupture. MC chymase and tryptase also cleave high-density lipoprotein (HDL) components (apolipoproteins A-1, A-2, and E) [15,16] and regulate nuclear receptor LXRα (liver X receptor α) activation [17], thereby reducing the ability of HDL in cholesterol efflux from lipid-loaded cells [18,19] and the expression of lipid metabolizing genes ABCG1 (ATP-binding cassette transporter G1), ABCA1, and SREBP-1 (sterol regulatory element-binding protein-1) [20,21]. In atherosclerosis-prone apolipoprotein E-deficient ($Apoe^{-/-}$) mice, oral administration of a chymase inhibitor reduced spontaneous thoracic atherosclerosis, prevented repetitive perivascular MC activation-induced carotid atherosclerosis, including reduced lesion necrotic core sizes, enhanced lesion collagen contents, and normalized the increased frequency and sizes of intraplaque hemorrhages [22].

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0021-9150/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosis.2013.05.025

MC-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice provided important reagent in testing a direct participation of MCs in atherosclerosis. At least three groups, including our own used both $Apoe^{-/-}$ mice and another atherosclerosis-prone low-density lipoprotein receptor-deficient ($Ldlr^{-/-}$) mice and demonstrated that absence of MCs reduced atherosclerotic lesions in thoracic-abdominal aorta, aortic arch, or aortic root, along with significant suppression of lesion inflammatory cell accumulation and matrix remodeling [8,23,24]. Therefore, MC activation or stabilization may affect the growth of atherosclerotic lesions in $Apoe^{-/-}$ and $Ldlr^{-/-}$ mice. In carotid artery semiconstrictive collar placement-induced atherosclerosis in $Apoe^{-/-}$ mice, MC activation with dinitrophenyl (DNP)-albumin [25] or substance P [26] greatly increased leukocyte adhesion, atherosclerotic lesion areas, lesion apoptosis, and intraplaque hemorrhage incidences. In mouse vein graft-induced carotid artery intimal thickness, MC stabilization with cromolyn reduced lesion area by 22% and total vessel area by 19%, without affecting lumen areas [27].

This current study was designed to test whether MC activation with compound 48/80 (C48/80) or MC stabilization with cromolyn expedites or prevents atherogenesis in $Ldlr^{-/-}$ mice and whether MC stabilization with cromolyn attenuates the progression of pre-established atherosclerosis in $Ldlr^{-/-}$ mice.

2. Materials and methods

2.1. Experimental atherosclerosis in $Ldlr^{-/-}$ mice

To test whether MC activation or stabilization affects atherogenesis, we fed six-week-old $Ldlr^{-/-}$ males (C57BL/6, N11, The Jackson Laboratory, Bar Harbor, ME) an atherogenic diet (Research Diets, Inc., New Brunswick, NJ) for 3 months or 6 months while giving mice intraperitoneal administration of 25 mg/kg/day disodium cromoglycate (DSCG, also known as cromolyn) or 4 mg/kg/day C48/80 (Sigma–Aldrich, St. Louis, MO). The same age male $Ldlr^{-/-}$ mice consumed the same atherogenic diet for 3 months or 6 months from an independent experiment were used as experimental controls.

To examine a possible therapeutic application of cromolyn in atherosclerosis, we fed $Ldlr^{-/-}$ mice an atherogenic diet for 3 months followed by giving mice cromolyn for additional 3 months. Control groups treated with vehicles used the same age male mice consumed the same atherogenic diet in an independent experiment. We analyzed mouse atherosclerotic lesions in longitudinal sections from a 3-mm segment of the lesser curvature of the aortic arch (defined using a perpendicular line dropped from the right side of the innominate artery) using previously published approaches [28].

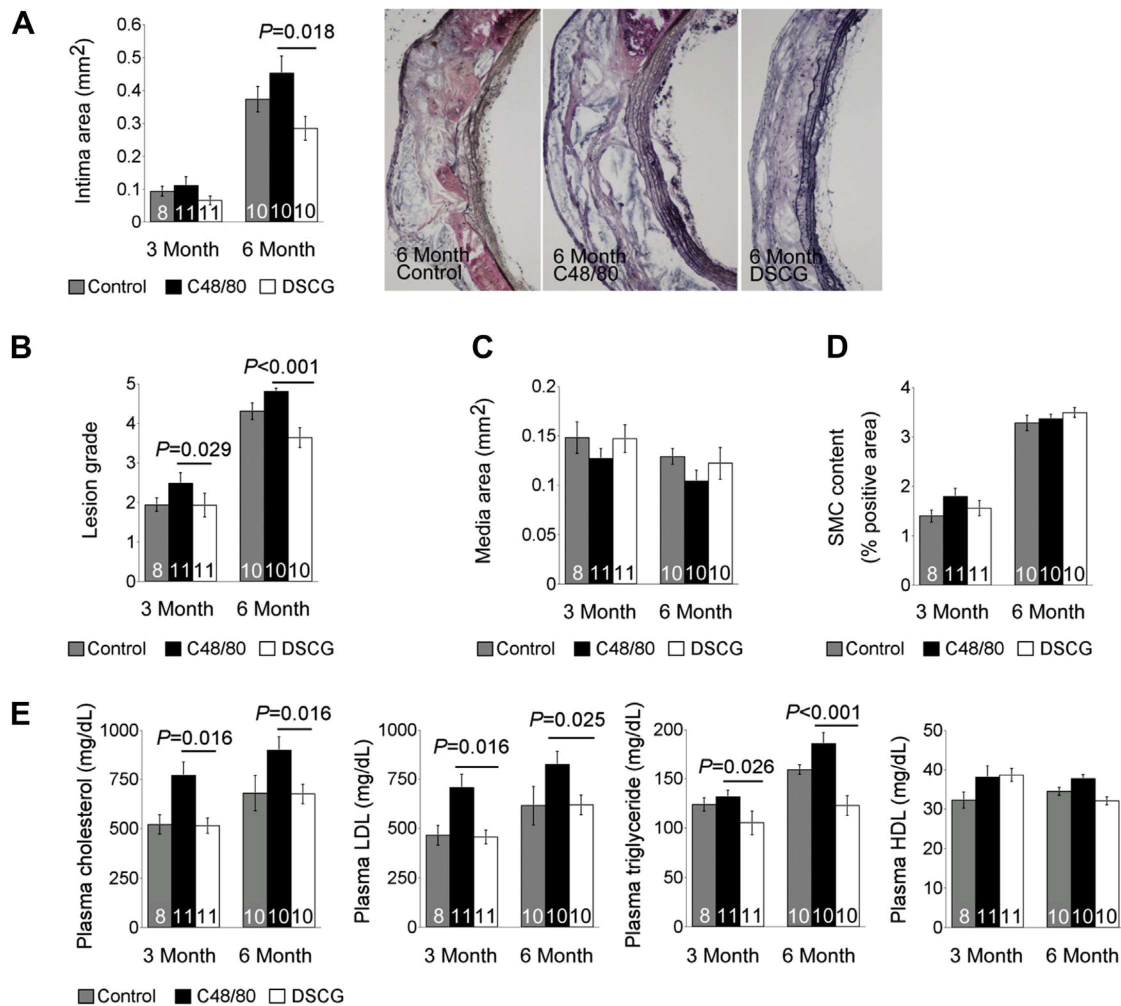

Fig. 1. MC activation and stabilization in atherosclerosis-prone $Ldlr^{-/-}$ mice. A. Aortic arch atherosclerotic lesion intima area in $Ldlr^{-/-}$ mice received daily intraperitoneal administration of C48/80 or DSCG or without treatment (Control) for 3 and 6 months while mice were consuming an atherogenic diet. Representative aortic arch lesions are shown to the right. B. Aortic arch lesion grade. C. Aortic arch lesion media area. D. Aortic arch media α-actin-positive SMC area in percentage. E. ELISA determined plasma lipid profile. Data were mean ± SE. The number of mice per group was indicated in each bar.

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