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Adding Reg3 β to the acute coronary syndrome prognostic marker list

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The regenerating islet-derived protein (Reg) family consists of four small secreted proteins: Reg 1, 2, 3, and 4. The Reg3 protein has three isoforms: Reg3 α , β , and γ . Reg3 β was first reported to be a lectin-related protein upregulated in a rat model of acute pancreatitis [1], and has since been shown to inhibit migration of cancer cells by impairing extracellular vesicle uptake [2], and facilitate pancreatic and cancer cell growth by inducing cell proliferation and inhibiting apoptosis [3,4]. In the heart, Reg3 β acts as a chemokine by promoting macrophage recruitment to the ischemic heart [5].

In the present issue, Lorchner and colleagues investigated the association of Reg3 β with cardiac inflammation and the possibility of Reg3 β as a prognostic marker for patients with acute coronary syndrome (ACS). Reg3 β was upregulated in the infarct and serum within the first 24 h post-myocardial infarction (MI) in mice, peaking at day 4 and remaining elevated by day 14 post-MI [6]. Flow cytometry experiments demonstrated a parallel between Reg3 β expression and early immune cell infiltration into the infarct. Additionally, the authors quantified and compared serum Reg3 β concentrations in patients with ACS to healthy individuals. ACS patients showed 1.7-fold higher serum Reg3 β levels than healthy controls, which remained significant even after adjusting for age and sex. Higher serum Reg3 β associated with an increased 6-month mortality. In summary, this study for the first time reveals that Reg3 β strongly correlates with the intensity of cardiac inflammation and may be useful as a prognostic biomarker for ACS patients.

Following MI, both infarct and serum Reg3 β levels are upregulated, whereas expression in the non-infarct remote region remains low. Colocalization of Reg3 β and α -sarcomeric actinin (a cardiomyocyte marker), but not vimentin (a fibroblast marker) in the infarct border zone suggests that Reg3 β is primarily derived from cardiomyocytes [5]. Macrophages isolated from the infarct region do not show detectable Reg3 β expression. In light of the

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Contributors

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Conflict of interest

The authors declare no conflicts of interest.

substantial presence of neutrophils and endothelial cells in the infarct, whether Reg3 β can be secreted by these cells needs to be evaluated. Oncostatin M, a member of the glycoprotein130 family of cytokines secreted by infiltrating macrophages and neutrophils following MI, is essential for Reg3 β induction in cardiomyocytes through activation of JAK1/STAT3 signaling. This study and previous work by Lorchner and co-workers emphasize the concept that myocytes are active initiators of the post-MI inflammatory response by secreting Reg3 β , as well as damage associated molecular patterns (DAMPs), including high-mobility group box 1, heat shock proteins, and interleukin-1 α [7].

Macrophages, a major target of Reg3 β , play a continuum of roles in cardiac remodeling and repair post-MI [8]. Excessive or prolonged presence of macrophages can cause tissue damage and impede cardiac wound healing; similarly, insufficient infiltration of macrophages can prevent adequate and timely removal of dead cells and matrix debris [9]. Thus, appropriate macrophage responses are required for favorable cardiac repair. Both in vitro and in vivo studies demonstrate that Reg3 β is a potent chemoattractant for macrophages [5]. Not surprisingly, Reg3 $\beta^{-/-}$ mice have fewer macrophages in the infarct region, as well as insufficient removal of apoptotic neutrophils and necrotic cardiomyocytes, enhanced matrix degradation, impaired scar formation, and elevated cardiac dilation [5]. Interestingly, the current study demonstrates that serum Reg3 β concentration positively correlates with mortality in patients presenting with ACS, which seems paradoxical with the animal findings showing that Reg3 β is required for normal wound healing. The median time for measuring serum Reg3 β was 265 min (4.4 h) after the onset of symptoms. For non-reperfused MI, substantial monocyte infiltration occurs after the peak of neutrophil infiltration (24 h post-MI) [10]. The first-wave of Reg3 β (within hours after ischemia) may represent the passive release from dying cardiomyocytes, while the second-wave of Reg3 β (hours to days after ischemia) may derive from the active secretion from surviving cardiomyocytes in the infarct border zone. It would be interesting to examine whether the first-wave of Reg3 β correlates with the degree of acute inflammation and can predict patient outcomes; in contrast, the second-wave of Reg3 β may signify the extent of cardiac wound healing. Serial measurements of circulating Reg3 β levels and evaluating their correlation with prognosis in human patients may address whether this concept is valid.

Macrophages in the infarct are heterogeneous and show a continuum of pro-inflammatory and anti-inflammatory phenotypes [8]. Pro-inflammatory macrophages dominate early post-MI and produce cytokines, chemokines, growth factors, and matrix metalloproteinases to clear debris and degrade extracellular matrix; in contrast, anti-inflammatory macrophages dominate later post-MI and secrete anti-inflammatory, pro-angiogenic, and pro-reparative factors to facilitate cardiac repair [9]. Reg3 β recruits monocytes that differentiate into M1 or M2 macrophages, indicating that the Reg3 β effect is primarily on migration and does not distinctly impact polarization [5]. In tumors, Reg3 β deficiency decreases the M2 to M1 ratio of tumor-associated macrophages, and in vitro, Reg3 β enhances M2 polarization induced by IL-4 plus IL-13 stimulation [4], indicating that Reg3 β has pro-M2 characteristics. The impact of Reg3 β on macrophage polarization is likely context-dependent and can change depending on what co-factors are present. Following MI, the impact of Reg3 β on macrophage polarization is likely influenced by the presence of polarization factors; and whether Reg3 β is an amplifier has not been examined.

In conclusion, this study, in conjunction with published studies by the same group, demonstrate that Reg3 β is required for adequate cardiac wound healing after MI. MI induces cardiomyocyte secretion of Reg3 β . Reg3 β , as a chemokine, mediates macrophage recruitment and accumulation in the infarct. Macrophages phagocytose dead cells and debris and generate a wide range of pro-reparative factors to promote angiogenesis and scar formation, thus contributing to cardiac wound healing (Fig. 1). In addition, Reg3 β may provide prognostic information for ACS patients. Larger cohort studies to validate the predictive value of Reg3 β for subsequent cardiovascular events after ACS, such as recurrent MI and acute heart failure, are warranted.

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Fig. 1.

Proposed mechanisms of Reg3β post-MI actions. Following MI, surviving cardiomyocytes in the infarct border zone secrete Reg3β. Reg3β recruits macrophages to the infarct region, where macrophages phagocytose dead cells and debris and secrete a wide range of pro-reparative factors to promote angiogenesis and scar formation, eventually contributing to cardiac wound healing. The images of the heart and cells were obtained from Servier Medical Art (www.servier.com).