S100A1: Another Step Toward Therapeutic Development for Heart Failure*

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It has been nearly 130 years since Sydney Ringer’s astute observations on the indispensability of extracellular Ca\(^{2+}\) to heart muscle contraction (1). At the cellular level, we now know that fluctuations of cytosolic Ca\(^{2+}\) are coordinated by several myocyte proteins in order to functionally couple the cardiac action potential to sarcomeric shortening and mitochondrial energy production. This elegant myocardial Ca\(^{2+}\)-cycling demands precise regulation of intracellular Ca\(^{2+}\), as evidenced by the numerous examples of cardiac dysfunction arising from altered expression or activity of Ca\(^{2+}\) handling proteins (2–5). One such protein, S100A1, has attracted the interest of cardiac scientists because of its myocardial enrichment, known interactions with several other Ca\(^{2+}\) handling proteins, including ryanodine receptors (RyR) and sarcoplasmic reticulum (SR) Ca\(^{2+}\) ATPase (SERCA), and the observation that its expression is progressively down-regulated in failing myocardium (6). Furthermore, cardi-specific S100A1 deletion accelerated the progression to heart failure (HF) after myocardial infarction in mice (7), whereas restoration of S100A1 expression via intracoronary adenoviral gene delivery to failing rat hearts normalized contractile performance (8).

In this issue of the Journal, Brinks et al. (9) provide the first evidence that S100A1 gene delivery can functionally improve human failing cardiomyocytes. Using ventricular tissue from ischemic HF patients, cardiomyocytes were isolated and infected with adenovirus encoding S100A1 (Ad-S100A1). The authors show that restoring S100A1 expression improved failing cardiomyocyte fractional shortening, relaxation rates, and Ca\(^{2+}\) transients compared with control cells. Moreover, Ad-S100A1 improved both rate-dependent and β-adrenergic–mediated contractile reserve, while ameliorating markers of abnormal energy metabolism in isolated cardiomyocytes and mitochondria from failing hearts. Despite increases in SR Ca\(^{2+}\) load, elevated S100A1 expression reduced diastolic SR Ca\(^{2+}\) leak and the propensity for aberrant depolarizations.

From a mechanistic standpoint, Brinks et al. (9) propose that S100A1 enhances failing cardiomyocyte contraction through improved cytosolic Ca\(^{2+}\) handling. In this regard, it is particularly interesting that the ability of S100A1 to improve Ca\(^{2+}\) transients and pathological shortening-frequency responses occurred without altering either pathological decreases in SERCA abundance or increases in sarcolemmal Na\(^+/Ca\(^{2+}\)\) exchanger that have been previously identified as major determinants of these defects in human myocardium (10–12). Although detailed proof of the molecular mechanism of S100A1’s actions is not reported, Brinks et al. speculate that they result from direct interaction of S100A1 with SR and mitochondrial proteins (i.e., RyR, SERCA, and F1-ATPase). Recent studies also indicate that S100A1 may enhance contractility and relaxation dynamics by regulating the interaction between the sarcomeric proteins titin and cardiac actin (13).

These findings represent an exciting initial step toward confirming S100A1 as a viable therapeutic target in human HF, concordant with prior data reported in various animal models. The physiological difference in Ca\(^{2+}\) handling between human and small mammal cardiomyocytes necessitates such work. The authors rightly caution, however, against prematurely extrapolating their in vitro, isolated cardiomyocyte findings to the intact organ or the human clinical setting. One reason is that S100A1 levels spike in the plasma after acute myocardial damage (14), and reports indicate that S100 proteins exert extracellular and perhaps paracrine effects (15–17), neither of which could be accounted for in the present study of isolated cells. In addition, S100A1 is also expressed in endothelial cells of the vasculature, and global deletion of S100A1 produces a hypertensive phenotype due to impaired nitric oxide–mediated vasorelaxation (18). This implies that the relative impact of S100A1 expression on both vascular and cardiac function remains to be determined.

These concerns aside, Brinks et al. (9) have furnished important in vitro data showing salutary effects of S100A1 on human myocardium. S100A1 is an especially intriguing prospect for HF treatment because it appears to serve critical functions in both the vasculature and the heart, and interacts with proteins at multiple nodes of the Ca\(^{2+}\) cycle (Fig. 1). In this regard, analogous studies involving virus-
mediated SERCA overexpression in human cardiac myocytes (19) inspired successful pre-clinical studies in pigs with cardiac dysfunction (20) which, in turn, led to encouraging pilot studies of SERCA gene therapy in humans with advanced heart failure. These prior studies provide a translational template and demonstrate the technical feasibility of myocardial gene therapy that is relevant to the present studies. Additionally, studies employing SERCA gene therapy and cardiac resynchronization therapy also support the conceptual argument that some therapies with positive inotropic effects may ultimately prove beneficial despite the many positive inotropic agents that have previously failed to improve outcomes among patients with advanced heart failure (21). In this context, although further studies and optimization of gene therapy delivery mode, vector, and safety profile are warranted, the current report suggests that S100A1-based gene therapy for HF could one day be translated to human benefit.

Figure 1 The Intersections of S100A1 and the Cardiac Ca\(^{2+}\) Cycle

Sarcolemmal membrane depolarization opens voltage-gated L-type Ca\(^{2+}\) channels, allowing Ca\(^{2+}\) to flow into the cell. This Ca\(^{2+}\) influx stimulates Ca\(^{2+}\) release from adjacent ryanodine receptors (RyR) of the sarcoplasmic reticulum (SR), causing a rise in [Ca\(^{2+}\)]\(_i\). Ca\(^{2+}\) then activates the myofilaments (contractile proteins), and the cell contracts. Some of the Ca\(^{2+}\) released from the SR enters the mitochondria via the mitochondrial Ca\(^{2+}\) uniporter (MCU), and is utilized to produce ATP. Relaxation is accomplished by removing Ca\(^{2+}\) from the cytosol, primarily by SR Ca\(^{2+}\) ATPase (SERCA). Shown in red, S100A1 interacts with multiple critical Ca\(^{2+}\) handling proteins in cardiac myocytes.

REFERENCES

1. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J Physiol 1883;4:29–42.

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