An association between hypertension and immune system activation has long been recognized as a potential mechanism of hypertensive end-organ damage. Indeed, recent accumulating evidence using mouse models of hypertension induced by angiotensin II (Ang II) supports the roles of T lymphocytes and macrophages in the pathogenesis of hypertension and its complications. Curiously, although neutrophil infiltration seems to be the earliest immune and inflammatory response observable with Ang II infusion, limited findings are available regarding the pathophysiological significance of neutrophil accumulation and its signaling mechanism in cardiovascular diseases. Neutrophil-derived myeloperoxidase was shown to be critical for atrial fibrosis and subsequent atrial fibrillation induced by Ang II, which involves hypochlorous acid-induced tyrosine chlorination and activation of matrix metalloprotease-9. Likewise, neutrophil-generated matrix metalloprotease-9 is required for aortic dissection induced by cotreatment with Ang II and a lysyl oxidase inhibitor. Thus, depletion of neutrophils with granulocyte differentiation antigen 1 antibody prevented the dissection. However, whether neutrophils and their signal transduction play a role in Ang II–induced hypertensive organ damage had not been investigated. In this issue of Hypertension, Wu et al provide the first compelling evidence supporting that neutrophil-generated S100a8/S100a9 proteins are the key molecules to initiate Ang II–induced cardiac inflammation and fibrosis independently from high blood pressure response. Consistent with the immediate and transient nature of neutrophil activation and infiltration, S100a8/S100a9 mRNAs and proteins demonstrated a sharp rise and fall in cluster of differentiation molecule 11b+/granulocyte differentiation antigen 1+ neutrophils infiltrating the heart on Ang II infusion. In vitro analysis also showed acute and dominant induction of S100a8 and S100a9 mRNA expression by Ang II in bone marrow–derived monocytes but was relatively lower in cardiac myocytes and cardiac fibroblasts. S100a8 (calgranulin A or migration inhibitory factor–related protein 8) and its binding partner S100a9 (calgranulin B, or MRP-14) are members of the S100 calcium-binding family of proteins primarily expressed in myeloid cells such as neutrophils and monocytes. These proteins show increased levels in several inflammatory states and have been characterized as significant immune regulatory multifunctional molecules through their intracellular and extracellular actions. They are also recognized as a potential biomarker for the pathophysiological condition including various types of cardiovascular diseases. The intracellular functions of S100a8 include scavenging reactive oxygen species generated by activated neutrophils, whereas the S100a8/S100a9 complex contributes to nicotinamide adenine dinucleotide phosphate oxidase activation in phagocytes. The extracellular functions seem to be mediated through membrane receptors including Toll-like receptor 4 and the receptor for advanced glycation end products (RAGE). The authors’ findings further suggest that RAGE, which activates nuclear factor-kB in cardiac fibroblasts, is the critical receptor for neutrophil-derived S100a8/S100a9 in mediating cardiac inflammation and subsequent fibrosis on Ang II infusion.

The involvement of S100a8/S100a9 in mediating cardiovascular inflammation is supported by several past studies (reviewed in Averill et al). For example, S100a9 gene deficiency in mice, which also depresses S100a8 expression, has reduced leukocyte accumulation, vascular inflammatory responses, and neointima formation in femoral artery on wire injury. Deletion of S100a9 also protected apolipoprotein E−/− mice from atherosclerosis, which was associated with less accumulation of macrophages in the plaques. Cardiac overexpression of S100a8 and S100a9 led to RAGE-dependent suppression of calcium flux and decreased ejection fraction in mice, whereas S100a9 knockdown attenuated lipopolysaccharide-induced cardiac dysfunction. The crucial role of RAGE in cardiovascular inflammation was also demonstrated by a recent study, in which formation of atherosclerosis and associated vascular inflammation in apolipoprotein E−/− mice were attenuated by RAGE-deficiency or dominant-negative RAGE expression.

Interestingly, using the same mouse model with Ang II infusion, the authors’ group has also demonstrated the crucial role of granulocyte colony stimulating factor as a key mediator for Ang II–induced recruitment of neutrophils into the heart and cardiac fibrosis. However, the cell type responsible for granulocyte colony stimulating factor production as well as its relation to the neutrophil S100a8/S100a9 system has not been addressed. Although accumulating evidence strongly implicates participation of Toll-like receptor 4 in inflammatory responses associated with atherosclerosis as well as ischemic heart diseases, potential S100a8/S100a9 signaling via Toll-like receptor 4 in cardiac fibrosis remains obscure.

See related article, p 1241–1250

Takashi Obama, Rosario Scalia, Satoru Eguchi

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From the Cardiovascular Research Center, Department of Physiology, Temple University School of Medicine, Philadelphia, PA.

Correspondence to Satoru Eguchi, Cardiovascular Research Center, Department of Physiology, Temple University School of Medicine, 3500 N. Broad Street, Philadelphia, PA 19140. E-mail seguchi@temple.edu


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S100a9 synergistically stimulates hypochlorous acid production with myeloperoxidase. Hypochlorous acid-modified albumin is a high affinity agonist for RAGE. Hypochlorous acid-modified S100a8/S100a9 proteins are also implicated in atherogenesis. A schematic diagram of the potential signal transduction stimulated by Ang II in neutrophil and cardiac fibroblast is illustrated in the Figure.

Taken together, the above information and the study by Wu et al provide new insight into the neutrophil-specific mechanism leading to hypertensive end-organ damage such as that occurring in the heart independently from high blood pressure regulation. However, occasional anti-inflammatory roles of the S100a8/S100a9 oppose the use of anti-S100a8/S100a9 therapy against cardiovascular diseases in general. Clinical studies to look for correlations of S100a8/S100a9 with hypertension, the risk factors, incidence of complication, and mortality with or without the usage of Ang II blockers seem to be critical. Limitations of the study include the lack of exploration into the intracellular mechanism by which Ang II enhances S100a8/S100a9 gene expression as well as the molecular link between secretion of S100a8/S100a9 by neutrophils and the ability of S100a8/S100a9 to act as autocrine factors for neutrophil infiltration. Therefore, further research is desired to look for the detailed molecular mechanisms by which neutrophil-derived S100a8/S100a9 participates in cardiac inflammation and fibrosis.

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References
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Takashi Obama, Rosario Scalia and Satoru Eguchi

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