Medical Hypotheses 81 (2013) 1025–1028

Contents lists available at ScienceDirect

Medical Hypotheses

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

Bone morphogenic protein-4: A potential novel target for preventing vein graft failure in coronary revascularization

Jia Hu *, Jing (Janice) Zhao

Department of Cardiovascular Surgery, West China Hospital, Sichuan University, Chengdu, People's Republic of China

ARTICLE INFO

Article history:
Received 5 November 2012
Accepted 18 September 2013

ABSTRACT

Coronary artery bypass surgery is an effective and durable therapy in both acute coronary syndrome and chronic coronary stenotic disease refractory to pharmacological treatment. Despite rapid development in operation-specific technologies and secondary prevention measures, the benefits of surgical revascularization are largely limited by inadequate patency of one of the most commonly used conduits, namely the autologous saphenous vein. However, apart from antiplatelet and lipid-lowering drugs, no other pharmacologic agent has hitherto proven clinically effective in preventing short- and long-term vein graft failure. Aiming at a large number of known biomolecules, multiple promising strategies failed to translate their beneficial effects observed in animal models into the clinical settings. Bone morphogenic protein-4 (BMP4), originally identified as a mediator in bone formation, has been recently demonstrated to participate in the process of arterial post-injury remodeling. Existing evidence has demonstrated that BMP4 is closely involved in the pathogenesis of thrombus formation, neointimal hyperplasia and superimposed atherosclerosis, all of which significantly contribute to arterial stenotic lesions. Although the post-injury responses inherent to arterial and venous vessel are unique, they share common elements and present with similar physiologic characteristics and clinical sequelae. Therefore, with regard to the multifaceted effects of BMP4 in regulating arterial wall remodeling, we hypothesize that BMP4 may play an important role in mediating the pathological responses of the venous wall to the arterial circulation. If our hypothesis is demonstrated correct, BMP4 inhibition could presumably serve as a novel strategy for preventing vein graft failure in coronary revascularization.

Introduction

With the ever-growing threat of ischemic heart disease worldwide, the past decades had witnessed continually advancement of coronary artery bypass grafting (CABG) and percutaneous coronary intervention. Despite the increasing use of intracoronary stents and a debate over the most appropriate revascularization strategies, current evidence maintains the use of CABG as an optimal therapy for patients with unprotected left-main and multivessel coronary lesions [1,2]. Unfortunately, however, the long-term success of surgical revascularization is largely limited by the inadequate patency rate of one of the most commonly used conduits, namely the autologous saphenous vein [1,3].

Saphenous vein graft failure represents a clinical entity affected by a complex series of interrelated factors, including surgical techniques, patient-specific risk factors, hemodynamics and inherent biologic responses. Although the underlying mechanisms are still incompletely elucidated, thrombosis, neointimal hyperplasia and superimposed atherosclerosis are well-recognized as the prime culprits which, logically, have gained the most attention of current therapeutic explorations [3,4]. However, apart from antiplatelet and lipid-lowering therapy, no other intervention has hitherto proven clinically effective in improving short- or long-term vein graft patency [5]. Aiming at a variety of known biomolecules, novel pharmacological agents, drug-releasing external supports and gene therapy failed to translate their beneficial effects observed in animal models into the clinical settings [3–6]. Given the persistent increase in the incidence of CABG patients living with symptomatic vein graft diseases that need repeat revascularization procedures [2–4], further investigations of novel molecules and associated pathways [3–7] that can be best targeted are urgently required.

Bone morphogenic protein-4 (BMP4) is one of the structurally related members of transforming growth factor β superfamily, and its activities are originally identified in human embryonic development, differentiation, and endochondral formation [8]. Recently, BMP4 has been proposed to play a significant role in vascular injury responses and in the development of inflammation and atherosclerotic lesions within the arterial wall. Overexpression of BMP4 could lead to endothelial dysfunction and induce arterial endothelial cells (AECs) apoptosis through reactive oxygen species (ROS)-dependent pathways [9,10]. Such an increase of BMP4 level

* Corresponding author. Tel./fax: +86 028 85421833.
E-mail address: humanjia@msn.com (J. Hu).

0306-9877/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mehy.2013.09.023

was also demonstrated to enhance intercellular adhesion molecules expression and facilitate circulating leukocytes infiltration, a critical early step in atherogenesis [11]. Moreover, BMP4 was found to be highly effective in promoting the activation of vascular smooth muscle cells (VSMCs) which contributes significantly to vascular neointima formation and medial thickening [12,13]. Nevertheless, the involvement of BMP4 in the process of vein graft remodeling remain largely unknown, and BMP4-activated pathways that may result in venous wall over-thickening are not well characterized. With regard to the proinflammatory, proatherogenic and pro-hyperplastic effects of BMP4 in regulating arterial post-injury remodeling, we hypothesize that BMP4 might play an important role in promoting the pathological responses of the venous wall to the arterial circulation, and BMP4 inhibition could presumably serve as a novel strategy for preventing vein graft failure in coronary revascularization.

The hypothesis

BMP4 might promote and accelerate the progression of vein graft failure. The hypothesis stems from lines of evidence demonstrating the vigorous interactions between BMP4 and the living components within the vascular wall, including endothelial cells, VSMCs and fibroblasts. Furthermore, the multifaceted effects of BMP4 in enhancing inflammatory responses and subsequent atherogenesis might also contribute to the development of vein graft stenotic diseases (Fig. 1).

BMP4 and the impairment of endothelial barrier function

All grafted saphenous veins initially experience abrupt hemodynamic changes in elevated arterial blood pressure, shear stress, wall tension and pulsatile flow [3,6]. The geometric and compliant mismatches between vein grafts and recipient coronary arteries would lead to distinct flow discrepancies, particularly prominent at the site of luminal irregularities (i.e. anastomosis and venous valves) [6]. As a mechanosensitive autocrine cytokine, BMP4 is easily detected in human and mouse AECs cultured in disturbed flow [11]. Overexpression of BMP4 in endothelial cells stimulates expression and activity of nicotinamide adenine dinucteotide phosphate oxidases, which causes overproduction of ROS, upregulated intercellular adhesion molecule expression, and subsequent increased monocytes adhesivity. The endothelial origin production of ROS induced by BMP4 was responsible for the decreased levels of the endothelial-derived anti-thrombotic biofactors (principally nitric oxide, prostacyclin and heparin-like substance) and impaired endothelium-dependent relaxations [9]. Moreover, BMP4 has been demonstrated to directly induce endothelium apoptosis through oxidative stress-dependent p38 mitogen-activated protein kinase and c-Jun N-terminal kinases pathways in human and rat arteries *in vitro* [10]. Taken together, upregulated BMP4 expression is linked to the impairment of the functional and structural integrity of the endothelial layer. The damaged endothelium quite rapidly acts as a theatre for platelet aggregation and subsequent coagulant cascades, which lead to acute thrombosis and predispose to early vein graft failure.

The interactions between BMP4 and VSMCs and fibroblasts

Pathological intimal thickening characterized by migrating VSMCs and fibroblasts proliferation along with extracellular matrix (ECM) deposition is the basis for the mid- and long-term graft failure. Existing evidence has indicated that BMP4 signaling pathway plays an important role in the development of arterial proliferative disorders [12–14]. As demonstrated in an *in vitro* study, Yang et al. [11] found induction of exogenous BMP4 in cultured peripheral pulmonary artery could enhance medial VSMCs proliferation/survival through p38 mitogen-activated protein kinase-dependent pathway. Similarly in a mouse of pulmonary hypertension model [12], pulmonary AECs secrete BMP4 in response to hypoxia and

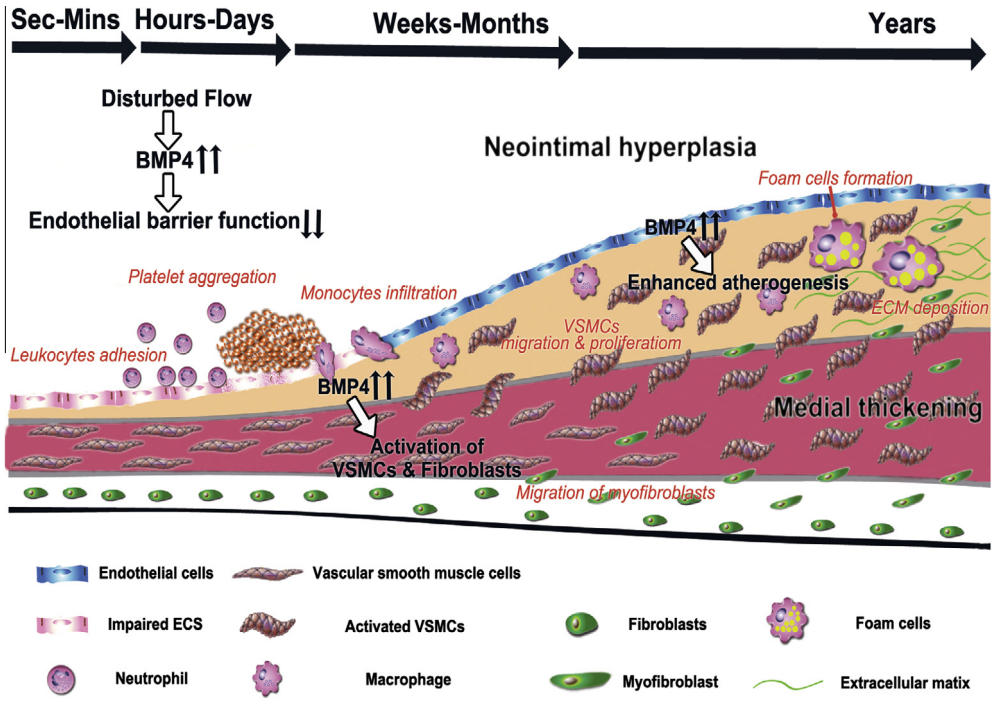

Fig. 1. Schematic diagram illustrating the potential mechanisms of bone morphogenic protein 4 (BMP4)-related negative (inward) vein graft remodeling. Overexpression of BMP4 induced by disturbed flow leads to impaired endothelial barrier function, activated vascular smooth muscle cells and fibroblasts, as well as enhanced atherogenesis. ECs, endothelial cells; VSMCs, vascular smooth muscle cells; ECM, extracellular matrix.