In their study published in this issue, Iglesias et al. give the first evidence that ghrelin is synthesized and secreted by cardiomyocytes. Ghrelin is a 28-amino acid peptide containing an n-octanoyl modification at serine 3. It acts on the pituitary and hypothalamus to stimulate growth hormone (GH) release, food intake, and adiposity. It has been newly identified as the endogenous ligand of the orphan GH secretagogues (GHS) receptor, GHSR-1a, that is mostly expressed in pituitary and hypothalamus. Acylation of ghrelin is required for activation of GHSR-1a, whereas des-acyl ghrelin, which is far more abundant than ghrelin, does not bind GHSR-1a and is devoid of any endocrine activity [1,2].

GH and its mediator, insulin-like growth factor (IGF)-1, are anabolic hormones that are essential for myocardial development and performance. Receptors for both GH and IGF-1 are expressed by cardiac myocytes; therefore, GH may act directly on the heart or via the induction of local or systemic IGF-1, whereas IGF-1 may act by endocrine, paracrine, or autocrine mechanisms [3]. Studies on animal models of pressure and volume overload report up-regulation of cardiac IGF-1 production and expression of GH and IGF-1 receptors, implying that the local regulation of these factors is influenced by haemodynamic changes. Other studies further show that GH administration improves cardiac performance in experimental heart failure [3]. However, the overall clinical benefits of GH therapy for patients with coronary artery disease. Those effects are not reproduced by recombinant GH or other synthetic GHS. The existence a novel GHSR in heart distinct from GSHR-1a is further supported by the finding that both ghrelin and des-acyl ghrelin inhibit apoptosis of cardiomyocytes and endothelial cells through activation of a intracellular survival pathway [8].

Major metabolic effects of ghrelin, in particular stimulation of food intake and inhibition of fat depot utilization, do rely on GH-independent mechanisms [9]. Vasodilatory actions and anticachectic effects of ghrelin administration, described in rats with heart failure, also appear to be independent of GH [10]. This is in keeping with the very recent study of Iwase et al. [11] aiming to compare the effects of the GSH compound, GHRP-6, and GH on progressive LV dysfunction in the TO-2 hamster model of cardiomyopathy. It is shown that GHRP-6 can ameliorate the development of progressive LV dysfunction independently of its ability to elicit GH secretion. However, in her comments about the paper of Iwase et al. [11], Lucchesi [12] points out that very little is known as to the cellular mechanisms that transduce the protective effect of GHRP-6. At least two different receptors for this peptide, GHSR and the b-type scavenger receptor CD36 that does not bind ghrelin, have been identified in the myocardium. The question as to the origin of endogenous ghrelin that accesses cardiac GSHR becomes crucial.
Plasma ghrelin comes essentially from the stomach. Significant levels of ghrelin are also expressed in other tissues including placenta, testis, kidney, pituitary, small intestine, pancreas, lymphocytes, brain, lung, and ovary [2]. Accordingly, it is agreed that ghrelin, as well as being a circulating factor, exerts local paracrine and/or autocrine actions in those different tissues. Iglesias et al. describe the synthesis and secretion of ghrelin by a mouse atrial cardiomyocyte HL-1 line and cultured human atrial cardiomyocytes. The authors also found that HL-1 cells express GHSR that bind ghrelin efficiently and that human myocardium expresses GHS-R1a mRNA. Exogenously added ghrelin inhibits cardiomyocyte AraC-induced apoptosis.

Taken together, these results strongly argue for a paracrine/autocrine activity of ghrelin in the heart. But as any new findings, they raise several questions. The first question concerns the role of ghrelin in the physiological control of cardiac function. Such a question has been previously asked by Torsello et al. [13]. In their study, the authors use hypophysectomized rats treated or not treated with ghrelin, and examine damage in hearts subjected in vitro to an ischemia/reperfusion procedure. They conclude that ghrelin plays a minor role in the control of heart function. However, such a proposal is now quite questionable because endogenous ghrelin can hinder possible effects of the exogenously added ghrelin. A second question is what is the form of ghrelin that is produced by the heart. Des-acyl ghrelin is far more abundant than ghrelin and may act as a survival factor in the cardiovascular system [8]. Would des-acyl ghrelin be the active cardiac form of ghrelin? The third question regards the regulation of the expression of ghrelin/des-acyl ghrelin in the heart. It has already been emphasized that atrial myocardium plays a predominant paracrine/autocrine role of under normal conditions and early LV dysfunction, producing atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), and adrenomedullin. These factors exert various protective effects and their administration has proven to be favorable in the treatment of heart failure [14,15]. In normal ventricle, BNP expression is null and that of adrenomedullin considerably lower than in atrium. In contrast, in the failing heart, expression of both factors in ventricle and atrium are comparable [16,17]. Administration of ghrelin improves left ventricular dysfunction in rats with heart failure [10]. Iglesias et al. show that not only is ghrelin produced by atrial cells, but also that it protects cardiomyocytes against apoptosis. Is ghrelin a new protective weapon in the atrial arsenal? Is ghrelin expressed in the failing ventricle? Ghrelin expression is up-regulated after fasting hypoglycemia or leptin administration, and it is increased by chronic undernutrition in animal models, suggesting that ghrelin expression and secretion are enhanced in situations of negative energy balance. Does this apply to the cachectic heart?

Finally, the most intriguing observation in the study of Iglesias et al. is that in HL-1 cells, the protective effect of GH against AraC-induced apoptosis is related to an increased expression of ghrelin mRNA. The authors do not comment on this last finding of the study, which leads to the ambiguous dual conclusion that cardiac effects of ghrelin may rely on GH release, or not, and that ghrelin may mediate cardiac effects of GH. Thus, the study of Iglesias et al. leads to a new question: between ghrelin and growth hormone, which is chicken, which is egg?

References