Novel Role for Osteopontin in Cardiac Fibrosis

Peter Zahradka

Wound healing is a normal physiological process that is required for the repair of tissue damage.1 The initial stages of this process result in the formation of a scar through deposition of extracellular matrix (ECM) proteins. In the subsequent stages, scar tissue is slowly replaced by new cells. The final result is regeneration of the original tissue and significant restoration of function.

The primary mediator of wound healing is the fibroblast, a nondescript cell found in all tissues.2 Activated fibroblasts or myofibroblasts are the source of the ECM proteins that form the scar. Myofibroblasts also help to maintain the integrity of the damaged tissue by contracting the newly deposited ECM, thus promoting wound closure. The scar subsequently serves as a matrix for cell recolonization during tissue regeneration. Accordingly, the scar is a temporary structure that is slowly removed as new cells are produced. Once regeneration is complete, the myofibroblasts revert to their original inactive state.

The interconversion of fibroblasts and myofibroblasts is intended to enable a rapid response to injury while ensuring excessive ECM deposition or fibrotic scarring does not occur. Nevertheless, failure to terminate the wound-healing program, thus leading to persistent activation of fibroblasts, does happen, and is the primary cause of fibrotic disease.2,3 Because excessive scar production or fibrosis can seriously compromise organ function, there is considerable effort underway to identify methods of preventing this currently untreatable condition.

Unlike most tissues, the heart is unable to repair itself because of the lack of sufficient cardiomyocyte proliferation. Consequently, neither scar removal nor regeneration occurs following a myocardial infarction. Nevertheless, wound healing plays a critical role in maintaining adequate heart function in the face of tissue loss.4 More specifically, the presence of the scar aids with myocardial remodeling, the adaptive change in heart morphology that is necessary for successful continuation of its function in the face of the restrictions placed on its pumping capability. On the other hand, because of the lack of scar flexibility, contraction of the heart places continual stress on the viable myocardial tissue that surrounds the scar, and this maintains fibroblasts in their activated state. As a result, there is chronic ECM deposition by myofibroblasts and further expansion of the scar. Eventually, the scar begins to interfere with cardiac compliance, thus further impairing function and instigating additional remodeling that in due course leads to failure.4

Mechanical stress and angiotensin II, which is released from injured cardiomyocytes, can trigger the activation of fibroblasts. In a process that parallels the phenotypic modulation of smooth muscle cells,5 fibroblasts with limited proliferative capacity undergo a conversion to myofibroblasts, which are capable of proliferation, migration, and ECM protein synthesis. The change in fibroblast properties is initiated by transformation growth factor (TGF)-β.6 This cytokine is produced in response to cellular damage and hormones such as angiotensin II. TGF-β, in turn, stimulates the expression of genes that are characteristic of myofibroblasts, including α-smooth muscle actin, ED-A fibronectin, connective tissue growth factor (CTGF), and osteopontin (OPN).

OPN is a phosphoprotein identified originally in osteoblasts and osteoclasts but has since been shown to be secreted by many different cell types.7 Although initially linked to bone mineralization, it is now recognized that OPN promotes cell adhesion and can mediate immune responses.8 OPN is not found in the unstressed heart; however, several studies from the laboratory of Hsueh in the late 1990s established that OPN expression correlated with onset of cardiac hypertrophy,9 presumably as a result of fibroblast activation.10 At approximately the same time, a correlation between OPN and onset of heart failure was also reported.11 Later studies demonstrated that OPN was necessary for maintaining effective cardiac function, because animals lacking OPN exhibit exaggerated left ventricular hypertrophy.12 Regardless, it has been generally accepted that OPN operates in the postinfarct heart by coordinating the intercellular signals required to integrate myofibroblast proliferation, migration, and ECM deposition with the recruitment of macrophages and initiation of collateral vessel formation, thus ensuring the mechanical properties of the heart are not compromised further.

Whereas it is generally accepted that the cardiac functions of OPN require its secretion by myofibroblasts,13 Lenga et al.14 recently examined the premise that OPN has a more active role in the formation of the myofibroblastic state. In this issue of Circulation Research, the authors identified a causal relationship between OPN expression and differentiation of fibroblasts into myofibroblasts. The concept that OPN was required for modulating fibroblast activation was based, in part, on the observation that α-smooth muscle actin is not expressed in TGF-β-treated cardiac fibroblasts isolated from OPN-null mice. This single finding establishes that OPN is absolutely required for expression of the myofibroblast phenotype and was confirmed by small interfering RNA knockdown of OPN in fibroblasts from wild-type mice.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the University of Manitoba and St. Boniface Research Centre, Winnipeg, Canada.

Correspondence to Peter Zahradka, St. Boniface Research Centre, Canadian Centre for Agri-food Research in Health & Medicine, 351 Tache Ave, Winnipeg, MB R2H 2A6, Canada. E-mail peterz@sbrc.ca

(Circ Res. 2008;102:270-272.)

© 2008 American Heart Association, Inc.

Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.107.170555
Other markers of myofibroblast differentiation were also monitored by Lenga et al. It was found that CTGF expression, formation of stress fibers, and focal adhesion, contractility, adhesion, and cell spreading were altered in the absence of OPN. In general, fibroblasts from OPN−/− mice retained a rounder morphology because of the presence of fewer adhesions. Nevertheless, these cells were still responsive to the chemoattractant actions of TGF-β, as determined in a migration assay, indicating that this property was unaffected. On examining the components of the adhesion complexes by mass spectrometry, Lenga et al found that HMGB1 (high-mobility group box 1 protein) was present in the focal adhesions of wild-type fibroblasts but not detectable in the absence OPN. In cells from OPN−/− mice, HMGB1 was located solely in the nucleus.

HMGB1 is a nonhistone chromosomal protein that was initially isolated more than 30 years ago. More recently, it has been reported that HMGB1 is a proinflammatory cytokine released by activated macrophages. On release, it can bind to RAGE, the receptor for activated glycation products, and stimulate the release of proinflammatory cytokines. Interestingly, HMGB1 may have a dual function in the heart: to enhance progression of ischemic injury and to promote cardiac regeneration through recruitment of stem cells. Based on these properties, it is likely that HMGB1 serves to mediate the immune response attributed to OPN. With respect to Lenga et al, no evidence was provided to suggest HMGB1 is released from myofibroblasts, although such a result may be predicted. However, it is also plausible that sequestration of HMGB1 in focal adhesions has specific effects on gene expression that promote fibroblast differentiation (Figure). It is also possible that the interaction between OPN and HMGB1 is a general phenomenon that modulates their functions, because it was recently shown that OPN can also shuttle between the nucleus and cytoplasm.

The other unique finding made by Lenga et al is the fact that OPN controls CTGF expression. It has been established that both OPN and CTGF are induced by the binding of SMAD proteins to their respective promoters following treatment with TGF-β. However, Chen et al have shown that the extracellular signal-regulated kinase pathway must also be activated for induction of the CTGF gene expression. Based on the findings of Lenga et al, it is likely that OPN performs this function, but whether activation of extracellular signal-regulated kinase via focal adhesion kinase is the mechanism through which OPN operates still remains to be determined. A role for integrin-linked kinase in this process, however, appears unlikely.

The study by Lenga et al has provided a unique insight into the mechanisms that control fibroblast differentiation in response to TGF-β. Not only has a novel regulatory mechanism for CTGF expression been formulated, a new factor, HMGB1, has been identified that likely integrates the key immunogenic events that participate in the cardiac response to injury. However, addressing these issues also has led to further questions. More details regarding the role of OPN in CTGF gene expression are called for. In particular, the role of focal adhesion activation in this process needs to be explored. Likewise, how does OPN modulate the cellular location of HMGB1, and is this protein secreted by cardiac myofibroblasts? In parallel, does HMGB1 mediate the expression of genes essential for differentiation of fibroblasts into myofibroblasts? Finally, does OPN function through its adhesive domains postsecretion, or does it operate via an intracellular mechanism? Lenga et al have done a significant service by making us aware that OPN acts as a humoral factor responsible for integrating the processes that maintain cardiac function postinfarction. This report is certain to generate significant interest in resolving these issues.

Sources of Funding
This work was supported by the Canadian Institutes of Health Research.

Disclosures
None.

References


Key Words: osteopontin □ myofibroblast differentiation □ HMGB1 □ cardiac fibrosis
Novel Role for Osteopontin in Cardiac Fibrosis
Peter Zahradka

*Circ Res.* 2008;102:270-272
doi: 10.1161/CIRCRESAHA.107.170555

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/102/3/270

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at: http://circres.ahajournals.org/subscriptions/