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REVIEW ARTICLE

Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets

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Abstract The onset of heart failure is typically preceded by cardiac hypertrophy, a response of the heart to increased workload, a cardiac insult such as a heart attack or genetic mutation. Cardiac hypertrophy is usually characterized by an increase in cardiomyocyte size and thickening of ventricular walls. Initially, such growth is an adaptive response to maintain cardiac function; however, in settings of sustained stress and as time progresses, these changes become maladaptive and the heart ultimately fails. In this review, we discuss the key features of pathological cardiac hypertrophy and the numerous mediators that have been found to be involved in the pathogenesis of cardiac hypertrophy affecting gene transcription, calcium handling, protein synthesis, metabolism, autophagy, oxidative stress and inflammation. We also discuss new mediators including signaling proteins, microRNAs, long noncoding RNAs and new findings related to the role of calcineurin and calcium-/calmodulin-dependent protein kinases. We also highlight mediators and processes which contribute to the transition from adaptive cardiac remodeling to maladaptive remodeling and heart failure. Treatment strategies for heart failure commonly include diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and β-blockers; however, mortality rates remain high. Here, we discuss new therapeutic approaches (e.g., RNA-based therapies, dietary supplementation, small molecules) either entering clinical trials or in preclinical development. Finally, we address the challenges that remain in translating these discoveries to new and approved therapies for heart failure.

Keywords Heart failure · Pathological hypertrophy · Maladaptive heart growth · Therapeutic applications · Signaling cascades

Overview and clinical implications

Heart failure (HF) is a debilitating condition in which the heart cannot sustain the supply of oxygenated blood to the body. This can result as a consequence of exposure to a chronic cardiac stress or injury including pressure or volume overload (e.g., hypertension, valvular heart disease), myocardial infarction (MI) or ischemia, as well as inherited diseases. The heart initially undergoes a compensatory response to the additional load or cardiac insult by increasing in size and mass to normalize wall stress and allow normal cardiovascular function at rest (Grossman et al. 1975). This cardiac enlargement is typically referred to as pathological cardiac hypertrophy (as a consequence of MI, the heart undergoes regional hypertrophy). During the compensatory stage of hypertrophy, the increase in heart size and mass is considered to be accompanied by biochemical, molecular, structural and metabolic changes in order to maintain cardiac function. Over time, however, chronic stress or disease will result in ventricular dilation, fall in contractile function and eventually progress to HF (Fig. 1).

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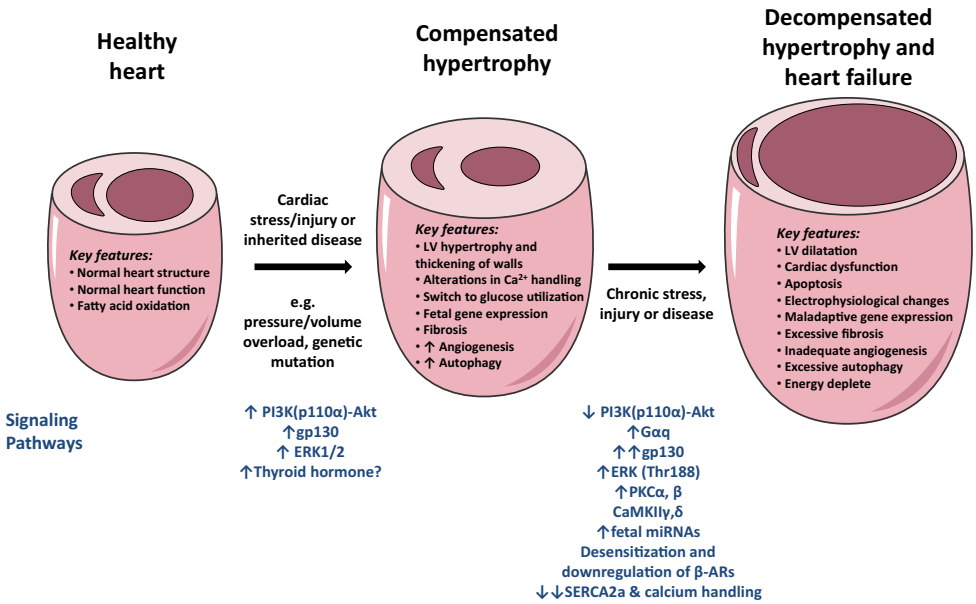

Fig. 1 Processes and main signaling pathways involved in cardiac remodeling. A schematic displaying the morphological, molecular and biochemical changes and altered signaling pathways associated with the transition from compensated hypertrophy to decompensated hypertrophy and heart failure. *β-AR* β-adrenergic receptors, *CaMK* calcium-/calmodulin-dependent protein kinase, *ERK* extracellular signal-regulated kinase, *gp130* glycoprotein 130, *LV* left ventricular, *PI3K* phosphoinositide 3-kinase, *PKC* protein kinase C, *SERCA2a* sarco/endoplasmic reticulum Ca^{2+}-ATPase

Cellular, molecular and biochemical changes associated with cardiac hypertrophy

The heart contains multiple cell types including cardiomyocytes (heart muscle cells, approximately 30 % of total cell number but account for 70–80 % of the heart's mass), fibroblasts, vascular smooth muscle cells, endothelial cells and immune cells (Bernardo et al. 2010). As most cardiomyocytes are unable to divide, cardiac hypertrophy is associated with cardiomyocyte enlargement (Porrello et al. 2011; Soonpaa and Field 1998). As described in subsequent sections, cardiac hypertrophy is accompanied by alterations within cardiomyocytes including calcium handling, metabolism and gene expression, as well as cell death (e.g., apoptosis and autophagy), and changes in extracellular matrix (ECM) (fibrosis) and angiogenesis (Figs. 1, 2).

Calcium handling

Contraction of the heart is regulated by cyclic changes in calcium (Ca^{2+}) within cardiomyocytes. During cardiac excitation–contraction coupling, a high action potential causes Ca^{2+} to enter the cardiomyocyte via L-type Ca^{2+} channels (LTCC) located within t-tubules (Fig. 2). Binding of Ca^{2+} to type 2 ryanodine receptors (RyR2) in opposing sarcoplasmic reticulum (SR) membranes leads to Ca^{2+} release from the SR, a process known as Ca^{2+}-induced Ca^{2+} release (Bers 2014). An increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) enhances binding of Ca^{2+} to troponin C within the thin filament of sarcomeres (basic contractile unit of the heart). This alters protein–protein interactions within the thin filament, promoting the formation of cross bridges between the thick and thin filaments and resulting in contraction (Solaro 2010). Relaxation occurs when Ca^{2+} is pumped back into the SR by sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) or out of the cell by the Na^+/Ca^{2+} exchanger (NCX) (Bers 2006). SERCA2a activity is regulated by phospholamban (PLN), a protein that inhibits SERCA2a when in its dephosphorylated form. Upon phosphorylation by protein kinase A (PKA) or Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), PLN alleviates the inhibitory effects of PLN on SERCA2a pump function (Kranias and Hajjar 2012).

In the failing heart, calcium-handling abnormalities contribute to contractile dysfunction (Feldman et al. 1987; Gwathmey et al. 1987; Lindner et al. 2002; Yeh et al. 2008). Impaired SERCA2a function resulting from reduced expression of SERCA2a (Hasenfuss 1998) or reduced PLN phosphorylation (Schwinger et al. 1999) leads to accumulation of Ca^{2+} in the cytosol, which prevents relaxation and reduces the pool of Ca^{2+} available for release from the SR during systole. Downregulation of SERCA2a has been observed in numerous experimental models of HF (Kawase et al. 2008; Kiss et al. 1995; O'Rourke et al. 1999) as well as in the failing human heart (Arai et al. 1993; Hasenfuss et al. 1994).

Ca^{2+} leak from the SR due to dysfunctional RyR2 may contribute to contractile dysfunction by depleting SR Ca^{2+} stores, elevating $[Ca^{2+}]_i$, increasing the incidence of arrhythmias and increasing the cell's energy requirements (to extrude the leaked Ca^{2+} or pump it back into the SR) (Bers 2014). Hyperphosphorylation of RyR2 has been observed in the failing human heart (Marx et al. 2000; Respress et al. 2014); however, the precise role of RyR2 phosphorylation in the pathogenesis of HF and arrhythmias is the subject of intense debate (Dobrev and Wehrens 2014;

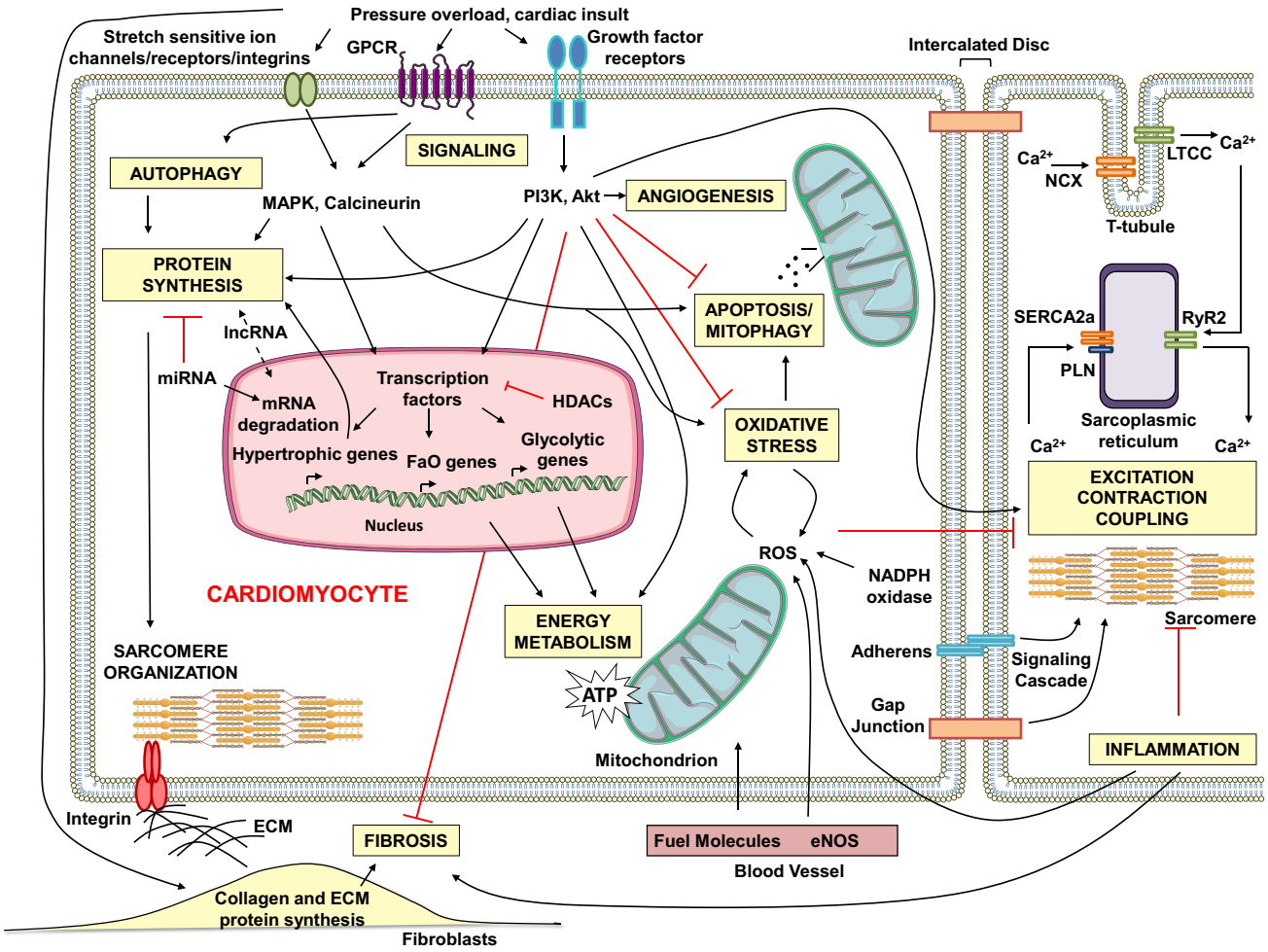

Fig. 2 Overview of cellular processes that contribute to remodeling in cardiac hypertrophy. *ECM* extracellular matrix, *eNOS* endothelial nitric oxide synthase, *FaO* fatty acid oxidation, *GPCR* G protein-coupled receptor, *HDAC* histone deacetylase, *lncRNA* long noncoding RNA, *LTCC* L-type Ca^{2+} channels, *miRNA* microRNA, *NADPH* nicotinamide-adenine dinucleotide phosphate, *NCX* Na^{2+}/Ca^{2+} exchanger, *PLN* phospholamban, *ROS* reactive oxygen species, *RyR2* type 2 ryanodine receptors, *SERCA2a* sarco/endoplasmic reticulum Ca^{2+}-ATPase

Houser 2014). Enhanced phosphorylation of RyR2 may result from increased phosphorylation by CaMKII or PKA, or reduced activity of protein phosphatase 1 (PP1) or protein phosphatase 2A (PP2A), all of which target RyR2 and are dysregulated in HF (Ather et al. 2013).

Dysregulation of t-tubules also appears to contribute to contractile dysfunction in settings of HF, as close association of LTCC in t-tubules with RyR2 in opposing SR membranes is necessary for rapid, synchronized Ca^{2+} release from the SR (Ibrahim et al. 2011). Crossman and colleagues used high-resolution fluorescence imaging to investigate t-tubule organization in healthy and failing human hearts (Crossman et al. 2011). In healthy myocardium, the t-tubular network was highly organized, with t-tubules uniformly spaced along the length of the cardiomyocyte. In contrast, the t-tubular system in failing myocardium was in disarray and was associated with a reduction in the density of RyR2 clusters as well as reduced colocalization between RyR2 and LTCC.

Metabolism in the normal heart and stressed heart

Metabolism in the normal heart

Each day the normal adult heart consumes 15–20 times its weight in adenosine triphosphate (ATP) (Kolwicz et al. 2013). Mitochondria are the organelles within cardiomyocytes responsible for generating ATP, allowing cardiomyocytes and the heart to continuously contract. Due to this high energy demand on the heart, mitochondria constitute at least 30 % of the cardiomyocyte volume (Schaper et al. 1985). The heart derives the majority (60–90 %) of its

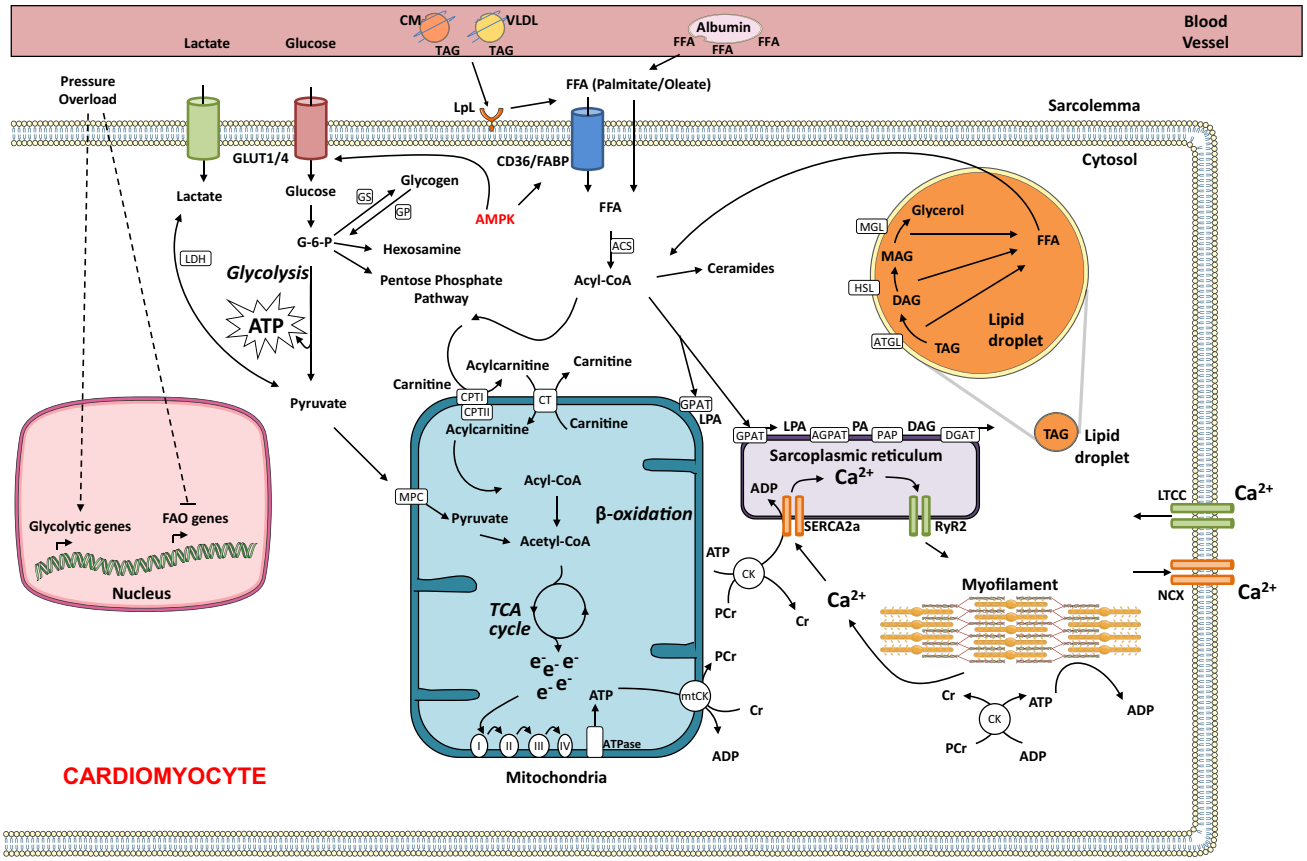

Fig. 3 Overview of energy metabolism in normal cardiomyocytes. Circulating fatty acids, glucose and lactate are taken up by the cardiomyocytes via active/passive transport. Fatty acids enter the mitochondria via carnitine palmitoyltransferase 1 (CPT I) conversion of acyl-CoA to acylcarnitine. Acylcarnitine is then shuttled into the mitochondria by carnitine:acylcarnitine translocase (CT) where CPT II then reverts acylcarnitine to acyl-CoA. Acyl-CoA then undergoes β-oxidation and oxidative phosphorylation to generate ATP. ATP generated is transported via the creatine kinase (CK) shuttle to be utilized in calcium cycling processes and contraction of myofilaments. Additional fatty acids that are unused undergo enzymatic conversion into TAG lipid droplets for storage till further use. ATP can be generated from glucose via glycolysis, or similar to lactate, can be converted to pyruvate before converging with the fatty acid oxidation pathways. *ACS* acyl-CoA synthase, *ADP* adenosine diphosphate, *AGPAT* 1-acyl-glycerol-3-phosphate-O-acyltransferase, *ATGL* adipose triglyceride lipase, *ATP* adenosine triphosphate, *CD36* fatty acid translocase, *CK* creatine kinase, *CM* chylomicron, *Cr* creatine, *DAG* diacylglycerol, *DGAT* diacylglycerol acyltransferase, *FABP* fatty acid binding protein, *FaO* fatty acid oxidation, *FFA* free fatty acid, *G-6-P* glucose-6-phosphate, *GLUT1/4* glucose transporter 1/4, *GP* glycogen phosphorylase, *GPAT* glycerol phosphate acyltransferase, *GS* glycogen synthase, *HSL* hormone sensitive lipase, *LDH* lactate dehydrogenase, *LPA* lysophosphatidic acid, *LpL* lipoprotein lipase, *LTCC* L-type Ca^{2+} channels, *MAG* monoacylglycerol, *MGL* monoacylglycerol lipase, *MPC* mitochondrial pyruvate carrier, *mtCK* mitochondrial creatine kinase, *NCX* Na^{2+}/Ca^{2+} exchanger, *PA* phosphatidic acid, *PCr* phosphocreatine kinase, *RyR2* type 2 ryanodine receptors, *SERCA2a* sarco/endoplasmic reticulum Ca^{2+}-ATPase, *TAG* triacylglycerol, *TCA cycle* tricarboxylic cycle, *VLDL* very low density lipoprotein

energy source from fatty acids (FAs), with glucose and lactate providing the remaining 10–40 % (Stanley and Chandler 2002). As conditions such as cardiac workload, oxygen supply and nutritional supply are altered, the heart is able to adapt and rely on varying proportions of substrates as a source of ATP to ensure that a constant supply of energy can be generated (Hue and Taegtmeyer 2009).

Circulating FAs are supplied to the heart via two sources (Fig. 3). The first form is as a component of triacylglycerol (TAGs) contained in circulating chylomicrons from the liver or very low density lipoprotein (VLDL) from the gut, or secondly as free fatty acids (FFAs) bound to plasma albumin. Chylomicron and VLDL-TAGs undergo lipoprotein lipase (LpL)-mediated lipolysis to release the FFAs, which enter the cardiomyocyte either through fatty acid translocase (CD36) or passive 'flip-flop' (Bharadwaj et al. 2010). FFAs from albumin can enter the cardiomyocyte either by passive diffusion or via a protein carrier-mediated pathway such as CD36 fatty acid binding protein or fatty acid transport protein 1/6 (Lopaschuk et al. 2010).

Upon entry into the cytosol, the majority of FFAs undergo β-oxidation in the mitochondria for ATP production, while the remaining FFAs undergo esterification to TAGs and are stored in lipid droplets (Kienesberger et al.

2013). Myocardial TAGs serve as a critical fuel storage depot and are also an important endogenous source of FAs utilized for ATP generation (Saddik and Lopaschuk 1991).

Metabolism in a setting of pathological cardiac hypertrophy

Pathological cardiac hypertrophy is associated with a decline in FA oxidation and a shift to glucose utilization (Figs. 1, 3). This is often referred to as a 'substrate switch' (Taegtmeyer 2002). Concurrent to this switch is the change in expression and activity of transcriptional proteins involved in glycolysis and FA oxidation such as peroxisome proliferator-activated receptor-α (PPARα), PPARγ co-activator-1α (PGC1-α) and hypoxia-inducible factor 1-α (HIF1-α) (Allard et al. 1994; el Alaoui-Talibi et al. 1992; Lopaschuk et al. 2010; Morissette et al. 2003). These changes act in concert leading to an increase in glucose uptake, glycolysis rates and decrease in FA oxidation. It has been noted in several studies, however, that glucose oxidation does not increase, leading to elevated uncoupling of glycolysis and glucose oxidation (Akki et al. 2008; Lydell et al. 2002; Sorokina et al. 2007). This creates a severe limitation in acetyl-coA availability for the TCA cycle to sustain sufficient ATP production. Anaplerosis is a mechanism suggested to occur as a 'quick fix' to maintain metabolic homeostasis by introducing carbons at various sites in the tricarboxylic acid (TCA) cycle (Sorokina et al. 2007). In the long run, however, as this process consumes ATP, it will result in net energy loss.

Hypertrophy results in increased cardiac workload and the need for additional ATP. It also increases the diffusion distance of oxygen and other substrates, eventually resulting in hypoxia (Friehs and del Nido 2003). The substrate switch noted earlier is hence thought to be more favorable and provides a protective mechanism as ATP generation from glucose requires less oxygen (6 mol oxygen per mol glucose) as compared to FAs (23 mol oxygen per mol palmitic acid) (Stanley et al. 2005). This resembles what occurs in fetal cardiac development, where glucose is used as the primary source of energy due to underdeveloped FA transport and metabolism enzymes as well as limited oxygen supply (Bernardo et al. 2010).

Eventually, the increased energy demands of pathological hypertrophy lead to the depletion of the energy reserve compound observed in reduced phosphocreatine (PCr)/ATP ratios (Liao et al. 1996; Tian et al. 1997). PCr is a small molecule that is part of the creatine kinase energy shuttle that transfers energy from ATP generated from the mitochondria to myofibrils (Fig. 3). Mitochondrial creatine kinase catalyzes the transfer of the high-energy phosphate bond from ATP to creatine to form PCr and adenosine diphosphate (ADP). PCr diffuses from the mitochondria into the myofibrils where the myofibril isoform of creatine kinase reforms ATP from PCr. Free creatine which is created from the removal of phosphate from PCr diffuses back into the mitochondria (Neubauer 2007). In a setting of pathological hypertrophy when increased energy requirements outstrip energy supply, the creatine kinase system serves as an energy buffer. PCr levels decrease in order to maintain ATP levels at the cost of elevated levels of ADP, which have been shown to inhibit many intracellular enzymes leading to an impairment of cardiac contractility (Neubauer 2007). This results in the progression into HF, where myocardial ATP levels are significantly reduced to 30–40 %. Factors including a decrease in creatine, PCr levels and creatine kinase activity contribute to impaired energy delivery to the myofibrils, further exacerbating contractile dysfunction and loss of ATP reserves. Decreased PCr/ATP ratios are observed in patients with HF and have been reported to be better predictors of mortality than ejection fraction (Neubauer et al. 1997).

Cardiac fibrosis

Fibrosis is the net accumulation of ECM proteins (consisting of collagens, fibronectin, matrix metalloproteinases (MMPs) and tissue inhibitor of matrix metalloproteinases (TIMPs)) in the heart which is a common feature of pathological cardiac conditions (Kong et al. 2014) (Fig. 2). In a normal heart, cardiac fibroblasts which are located within the ECM surrounding cardiomyocytes, produce the ECM components, primarily collagen type I and III. This is a constant process in the heart, with new collagen being synthesized and old collagen being degraded. Fibroblasts maintain the fine balance in collagen levels via the secretion of cytokines, growth factors and MMPs (Baum and Duffy 2011). The ECM provides an organized network around the cardiomyocytes, which not only serves as scaffolding for the cellular components, but also helps support a range of mechanical, chemical and electrical processes that maintain homeostasis and coordinate contractile function and electrical coupling between cardiomyocytes (Martin and Blaxall 2012).

Cardiomyocyte death (e.g., in response to MI) as well as pathological stimuli (such as chronic pressure or volume overload) will trigger pro-fibrotic pathways. There are various cell types that can contribute to fibrosis directly by producing matrix proteins (fibroblasts) or indirectly by secreting fibrogenic mediators [macrophages, mast cells, lymphocytes, cardiomyocytes and vascular cells, e.g., secretion of tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β) and endothelin-1 (ET-1)]. The differentiation of cardiac fibroblasts to myofibroblasts is also a crucial event that drives the fibrotic response (Kong et al. 2014). Myofibroblasts have enhanced proliferative and

secretory properties that migrate to sites of injury, playing an important role in tissue repair and wound healing (Martin and Blaxall 2012). Chronic stress, however, results in the persistent activation and proliferation of myofibroblasts, leading to the aberrant deposition (interstitial/replacement) and subsequent accumulation of collagen in the heart. This causes mechanical stiffening, contributing to diastolic dysfunction and can progress to systolic dysfunction. Fibrosis also promotes arrhythmogenesis by impairing conduction, which induces slowing of electrical conduction velocities and subsequently generating re-entry circuits (Khan and Sheppard 2006).

Oxidative stress

Oxidative stress occurs when there is an imbalance between reactive oxygen species (ROS) produced and the heart's ability to detoxify or remove the reactive intermediates by intrinsic antioxidant systems (e.g., superoxide dismutase, catalase and glutathione peroxidase) (Nordberg and Arner 2001). Excessive ROS production has been associated with pathological cardiac hypertrophy and HF in humans and animal models (Huynh et al. 2014; Keith et al. 1998; McMurray et al. 1993; Murdoch et al. 2006). The three major sources of ROS in the heart include: (1) the membrane-bound enzyme complex nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, (2) mitochondrial respiratory chain and (3) uncoupled endothelial nitric oxide synthase (eNOS). Elevated ROS from each of these sources have been associated with cardiac disease, and studies in which ROS have been genetically or pharmacologically regulated suggest elevated ROS contribute to adverse cardiac remodeling (Huynh et al. 2014).

Studies have demonstrated that hypertrophic stimuli such as angiotensin II (Ang II), ET-1, catecholamines, cytokines and biomechanical stretch can induce increased ROS production in cardiomyocytes (Laskowski et al. 2006; Liu et al. 2004), and this can activate a range of hypertrophic signaling mediators and transcription factors such as ERK1/2 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Takimoto and Kass 2007). Elevated ROS produced by NADPH oxidase or the mitochondria in settings of cardiac pathology can contribute to (or are associated with) the development of pathological hypertrophy, fibrosis, depressed contractility and apoptosis (Dai et al. 2011; Murdoch et al. 2006; Schwarzer et al. 2014; Takimoto and Kass 2007) (Fig. 2).

Balance between cardiomyocyte survival and death-apoptosis, necrosis and autophagy

Depending on the type of stress and severity, cells will respond by activating pathways/mechanisms, which promote cell survival or elicit cell death to remove damaged cells. A key feature which characterizes the transition from compensated heart growth to decompensated heart growth and HF is cardiomyocyte cell death. Thus, it has been proposed that inhibiting modes of cell death may represent a promising therapeutic approach. Types and/or processes associated with cell death include necrosis, apoptosis and autophagy (Diwan and Dorn 2007; Konstantinidis et al. 2012) (Fig. 2).

Apoptosis is morphologically defined by cell shrinkage, fragmentation into membrane-enclosed dense apoptotic bodies (Martelli et al. 2001) and phagocytosis of these bodies without inducing an inflammatory response (Diwan and Dorn 2007; Konstantinidis et al. 2012). In the normal heart where cellular regeneration is limited, apoptosis occurs at extremely low rates (Soonpaa and Field 1998). However, in a setting of heart disease, the rate of cardiomyocyte apoptosis can increase in the human heart (Hein et al. 2003; Narula et al. 1996; Olivetti et al. 1997) and based on animal studies contributes to decompensated hypertrophy and HF (Hayakawa et al. 2003; Wencker et al. 2003). In contrast to apoptosis, necrosis is associated with loss of membrane integrity, swelling of organelles and cells, and an inflammatory response (Diwan and Dorn 2007; Konstantinidis et al. 2012). Mediators of apoptosis and necrosis by death receptor pathways (extrinsic, e.g., binding of cytokines such as tumor necrosis factor α (TNF-α) to cell surface receptors and subsequent activation of caspases), mitochondrial pathways (intrinsic, involving proapoptotic mitochondrial proteins, e.g., Bax and Bak, and release of cytochrome C) and interactions have previously been reviewed in detail (Konstantinidis et al. 2012).

Autophagy is a cellular process recognized to degrade and recycle aged proteins and clear damaged organelles via a lysosomal-mediated pathway (Bernardo et al. 2010; Wang et al. 2012). In a setting of cardiac stress, autophagy levels are considered to increase to account for the synthesis of additional proteins, contributing to increased myocyte size and sarcomeric remodeling (Rothermel and Hill 2008). The increased autophagy protects cardiomyocytes by clearing ubiquitinated protein aggregation that would otherwise accumulate when the degradative capacity of the proteasome is surpassed and proteotoxicity would occur (Tannous et al. 2008). Regulation of key autophagy proteins (Atg5 and Atg7) in the heart using genetic mouse models suggest that autophagy protects against pathological remodeling and contractile dysfunction (Bhuiyan et al. 2013; Nakai et al. 2007). Furthermore, knockout (KO) of atrogin-1, a muscle-specific ubiquitin ligase that targets signaling proteins involved in cardiac hypertrophy for degradation in mice, leads to impaired autophagy, and accumulation of intracellular protein aggregates eventually leading to cardiomyocyte death (Zaglia et al. 2014). However, it

has also been suggested that excessive levels of autophagy may lead to cellular dysfunction and cell death (Maejima et al. 2014).

Initially, acute cellular responses to a stress including the heat shock protein (Hsp) response, unfolded protein response, DNA damage response and response to oxidative stress are elicited to provide protection (Fulda et al. 2010). However, chronic and/or excessive exposure leads to cell death. The mechanism by which the cell dies appears to be dependent on the type of stress, intensity and time frame of exposure (Fulda et al. 2010). Below, we provide one example of the balance between adaptive and maladaptive responses related to ROS produced by the mitochondria.

As described earlier, mitochondria are responsible for providing cardiomyocytes with a continuous supply of ATP, but also participate in regulating cell death due to the production of ROS (Kubli and Gustafsson 2012). Mitochondria produce ATP largely from the electron transport chain located on the inner mitochondrial membrane during oxidative phosphorylation. However, electron leakage from the electron transport chain together with the production of byproducts of ATP synthesis (O_2^- and H_2O_2) makes mitochondria a source of ROS (Wallace 1999, 2005). Under normal physiological conditions, ROS act as mediators to induce adaptive responses in the heart (Song et al. 2014), and the formation of excessive ROS is prevented by intrinsic antioxidant systems within the cell (Giordano 2005). However, in settings of chronic cardiac stress which damage mitochondrial proteins, ROS production increases leading to mitochondrial dysfunction. To adapt to the cellular stress, mitochondria will undergo fusion, fission and mitochondrial autophagy (mitophagy, a specialized form of autophagy to eliminate damaged mitochondria). Increased mitophagy is considered an early response to promote survival by removing damaged mitochondria. However, in a setting of excessive mitochondrial damage, apoptosis becomes dominant and is followed by cell death (Dorn and Kitsis 2015; Kubli and Gustafsson 2012).

Inflammation

A pathological insult such as pressure overload or MI can activate the innate immune system and trigger inflammation (Baumgarten et al. 2002; Vanderheyden et al. 2005) (Fig. 2). Many studies have demonstrated increased levels of the pro-inflammatory cytokine TNF-α in animal models of cardiac disease (Aker et al. 2003; Marin-Garcia et al. 2001; Recchia et al. 2000) and patients with HF (Aukrust et al. 1999; Kubota et al. 1998; Levine et al. 1990; Munger et al. 1996; Petretta et al. 2000; Torre-Amione et al. 1996). More recently, other cytokines such as toll-like receptors (TLR) and interleukin (IL) were shown to be involved in pathological cardiac remodeling and contribute to impairment of contractile function, increased generation of ROS, apoptosis and fibrosis (Gonzalez et al. 2015; Kleinbongard et al. 2011; Mann 2011). However, evidence suggests that the initial short-term inflammatory response is an adaptive response, which is important for cardiac repair (Mann 2002). For example, TLR-2 was shown to be crucial for the cardiac adaptation in response to pressure overload (Higashikuni et al. 2013). Chronic inflammation, however, is considered detrimental and will lead to tissue damage, maladaptive cardiac remodeling and HF (Mann 2011).

Angiogenesis

Angiogenesis is a key component of cardiac remodeling, arising from paracrine signaling between cardiomyocytes and the vasculature (Oka et al. 2014; Walsh and Shiojima 2007). Myocardial angiogenesis is thought to be critical for maintaining perfusion and an adequate nutrient supply to hypertrophying myocytes, as disruption of angiogenesis during adaptive hypertrophy leads to contractile dysfunction (Izumiya et al. 2006; Shiojima et al. 2005), while stimulation of angiogenesis during pressure overload is protective and prevents the transition from compensatory cardiac hypertrophy to HF (Friehs et al. 2006). Maintained or enhanced myocardial capillary density has been observed in experimental models of beneficial physiological hypertrophy (Weeks et al. 2012; White et al. 1998), and there was a strong correlation between myocardial blood vessel density and left ventricular (LV) mass index in patients with aortic stenosis and preserved ejection fraction (i.e., compensatory hypertrophy) (Lee et al. 2014). In contrast, advanced pathological remodeling and HF are associated with significant reductions in myocardial capillary density (Karch et al. 2005; Rengo et al. 2013).

The importance of adequate angiogenesis in a setting of cardiac hypertrophy was highlighted by a key study by Shiojima and colleagues (Shiojima et al. 2005). Increased expression of Akt1, a key mediator of adaptive physiological cardiomyocyte growth (see section on the IGF1–PI3K–Akt pathway) for 2 weeks, led to adaptive heart growth with preserved contractile function. In contrast, 6 weeks of Akt1 expression induced pathological cardiac hypertrophy, characterized by cardiac fibrosis, depressed systolic function and reduced capillary density. Utilizing tools to regulate vascular endothelial growth factor (VEGF), a factor critical for regulating angiogenesis, it was demonstrated that maintenance of cardiac function during short-term Akt expression (i.e., 2 weeks) was dependent on adequate angiogenesis, which was inadequate with longer-term Akt expression (i.e., 6 weeks). In this context, enhancing myocardial angiogenesis during pathological remodeling has been shown to improve outcome in preclinical models of HF (Banquet et al. 2011; Huusko et al. 2012).

Typical cardiac gene expression changes associated with pathological cardiac hypertrophy

Alongside morphological changes noted earlier, the development of pathological cardiac hypertrophy is commonly associated with the reinduction of fetal genes not usually expressed in the adult heart (Fig. 1). Studies in both human and animal models (Arai et al. 1993; Iemitsu et al. 2001; Takahashi et al. 1992) have shown increased mRNA expression of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and α-skeletal actin. Other typical changes, particularly in a setting of established cardiac dysfunction, include the downregulation of SERCA2a and a shift in expression from α-myosin heavy chain (α-MHC, fast contractile isoform) to β-MHC (slow MHC isoform) (Bernardo et al. 2010).

Signaling pathways associated with cardiac hypertrophy and remodeling

Numerous signaling cascades have been implicated in mediating cardiac growth in response to a cardiac stress or insult. Signaling within cardiomyocytes as well as the cross talk with other cardiac cell types is incredibly complex. In addition, the contribution of different signaling cascades in contributing specifically/selectively to compensated heart growth and the transition to decompensated heart growth and HF requires further investigation. Signaling cascades within the heart have been extensively reviewed by us and others (Bernardo et al. 2010; van Berlo et al. 2013). Below, we have focused on signaling pathways, which have been associated with different stages of cardiac hypertrophy and/or have been targeted with therapies (Figs. 4, 5).

Signaling pathways associated with compensated heart growth and beneficial processes

IGF1–PI3K–Akt pathway

Our laboratory and others have extensively assessed the role of the insulin-like growth factor 1 (IGF1)—phosphoinositide-3-kinase (PI3K)–protein kinase B (Akt) signaling pathway in mediating beneficial physiological heart growth (e.g., postnatal heart growth and exercise-induced growth) (Fig. 4). There are three major classes of PI3K (I, II and III). The role of PI3Ks with catalytic subunits p110α and p110β (Class 1_A, coupled to receptor tyrosine kinases, e.g., IGF1 receptor, IGF1R) and p110γ (Class 1_B, coupled to G protein-coupled receptors, GPCRs) has been best characterized in the heart (Bernardo et al. 2010). While there are some inconsistencies between genetic mouse models and downstream signaling (particularly in relation to Akt) (Bernardo et al. 2010), the majority of data indicate that IGF1R, PI3K (p110α) and Akt1 play critical roles in the induction of adaptive physiological heart growth (DeBosch et al. 2006; Kim et al. 2008; Luo et al. 2005; McMullen et al. 2003, 2004; Shioi et al. 2000). There is also evidence to suggest that this pathway is activated during the compensated phase of hypertrophy in response to a pathological insult. Increased cardiac generation of IGF1 was identified in patients with compensatory hypertrophy due to aortic stenosis or regurgitation, and there was a positive correlation between IGF1 formation and a measure of cardiac performance. By contrast, IGF1 levels were not elevated in patients with inadequate hypertrophy and in the transition to HF (Serneri et al. 1999).

IGF1, IGF1R, PI3K (p110α, p110β) and/or Akt have been shown to protect the heart and preserve cardiac function in settings of stress by numerous mechanisms including promoting adaptive cardiomyocyte growth, cardiomyocyte survival, angiogenesis, attenuating fibrosis and cell death, favorable electrical remodeling, and providing protection against mitochondrial dysfunction and excessive ROS generation (Lin et al. 2015; McMullen et al. 2004, 2007; McMullen 2008; O'Neill et al. 2007; Yang et al. 2012). Though, of note, not all these properties are necessarily dependent on Akt. The glycogen synthase kinase-3 (GSK3) family (GSK3α and GSK3β) has also been implicated in mediating cardiac responses downstream of the PI3K–Akt pathway (as well as other pathways) and has recently been extensively reviewed (Lal et al. 2015). While it is recognized that GSK3 plays a role in regulating cardiac remodeling, the exact role of each isoform in different cardiac disease settings has been difficult to dissect (See Lal et al. 2015 for a review of numerous genetic mouse models: global, conditional, myocyte specific and fibroblast specific). Nonetheless, collectively it appears that inhibition of GSK3α could be a strategy for attenuating maladaptive remodeling after MI (Lal et al. 2015).

More recently, other mediators associated with the IGF1–PI3K–Akt pathway have been identified including CCAAT/enhancer-binding protein β (CEBP/β), proline-rich Akt substrate of 40Kda (PRAS40) and PH domain leucine-rich repeat protein phosphatase 1 (PHLPP1) (Fig. 4).

CEBP/β

Current studies suggest that the transcription factor CEBP/β regulates cardiomyocyte proliferation. Exercise-induced activation of the PI3K–Akt pathway attenuated expression of CEBP/β, which was found to regulate and inhibit CBP/p300-interacting transactivator 4 (CITED4)-induced proliferation of cardiomyocytes. CEBP/β also interacted with

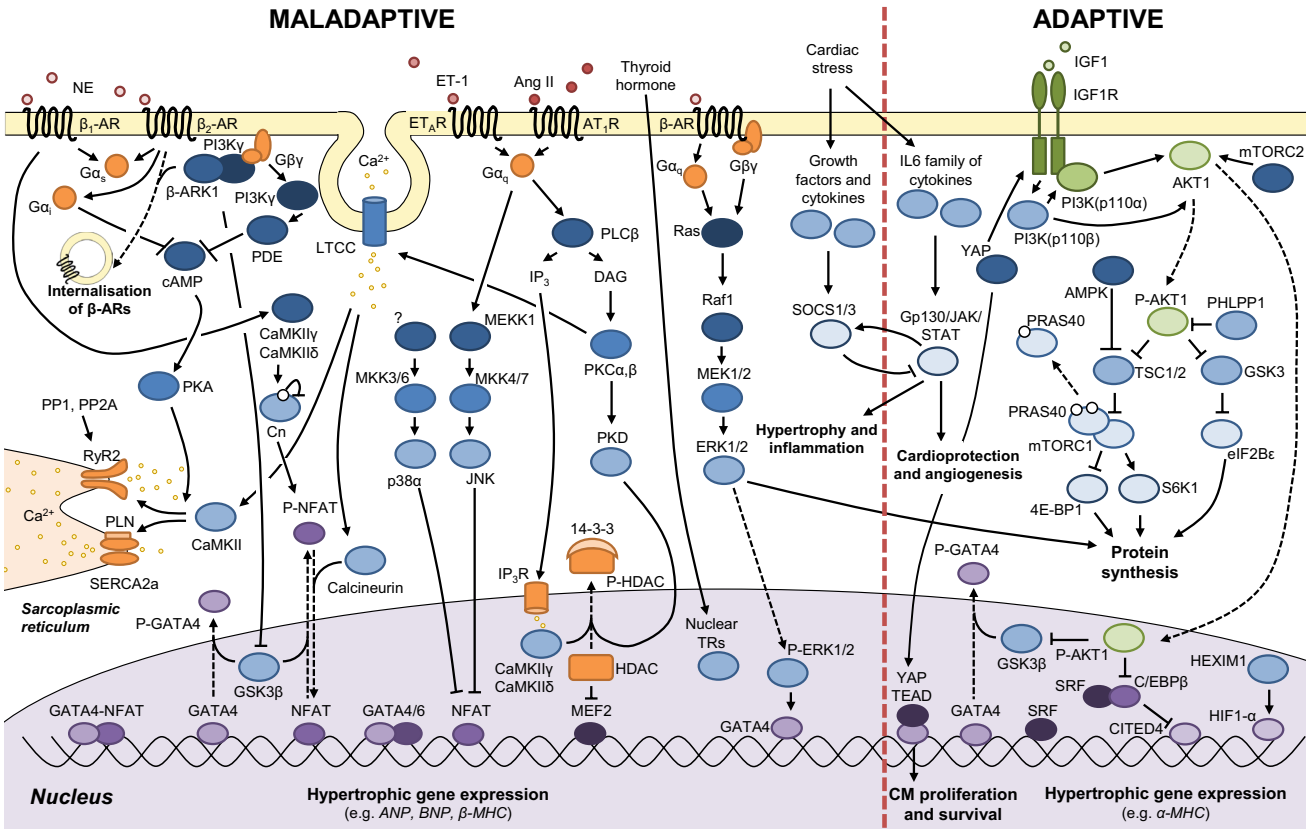

Fig. 4 A schematic of the major signaling pathways involved in maladaptive and adaptive cardiac hypertrophy. Signaling is complex, and there is extensive cross talk and integration between various components of the pathways. Dashed lines indicate translocation to a different intracellular compartment. Proteins in green have been shown to be critical for adaptive cardiac hypertrophy. *4E-BP1* eukaryotic translation initiation factor 4E-binding protein 1, *α-MHC* α-myosin heavy chain, *Akt1* protein kinase B, *AMPK* AMP-activated protein kinase, *Ang II* angiotensin II, *ANP* atrial natriuretic peptide, *AT-R* angiotensin II receptor, *β-AR* β-adrenergic receptor, *β-ARK* β-adrenergic receptor kinase, *β-MHC* β-myosin heavy chain, *BNP* B-type natriuretic peptide, *CAMK* Ca^{2+}/calmodulin-dependent protein kinase, *cAMP* cyclic adenosine monophosphate, *C/EBPb* CCAAT/enhancer-binding protein b, *CITED4* CBP/p300-interacting transactivator 4, *Cn* calcineurin, *DAG* diacylglycerol, *eIF2B* eukaryotic translation initiation factor 2B, *ERK* extracellular signal-related kinase, *ET-1* endothelin-1, *ET-R* endothelin receptor, *GATA* GATA binding protein, *gp130* glycoprotein 130, *GSK3* glycogen synthase kinase 3, *HDACs* histone deacetylases, *HEXIM1* hexamethylene-bis-acetamide-inducible 1, *HIF-1α* hypoxia-inducible factor 1α, *IGF1* insulin-like growth factor 1, *IGF1R* insulin-like growth factor 1 receptor, *IL-6* interleukin-6, IP_3 inositol trisphosphate, IP_3R inositol triphosphate receptor, *JAK* janus kinase, *JNK* jun amino-terminal kinase, *LTCC* L-type calcium channel, *PI3K* phosphoinositide 3-kinase, *MEF2* myocyte enhancer factor-2, *MEKK* MAP kinase, mTORC, mammalian target of rapamycin complex, *NE* noradrenaline, *NFAT* nuclear factor of activated T cells, *PDE* phosphodiesterase, *PHLPP1* PH domain and leucine-rich repeat protein phosphatase 1, *PKA* protein kinase A, *PKC* protein kinase C, *PKD* protein kinase D, *PLC* phospholipase C, *PLN* phospholamban, *PP1* protein phosphatase 1, *PP2A* protein phosphatase 2, *PRAS40* proline-rich AKT substrate, *RYR2* Ryanodine receptor 2, *S6K1* ribosomal protein s6 kinase 1, *SERCA2a* sarco/endoplasmic reticulum Ca^{2+}-ATPase, *SOCS* suppressor of cytokine signaling proteins, *SRF* serum response factor, *STAT* signal transducer and activator of transcription, *Raf1* RAF proto-oncogene serine/threonine-protein kinase, *TEAD* transcriptional enhancer factor TEF-1, *TR* thyroid hormone receptor, *TSC1/2* tuberous sclerosis complex 1/2, *YAP* Yes-associated protein

serum response factor (SRF) to regulate protective genes such as PGC1-α and genes associated with cardiomyocyte proliferation such as Tbx5, Gata and Nkx2.5 (Boström et al. 2010) (Fig. 4).

PRAS40

PRAS40 is highly expressed in cardiomyocytes and is phosphorylated via activation of Akt. Upon phosphorylation, disassociation of PRAS40 relieves inhibition on mTOR complex 1 (mTORC1), allowing physiological heart growth to occur via downstream mediators, which regulate protein synthesis including ribosomal S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E binding protein 1 (4EBP) (Fig. 4). Cardiac transgenic overexpression of PRAS40 was shown to attenuate pressure overload-induced hypertrophy and prevent cardiac dysfunction (Volkers et al. 2013).

PHLPP1

The novel protein phosphatase PHLPP1 was recently shown to dephosphorylate Akt to terminate signaling (Fig. 4). Swim training of PHLPP1 KO mice demonstrated accentuated physiological hypertrophy, while also showing an attenuated pathological hypertrophic response to pressure overload. The protective phenotype observed in PHLPP1 KO mice subjected to pressure overload was attributed to increased angiogenesis, as PHLPP1 KO mice had elevated angiopoietin-2 and VEGF-A levels and increased myocardial capillary density compared with control mice, and knockdown of PHLPP1 in cardiomyocytes increased VEGF-A expression and endothelial tube formation in myocyte/endothelial cell cocultures (Moc et al. 2015).

HEXIM1

Hexamethylene-bis-acetamide-inducible protein 1 (HEXIM1) is a transcription factor, which has also been implicated in mediating adaptive heart growth but may act independently of PI3K and Akt (Fig. 4). Inducible transgenic expression of HEXIM1 led to heart growth characteristic of physiological hypertrophy including increased angiogenesis and improved ejection fraction (Montano et al. 2013). HEXIM1-induced hypertrophy was associated with the regulation of transcription factors, which regulate angiogenesis (e.g., HIF1-α, VEGF) and metabolism [PPAR-α, glucose transporter type 4 (GLUT4)].

ERK1/2

Mitogen-activated protein kinases (MAPKs) are broadly divided into three subfamilies: extracellular signal-regulated kinases (ERKs), c-Jun amino-terminal kinase (JNK) and p38 (Fig. 4). Activation of ERK1/2 has been reported to mediate both adaptive and maladaptive processes in the heart (Fig. 4). As previously reviewed (Bernardo et al. 2010), results from in vitro studies and genetic mouse models have been difficult to interpret with a range of phenotypes reported (including no phenotype or contributions to both adaptive and maladaptive processes). For instance, constitutive transgenic expression of MEK1 (upstream of ERK1/2) in mice induced an adaptive cardiac response (enhanced cardiac function with no fibrosis) (Bueno et al. 2000). However, more recently it was shown that loss of ERK1 and ERK2 from cardiomyocytes did not attenuate cardiac enlargement in response to transverse aortic constriction (TAC) or exercise. However, loss of ERK1 and ERK2 induced eccentric cardiomyocyte growth (i.e., lengthening of cardiomyocytes as occurs when the heart decompensates and dilates) (Kehat et al. 2011).

It has been proposed that the adaptive and maladaptive roles of ERK1/2 may be related, at least in part, to the activation of ERK1/2 at two distinct phosphorylation sites via G protein subunits. Adaptive growth has been associated with the phosphorylation of ERK1/2 within the TEY motif (Gαq mediated) and phosphorylation of cytosolic targets inducing protein synthesis. In contrast, maladaptive processes have been associated with autophosphorylation of ERK1/2 at Thr188 (via Gβγ) leading to nuclear localization and the transcription of genes associated with pathology (Lorenz et al. 2009). Indeed, a follow-up study showed that interference of ERK1/2 autophosphorylation at Thr188 attenuated the hypertrophic response to phenylephrine and pressure overload, but did not interfere with the physiological hypertrophic growth response (Ruppert et al. 2013).

The other two major subfamilies, JNK and p38, are typically activated in settings of stress and injury. Numerous groups have studied the role of these MAPKs under basal conditions or in settings of disease by utilizing genetic mouse models, which directly or indirectly regulate JNK or p38, or by using pharmacological inhibitors. Results of these studies have previously been extensively reviewed (Bernardo et al. 2010; Martin et al. 2014; Rose et al. 2010). Collectively, the findings remain inconclusive with some studies suggesting that p38 and JNK contribute to pathology and the transition to HF, while others suggesting that these MAPKs are required for protecting the heart in settings of stress. Further studies with better tools for understanding the complex regulation, activation, localization and interaction of MAPKs will be required to target MAPKs as therapeutic targets.

Adaptive PKC isoform: PKCε

Protein kinase C (PKC) is a family of serine/threonine kinases that regulate a multitude of signaling cascades. PKC is activated in settings of cardiac stress and lies downstream of GPCR. Numerous PKC isoforms exist, but the four isoforms which appear to play key roles in regulating cardiac hypertrophy and/or contractility are PKCα, PKCβ, PKCδ and PKCε. A description of each isoform has previously been reviewed extensively (Dorn II and Force 2005). Here and in subsequent sections, we focus on those isoforms which have been linked with the compensatory response of cardiac hypertrophy or pathology associated with the transition to HF (refer to section on maladaptive PKC isoforms—PKCα and PKCβ). PKCε, a Ca^{2+}-independent isoform, appears to play an adaptive role in the heart (Dorn II and Force 2005). Cardiac-specific transgenic mice overexpressing a constitutively active mutant of PKCε developed mild cardiac hypertrophy associated with preserved cardiac function (Takeishi et al. 2000). Interestingly, ANP was not elevated in hearts of PKCε transgenic mice (consistent with an adaptive response) but β-MHC was elevated. Transgenic mice with increased subcellular PKCε translocation attenuated pathological

hypertrophy induced by Gq and improved cardiac function (Wu et al. 2000). By contrast, PKCε KO mice developed more fibrosis and diastolic dysfunction than wild-type mice in response to TAC; cardiac hypertrophy was similar between the two groups (Klein et al. 2005). Studies in PKCε KO mice have also shown that PKCε confers protection in a setting of ischemia (Gray et al. 2004).

Hsps and HSF1

Hsps are a family of molecular chaperones that are induced by heat shock or other stresses (De Maio 1999), and are also elevated in the heart in response to exercise training (Hamilton et al. 2003; Melling et al. 2007; Sakamoto et al. 2006). Heat shock transcription factor 1 (HSF1), which regulates Hsps, was identified in a genetic profiling screen as being elevated in the rat heart in response to exercise training but not pressure overload-induced hypertrophy, suggesting that HSF1 may play a distinct role in adaptive physiological heart growth versus growth in a disease setting (Sakamoto et al. 2006). Interestingly, exercise-induced hypertrophy was comparable in HSF1+/− and wild-type mice but HSF1+/− mice displayed cardiac dysfunction. Supporting a role for HSF1 playing an adaptive role, transgenic mice with constitutive activation of HSF1 developed less hypertrophy, fibrosis, apoptosis and cardiac dysfunction in response to TAC compared with wild-type mice (Sakamoto et al. 2006).

Of the Hsps, Hsp70 has been the most comprehensively studied in settings of cardiac stress (Kim et al. 2006; Marber et al. 1995; Plumier et al. 1995). Studies in Hsp70 genetic mouse models suggest that Hsp70 plays a protective role in settings of ischemic injury (Kim et al. 2006; Marber et al. 1995). However, whether Hsp70 provides any protection in a setting of pressure overload-induced hypertrophy is less clear (Weeks et al. 2012). More recently, the role of other Hsps in mediating cardioprotection has been explored. HspB2/Hsp27 KO mice and wild-type mice showed a similar hypertrophic and functional response to pressure overload, but loss of Hsp27 resulted in a decrease in mitochondrial respiration and ATP production rates. This suggests a role for Hsp27 in the energetics of compensatory hypertrophy (Ishiwata et al. 2012). HspB6/Hsp20 is another small Hsp, which has been implicated in mediating protection in the heart (Fan et al. 2005). Hsp20 was demonstrated to confer cardioprotection by enhancing contractile function and suppressing pro-apoptotic pathways in settings of ischemia/reperfusion injury and β-adrenergic receptor (β-AR)-induced hypertrophy. Enhanced contractile function was mediated in part by phosphorylating PLN, relieving its inhibition of SERCA2a and also by inhibiting the activity of PP1, a known regulator of PLN (Qian et al. 2011). In other studies using a model of β-AR-induced hypertrophy and remodeling, Hsp20 provided protection by attenuating apoptosis by preventing the translocation of Bax to the mitochondria to trigger mitochondrial death (Fan et al. 2004) and via the inhibition of the apoptosis signal-regulating kinase 1 (ASK1) pathway (Fan et al. 2006).

Thyroid hormone receptor signaling

Thyroid hormone (TH) plays a critical role in the maturation of the myocardium after birth (Hudlicka and Brown 1996; Mai et al. 2004) and appears to induce cardiac growth in adults, which is more similar to adaptive physiological hypertrophy (e.g., exercise-induced heart growth) than pathological hypertrophy (Bernardo et al. 2010; Janssen et al. 2014). Studies have demonstrated that increasing TH, thyroxine (T_4, prohormone) or triiodothyronine (T_3, active form of TH) in animal models or patients with hyperthyroidism induces hypertrophy, which is not maladaptive or associated with pathological features such as fibrosis (Bedotto et al. 1989; Bernardo et al. 2010; Ghose Roy et al. 2007; Janssen et al. 2014). T_3 binds to nuclear thyroid hormone receptors including TRα1 (predominant isoform), TRα2 and TRβ1, and regulates the transcription of a number of cardiac genes including α-MHC, β-MHC, SERCA2a and PLN (Arsanjani et al. 2011; Belakavadi et al. 2010; Bernardo et al. 2010) (Fig. 4).

Animal studies suggest that low levels of TH/T3 in cardiac disease settings are associated with cardiac dysfunction, and restoration improves outcome including more favorable expression of MHC isoforms. However, very high levels of TH may have an adverse effect (Henderson et al. 2009; Mourouzis et al. 2012; Pantos et al. 2011). It has also been shown that cytosol-localized TRα1 can interact with the p85α subunit of PI3K and that T3 regulates microRNAs (miRNAs) with targets that could promote physiological growth (Janssen et al. 2014; Kenessey and Ojamaa 2006). This represents potential mechanisms via which TH could mediate adaptive physiological growth. Consistent with these reports, it was suggested that TRα1 may play a role during the compensatory phase of cardiac hypertrophy. Following acute MI, nuclear TRα1 expression in rat hearts was increased alongside activation of ERK1/2 and mammalian target of rapamycin (mTOR, downstream of PI3K–Akt) during the compensatory growth phase. As the hearts regressed into HF, TRα1, pERK1/2 and phospho-mTOR levels were reduced (Pantos et al. 2010).

Gp130/JAK/STAT pathway

The gp130/JAK/STAT pathway is activated by the IL-6 family of cytokines (IL-6, cardiotrophin 1, leukemia inhibitory factor), which are produced by cardiomyocytes in response to a cardiac stress (Shi and Wei 2012) (Fig. 4). In general, genetic models or gene transfer of gp130, STAT and suppressors of cytokine signaling (SOCs, a negative

regulator of the JAK/STAT pathway) in rodents suggest that activation of the JAK/STAT pathway is initially important for mediating protection by inducing anti-apoptotic genes, ROS scavengers, and promoting angiogenesis (Cittadini et al. 2012; Hirota et al. 1999; Kunisada et al. 2000). However, chronic excessive activation of this pathway may lead to oxidative stress and inflammation, and contribute to the progression to HF (Shi and Wei 2012).

AMPK

Adaptive heart growth requires the coordination of increased cardiomyocyte size with changes in metabolism. Adenosine monophosphate-activated protein kinase (AMPK) is a key regulator of energy metabolism in the heart and is activated by stimuli that increase AMP and deplete ATP production. AMPK is also activated by increased ROS production or alterations in the concentration of calcium and is phosphorylated by upstream kinases LKB1-STRAD-MOD25 complex and calcium-/calmodulin-dependent protein kinase kinase-β (CaMKK2β) (Hardie et al. 2012; Kim and Dyck 2015). It is also known to activate multiple downstream targets (e.g., PGC-1α, FoxO proteins, PPARγ, GLUT4) to regulate cardiac energetic homeostasis, as well as act on several signaling cascades that limit cell growth (reviewed in Hardie et al. 2012; Kim and Dyck 2015) (Fig. 4).

Activation of AMPK has been reported in numerous rodent models of cardiac injury (including pressure overload, hypoxia and ischemia) as an adaptive response and was associated with enhanced glucose uptake (Huang et al. 2014; Nishino et al. 2004; Tian et al. 2001). Elevated AMPK protein expression and activity have been demonstrated in human failing hearts, although AMPK expression has not been extensively studied in all forms of HF (Kim et al. 2012). Pharmacological activation of AMPK has been shown to inhibit the mTOR pathway and attenuate pressure overload-induced hypertrophy (Chan et al. 2004, 2008; Li et al. 2007). Conversely, mice with depleted AMPK activity had an exacerbated degree of LV hypertrophy, adverse remodeling and dysfunction following cardiac injury (Shibata et al. 2004; Xu et al. 2014; Zarrinpashneh et al. 2008; Zhang et al. 2008). Collectively, these studies suggest an important role of AMPK in controlling the growth processes in hypertrophy and in controlling cardiac energy metabolism.

Signaling pathways associated with processes contributing to cardiac pathology and transition to HF

Signaling via GPCR pathways

GPCRs are a family of transmembrane proteins activated by multiple factors which are typically elevated in settings of cardiac stress and HF. Signaling via GPCR occurs via the interaction of GPCR with heterotrimeric G proteins made up of three subunits, Gα (including $G\alpha_q$, $G\alpha_i$, $G\alpha_s$), Gβ and Gγ. In the heart, $G\alpha_q$ has been shown to play a major role in regulating pathological cardiac hypertrophy. Hormones/factors including Ang II, ET-1 and α-adrenergic agonists (e.g., noradrenaline) bind to GPCR [Ang II receptor type 1 (AT_1 receptor), endothelin receptors (ET_A and ET_B) and α_1-adrenergic receptors (ARs), respectively] and activate numerous downstream signaling proteins including phospholipase C (PLC), PKC and MAPKs (Bernardo et al. 2010) (Fig. 4). $G\alpha_q$ has also been associated with elevated CaMKII signaling as a consequence of increases in intracellular calcium (Anderson et al. 2011). The key role of $G\alpha_q$ in mediating maladaptive heart growth was demonstrated by studies in genetic mouse models. Mice with cardiac-specific overexpression of $G\alpha_q$ developed HF and died prematurely (D'Angelo et al. 1997; Mende et al. 1998). By contrast, reduced cardiomyocyte $G\alpha_{q/11}$ signaling was associated with an attenuated hypertrophic response in a setting of pressure overload (Wettschureck et al. 2001).

As discussed in a later section (see current pharmacological therapeutics targeting maladaptive processes associated with pathological cardiac hypertrophy and remodeling), current drug therapies including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and β-blockers target GPCR and the role of these receptors (e.g., Ang II receptors and β-ARs) in regulating pathological cardiac hypertrophy and maladaptive processes has been studied in animal models using genetic approaches and pharmacological agents. While it has been well demonstrated that treatment with ACE inhibitors attenuates pressure overload-induced cardiac hypertrophy in animal models (Lijnen and Petrov 1999; Modesti et al. 2000; Sadoshima et al. 1996; Yamazaki et al. 1999; Zhu et al. 1997), results from genetic models involving global or cardiac-specific overexpression/KO of the Ang II receptor isoforms AT_{1A}, AT_{1B} and AT_2 have been difficult to interpret. Some studies have suggested a role for specific Ang II receptor subtypes but others observed no clear phenotype. This may be due, in part, to compensation by other Ang II receptor subtypes and confounding factors such as differences in blood pressure (Bernardo et al. 2010).

ARs are activated by catecholamines and have previously been extensively studied and reviewed (Du 2008; O'Connell et al. 2014). ARs are broadly classified into three subfamilies: α_1-AR, α_2-AR and β-AR. Subtypes present within the heart which have been well characterized include α_{1A}, α_{1B}, α_{1D} (couple to $G\alpha_q$) and β_1, β_2 (couple to $G\alpha_i$ and/or $G\alpha_s$). β_1-AR represents the predominant isoform in the healthy heart (Xiang and Kobilka 2003). Human and mouse studies suggest that acute activation of β/β_1-AR may initially be adaptive because it increases contractility (Du

2008; Engelhardt et al. 1999; Lefkowitz et al. 2000; Rockman et al. 2002). However, chronic activation results in cardiac dysfunction and HF associated with desensitization and downregulation of β-ARs (Bristow 2000). The contribution of ARs in regulating cardiac hypertrophy and the transition to HF has previously been extensively reviewed (Du 2008). In brief, in a setting of pressure overload, β_1-AR and β_2-AR contribute to cardiac enlargement, α_{1B}-AR and β_2-AR contribute to the transition to HF, and α_{1A}-AR may play a protective role (Du 2008; Kiriazis et al. 2008).

PI3K (p110γ) signaling

In contrast to PI3K (p110α), PI3K (p110γ) is activated by GPCR pathways and negatively regulates cardiomyocyte contractility by modulating the activity of phosphodiesterases (PDEs) and cAMP (Patrucco et al. 2004) (Fig. 4). PI3K (p110γ) activity is enhanced in the murine heart in response to stress (Naga Prasad et al. 2000); however, the role of PI3K (p110γ) in the diseased heart is complex and it appears that the response differs depending on the pathological stress. Transgenic mouse models in which PI3K (p110γ) was depleted had enhanced basal contractility but increased susceptibility to pressure overload and ischemic myocardial injury (Crackower et al. 2002; Guo et al. 2010; Oudit and Kassiri 2007; Patrucco et al. 2004). However, these mice were protected from HF induced by isoproterenol, suggesting that PI3K (p110γ) contributes to pathological remodeling downstream of β-AR activation (Oudit et al. 2003). Similarly, mice expressing a kinase-dead mutant of PI3K (p110γ) or cardiac-specific overexpression of an inactive mutant displayed less hypertrophy and fibrosis than wild-type mice when subjected to pressure overload (Nienaber et al. 2003; Patrucco et al. 2004) or were protected from ischemia–reperfusion injury (Haubner et al. 2010). A more recent study has demonstrated that long-term inactivation of both PI3K (p110α) and PI3K (p110γ) in the mouse heart activates pathological remodeling resulting in cardiomyopathy (Zhabyeyev et al. 2014).

Maladaptive PKC isoforms: PKCα and PKCβ

As previously described, multiple PKC isoforms exist. PKCα and PKCβ are the two isoforms, which have been associated with maladaptive processes in the heart. PKCα and PKCβ expression is elevated in the human failing heart (Bowling et al. 1999). Genetic mouse studies suggest that PKCα contributes to contractile dysfunction (Braz et al. 2002, 2004; Hahn et al. 2003). PKCα overexpressing transgenic mice exhibited depressed contractile function, while PKCα null mice displayed improved cardiac contractility (Braz et al. 2004). Similar findings were observed when PKCα was modulated in cardiomyocytes using an adenoviral-mediated approach (overexpression of PKCα or dominant negative mutant) (Braz et al. 2004).

Increased activity of the PKCβ isoform has been shown to induce pathological heart growth. A number of groups found that cardiac-specific transgenic overexpression of PKCβ led to cardiac enlargement associated with dysfunction, fibrosis and premature death (Bowman et al. 1997; Chen et al. 2001; Wakasaki et al. 1997). However, while PKCβ is sufficient to induce maladaptive heart growth, it does not appear to be required. PKCβ-null mice displayed an equivalent hypertrophic response to aortic banding or phenylephrine infusion to that of wild-type mice (Roman et al. 2001). However, ruboxistaurin (a PKCβ inhibitor) was able to attenuate myocyte hypertrophy, fibrosis and diastolic dysfunction in a rat model of diabetic cardiomyopathy (Connelly et al. 2009).

Calcineurin and CaMK

Calcineurin and CaMKII are calcium-dependent signaling proteins, which have been proposed to play key roles in the development of cardiac hypertrophy and adverse remodeling.

Calcineurin dephosphorylates and induces the translocation of cytoplasmic NFAT to the nucleus. Subsequently in the nucleus, NFAT activates the transcription of pro-hypertrophic target genes (Bueno et al. 2002) (Fig. 4). Calcineurin activity was elevated in hearts from patients with HF and cardiac hypertrophy (Haq et al. 2001), and transgenic mice with cardiac expression of the activated from of calcineurin or NFAT3 developed severe pathological hypertrophy and HF (Molkentin et al. 1998). Furthermore, calcineurin inhibition in mice was shown to attenuate of pathological cardiac hypertrophy (Sussman et al. 1998).

CaMKII is a downstream signaling effector of Gq signaling and can also be activated by oxidative stress (Luczak and Anderson 2014). Of the four CaMKII isoforms (α, β, δ and γ), CaMKIIδc (a splice variant of CaMKIIδ) is the predominant isoform in the heart. Cardiac-specific transgenic overexpression of CaMKIIδc induced cardiac hypertrophy associated with dilatation of ventricular chambers and transitioned to HF (Zhang et al. 2003). In contrast, CaMKIIδ KO mice were protected against pressure overload-induced pathological hypertrophy and HF. These phenotypes closely resemble findings previously observed in $G\alpha_q$ transgenic mice and $G\alpha_{q/11}$ KO mice (D'Angelo et al. 1997; Wettschureck et al. 2001). It was recently demonstrated that CaMKIIδ plays a key role in contributing to mitochondrial dysfunction and the transition from hypertrophy to HF in a setting of increased Gq signaling (Westenbrink et al. 2015).

Recent studies have also uncovered new findings related to the role of calcineurin and CaMKII in the heart and

highlight complexities involving cross talk between CaMKII and calcineurin in some settings. For instance, in a setting of pressure overload and β-AR stimulation, mice lacking CaMKII δ and γ in cardiomyocytes were protected against cardiac dysfunction, fibrosis and transition to HF, but displayed a similar hypertrophic response to control mice. The favorable phenotype was attributed to inhibition of CaMKII-induced maladaptive remodeling and the induction of non-maladaptive growth by calcineurin–NFAT (Kreusser et al. 2014).

In another study, a new regulatory mechanism for calcineurin–NFAT signaling was identified. Interferon regulatory factor 8 (IRF8) is typically found to influence the innate immune response. IRF8 was decreased in hearts from patients with dilated/hypertrophic cardiomyopathy, and cardiac-specific overexpression of IRF8 in mice was protective against aortic banding. The authors provide mechanistic data to show that IRF8 interacts with NFAT to prevent nuclear translocation, thereby inhibiting the hypertrophic response. By contrast, in mice that lacked IRF8, the hypertrophic response to pressure overload was further exacerbated (Jiang et al. 2014).

HDACs

Histone deacetylases (HDACs) are chromatin-remodeling enzymes which have been well studied in the heart because they have been implicated in the re-expression of the fetal gene program which occurs in a setting of pathological hypertrophy (McKinsey et al. 2002). HDACs constitute a large family of enzymes that catalyze the removal of acetyl groups from lysine residues within histone and non-histone protein substrates (Choudhary et al. 2009). Histone deacetylation represses gene transcription by stabilizing the interaction between histones and DNA, leading to a more compact chromatin structure that is less accessible to components of the transcriptional machinery. The HDAC superfamily consists of four classes. Class I, II and IV HDACs are Zn^{2+}-dependent enzymes (Finnin et al. 1999; Lahm et al. 2007), while class III HDACs (also known as sirtuins) are an unrelated class of NAD-dependent deacetylases (Gregoretti et al. 2004; Landry et al. 2000). Class II HDACs can be further divided into two subclasses, class IIa and IIb. Compared with class I HDACs (HDAC1, 2, 3 and 8) and class IIb HDACs (HDAC6 and 10), class IIa HDACs (HDAC4, HDAC5, HDAC7 and HDAC9) have very low enzymatic activity (Bradner et al. 2010; Lahm et al. 2007) and repress gene transcription primarily via protein–protein interactions with transcription factors, such as members of the myocyte enhancer factor-2 (MEF2) family (Lu et al. 2000; Miska et al. 1999), and via the recruitment of class I HDACs and other co-repressors (Fischle et al. 2002; Hohl et al. 2013; Zhang et al. 2002b). Nucleo-cytoplasmic shuttling is a key mechanism regulating class IIa HDAC function (Grozinger and Schreiber 2000; Harrison et al. 2004; McKinsey et al. 2000a; Vega et al. 2004).

In contrast to 'pro-hypertrophic' class I HDACs, class IIa HDACs have been identified as negative regulators of cardiac hypertrophy, as genetic deletion of HDAC5 or HDAC9 in mice exacerbated the hypertrophic response to pressure overload and to transgenic expression of activated calcineurin (Chang et al. 2004; Zhang et al. 2002a). Interestingly, however, nuclear export (i.e., inactivation) of class IIa HDACs is required for cardiomyocyte hypertrophy in vitro (Harrison et al. 2004; Zhang et al. 2002a). Thus, it seems likely that dynamic regulation of class IIa HDACs is required to mount an appropriate hypertrophic response to hemodynamic overload. In this context, acute β-adrenergic stimulation leads to PKA-mediated cleavage of HDAC4, accumulation of the resulting N-terminal fragment in the nucleus and subsequent inhibition of MEF2 (Backs et al. 2011). This may be a protective mechanism to prevent pathological remodeling in response to transient elevations in catecholamines, which occur during exercise or in settings of acute stress (Backs et al. 2011).

Class IIa HDACs are subject to various posttranslational modifications, such as phosphorylation, oxidation and proteolytic cleavage (Weeks and Avkiran 2014). Among these, phosphorylation is the best studied. Phosphorylation of class IIa HDACs by CaMKII [following $InsP_3$-induced Ca^{2+} release from the nuclear envelope (Wu et al. 2006)] or PKD [downstream of PKC or following activation by diacylglycerol (DAG) at the plasma membrane (Bossuyt et al. 2011; Vega et al. 2004)] leads to association with 14-3-3 proteins and exclusion from the cell nucleus (McKinsey et al. 2000b). This, in turn, alleviates the repressive interaction of class IIa HDACs with transcription factors and allows the recruitment of other epigenetic regulators, such as histone acetyltransferases and histone demethylases, to gene promoter regions (Hohl et al. 2013; Wei et al. 2008).

Role of noncoding RNAs in regulating pathological hypertrophy and remodeling

Noncoding RNAs

Noncoding RNAs have emerged as new mediators in the pathophysiology of the heart. miRNAs and long noncoding RNAs (lncRNAs) have been implicated in multiple biological processes and diseases such as development, cell cycle, cancer, apoptosis and cardiovascular diseases (CVDs) (Batista and Chang 2013; Sayed and Abdellatif 2011). Protein-coding sequences constitute <2 % of the human genome, while the vast majority of the remaining sequences are transcribed as nonprotein-coding RNAs

in many cell types and tissues. Among noncoding RNAs, miRNAs and lncRNAs have received the most attention and will be the focus in this review.

MiRNAs

miRNAs are short single-stranded RNAs approximately 22 nucleotides in length. miRNAs are evolutionarily conserved and repress gene expression through base pairing to the 3′ untranslated region of target mRNA (leading to mRNA cleavage) and/or translational repression (Bernardo et al. 2012a; Olson 2014; Papoutsidakis et al. 2013). miRNAs can target single/multiple mRNAs and often act by suppression of functionally related gene networks.

The first miRNA (lin-4) was discovered to regulate the development of *Caenorhabditis elegans* almost 20 years ago (Lee et al. 2004; Wightman et al. 1993). In the heart, several studies highlight the importance of miRNAs. Mice with cardiac deletion of Dicer, the enzyme involved in miRNA processing, developed HF and died 4 days after birth (Chen et al. 2008). Targeted Dicer deletion in the postnatal myocardium (3- and 8-week-old mice) induced spontaneous adverse cardiac remodeling and activation of fetal cardiac genes (da Costa Martins et al. 2008). In addition to functional data, Thum et al. (2007) used genome-wide profiling and demonstrated similarities between miRNAs expressed in failing and fetal hearts. Thus, reactivation of a fetal miRNA program may regulate gene expression changes in the failing myocardium, which resembles the fetal heart.

Approximately 8 years ago, the first cardiac miRNA (miR-208) was discovered to regulate MHC gene expression and LV cardiac hypertrophy (van Rooij et al. 2007). Since then, there has been extensive research investigating the role of miRNAs regulating numerous processes associated with pathological cardiac remodeling in disease settings including cardiomyocyte hypertrophy, fibrosis, calcium handling and angiogenesis; refer to reviews (Kumarswamy and Thum 2013; Matkovich 2014; Olson 2014; Thum 2014). To name a few, multiple groups have shown that the expression of miR-24, miR-21 and miR-199a is upregulated in the LV of mice and human failing myocardium (Kumarswamy and Thum 2013; Small et al. 2010; van Rooij et al. 2006). In contrast, fewer studies have set out to identify changes in miRNAs during beneficial physiological heart growth or compensated hypertrophy (Da Silva Jr. et al. 2012; Lin et al. 2010; Ma et al. 2013; Ooi et al. 2014). Most miRNA studies have also focused on LV remodeling, and right ventricular failure remains understudied. Recently, an unbiased screening of miRNAs in a model of decompensated right ventricular hypertrophy showed decreased expression of miR-208a in the right myocardium (Paulin et al. 2015). This result highlights the distinct regulation of miR-208a expression in left and right ventricular remodeling and suggests that miRNAs may play different roles in different chambers of the heart. As miRNAs are aberrantly expressed in disease, many studies have demonstrated the therapeutic potential of targeting stress induced miRNAs using miRNA inhibitors/mimics in preclinical models of HF (van Rooij et al. 2012) (discussed further in the section on miRNA-based therapeutics).

The role of circulating miRNAs has also received considerable attention because they have been detected in serum and plasma of animals and patients with failing hearts, opening the possibility of using miRNAs as biomarkers of disease states (Creemers et al. 2012). Despite the existence of ribonucleases, extracellular miRNAs remain stable in body fluids due to loading of the miRNAs into proteins, lipids or lipoprotein complexes such as exosomes or microvesicles (Creemers et al. 2012; Olson 2014). The levels of plasma miR-208b and miR-499 (cardiac-specific miRNAs) were present after cardiac stress, suggesting that these miRNAs are specifically released from the heart after myocardial injury (Gidlof et al. 2013). In another study, the increase in circulating miR-208 levels in patients with cardiac injury was consistent with the time course elevation of cardiac troponin 1 levels, the gold standard for the diagnosis of myocardial injury (Ji et al. 2009).

LncRNAs

Up until approximately 2 years ago, research had largely focused on the role of miRNAs in settings of cardiac disease. In 2013, a novel lncRNA, Braveheart, was identified to regulate cardiac development (Klattenhoff et al. 2013). This study underscores the significance of other noncoding RNAs in the heart, and since then, many more lncRNAs have been shown to play roles in heart physiology and disease.

LncRNAs are defined as RNA transcripts larger than 200 nucleotides with no evidence of protein-coding function. The term lncRNA is a broad definition that includes intergenic sequences, transcripts that overlap with other coding regions in either sense or antisense orientation, and enhancer RNAs (Batista and Chang 2013; Orom and Shiekhattar 2013). Several studies have shown that lncRNA expression is more cell type specific than protein-coding genes (Cabili et al. 2011; Ravasi et al. 2006), suggesting that lncRNAs can play a regulatory role. Unlike miRNAs, the mechanism of lncRNA gene regulation involves both activation and inhibition of mRNA expression, as well as regulation of chromatin architecture (Batista and Chang 2013; Mercer and Mattick 2013). The precise mechanism of lncRNA action has not been fully elucidated. LncRNA can act locally (in cis) to regulate the expression

of neighboring genes or distally (in trans) to influence the expression across multiple chromosomes (Batista and Chang 2013). In addition, they can also interact with proteins (to form scaffolds) and miRNAs (competing endogenous RNA) for an additional level of transcription regulation (Batista and Chang 2013; Mercer and Mattick 2013).

Several recent studies have profiled lncRNAs in human patients with HF (Yang et al. 2014) and mouse models of MI (Ounzain et al. 2015; Zangrando et al. 2014). Using RNA profiling, approximately 500–700 lncRNAs were dynamically regulated in the LV tissue of patients with HF, and 10 % of these transcripts were normalized after LV assisted implantation (Yang et al. 2014). This study suggests that lncRNAs not only play a role in the pathogenesis of HF but also in reverse remodeling. The lncRNAs and myocardial infarction-associated transcripts 1 and 2 (MIRT1, MIRT2) are upregulated, while novel lncRNA Novlnc6 expression is decreased in the hearts of mice with MI (Ounzain et al. 2015; Zangrando et al. 2014). Ounzain et al. (2015) extended their murine genome-wide studies to validate human orthologues in patient samples. The levels of Novlnc66 and Novlnc44 were reduced in patients with heart pathologies.

The mechanistic function of lncRNA in the heart is still unclear. LncRNAs have been reported to function as a sponge/sink for miRNA and chromatin-remodeling proteins (Han et al. 2014; Wang et al. 2014). Cardiac hypertrophy-related factor (CHRF) sequesters miR-489, therefore inhibiting its ability to repress the expression of its target mRNA, Myd88. Downregulation of Myd88 expression led to cardiomyocyte hypertrophy (Wang et al. 2014). The expression of MHC-associated RNA transcript (Myheart or Mhrt) was downregulated in response to a cardiac stress (Hang et al. 2010), and restoring Mhrt levels in vivo was cardioprotective (Han et al. 2014). Mhrt antagonizes the role of Brg1 (an ATP-dependent chromatin remodeler), preventing recognition of genomic DNA targets and pathological gene activation of MHC (Han et al. 2014). These studies uncovered a novel hypertrophic mechanism, comprising the interplay between lncRNAs and miRNAs or nucleosome remodeling, acting on hypertrophic gene expression.

Similar to miRNAs, lncRNAs are also detected in body fluids and may serve as biomarkers for CVDs. During a screen for lncRNA in plasma of patients with MI, the investigators reported the circulating mitochondrial long noncoding RNA uc022bqs.1, LIPCAR, as a predictor for survival in patients with HF (Kumarswamy et al. 2014). In an independent study, the group took another approach to analyze lncRNA in whole blood of patients with MI and identified increased levels of hypoxia-inducible factor 1A antisense RNA 2 (aHIF), potassium voltage-gated channel KQT-like subfamily member 1 opposite strand/antisense transcript 1 (KCNQ1OT1), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and decreased levels of cyclin-dependent kinase inhibitor 2B antisense RNA 1 (ANRIL) (Vausort et al. 2014). Using multivariable and reclassification analyses, ANRIL and KCNQ1OT1 were found to improve prediction of LV dysfunction after MI (Vausort et al. 2014).

LncRNA research is still at its infancy, and future studies will help us understand the role and molecular mechanisms of these noncoding RNAs in the diseased heart. Next-generation sequencing studies suggest that lncRNAs are highly tissue specific and implies that heart-specific lncRNAs have potential therapeutic possibilities as targeting molecules in CVDs, similar to miRNAs.

A list of miRNAs studied in settings of cardiac disease has previously been well summarized (Kumarswamy and Thum 2013; Olson 2014). Here, we provide a list of lncRNAs studied in cardiac hypertrophy and HF (Table 1).

Current pharmacological therapeutics targeting maladaptive processes associated with pathological cardiac hypertrophy and remodeling

Treatment options for HF include pharmacologic therapy, lifestyle modifications (e.g., exercise), implantable devices and surgery. The overall goal of HF therapy is to relieve symptoms, decrease hospitalization rates and prevent premature death. Regular physical activity has been shown to improve the quality of life in patients with stable chronic HF, reverse pathological remodeling and improve heart function of patients with systolic HF, although patient non-adherence remains a major challenge (reviewed in De Maeyer et al. 2013; Piña et al. 2003; Wisloff et al. 2007). Implantable devices such as cardioverter defibrillators and LV assist devices have been shown to reduce the risk of sudden death or improve survival, but limited economic resources affect the usage of device therapy (reviewed in McMurray 2010). Although cardiac transplantation has been shown to prolong survival and improve quality of life in patients with end stage HF (Augoustides and Riha 2009), it is limited by insufficient donor organs and contraindications, as well as other barriers including socioeconomic factors, financial resources and is limited to a small number of patients (Fischer and Glas 2013). Drug therapy is more widely available, mainly due to its lower cost. Here, we review current pharmacological therapeutics commonly prescribed to patients with HF and the mechanisms via which they act.

ACE inhibitors

ACE inhibitors are a well-established pharmacotherapy for the treatment of hypertension and HF. ACE inhibitors

Table 1 List of lncRNAs studied so far in CVDs

LncRNA	Key observation	References
CHRF	Upregulated in cardiomyocytes in response to Ang II stimulation	Wang et al. (2014)
Mhrt	Downregulated in response to pressure overload in mice Downregulated in patients with hypertrophic, ischemic or idiopathic cardiomyopathy Cardiac-specific Mhrt transgenic mice were protected from pressure overload-induced cardiac hypertrophy	Han et al. (2010, 2014)
Novlnc6	Downregulated with MI in mice Downregulated in patients with dilated cardiomyopathy	Ounzain et al. (2015)
Novlnc44	Downregulated in patients with aortic stenosis	Ounzain et al. (2015)
MIRT1	Upregulated with MI in mice	Zangrando et al. (2014)
MIRT2	Upregulated with MI in mice	Zangrando et al. (2014)
LIPCAR (circulation)	Downregulated early but upregulated during later stages in patients with MI	Kumarswamy et al. (2014)
aHIF (circulation)	Upregulated in patients with MI	Vausort et al. (2014)
KCNQ1OT1 (circulation)	Upregulated in patients with MI	Vausort et al. (2014)
MALAT1 (circulation)	Upregulated in patients with MI	Vausort et al. (2014)
ANRIL (circulation)	Downregulated in patients with MI	Vausort et al. (2014)

prevent the formation of Ang II and reduce pathological signaling through the AT_1 receptor (Fig. 5). This causes relaxation of blood vessels, facilitation of salt and water excretion, and thus, subsequent lowering of blood pressure (Sweitzer 2003). ACE inhibitors improve symptoms of HF, improve heart function, decrease admissions to hospital and enable patients to live longer. These benefits were seen in patients irrespective of the severity of HF symptoms and in patients with or without coronary artery disease (CONSENSUS Trial Study Group 1987; SOLVD Investigators 1991). In addition, ACE inhibitor therapy has been shown to reduce the risk of MI and decrease the risk of asymptomatic patients with LV dysfunction later developing symptoms of HF (AIRE Investigators 1993; Pfeffer et al. 1992; SOLVD Investigators 1992).

The efficacy of ARBs is similar to that of ACE inhibitors and is used in HF patients who are ACE inhibitor intolerant or those that develop a cough as a result of ACE inhibitor therapy (McMurray 2010; Yancy et al. 2013). More recently, the dual angiotensin–neprilysin receptor inhibitor has been shown to be more effective than the current standard treatment (the ACE inhibitor enalapril) at preventing the progression of HF (McMurray et al. 2014; Packer et al. 2015). This dual inhibitor targets both neurohormonal systems by preventing peptide degradation (e.g., natriuretic, bradykinin, adrenomedullin that mediate beneficial cardiorenal effects and are impaired in HF), while concomitantly blocking the AT_1 receptor (Langenickel and Dole 2012). ACE inhibitors and ARBs may have a direct effect on heart growth via inhibition of AT_1 receptors (as discussed earlier in section on signaling via GPCR pathways). Therefore, ACE inhibitors and ARBs are important components of standard HF therapy in patients with HF.

β-Blockers

β-Blockers are administered to control HF symptoms (such as shortness of breath or weakness), which occur due to the release of catecholamines (Fig. 5). β-Blockers may work by slowing heart rate, thus allowing the chambers of the heart to fill more effectively and improve function of the heart, and also by decreasing blood pressure by dilating blood vessels (Frishman 2003).

β-Blockers are often used in conjunction with ACE inhibitors and have been shown to be effective for treating most people who have HF. Evidence from clinical trials shows that β-blocker therapy can improve cardiac function, decrease hospitalization, reduce symptoms and reduce the risk of death in patients with HF (CIBIS-II Investigators 1999; MERIT-HR Study Group 1999; Packer et al. 2001).

MRAs

Mineralocorticoid receptor activation in the heart drives cardiac fibrosis and inflammation, which leads to HF (Bienvenu et al. 2013; Young 2013). Thus, mineralocorticoid receptor blockade in the heart represents an attractive therapeutic option for the treatment of HF (Fig. 5). Mineralocorticoid receptor antagonists (MRAs) are prescribed in addition to ACE inhibitors, ARBs and β-blockers. Several randomized controlled clinical trials have demonstrated the benefits of MRA therapy. The first MRA developed was spironolactone and was shown to reduce hospitalization and total mortality in patients with severe HF (Pitt et al. 1999). Subsequently, the more selective MRA eplerenone significantly reduced mortality, morbidity and had fewer hospitalizations in a wider range of HF patients (e.g., patients with mild HF or acute MI complicated by HF) (Pitt

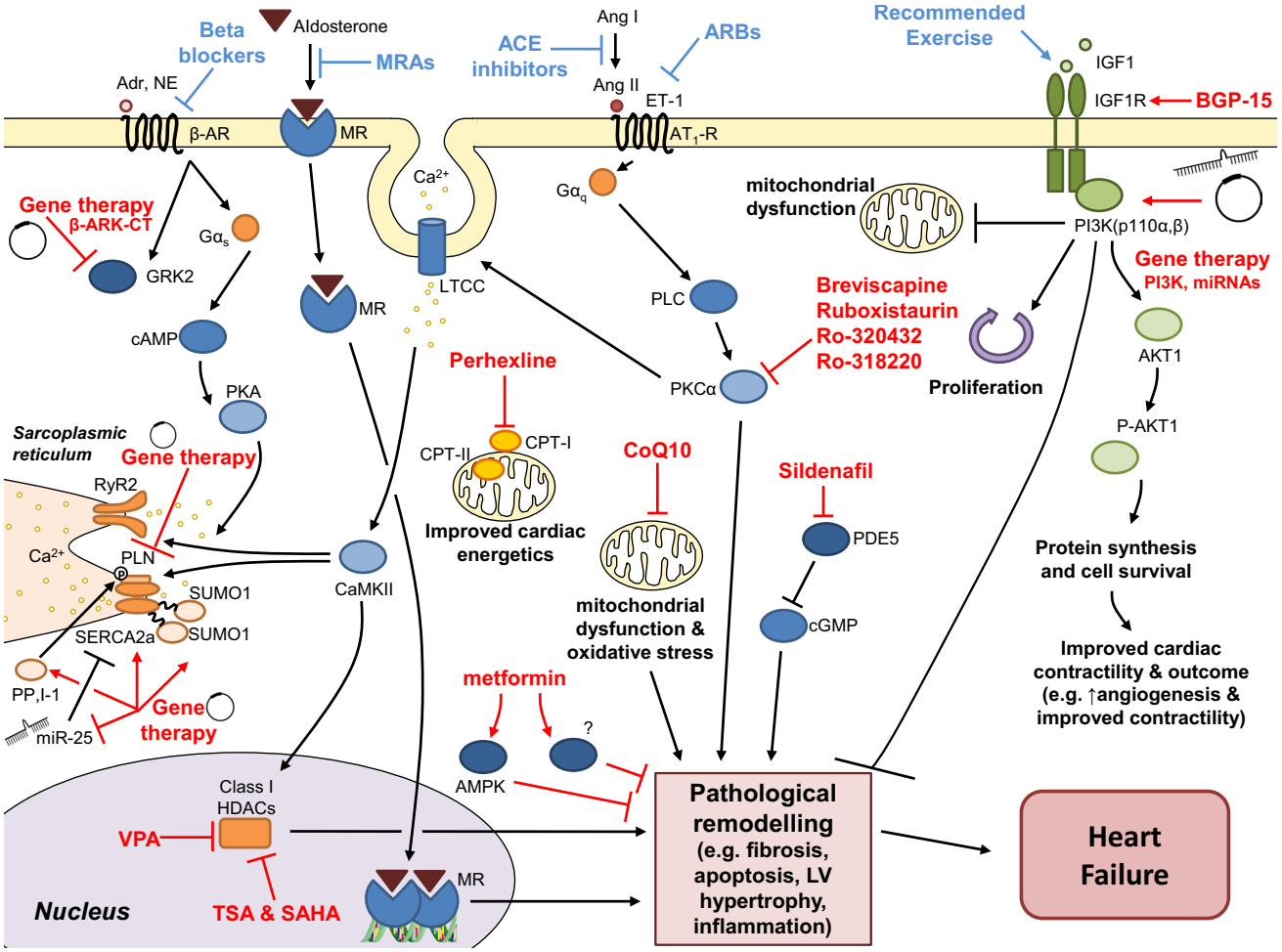

Fig. 5 Drug therapies for the treatment of heart failure. Current drug therapies commonly prescribed for the treatment of heart failure (*blue text*) and new therapies that hold promise for the treatment of heart failure (gene technology, microRNA inhibitors or small molecules) that are in preclinical or clinical development (*red text*). *ACE* Angiotensin II converting enzyme, *Adr* adrenaline, *AMPK* adenosine monophosphate-activated protein kinase, *Ang* angiotensin I, II, *ARBs* angiotensin receptor blockers, *AT-R* angiotensin type receptor, *β-AR* beta-adrenergic receptor, *CaMK* calcium-/calmodulin-dependent protein kinase, *cGMP* cyclic guanosine monophosphate, *CoQ10* coenzyme Q_{10}, *CPT* carnitine palmitoyltransferase, *ET-1* endothelin-1, *GRK* G protein-coupled receptor kinase, *HDAC* histone deacetylase, *I-1* inhibitor-1 of PP1, *IGF1* insulin like growth factor 1, *IGF1R* IGF1 receptor, *LTCC* L-type Ca^{2+} channels, *LV* left ventricular, *miRNAs, miR* microRNA, *MRAs* mineralocorticoid receptor antagonists, *NE* noradrenaline, norepinephrine, *PDE* phosphodiesterase, *PI3K* phosphoinositide 3-kinase, *PKA* protein kinase A, *PKC* protein kinase C, *PLC* phospholipase C, *PLN* phospholamban, *PP* protein phosphatase, *RyR2* type 2 ryanodine receptors, *SAHA* suberoylanilide hydroxamic acid, *SERCA2a* sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2a, *SUMO* small ubiquitin-like modifier, *TSA* trichostatin A, *VPA* valproic acid

et al. 2003; Zannad et al. 2011). The improved outcomes may be due to alteration of renal sodium or potassium handling, and beneficial effects on cardiac ECM remodeling (Leopold 2011).

Diuretics for the relief of HF symptoms

Diuretics remain a major component of drug therapy in both hypertension and HF; however, diuretics only relieve symptoms and are combined with an ACE inhibitor, β-blocker or MRA. Diuretics provide rapid relief of fluid retention and shortness of breath, but the effect of diuretics on morbidity and mortality is not known (Yancy et al. 2013). Common side effects associated with the use of diuretics include hypotension, electrolyte depletion and resistance, and some patients display adverse outcomes to diuretics (ter Maaten et al. 2015).

Limitations/risks of current therapies

The use of current pharmacological agents mentioned above largely slow down the progression of the disease; however, mortality remains high. While these medications are generally well tolerated and have been used in patients

for a few decades, it is not uncommon for patients to experience adverse side effects. ACE inhibitors can lower blood pressure, and thus, lightheadedness and dizziness may result if blood pressure becomes too low. However, the most common side effect is an ACE inhibitor-induced cough, experienced by 15–20 % of patients (Sweitzer 2003; Yancy et al. 2013). Possible side effects for patients on β-blockers include fluid retention, bradycardia, fatigue and worsening HF during initiation of treatment (Frishman 2003; Yancy et al. 2013), and the major risk associated with MRA use is hyperkalemia (Maron and Leopold 2010; Yancy et al. 2013). Comorbidity is an increasing problem as many HF patients commonly present with comorbidities such as chronic kidney disease, hypertension, diabetes, osteoarthritis, depression and anemia. This increases the potential for drug intolerance and incompatibility limiting the effectiveness of proven treatments (McMurray and Pfeffer 2005).

New pharmacological therapies in clinical trials

Cardiac energetic impairment is a common feature of HF and is associated with decreased myocardial PCr: ATP ratio (Neubauer 2007; Taha and Lopaschuk 2007). Current pharmacotherapies (e.g., ACE inhibitors, β-blockers) do not directly affect energy metabolism; thus, metabolic intervention for HF represents a promising therapeutic prospect. Perhexiline inhibits carnitine palmitoyltransferase I (CPT I) and CPT II, thereby shifting substrate utilization to more efficient carbohydrate metabolism (Fig. 5) (Ashrafian et al. 2007; Jeffrey et al. 1995). Results from clinical trials with perhexiline have been encouraging. Treatment with perhexiline in patients with chronic HF led to significant improvements in aerobic capacity (i.e., VO_{2max}), cardiac function and quality of life (Lee et al. 2005). A separate study conducted in hypertrophic cardiomyopathy patients demonstrated that perhexiline increased the myocardial PCr:ATP ratio (i.e., improved cardiac energy metabolism) and increased exercise capacity (Abozguia et al. 2010). Side effects in these studies were limited to dizziness and nausea (Abozguia et al. 2010; Lee et al. 2005). Thus, perhexiline represents a promising treatment targeting cardiac energetics, which can be extended to other cardiac disorders that have metabolic and energetic dysfunction (e.g., diabetic cardiomyopathy). However, extensive clinical trials will need to be conducted to assess the efficacy of perhexiline, especially effects of long-term use.

The risk of developing HF is greater in diabetic patients than nondiabetic patients (Huynh et al. 2014). Metformin, an antidiabetic drug, has been shown to reduce mortality and morbidity of type 2 diabetic patients with CVD and is associated with better prognosis when compared to other antidiabetic treatments in diabetic patients with chronic HF (Eurich et al. 2013). Metformin is currently recommended as the first drug of therapy for diabetic patients with HF; however, more clinical trials are required to investigate the full cardioprotective effects and safety of metformin (Foretz et al. 2014). Studies in HF mouse models suggest that metformin protects against adverse cardiac remodeling, although the precise mechanism by which metformin exerts these cardioprotective effects remains unclear, whether it is dependent or independent of the AMPK pathway (Gundewar et al. 2009; Kim and Dyck 2015; Xu et al. 2014) (Fig. 5).

Therapeutic agents that target mitochondrial dysfunction and oxidative stress (two processes that have a role in the pathophysiology of cardiac remodeling and HF) are currently being explored. Coenzyme Q_{10} (CoQ_{10}) is an antioxidant and a cofactor for mitochondrial energy production, and is thought to target oxidative stress and mitochondrial dysfunction. A recent clinical trial suggested that long-term CoQ_{10} treatment (in addition to standard therapy) of patients with chronic HF was safe, improved symptoms and reduced adverse cardiovascular events (Mortensen et al. 2014) (Fig. 5). Despite the limitations of this study (e.g., low study population and long duration), a larger clinical trial is required to establish safety and efficacy before the use of CoQ_{10} can be recommended to patients with chronic HF (Okonko and Shah 2015).

New therapeutic strategies to promote adaptive processes and restore heart function

Targeting the adaptive phosphoinositide 3-kinase pathway as a novel therapeutic approach

PI3K (p110α) is activated in the heart during exercise (Perrino et al. 2006) and is critical for postnatal heart growth and exercise-induced physiological hypertrophy (McMullen et al. 2003; Shioi et al. 2000). Activation of PI3K (p110α) in the heart (utilizing cardiac-specific transgenic mouse models with increased or decreased PI3K activity) has demonstrated that PI3K (p110α) protects the heart against cardiac dysfunction and adverse cardiac remodeling. Mice with increased PI3K (p110α) activity had better cardiac function or lifespan in a setting of MI (Lin et al. 2010), pressure overload (McMullen et al. 2007) or dilated cardiomyopathy (McMullen et al. 2007); reduced atrial fibrosis and improved cardiac conduction in atrial fibrillation (AF) (Pretorius et al. 2009); and was associated with no apoptosis or superoxide generation thus preventing diabetes-induced cardiomyopathy (Ritchie et al. 2012). While these studies indicate a role of PI3K (p110α) in mediating cardiac protection, increased PI3K activity is

an important and a common contributor to tumorigenesis and cancer progression (Fruman and Rommel 2014). Thus, we recently employed a gene therapy approach (recombinant adeno-associated viral vectors) to deliver PI3K (p110α) specifically to hearts of adult mice with established cardiac dysfunction caused by pressure overload. We showed that muscle-specific delivery of PI3K (p110α) was able to improve function of the failing heart, without any transgene expression observed in other tissues (Weeks et al. 2012) (Fig. 5). More recently, it was demonstrated that AAV9:Pik3cb (p110β isoform of PI3K) acts downstream of Yes-associated protein (YAP) (nuclear effector of the Hippo cascade) to regulate Pik3ca (p110α isoform of PI3K), Akt and p27 in the heart. AAV9:Pik3cb in the mouse MI model promoted cardiomyocyte survival after MI (Lin et al. 2015).

Therapies that correct abnormal calcium handling in HF

Calcium is essential in the control of contractile function and cardiac growth, and regulating excitation–contraction coupling. Abnormal handling of calcium ions by cardiomyocytes is a key pathophysiological mechanism in HF (Lou et al. 2012). As described previously (see section on calcium handling), the SERCA2a pump is responsible for calcium re-uptake during excitation–contraction coupling, and is regulated by PLN. Diminished reuptake of calcium in the failing heart is due to decreased SERCA2a activity and decreased PLN phosphorylation. The importance of SERCA2a has been reflected in numerous studies that demonstrate reduced SERCA2a activity and expression in HF animal models (Kawase et al. 2008; Kiss et al. 1995) and in the human failing myocardium (Hasenfuss et al. 1994). Thus, therapies that can normalize cardiac SERCA2a activity and/or expression are being actively explored. Results from preclinical HF models have convincingly shown significant improvement in cardiac function and remodeling as a consequence of overexpression of SERCA2a using adenoviral vectors (Byrne et al. 2008; Kawase et al. 2008; Miyamoto et al. 2000). Following this, gene therapy clinical trials have been designed to increase SERCA2a in the myocardium of patients with HF using recombinant adeno-associated viral vectors (Greenberg et al. 2014; Hajjar et al. 2008; Jaski et al. 2009; Jessup et al. 2011; Zsebo et al. 2014) (Fig. 5). Results from early clinical trials indicated that intracoronary infusion of an AAV carrying the SERCA2a gene was able to increase SERCA2a protein levels, was safe and improved cardiac function (Jaski et al. 2009), and after a 12 month follow-up, patients with advanced HF displayed improved signs and symptoms of HF and cardiac function (Jessup et al. 2011). More importantly, after a 3-year follow-up and long-term treatment of AAV-SERCA2a, no adverse events in patients with HF were reported, and SERCA2a vector sequences were present in cardiac tissues from patients for at least 31 months (Zsebo et al. 2014). A phase 2b clinical trial is underway which will evaluate whether increasing SERCA2a activity by AAV improves clinical outcome in patients with moderate to severe HF (Greenberg et al. 2014). In addition, reducing the inhibitory effects of PLN on SERCA2a activity via AAV- or adenoviral-mediated delivery of a pseudophosphorylated mutant of PLN has also been shown to improve cardiac contractility in hamster and sheep models of HF, respectively (Hoshijima et al. 2002; Kaye et al. 2007). PLN activity is also regulated by the inhibitor-1 of PP1 (I-1) (Kranias and Hajjar 2012) (Fig. 5). Studies have demonstrated that activating the expression of the inhibitor I-1c using an AAV gene therapy approach enhanced PLN phosphorylation, improved contractility and decreased fibrosis in murine and porcine models of HF (Pathak et al. 2005; Fish et al. 2013; Ishikawa et al. 2014) (Fig. 5).

An alternate way that SERCA2a activity can be manipulated is through modification of small ubiquitin-like modifier-1 (SUMO1), which is required for preserving SERCA2a function by SUMOylation (Fig. 5). SUMO1 protein expression is decreased in experimental models of HF and in cardiomyocytes isolated from failing human hearts (Kho et al. 2011). Studies in a murine model of HF induced by TAC demonstrated that cardiac restoration of the SUMO1 gene using AAV gene therapy was able to improve cardiac function, reduce mortality and prevent TAC-induced cardiac hypertrophy (Kho et al. 2011). Further investigation in a swine ischemia–reperfusion HF model demonstrated that SUMO1 gene therapy improved cardiac contractility and restored SERCA2a protein levels (Tilemann et al. 2013). Additional studies are required to determine the precise mechanism of how SUMO1 treatment exerts beneficial cardiac effects, but these results demonstrate a new strategy for the treatment of HF that can be further explored.

Targeting cardiac β-adrenergic signaling through GRK2 inhibition as a novel HF therapy

G protein-coupled receptor kinase 2 (GRK2) is upregulated in HF and regulates β-ARs. In the stressed heart, GRK2 initiates the deactivation and down-regulation of β-ARs, ultimately impairing myocardial contractility (Cannavo et al. 2013; Woodall et al. 2014). Studies performed in animal models of HF have demonstrated that lowering GRK2 could be of therapeutic benefit. Cardiac-specific deletion of GRK2 in mice following MI increased survival, reversed ventricular remodeling and enhanced cardiac function (Raake et al. 2008). Furthermore, transgenic or AAV expression of β-ARKct, a small peptide inhibitor of GRK2, in different preclinical models of HF, has been shown to improve functional and morphological parameters

of the failing heart (Brinks et al. 2010; Raake et al. 2013; Rengo et al. 2009; Shah et al. 2001; White et al. 2000) (Fig. 5). These studies demonstrate the clinical potential of βARKct-mediated gene therapy, and phase I clinical trials are being planned (Cannavo et al. 2013).

PKC inhibitors

PKC isoforms regulate a number of cardiac responses, including those associated with HF (reviewed in Liu and Molkentin 2011; Palaniyandi et al. 2009). Pharmacological inhibition of PKCα with either breviscapine, ruboxistaurin, Ro-320432 or Ro-318220 enhanced cardiac contractility, reduced mortality and improved cardiac pathology in multiple rodent models of heart disease, providing good evidence that inhibition of PKCα protects the heart following injury (see reviews Dhalla and Müller 2010; Liu and Molkentin 2011; van Berlo et al. 2013) (Fig. 5). These findings were supported in a larger animal model where ruboxistaurin treatment improved cardiac function and attenuated HF in pigs following MI (Ladage et al. 2011). Although ruboxistaurin has been used in clinical trials in patients with diabetic retinopathy (Aiello et al. 2011; Sheetz et al. 2011), its efficacy has not yet been evaluated in HF patients.

HDAC inhibitors

Both class I and class IIa HDACs have been identified as important regulators of cardiac remodeling and potential therapeutic targets for the treatment of HF (Lehmann et al. 2014; McKinsey 2011; Xie and Hill 2013) (Fig. 5). Administration of pan-HDAC inhibitors, such as trichostatin A (TSA) or valproic acid, has been shown to prevent, attenuate and even reverse LV hypertrophy in rodents subjected to aortic banding or chronic infusion with hypertrophic agonists such as Ang II or isoprenaline (Kee et al. 2006; Kong et al. 2006; Kook et al. 2003). HDAC inhibitors are also anti-fibrotic, reducing interstitial collagen deposition in spontaneously hypertensive and DOCA-salt hypertensive rats (Cardinale et al. 2010; Iyer et al. 2010; Kee et al. 2013). In a recent preclinical study, administration of suberoylanilide hydroxamic acid (SAHA), an HDAC inhibitor that has been approved by the US Food and Drug Administration for the treatment of cutaneous T cell lymphoma, reduced infarct size and improved systolic function in rabbits subjected to ischemia–reperfusion injury (Xie et al. 2014). As many HDAC inhibitors function by chelating the Zn^{2+} ion required for catalytic activity (Finnin et al. 1999), and class IIa HDACs have negligible deacetylase activity in vivo (Lahm et al. 2007), the cardioprotective effects of pan-HDAC inhibitors such as TSA and SAHA have been attributed to inhibition of class I and IIb isoforms. The development of class- and isoform-selective HDAC inhibitors has helped to elucidate which isoforms are responsible for mediating pathological processes such as fibrosis (Williams et al. 2014), and may be less toxic than pan-HDACs in clinical settings (McKinsey 2011).

RNA based therapies

ShRNA

RNA interference (RNAi) is a sequence-specific gene silencing event mediated by double-stranded RNA. The most common form of RNAi application is the introduction of a synthetic short hairpin RNA (shRNA) that binds with perfect sequence complementarity to the target gene and directs mRNA cleavage of the gene of interest. A number of studies have used AAV technology to deliver shRNA in vivo. There are numerous serotypes of AAV depending on the different cellular receptors that each AAV interacts with and the natural tropism of each individual AAV toward different organs (Asokan et al. 2012). AAV type 6 and type 9 display preferential tropism for skeletal muscle and heart when delivered systemically in rodents (Bish et al. 2008; Gregorevic et al. 2004). In the heart, AAV shRNA vectors have been used to successfully silence PLN in a HF model in rats (Suckau et al. 2009) and sheep (Kaye et al. 2007) (Fig. 5). Silencing of PLN attenuated preexisting cardiac hypertrophy, cardiomyocyte diameter and reduced cardiac fibrosis (Kaye et al. 2007; Suckau et al. 2009).

MiRNAs

The expression and function of miRNAs can be pharmacologically manipulated through systemic or local delivery of miRNA mimics (to elevate expression of beneficial miRNAs) or anti-miRs (inhibition to block the binding of miRNA to their target mRNAs) (Olson 2014; Ooi et al. 2014; van Rooij et al. 2012). To enhance cellular uptake and stability, anti-miRs are subjected to chemical modifications such as covalent attachment of cholesterol and locked nucleic acid (LNA) modification. While much of the research in the field has focused on anti-miR therapy, data on miRNA mimics have been lacking as miRNA mimics do not tolerate chemical modifications well (Olson 2014). The first miRNA-based therapy that has been successfully translated from animal studies and reached the clinic is miravirsen, a miR-122 LNA inhibitor to treat hepatitis C in a Phase IIa clinical trial (Janssen et al. 2013). Results from the clinical trial indicate that the drug was effective, well tolerated in patients and the inhibition sustained after termination of drug treatment (Janssen et al. 2013).

Although miRNA-based therapies have not reached clinical trials for CVDs, inhibition of miRNAs by

LNA-anti-miRs has shown promising results in preclinical models of cardiac pathology/HF with effective long-term silencing and no evidence of toxicity (Bernardo et al. 2012b, 2014a, b; Montgomery et al. 2011; Wahlquist et al. 2014). Here, we present some examples of miRNAs (miR-34a/miR-34 family, miR-652, miR-208a and miR-25) that have been successfully targeted in preclinical animal studies. We targeted miR-34a/miR-34 family (miR-34a, miR-34b, miR-34c) and miR-652 because these miRNAs were distinctly regulated in settings of adaptive/physiological and pathological heart growth, i.e., decreased in a setting of increased PI3K (110α) signaling associated with physiological hypertrophy and increased in a setting cardiac stress (Bernardo et al. 2012b, 2014b; Lin et al. 2010) (Fig. 5). Inhibition of miR-34a and miR-652 was beneficial in a setting of moderate pressure overload, with favorable effects on heart size, fibrosis and function (Bernardo et al. 2012b, 2014a, b). Boon and colleagues also demonstrated that following acute MI, inhibition of miR-34a reduced apoptosis and fibrosis as well as improved recovery (Boon et al. 2013). However, interestingly, inhibition of miR-34a alone was unable to provide significant protection in models of severe pressure overload or established MI (Bernardo et al. 2012b, 2014a). Collectively, this suggests that it may be necessary to target a larger panel of miRNAs in more severe disease settings. More recently, miRNAs regulated by TH which also induces hypertrophy resembling physiological hypertrophy were identified. Targets of the TH-dependent miRNAs are predicted to enhance physiological signaling and suppress pathological signaling (Janssen et al. 2014). Thus, regulation of TH-dependent miRNAs may represent a future therapeutic approach. Other studies have targeted miRNAs that target genes associated with cardiac contractile function (e.g., miR-208a targets MHC) and calcium handling (miR-25 targets SERCA2a) (Montgomery et al. 2011; Wahlquist et al. 2014). Silencing of miR-208a prevented cardiac remodeling and cardiac dysfunction, as well as prolonged survival in hypertension-induced HF rats (Montgomery et al. 2011). As noted earlier, restoration of SERCA2a levels via gene therapy improved cardiac function during HF. MiR-25 was identified as a repressor for SERCA2a expression. Increasing levels of miR-25 in vivo was associated with downregulation of SERCA2a activity and declining contractile function (Fig. 5). Meanwhile, inhibition of miR-25 restored SERCA2a activity, attenuated cardiac remodeling and improved cardiac contractility, function and survival in a mouse model of pressure overload (Wahlquist et al. 2014).

Since most miRNAs are ubiquitously expressed, and miRNA-based therapies are taken up by multiple organs upon delivery, AAV vectors have been combined with miRNA-based therapies for tissue-selective delivery. This approach allows investigators to enhance miRNA function or replace miRNAs that are downregulated in preclinical models of cardiac diseases (Ganesan et al. 2013; Wahlquist et al. 2014). AAV delivery of RNAi provides temporal control over gene knockdown and is less subject to compensatory mechanisms that may develop over generations of selection in KO mice (Mingozzi and High 2011). The safety and efficacy of AAV-based delivery in clinical trials are promising, though this approach requires further development of strategies to overcome immune responses (Mingozzi and High 2013).

LncRNA

LncRNA research is still in its infancy, and few studies have explored the potential of targeting lncRNAs as therapies for diseases. A study in 2014 reported that lncRNAs can be inhibited by small interfering RNAs in vitro and LNA gapmers (DNA oligonucleotides with LNA residues at the 3′ and 5′ end which induce RNas-H-mediated degradation of nuclear lncRNA) in vivo (Michalik et al. 2014). The investigators inhibited the expression of MALAT1 and reported impaired endothelial cell proliferation and retinal vessel growth in vitro (VEGF-stimulated angiogenesis in endothelial cells) and in vivo (mice with hindlimb ischemia) (Michalik et al. 2014).

Synthetic chemically modRNA

Modified mRNA (modRNA) is a relatively new approach in which one or more nucleotides within an mRNA are replaced by modified nucleotides (Chien et al. 2014). The modification of nucleotides overcomes the issue of potential immune responses, which can be encountered with AAVs. The modification of nucleotides leads to a change in the secondary structure of the mRNA, escaping detection by the innate immune response but still being efficiently expressed. ModRNA technology is currently a gain-of-function approach for short-term, localized expression. In vivo studies in the mouse heart showed peak expression at approximately 8 h after injection with little expression after 72 h (Chien et al. 2014). Zangi and colleagues demonstrated that VEGF-A modRNA administered at the time of coronary artery ligation in the MI mouse model by direct intramyocardial injection improved heart function and survival after MI (Zangi et al. 2013).

Therapies involving dietary supplementation

While in the past, the general guidelines for reducing the risk of CVD were to reduce total fat consumption, it is now recognized that the type of fat (fish, plant or animal derived) consumed is more important (van Bilsen and

Planavila 2014). A dietary intervention trial showed that a Mediterranean style diet rich in FAs derived from olive oil or nuts lowered the incidence of CVD as compared to a control, low-fat diet (Estruch et al. 2013). Conversely, hydrogenated or trans FAs have been implicated in increasing cardiovascular risk factors (Lichtenstein et al. 1999; Willett 2006). As noted previously, a substrate shift occurs from FA oxidation to glucose utilization with progression of pathological hypertrophy. As such, shifting the dietary balance to include more beneficial FAs may drive increased FA oxidation and provide an alternate form of therapy to attenuate or reverse heart conditions.

N3-PUFA supplementation

Early observational studies of Eskimo and Okinawa islander populations with diets high in n-3 long-chain polyunsaturated fatty acids (LCPUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from oily fish were shown to lower risk of death from coronary heart disease (Bang et al. 1976; Kagawa et al. 1982). Research conducted in the diet and reinfarction trial (DART) showed that in men recovering from MI, consumption of two weekly portions (200–400 g) of oily fish had a 29 % reduction in 2 year all-cause mortality (Burr et al. 1989). In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione trials, patients recently surviving MI that were assigned daily n3-polyunsaturated fatty acids (PUFAs) supplements had a 10 % reduced risk of death, nonfatal MI and nonfatal stroke (GISSI-Prevenzione Investigators 1999). Furthermore, a cohort from the Kuopio Ischemic Heart Disease Risk Factor Study showed an association of increased plasma levels of n-3 LCPUFAs to reduced risk of AF (Virtanen et al. 2009). This association was replicated in rabbits that were started on diets containing n-3 LCPUFAs before induction of combined pressure and volume overload that were protected against development of hypertrophy, electrical remodeling and arrhythmias (Den Ruijter et al. 2012). EPA supplementation also successfully reduced AF and remodeling in rabbits after ventricular tachypacing (Kitamura et al. 2011).

N3-PUFA supplemented diet fed to a transgenic rat model of hypertensive heart disease was associated with reduced levels of arrhythmia and fibrosis, although the rats still developed cardiac hypertrophy. The reduction in arrhythmia was associated with normalized expression and subcellular localization of connexin-43, a transmembrane protein that forms intermyocyte gap junctions (Fischer et al. 2008). Dietary supplementation of fish oil to mice subjected to TAC attenuated the development of cardiac hypertrophy and fibrosis, blocked cardiac fibroblast activation and improved cardiac function (Chen et al. 2011).

For the human studies described above, there are also others that have shown no association between fish oil supplementation and CVD (Belin et al. 2011; Dijkstra et al. 2009; Jarvinen et al. 2006; Levitan et al. 2009; Nakamura et al. 2005). The inconsistency in results highlights the limitations of randomized controlled trials and prospective cohort studies; thus further studies exploring the therapeutic potential of fish oil supplementation are warranted.

FFAs

Of the circulating FAs used in the production of cardiac ATP, some are sourced from the liver and peripheral adipose tissues; however, the majority are derived from dietary FAs, mainly palmitate and oleate (Banke et al. 2010) (Fig. 3). Palmitate treatment of neonatal rat ventricular myocytes was associated with increased apoptosis and oxidative stress, while treatment with oleate was able to attenuate that effect (Miller et al. 2005). Similarly in another study, TNF-α-induced oxidative stress in adult rat cardiomyocytes was also prevented by oleate treatment (Al-Shudiefat et al. 2013). More recently, isolated hearts from rats that underwent TAC surgery perfused with oleate showed improved contractility while maintaining TAG turnover and oxidation levels. This was attributed to the increased affinity of oleate to TAG incorporation, thereby maintaining the normal rate of fatty acid metabolism in the hypertrophied heart (Lahey et al. 2014). To our knowledge, there are currently no oleate-specific dietary trials being conducted to treat HF patients. However, oleate is a naturally abundant FA (70–80 %) found in olive oil (Benito et al. 2010), which features prominently in Mediterranean style diets. Meta-analysis from a systemic review conducted in 2014 showed a significant correlation between increased consumption of olive oil and reduced risk of all-cause mortality, cardiovascular events and strokes (Schwingshackl and Hoffmann 2014). The Prevencion con Dieta Mediterranea (PREDIMED) study found a reduced occurrence of major cardiovascular events among people with high cardiovascular risk that consumed a Mediterranean style diet supplemented with extra-virgin olive oil (Estruch et al. 2013). Analysis of a cohort from PREDIMED showed that those with the highest consumption of virgin olive oil and vegetable consumption had lower plasma inflammatory biomarkers for coronary heart disease compared to those who consumed less (Urpi-Sarda et al. 2012). These studies all serve to highlight the therapeutic potential oleate supplementation could provide for HF patients.

L-Carnitine

Carnitine is produced from the amino acids lysine and methionine, and it exists in two stereoisomers, where

L-carnitine is the biologically active form. L-Carnitine levels are maintained via endogenous synthesis predominantly in the kidney and liver and via dietary intake, mostly from dairy and meat (Demarquoy et al. 2004; Siliprandi et al. 1991). L-Carnitine is primarily involved in mitochondrial metabolism and function (Fig. 3). It serves as an essential cofactor for the transport of acyl-CoA into the mitochondria matrix for the generation of ATP through β-oxidation (Broderick et al. 1993). L-Carnitine also increases the rate of glucose oxidation by stimulating pyruvate dehydrogenase when there are elevated levels of unused FAs (Calvani et al. 2000). Depletion of the L-carnitine pool will therefore lead to a decreased rate of β-oxidation. In settings of HF, cardiac L-carnitine levels are shown to be reduced (Masumura et al. 1990; Regitz et al. 1990). Its supplementation therefore is viewed by many as a potential form of therapy to restore ATP levels to the heart.

An early study demonstrated that acute L-carnitine perfusion reversed the depressed cardiac function in isolated carnitine-deficient rat hearts and was protective against ex vivo ischemia/reperfusion injury (Broderick et al. 1993). Rats with mild surgically induced hypertrophy exhibited increased glucose oxidation rates and improved contractile function when treated with propionyl-L-carnitine, a derivative of L-carnitine (Schonekess et al. 1995) while another rat model of HF with preserved ejection fraction showed improved survival rates, attenuation of LV fibrosis and restoration of LV free-carnitine levels after being provided with a L-carnitine supplemented diet (Omori et al. 2012). Perfusion of L-carnitine in dog and pig hearts was also shown to improve contractility and LV pressure (Liedtke et al. 1988; Suzuki et al. 1981).

A small cohort of patients with congestive HF treated with propionyl-L-carnitine showed increased peak heart rate, exercise capacity and peak oxygen consumption, along with a significant reduction in pulmonary arterial pressure, atrial and ventricular size (Anand et al. 1998); 1500 mg L-carnitine administered to patients daily with New York Heart Association (NYHA) class II symptoms and preserved ejection fraction showed improvement in diastolic parameters as well as dyspnea after 3 months (Serati et al. 2010). A separate study showed that patients with dilated cardiomyopathy who received daily 2 g doses of L-carnitine had increased mortality benefit against those who received the placebo (Rizos 2000). Of note, a recent study in mice suggested that intestinal microbiota metabolism of L-carnitine may contribute to increased risk of atherosclerosis (Koeth et al. 2013). However, potential limitations of this study have also been highlighted (Ussher et al. 2013). In summary, while a number of clinical studies show promising results, larger randomized trials and mechanistic studies should be undertaken to comprehensively assess the therapeutic potential of L-carnitine supplementation.

Small molecules

Small molecules are chemically synthesized drugs with low molecular weights (<1000 Da). They can usually be administered orally and can enter the systemic circulation via capillaries (Samanen 2013). Thus, a number of investigators have assessed the potential of using small molecules to target specific intercellular signaling pathways to treat HF.

Sildenafil

Sildenafil is a selective inhibitor of type 5 phosphodiesterase (PDE5) that inhibits the degradation of cGMP resulting in an antihypertrophic signaling effect (Vandeput et al. 2009) (Fig. 5). Several animal studies have shown that sildenafil attenuates cardiac remodeling, with an antihypertrophic and anti-fibrotic effect, and protects the heart against cardiac injury including MI and TAC (Chau et al. 2011; Nagayama et al. 2009; Takimoto et al. 2005). Sildenafil has been tested in a number of clinical trials in various clinical conditions, including HF, MI and diabetic cardiomyopathy, with studies showing improved cardiac performance and outcomes and a good safety profile (Giannetta et al. 2012, 2014; Schwartz et al. 2012). HF patients with NYHA class II–III symptoms treated with 50 mg of Sildenafil three times daily for a year showed improved cardiac functional capacity, reversed remodeling of the left atria and ventricle, and was associated with improvement in exercise performance (Guazzi et al. 2011).

BGP-15

We recently assessed the potential of a small molecule called BGP-15 in a transgenic mouse model with HF and AF. BGP-15 is a hydroxamic acid derivative that is administered orally, and is a co-inducer of the stress-inducible form of hsp70 (HSP70/72). BGP-15 was previously found to be effective in preventing insulin resistance in genetic- and diet-induced mouse models of obesity (Chung et al. 2008), and shown to provide protection in genetic mouse models of Duchenne muscular dystrophy, in part by attenuating fibrosis in the diaphragm muscle and increasing SERCA2a in skeletal muscle (Gehrig et al. 2012). Finally, BGP-15 represented an attractive drug to test in our mouse model with HF and AF because BGP-15 had previously been tested for safety and efficacy in human clinical trials and shown to have no adverse cardiac effects (healthy volunteers, patients with insulin resistance and patients with type 2 diabetes mellitus) (Literati-Nagy et al. 2009, 2010, 2012). Oral administration of BGP-15 for 4 weeks in the AF and HF mouse model was associated with reduced episodes of arrhythmia, improved cardiac function, smaller atrial

size, reduced ventricular fibrosis and increased cardiac SERCA2a expression (Sapra et al. 2014). While we had hypothesized that BGP-15 treatment may provide benefit in the HF and AF model by increasing expression of hsp70, BGP-15-induced protection was associated with increased phosphorylation of IGF1R and reduced atrial levels of the lipid GM3 ganglioside, without changes in hsp70 (Sapra et al. 2014) (Fig. 5).

Stem cell therapies and cardiac regeneration

The adult heart has a very limited regenerative capacity following injury. It was envisaged that implantation of stem cells into the failing heart would cause regeneration of heart muscle and improve heart function; thus, a number of cell therapies for cardiac regeneration have been experimentally investigated (reviewed in Braunwald 2014; Hudson and Porrello 2013; Sanganalmath and Bolli 2013; van Berlo and Molkentin 2014). Initial studies revealed that bone marrow-derived stem cells and skeletal myoblasts had limited effect on cardiac function in clinical trials and did not affect survival (Abdel-Latif et al. 2007; Menasche et al. 2008). Cardiac progenitor cells appear to be safe when injected into a small number of patients, and thus, a larger trial is planned (Bolli et al. 2011). Cardiosphere-derived cells also appear to be safe and associated with reduced scar size (Makkar et al. 2012; Malliaras et al. 2014). A clinical trial to assess safety and efficacy of cardiospheres in patients post-MI with cardiac dysfunction is now being undertaken (Braunwald 2014). Human-induced pluripotent stem cells have been shown to reduce infarct size and improve cardiac function in a porcine ischemia–reperfusion model (Xiong et al. 2013) but have not yet been used in a clinical setting. A recent study has produced human embryonic stem cell-derived cardiomyocytes (hESC-CMs) at a clinical scale and demonstrated sufficient myocardial regeneration following transplantation in infracted hearts of nonhuman primates (Chong et al. 2014). Despite the limitations of the study (e.g., small animal numbers, high cost, hESC-CM induced arrhythmias, discussed in detail in the following commentaries (Anderson et al. 2014; Murry et al. 2014; Sussman and Puceat 2014), this study was able to generate 10-times more hESC-CMs than previous studies and identified ventricular arrhythmias as a challenge that needs to be addressed before this therapy is used in the clinic. Thus, in order for cell therapy to become a reality, several important questions regarding optimal cell type, route of administration, optimal cell dose and timing of their administration need to be answered, and large-scale, carefully designed, randomized clinical trials need to be performed (Sanganalmath and Bolli 2013).

Challenges that need to be overcome

A wide gap exists between our ever increasing knowledge of heart disease biology and the difficulty in translating these discoveries to new and approved therapies for HF. The drug development process is typically lengthy due to requirements of extensive pharmacological studies in different types of animal models and the complexity of the animal systems, which may differ to that of humans. Ensuring the safety of new cardiac drugs remains a major challenge and is of paramount importance. In the USA, cardiac safety is the leading cause for drug discontinuation at all phases of development (Finkle et al. 2009; Piccini et al. 2009). Efficacy needs to be achieved, and this is often the result of selecting the appropriate delivery method and clinical endpoint measurement (Scimia et al. 2014). In addition, recent data suggest that taking just one discovery from the laboratory to development and delivery to patients costs millions of dollars (Mullard 2014). Another common challenge is matching the study drug to the right patient cohort. Patients with HF often have multiple comorbidities, and given the wide heterogeneity of the patient population with HF, clinical studies need to identity the appropriate target population in order to maximize the success of new drug therapies (Vaduganathan et al. 2013).

The very lengthy process of transferring preclinical studies performed in small to large animal models and then into clinical trials (i.e., bench to bedside) can take up to 20 years and poses a major barrier to clinical translation. In order to accelerate preclinical development, it has been suggested that academic centers could be provided with small and large animal study facilities and the necessary personnel to test efficacy of novel drug targets. This would allow simultaneous testing of investigational drugs on small and large animal models. Collaboration is critical, and thus, interactions between scientists and clinicians should be encouraged and appropriate personnel employed to negotiate the regulatory maze. Together, this may increase the speed and efficiency with which research discoveries are translated into advances in patient care (Scimia et al. 2013, 2014).

For both cardiac and noncardiac investigational drugs, efficient and sensitive evaluation of cardiac safety in research and development is a priority. A common side effect of chemotherapy drugs or other anticancer therapies is cardiotoxicity. Earlier, we discussed the potential of PI3K (p110α) gene therapy for the treatment of HF. However, PI3K inhibitors and other tyrosine kinase inhibitors (e.g., ibrutinib) are a promising class of anticancer drugs, but at the same time, are likely to lead to considerable toxicity to the cardiovascular system (McLean et al. 2013; McMullen et al. 2014). Mice that are deficient for both PI3K (p110α) and PI3K (p110γ) have impaired cardiac function and increased pathology (e.g., fibrosis, upregulation of fetal genes) ultimately resulting in cardiomyopathy at

1 year of age, suggesting that long-term use of PI3K inhibitors may lead to cardiac defects and toxicity (Zhabyeyev et al. 2014). Furthermore, inhibition of PI3K signaling by the tyrosine kinase inhibitors nilotinib and dasatinib (anticancer drugs that have entered clinical use) can cause drug-induced cardiac arrhythmias (Ballou et al. 2015). Similarly, while we and others have shown that inhibition of miR-34a and the miR-34 family is protective in the diseased hearts of mice (Bernardo et al. 2012b, 2014a; Boon et al. 2013), the effect of prolonged/chronic inhibition of miR-34a and its family members may not be ideal because of its ability to drive tumorigenesis (Wong et al. 2011). Conversely, miR-34a replacement therapy as a cancer therapeutic (as is being developed by Mirna Therapeutics) may have adverse affects on the heart (Bader 2012; Daige et al. 2014; Kasinski et al. 2014). Thus, miRNA-34 replacement therapies, PI3K inhibitors and other anticancer therapeutics are to be used with care in cancer patients with preexisting cardiac risk factors or disease. In addition, patients should be carefully monitored and management plans developed (Yeh et al. 2004).

Conclusions

Mechanisms contributing to the development of cardiac hypertrophy are very complex, and our understanding of the key processes responsible for the transition to HF remains incomplete. In the last decade, our improved understanding of known mechanisms and the identification of new regulators/signaling mediators and processes associated with cardiac remodeling (e.g., noncoding RNAs, autophagy etc.) have opened up new areas of research. HF remains challenging to treat, and the incidence continues to rise with an aging population. With current HF drugs largely delaying HF progression, it is hoped that some of the new therapeutic approaches discussed in this review will show potential in improving heart function and reversing pathological remodeling. However, additional studies and research will be required to ascertain the efficacy, safety and mechanisms of action of these new treatments. With further advancements in our understanding of the mechanisms responsible for the transition from adaptive to maladaptive heart growth, and improved tools, technologies and drug design, we get closer to the reality of identifying new therapeutics, which can improve heart function and the quality of life of HF patients.

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