**Abstracts of 2009th Alumni Association Medical Research Fund Prize Memorial Lecture (4)**

# The Role of S100A8 in Atrial Fibrillation: Bridging the Gap between Basic Science and Clinical Practice

Yasumi Endoh

Division of Cardiology, Department of Internal Medicine, Nippon Medical School Tama Nagayama Hospital

S100A8 is a highly-expressed calcium-binding protein in neutrophils and activated macrophages, and has proposed roles in myeloid cell differentiation and host defense. The functions of S100A8 are not fully understood, partly because of difficulties in generating S100A8 knockout mice. Clinically, S100A8 is suggested to be a sensitive marker of inflammation in various conditions rather than a diagnostic indicator of specific diseases. For example, in psoriatic arthritis, the kinetics of elevation of serum levels reflect acute exacerbation, and levels rapidly decline in response to successful treatment[1]. There are strong correlations between S100A8 levels and the clinical disease activity scores in inflammatory bowel disease[2], Kawasaki disease[3], psoriatic arthritis[1], juvenile idiopathic arthritis, and HIV infection, and the heterodimeric complex of S100A8 and S100A9 has been proposed as a biomarker for monitoring disease activity in chronic inflammatory disorders.

S100A8 is found in macrophages, foam cells, and neovessels in human atherosclerotic plaques[4]. Normal arteries contain negligible S100A8, whereas atherosclerotic plaque contains multiple S100 complexes. High levels of serum S100A8 are found in Kawasaki disease, an acute systemic vasculitis that occurs in children and that leads to coronary artery abnormalities, implying the involvement of S100A8 in human vasculitis[3]. Among the expression of the various S100 genes in human atherosclerotic plaques, S100A8 is associated with neovascularization[4]. The S100A8 complex changes the adhesive and prothrombotic properties of the endothelium by inducing inflammation-associated genes and the secretion of factors that enhance platelet activation[5] and may also contribute to vascular changes.

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. The prevalence of AF is 1% in the general population and increases with age to about 6% in people older than 65 years[6]. Several atherosclerotic risk factors, such as obesity, diabetes, and hypertension, have been linked with the development of AF[7], and the majority of cases are associated with structural abnormalities, such as hypertensive heart disease, cardiomyopathy, valvular disease, or ischemic heart disease. Although increasing attention has been focused on the underlying pathophysiological mechanisms, the pathogenesis of AF is not fully understood, and its clinical management remains complex. Recent advances in genetics and molecular biology have provided new insights into the development of the disease, and accumulating evidence indicates that inflammation may be a predisposing factor in AF[8].

Our hypothesis is that S100A8 plays important roles in the pathogenesis of AF. To test this hypothesis, immunohistochemistry will be performed to evaluate S100A8 expression in human hearts with or without AF obtained at autopsy, and correlations between its expression and the patient's clinical background, particularly treatments for AF, will be examined. Moreover, the effect of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins on the expression of S100A8 in activated peripheral blood mononuclear cells will be examined with the real-time polymerase chain reaction.

Our approach for investigating S100A8 expression in the fibrillating atrium may assist in exploring its functions and lead to new insights concerning the regulation of inflammation in AF. Clinically, inflammation has been proposed to be involved in AF. Therefore, the therapeutic approaches to regulate inflammation may be useful for preventing AF. Determining the correlations of cellular mechanisms with clinical practice and physiological results represents a challenge but will help understand this missing link. These experiments are considered to provide new basic information regarding the role of S100A8 in AF.

## References


1. Kane D, Roth J, Frosch M, Vogl T, Bresnihan B, FitzGerald O: Increased perivascular synovial membrane expression of myeloid-related proteins in psoriatic arthritis. Arthritis Rheum 2003; 48: 1676.
2. Tibble JA, Bjarnason I: Fecal calprotectin as an index of intestinal inflammation. Drugs Today (Barc) 2001; 37: 85.
3. Hirono K, Foell D, Xing Y, et al.: Expression of myeloid-related protein-8 and -14 in patients with acute Kawasaki disease. J Am Coll Cardiol 2006; 48: 1257.
4. McCormick MM, Rahimi F, Bobryshev YV, et al.: S100A8 and S100A9 in human arterial wall. Implications for atherogenesis. J Biol Chem 2005; 280: 41521.
5. Viemann D, Strey A, Janning A, et al.: Myeloid-related proteins 8 and 14 induce a specific inflammatory response in human microvascular endothelial cells. Blood 2005; 105: 2955.
6. Kannel WB, Wolf PA, Benjamin EJ, Levy D: Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2N–9N.
7. Chung MK, Foldvary-Schaefer N, Somers VK, Friedman PA, Wang PJ: Atrial fibrillation, sleep apnea and obesity. Nat Clin Pract Cardiovasc Med 2004; 1: 56–59, quiz 1 p following 59.
8. Aviles RJ, Martin DO, Apperson-Hansen C, et al.: Inflammation as a risk factor for atrial fibrillation. Circulation 2003; 108: 3006–3010.