See article by Schneider et al. [13] (pages 40–50) in this issue.

Heart failure (HF) represents the common endpoint of many different kinds of cardiopulmonary diseases. Essentially, loss of myocardium triggers a sequence of molecular, cellular and physiological responses leading to ventricular remodelling and the inability of the ventricle to maintain an output sufficient for the metabolic requirements of the tissues of the body [1]. Although these responses may be viewed as compensatory in nature, many of them are or become counter-regulatory and lead to long-term adverse effects [1]. Thus, novel insight into the regulatory mechanisms that contribute to the compensation and subsequent decompensation is urgently needed to broaden our knowledge about HF and to develop therapeutic strategies that can prevent the progressive deterioration of cardiac function and ultimately avoid this disease.

S100 proteins constitute the largest subfamily of EF-hand Ca²⁺-binding proteins. Several biological activities, such as the regulation of myocardial and skeletal muscle contractility, hypertrophy, apoptosis, the regulation of metabolic enzymes, proliferation, migration, and cell differentiation, are affected by S100 proteins [2–4]. Members of the S100 protein family display a tissue- and cell type-specific expression pattern and exhibit distinct functional properties [2–4]. Interestingly, several in vitro and in vivo studies have shown that expression levels of members of the S100 protein family are differentially regulated in damaged myocardium [5–8].

S100A1 is abundant predominantly in the healthy heart and displays anti-hypertrophic and anti-apoptotic characteristics in cardiomyocytes [reviewed in 9]. Moreover, S100A1 is a positive inotropic regulator of myocardial function, and this effect is largely mediated by a significant gain in sarcoplasmic reticulum (SR) Ca²⁺ cycling [9]. Importantly, cardiac S100A1 expression is significantly downregulated in end-stage heart failure, which is mediated by Gq/11-protein and protein kinase C (PKC) signalling [8,10]. Downregulation of S100A1 is permissive for the induction of foetal gene expression in HF and critically contributes to contractile dysfunction, hypertrophy, and apoptosis, causing an increased mortality in post-myocardial infarction (MI) heart failure models [9,10]. Indeed, restoration of myocardial S100A1 protein expression was shown to have therapeutic potential and to rescue in vivo global cardiac function after acute MI as well as in chronic HF [9,11].

In contrast, expression of S100B is not found in mature myocardium, but expression of S100B is induced upon pro-hypertrophic signalling in the context of foetal gene re-expression [6,8]. Induction of S100B modulates left ventricular remodelling after MI and causes reduced hypertrophy, increased apoptosis, progressive deterioration of cardiac function, and an increased mortality post-MI [12]. Thus, despite opposite effects on cardiac hypertrophy, contrary alterations of cardiac S100A1 and S100B expression levels in transition to HF both appear to be detrimental [10,12].

Further S100 proteins were demonstrated to be upregulated in damaged myocardium [8]. Increased cardiac S100A6 expression was shown to display anti-hypertrophic properties [7]. However, functional consequences as well as long-term effects on cardiac remodelling remain largely unknown.

In the current issue of Cardiovascular Research, Schneider and colleagues underscore the significance of S100 proteins in damaged myocardium by reporting on novel functional aspects of S100A4 protein. The authors demonstrate increased expression of S100A4 in homogenates of hypertrophic hearts following aortic banding or MI [13]. Interestingly, S100A4 was shown to be a β-catenin target in
human colon cancer cell lines and this mechanism might also be relevant to regulate S100A4 expression in hypertrophied myocardium [14].

Immunofluorescence experiments revealed that increased appearance of S100A4 protein in injured myocardium was mainly due to invasion of neutrophils and macrophages as well as increasing numbers of fibroblast-like, endothelial, and smooth muscle cells, whereas S100A4 protein was found exclusively in cardiomyocytes after MI in the infarct border zone [13]. This result was consistent with data obtained from patients with ischemic cardiomyopathy, adding to the clinical relevance of their findings [13]. In situ hybridization analysis targeting S100A4 mRNA might suggest that S100A4 protein is being taken up by cardiac myocytes [13]. S100A4 might therefore be involved in the interplay between different cell types during cardiac remodelling, although the mechanism for uptake of S100A4 in the infarct border zone remains elusive. It is therefore of interest that S100A1 protein was shown to be endocytosed via a Ca\(^{2+}\)-dependent, clathrin-mediated process in neonatal cardiomyocytes [15]. Also noteworthy, a previous report demonstrated strong upregulation of S100A4 in failing myocardium after myocardial infarction due to activation of G\(_{q11}\)-protein, PKC as well as receptor-coupled tyrosine kinase- and serine–threonine kinase-dependent pathways [8]. However, the current work by Schneider et al. clearly shows distinct S100A4 staining in the infarct border zone, suggesting a role of S100A4 in post-infarct cardiac remodelling, and further studies are needed to investigate the functional impact of this finding.

What is also of interest from the current data of Schneider et al. is that, like other S100 proteins, S100A4 regulates hypertrophy and apoptosis of cardiomyocytes. Extracellular S100A4 was shown to be taken up by neonatal cardiomyocytes and exhibit pro-hypertrophic as well as anti-apoptotic actions in vitro [13]. One possible explanation for pro-hypertrophic effects of S100A4 might be S100A4-mediated downregulation of phosphatase and tensin homolog (PTEN) and thus increased activity of phosphatidylinositol 3-kinase (PI3K) [16]. Interestingly, although different members of the S100 protein family were shown to display distinct effects on cardiomyocytes, anti-apoptotic effects of both S100A4 and S100A1 proteins involve specific activation of the extracellular signal-regulated kinase 1/2 (ERK 1/2) [13,15]. Further studies will have to examine whether functional consequences of increased S100A4 protein levels in injured myocardium bear beneficial or detrimental effects.

Overall, differential regulation of S100 proteins is part of the compensatory or maladaptive process that takes place in damaged myocardium. Altered expression of S100 proteins in HF effects myocardial remodelling and function via modulation of key processes such as hypertrophy, apoptosis, and intracellular Ca\(^{2+}\) cycling. However, the functional properties of different S100 proteins on cardiomyocytes are very distinct and need to be investigated in more detail. Therefore, examination of the functional role of individual S100 proteins in HF might contribute to a better understanding of the regulatory and counterregulatory mechanisms causing the progressive deterioration of cardiac function in HF patients.

References