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REVIEW SERIES

Metabolic changes in hypertrophic cardiomyopathies: scientific update from the Working Group of Myocardial Function of the European Society of Cardiology

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Abstract Disturbed metabolism as a consequence of obesity and diabetes may cause cardiac diseases (recently highlighted in the cardiovascular research spotlight issue on metabolic cardiomyopathies).[1] In turn, the metabolism of the heart may also be disturbed in genetic and acquired forms of hypertrophic cardiac disease. Herein, we provide an overview of recent insights on metabolic changes in genetic hypertrophic cardiomyopathy and discuss several therapies, which may be explored to target disturbed metabolism and prevent onset of cardiac hypertrophy.

Keywords Hypertrophic cardiomyopathy • Mutations • Metabolism

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1. HCM: inefficient sarcomere contraction as primary defect

Hypertrophic cardiomyopathy (HCM) is the most frequent inherited cardiomyopathy with a recently reported prevalence of 1:200.[2] HCM has an extremely wide phenotypic variation. Its diverse appearance on cardiac imaging has only been recognized fully in the past decade since cardiac magnetic resonance has been introduced as the gold standard imaging assessment for diagnostic characterization and follow-up of these patients. The same genetic signature can translate into extreme cardiac morphological findings extending from an almost normal appearance or localized (segmental) hypertrophy to significant hypertrophy affecting predominantly the septum and/or the lateral wall and/or the apex.[3] Aside from the diastolic abnormalities of the hypertrophic phenotype *per se*, additional pathophysiological consequences accompany the HCM heart such as outflow tract obstruction where the mitral valve becomes involved in the acceleration of flow seen in the obstructed outflow tract. The latter may also result in mitral regurgitation, all of which contribute to the symptoms experienced by these patients. After the first identification of a sarcomeric gene mutation in 1989,[4,5] more than 1400 mutations have been identified, mostly in genes encoding sarcomeric proteins.[6] Most mutations (~90%) are found in the

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thick filament proteins myosin heavy chain (MyHC, *MYH7* gene) and cardiac myosin binding protein C (cMyBP-C, *MYBPC3* gene), and the thin filament protein troponin T (cTnT, *TNNT2* gene). Initial studies on mutation-induced changes in sarcomere function revealed an increase in myofilament Ca^{2+}-sensitivity as opposed to a decreased myofilament Ca^{2+}-sensitivity in dilated cardiomyopathy (DCM).[7–11] The opposite effects on myofilament Ca^{2+}-sensitivity appears to be a consistent observation for thin filament mutations causing HCM and DCM, respectively (see also 'Complex road from genotype to phenotype in dilated cardiomyopathies' in the current issue),[8,11] while the increase in myofilament Ca^{2+}-sensitivity appears to be mostly secondary to disease progression in HCM with thick filament mutations.[12] Rather than an increase in myofilament Ca^{2+}-sensitivity, a common cellular phenotype induced by HCM sarcomere mutations is an inefficient sarcomere contraction, which is attributed to diverse changes in sarcomere properties: (i) an increase in myofilament Ca^{2+}-sensitivity, which coincides with an increase in adenosine triphosphatase (ATPase) activity indicating increased adenosine triphosphate (ATP) utilization at the sarcomeres[13]; (ii) a blunted length-dependent activation, which will cause a less efficient sarcomere response to increased stress[14]; (iii) increased kinetics of activation and relaxation, which underlie increased tension cost, i.e. increased ATP utilization for force development at the sarcomere level[15–19]; and (iv) reduced super relaxed state of the cross-bridges, which will increase ATP utilization at low diastolic cytosolic calcium levels.[20] Evidence for a mutation-induced reduction in the efficiency of cardiac performance in asymptomatic mutation carriers comes from imaging studies combining [11C]-acetate positron emission tomography and cardiovascular magnetic resonance imaging to assess myocardial external efficiency (MEE, i.e. the amount of oxygen used for cardiac work).[18,21,22] These studies revealed reduced MEE in mutation carriers, indicating that inefficient cardiac contractility precedes the development of hypertrophy. Thus, recent *ex vivo* and *in vivo* analyses support the paradigm proposed by Ashrafian *et al.*[23] that energy depletion causes HCM.

2. Linking inefficient sarcomere contraction with metabolic changes

Energy depletion induced by increased ATP utilization for sarcomere contraction is expected to impair cellular mechanisms regulating Ca^{2+} homeostasis and metabolism. Increased diastolic Ca^{2+} levels have been reported in HCM mouse models and human HCM patient samples,[19,24] indicating impaired Ca^{2+} handling. In addition, a reduced PCr (phosphocreatine)/ATP ratio was observed in HCM with and without hypertrophy indicating deficits in cardiac energetics at an early stage of HCM.[25] In the healthy heart, creatine kinase (CK) catalyses the transfer of phosphate from PCr to adenosine diphosphate (ADP), thereby regenerating ATP, while preventing accumulation of cytosolic ADP (*Figure 1*). Reducing PCr or experimental inhibition of CK activity has been causally linked to the development of heart failure, as it elevates left ventricle end-diastolic pressure (i.e. diastolic dysfunction), reduces contractility and increases mortality in rats.[26–28] The consequence of low PCr and/or a reduced CK activity is that cytosolic levels of ADP will increase. Increases in (ADP) of >50% have been reported in HCM mouse models.[16,29] Selectively increasing ADP levels without altering cytosolic ATP levels has been shown to limit myocardial relaxation in rats.[30] High ADP levels impair relaxation of wild-type rat hearts via ADP-mediated defects in sarcomere function.[31] Moreover, ADP increased myofilament Ca^{2+}-sensitivity in human HCM samples.[32] Thus, enhanced Ca^{2+}-sensitivity is caused directly by the mutation and indirectly via increased ADP levels (*Figure 2*). These studies support the idea that energy depletion results in elevations of ADP, thereby causes diastolic dysfunction.

3. Mitochondrial dysfunction

Impaired sarcomere energetics also provokes mitochondrial dysfunction, increase reactive oxygen species (ROS) and lead to altered ion homeostasis and lethal arrhythmias.[33] Increased binding of Ca^{2+} to the myofilaments (via increased Ca^{2+}-sensitivity) will reduce the Krebs cycle activity. At the same time, high ATP utilization increases ADP, which will reduce the levels of NADH and NADPH, thereby triggers oxidative stress. The composition of intracellular metabolic substrates is essential to regulate ATP production and limit production of ROS by the mitochondria. In mitochondria, ADP accelerates ATP production via oxidation of NADH to NAD^+. At the same time Ca^{2+} stimulates the Krebs cycle (conversion of NAD^+ to NADH) to match the ADP-mediated reduction in NADH, thereby maintaining the NADH/NAD^+ redox state.[34,35] The mutation-induced increase in myofilament Ca^{2+}-sensitivity will enhance ATP utilization and increase ADP levels. The increase in ADP will increase oxidation of both NADH and NADPH and perturb the NADH/NAD^+ balance.[36] As NADPH is needed to detoxify ROS, the ADP-mediated NADPH oxidation will reduce the mitochondrial capacity to lower ROS. Moreover, as more Ca^{2+} will be bound to the sarcomeres due to the increased Ca^{2+}-sensitivity, less Ca^{2+} will be available to stimulate the mitochondrial Krebs cycle and regenerate NADH. Through these mechanisms, impaired sarcomere energetics may thus provoke mitochondrial dysfunction and increase ROS.

4. Vascular endothelial dysfunction and rarefaction

While inefficient sarcomere contraction and relaxation will increase energy demand of the heart, pathogenic vascular remodelling may disrupt energy supply. HCM patients have abnormal myocardial perfusion reserve, which is more pronounced in the endocardium vs. mid and epicardial layers. Reduced cardiac perfusion has been reported in HCM patients, which was most severe in patients with a sarcomere mutation.[37,38] No microvascular dysfunction was observed in asymptomatic mutation carriers.[21] The observation of reduced coronary flow reserve in HCM patients with normal coronary angiograms led to the concept of microvascular (endothelial) dysfunction as secondary pathomechanism in HCM development.[39,40] Blunted coronary flow in response to adenosine (i.e. endothelial dysfunction) has been observed in hypertrophied and non-hypertrophied regions of the heart.[40] These studies suggest that mutation-induced cardiac contractile dysfunction precedes and possibly causes vascular (endothelial) dysfunction, which subsequently initiates remodelling (hypertrophy) of the heart. The inability of the capillary network to match the hypertrophic and disarrayed myocardium increases proportionately with the measured wall thickness on cardiac imaging, i.e. the most hypertrophic segments have the poorest perfusion reserve.[41,42] Histological analysis revealed reduced capillary density (i.e. rarefaction) in septal tissue samples from patients with obstructive HCM.[43] A significant proportion of patients with HCM progress to develop myocardial replacement fibrosis, typically located within the area of maximal wall hypertrophy. The presence of fibrosis appears to predict those phenotypes that later progress onto heart failure[44] or are more likely to develop malignant ventricular arrhythmias.[45]

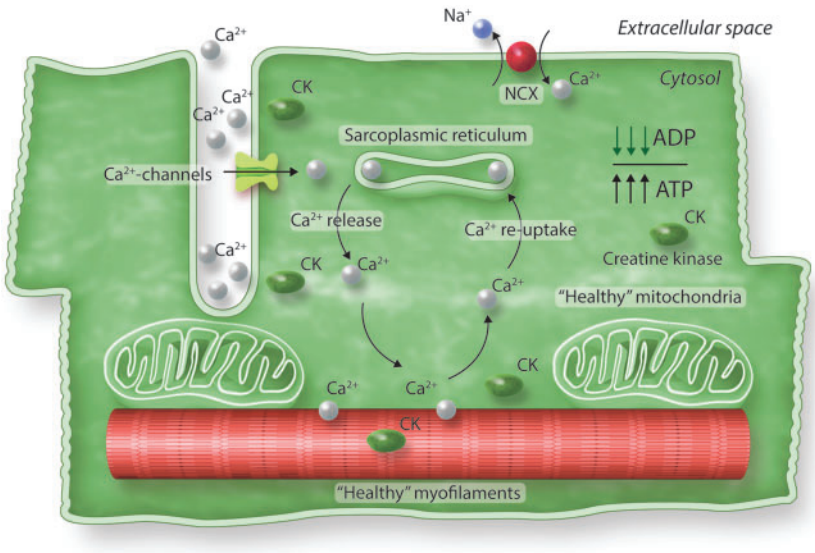

Figure 1 Excitation-contraction coupling in a healthy heart. Contraction is initiated upon Ca^{2+} entry in the muscle cell, which activates Ca^{2+} release from the SR. Ca^{2+} binds to the myofilaments, which causes contraction. To relax Ca^{2+} detaches from myofilaments and is pumped back into the SR. A small fraction of Ca^{2+} is removed out of the cell via the Na^{+}-Ca^{2+} exchanger (NCX). Mitochondria take care of sufficient ATP needed for proper contraction and relaxation of cardiomyocytes. In the healthy heart, CK catalyses the transfer of phosphate from phosphocreatine to ADP, thereby regenerating ATP, while preventing accumulation of cytosolic ADP.

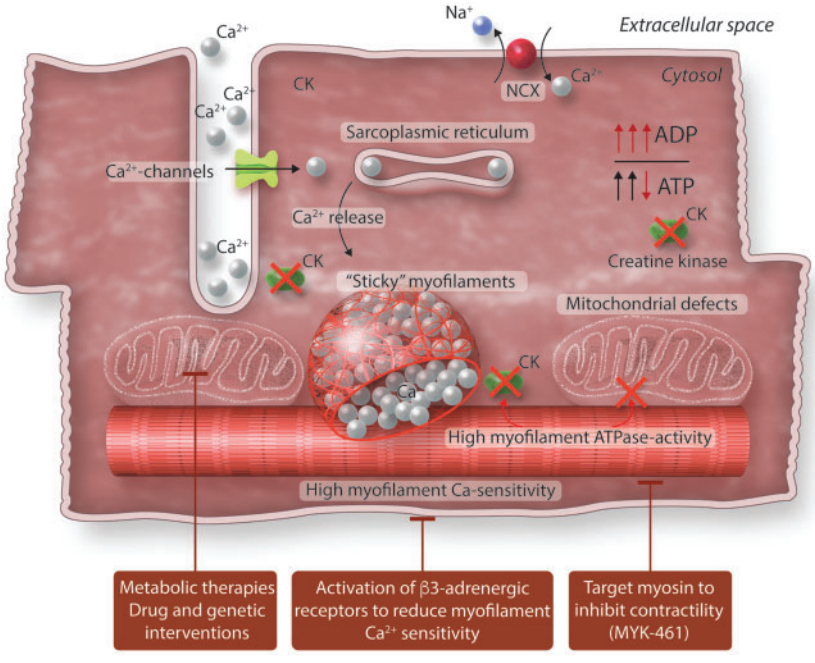

Figure 2 Excitation-contraction coupling in diseased heart and possible targets for therapy. Mutation-induced changes in myofilament properties increase ATP utilization. Cellular metabolism changes as a consequences of mutation-induced and ADP-mediated increases in myofilament Ca^{2+}-sensitivity, impaired mitochondrial function and reduced creatine kinase activity. Different therapies may target impaired metabolism in HCM.

5. Changes in substrate metabolism in hypertrophied muscle

The healthy heart has a wide substrate versatility because it is able to metabolize fatty acids, carbohydrates, lactate, ketone bodies, and specific amino acids.[46] In normal condition, cardiomyocytes generate more than two-thirds of the ATP by the oxidation of fatty acids and the remainder one-third by the oxidation of other substrates such as glucose. Interestingly, though, the oxidation of glucose is more energy efficient than that of fatty acids (ATP/O ratio = 3.17 for glucose vs. ±2 to 2.5 for fatty acids). In the case of acute increases in cardiac load, rapid supply of ATP is guaranteed by several mechanisms: increase in coronary flow and in oxygen extraction from the arterial coronary blood, and a metabolic shift from fatty acid oxidation to glucose oxidation (the Randle cycle). This 'glucose-fatty acid cycle' is a homeostatic mechanism that controls fuel selection and adapts substrate supply and demands in normal tissues and in the blood.[47] This shift from fatty acid oxidation to increased glucose metabolism is common in end-stage heart failure.[48] As a consequence, fatty acids and their derivatives accumulate into cells, causing lipotoxicity, [49] while glucose oxidation increases. This shift occurs mostly in mitochondria ('aerobic glycolysis' by oxidation of pyruvate) in order to guarantee more energy for the energy depleted failing heart. However, in failing hearts, a large part of glucose is converted to lactate through anaerobic glycolysis, which is less energy efficient. In the heart, it is possible that the latter process is the result of relative hypoxia caused by a reduced capillary density in combination with a higher workload of the hypertrophied heart. Recent findings indicate a central role for dihydrolipoyl succinyltransferase (DLST), the E2 subcomponent of the α-ketoglutarate dehydrogenase complex, a rate-controlling tricarboxylic acid cycle enzyme, in cardiac oxidative metabolism and hypertrophy. Its decrease in the diseased heart parallels a reduction of oxidative metabolism, whereas its cardiac overexpression improves oxidative metabolism and protects against cardiac hypertrophy and dysfunction.[50]

6. Atrial fibrillation

A high incidence of atrial fibrillation (AF) is observed in HCM, which worsens ventricular function. HCM patients with paroxysmal AF show reduced exercise capacity and is associated with markedly increased risk of death by stroke and heart failure.[51,52] Moreover, AF is associated with advanced disease progression in HCM patients.[52] AF may be caused by atrial dilatation in response to diastolic ventricular dysfunction. However, it may also involve a direct effect of the mutant protein on atrial myocyte function. A study in zebrafish harbouring an atrial-specific myosin light chain (*MYL4*) mutation, which was associated with early-onset AF in human, showed disrupted sarcomere structure, atrial enlargement and AF-like electrical abnormalities.[53] However, not all HCM sarcomere mutations are expressed in atrial cardiomyocytes. In a recent clinical study, no significant correlations were found between genotype and onset or severity of AF in a HCM cohort with mutations in *MYBPC3*, *MYH7* and 'other genotypes' (including thin filament gene mutations *TNNT2*, *TNNI3*, *TPM1*, and *MYL2* and Z-line).[54] Based on the latter study, the authors proposed that intrinsic atrial myopathy may be caused by rare (atrial-specific) mutations. If sarcomere mutations directly alter functional and structural properties of atrial cardiomyocytes warrants further experimental studies.

7. Non-myocyte compartment of the hypertrophied heart

The pathophysiology of HCM is not limited to sarcomere defects *within* cardiomyocytes but is also characterized by structural alterations in cardiomyocytes and the non-myocyte compartment of the heart. In a healthy heart, ~70% of the cardiomyocyte volume consists of myofibrils. This fraction is reduced in manifest human HCM, and largely explains the decreased cardiomyocyte maximal force generation capacity observed in HCM biopsies.[55] Cardiomyocytes solely account for 25–35% of all heart cells, while the non-myocyte populations are predominant and consist mostly of endothelial cells and cardiac fibroblasts.[56] Studies in HCM mice identified the pro-fibrotic transforming growth factor beta (TGF-β), most likely released from cardiac fibroblasts, as the main determinant of non-myocyte proliferation and myocardial fibrosis observed in HCM.[57] Since cardiac fibroblasts are responsible for extracellular matrix maintenance, and thus bridge biomechanical forces *to* and *from* cardiomyocytes, it has been speculated that the high basal myocardial activation observed in HCM cardiomyocytes (i.e. exacerbated biomechanical forces) is transmitted to the non-myocyte population, leading to increased expression of pro-fibrotic TGF-β.[58] This is supported by *ex vivo* culture studies of both cardiac fibroblasts and cardiomyocytes that showed increased expression of TGF-β following repetitive stretch procedures.[59,60] Early manifestation of myocardial fibrosis is a hallmark of HCM and correlates well with the degree of hypertrophy, diastolic dysfunction and energy consumption,[44,61] indicating that targeting the extracellular matrix via TGF-β may represent a way to modify disease progression.

8. Therapies

8.1 Targeting metabolism

On the basis of the consideration that inhibition of mitochondrial fatty acid oxidation leads to cardiac hypertrophy, a study in rats has recently shown that the restoration of fatty acid metabolism confers beneficial effects on the hypertrophic heart.[62] CD36-deficient (Cluster of differentiation 36, a major sarcolemmal fatty acid transporter) spontaneously hypertensive rats with established hypertrophy were treated with Tricaprylin, a triglyceride of caprylic acid, that stimulates fatty acid oxidation and maintains the cellular redox status. This treatment decreased cardiomyocyte cross-sectional area and reduced interstitial fibrosis, along decreased expression of BNP, calcineurin A and oxidative stress biomarkers. Cardiac function and energetics were also influenced by substrate availability. In fact, fenofibrate treatment in the absence of the appropriate metabolic substrate resulted in the mobilization of endogenous triglycerides and caused an imbalance of the cellular redox status, leading to enhanced free radical production and adverse cardiac changes. Conversely, medium-chain triglycerides have the capacity to bypass CD36 and serve as substrate for fatty acid oxidation,[63] maintaining the intracellular redox status. Perhexiline is a metabolic drug which shifts metabolism away from the preferred fatty acids toward carbohydrates, and would thereby increase ATP supply. Perhexiline treatment enhanced glycolysis and protected against catecholamine-induced cardiac damage in a mouse model of peripartum cardiomyopathy.[64]

Metabolic remodelling appears to be reversible as regression of left ventricular hypertrophy is preceded by improved cardiac energy metabolism, as indicated in a mouse study of aortic constriction surgery

followed by debanding.[65] Debanding—unloading of the hyperpertrophic heart—significantly reduced left ventricular mass and wall thickness, along with profound changes in transcripts and proteins of cardiac substrate metabolism. However, debanding did not normalize the transcripts of proteins regulating glucose and fatty acid metabolism. This paradox is likely explained by the fact that cardiac energy metabolism is regulated at multiple levels, including many post-translational modifications. These data agree with the only partial reversal of depressed metabolic gene expression in the failing heart after implantation of a left ventricular assist device.[66] Likewise, aortic valve replacement surgery in patients with aortic valve stenosis increased MEE, but MEE was not corrected to control values 4 months after surgery.[67] Although only partial correction of MEE was observed, the improvement of MEE closely correlated with increased exercise capacity.[67] These studies involve a hemodynamic, non-genetic overload of the heart, and may not translate to genetic forms of HCM. However, therapy targeting metabolism may be effective in HCM. Perhexiline treatment of HCM mice harbouring a *MYBPC3* mutation improved some features of the HCM phenotype (reduced cardiac mass), which was associated with metabolic changes.[68] Treatment of symptomatic HCM patients with improved exercise capacity.[69] The therapeutic benefit of perhexiline may be the resultant of its multiple pleiotropic actions.[70] Far from inducing a simple shift from fatty acid to glucose oxidation, perhexiline may cause complex rebalancing of carbon and nucleotide phosphate fluxes to increase metabolic flexibility and to maintain cardiac output.[71] The benefit of metabolic drug therapy may depend on the ability of the heart to shift from mitochondrial lipid to glucose oxidation. As described above, hypertrophied hearts shift their metabolism from fatty acids to glucose utilization and glycolytic metabolism in an attempt to optimize energetic status.[72] Mitochondrial oxidative metabolism decreases, while glycolysis as an alternate source of ATP production increases. Accordingly, *in vivo* imaging studies in advanced HCM patients suggest that metabolism shifted to the lower oxygen consuming glucose metabolism.[22] Though initially adaptive, in the long run the (chronic) metabolic shift is detrimental for the heart as increased glycolysis increases pyruvate and lactate. The latter is accompanied by accumulation of H^+ in the cytosol, which eventually leads to elevated calcium (i.e. impaired relaxation).[72] While several pathways are activated in the severe (hypertrophic) stage of disease as compensatory mechanism, paradoxically, chronic stimulation of these pathways is detrimental. Likewise, chronic metabolic therapy may be harmful for the heart. Based on positive effects of exercise in cardiac disease, which is intermittent by its very nature, one may consider if intermittent metabolic drug-therapy, as opposed to chronic drug-treatment, represents a more effective and novel approach to treat cardiomyopathy.

Noteworthy, combined proteomics and metabolomics analysis revealed impaired energy generating pathways in mice with very high creatine levels that subsequently develop cardiac hypertrophy and dysfunction. Overall, these studies indicate that either low or very high levels of creatine perturb cardiac performance, and suggests that there is a therapeutic window of optimizing the cardiac energy balance in the heart.[73]

In conclusion, the hypertrophied and failing heart shows several metabolic changes. Improving the efficiency of energy generation in the hypertrophied heart can be exploited in order to optimize specific therapies. Metabolic alterations are (partially) reversible and their early identification may represent a therapeutic option (*Figure 2*).

8.2 Stimulation of β_3-adrenergic receptors

Activation of β_3-adrenergic receptors (β_3AR) may be a way to modify altered energetic status of the HCM heart. β_3AR are expressed in human cardiac myocytes and endothelial cells.[74,75] They differ from the other two βAR isotypes in a number of ways; (i) in cardiac muscle, they exert effects that are antipathetic to those of $\beta_{1\text{-}2}$AR on contractility (i.e. they act as "endogenous $\beta_{1\text{-}2}$AR blockers")[74]; (ii) β_3AR expression increases in cardiac myocytes from diseased including failing, hearts[74]; (iii) β_3AR lack consensus sequences for phosphorylation by GRK2 or protein kinase A (PKA) in their C-terminal tail, which attenuates or suppresses their desensitization, depending on the cell context.[76] These characteristics make β_3AR attractive targets in the context of heart failure, a condition with prevailing hyperadrenergism, when $\beta_{1\text{-}2}$AR usually are desensitized/downregulated. Reduced β_1AR signalling has also been observed in human HCM evident from reduced PKA-mediated phosphorylation of sarcomeric target proteins.[12,14] Decreased PKA-mediated phosphorylation of troponin I (TnI) causes increased myofilament Ca^{2+}-sensitivity, which will further exacerbate the energetic defect in HCM. In human cardiac muscle, β_3AR couple through G-alpha-i to activation of the constitutive nitric oxide synthase (NOS),[77] endothelial NOS and neuronal NOS (nNOS), both expressed in cardiac myocytes.[78] β_3AR expression and activity correlates with tonic increases in cGMP.[77] Downstream activation of cGMP-dependent kinase (PKG)-I-alpha is expected to phosphorylate a number of targets functionally relevant to both excitation-contraction coupling and cardiac muscle remodelling. PKG modulates phospholamban phosphorylation to increase Ca^{2+} reuptake in the sarcoplasmic reticulum (SR),[79] resulting in improved diastolic relaxation as well as increased SR load. PKG phosphorylates TnI to decrease myofilament Ca^{2+}-sensitivity (*Figure 2*).[80] PKG also modulates the phosphorylation of titin on specific residues, with putative improvements in myocyte elastic properties.[81] nNOS also modulates PKA-mediated phospholamban phosphorylation and improves Ca^{2+} reuptake in the SR through cGMP-independent effects on protein phosphatase.[82]

These effects should directly improve relaxation and decrease myofilament Ca^{2+}-sensitivity, with expected beneficial effects on energetics in HCM. In addition, β_3AR uniquely exert antioxidant properties in hypertrophic cardiac muscle.[83,84] This may counteract the adverse pro-oxidant consequences of increased ADP and decreased Ca^{2+} uptake by mitochondria. In addition, activation of the β_3AR/NOS/cGMP pathway attenuates hypertrophic remodelling in several mouse models of neurohormonal or hemodynamic overload.[78,83,85] Fibrosis is also decreased, through β_3AR modulation of paracrine signalling from cardiac myocytes to fibroblasts, e.g. secondary to β_3AR/nNOS anti-oxidant effects.[83] Coronary perfusion is also expected to be improved, as β_3AR expressed in human coronary microvascular endothelial cells are coupled to both nitric oxide and EDHF-dependent relaxations,[75] as well as pro-angiogenic effects.[86] Finally, systemic activation of β_3AR in beige/brown fat may add indirect metabolic effects through increased lipolysis and improved systemic insulin sensitivity.[87] Direct effects on cardiac metabolism, i.e. on the selection of energetic fuels (lipids versus glucose), particularly in the stressed or failing heart, are currently being studied.

8.3 Targeting myosin

An alternative way to modify cardiac contraction is the use of small molecules which directly target myosin. Omecamtiv mercabil (OM), a myosin activator is currently tested in clinical trials in patients with systolic heart failure.[88] While a myosin activator may increase cardiac contractile performance, it may come at the expense of increased cardiac oxygen

consumption as the compound may also increase myosin ATPase activity.[89] Interestingly, a recent study showed that OM increases contractility at [Ca^{2+}], which are close to values at systole under basal conditions, while it decreased force at high (maximal) Ca^{2+} activation.[90] The latter study showed that the effect of OM depends on the concentration of both OM and intracellular Ca^{2+} levels, and the authors indicated that OM may be used to increase contractility and enhance function of a failing heart, while it may be used to reduce contractility in diastolic failure as observed in HCM dependent on its activating and inhibitory actions, respectively. A myosin inhibitor (mevacamten, also known as MYK-461), which was shown to reduce contractility,[91] and most likely reduces oxygen consumption of the hypertrophied heart, suppressed HCM in a mouse models with *MYH7* mutations.[92] MYK-461 is currently tested in HCM by Myocardia. The use of myosin activators and inhibitors is an attractive novel approach to correct cardiac dysfunction, thereby influence metabolism.

8.4 Genetic interventions

Recently, a novel role was identified for microRNA-146a in regulating cardiac metabolism via suppression of oxidative metabolism.[50] MicroRNA-146a targets a key component of the α-ketoglutarate dehydrogenase complex named DLST. Overexpression of DLST or inhibition of microRNA-146a blunted the hypertrophic response upon pressure overload in mice, which coincided with partial maintenance of oxidative metabolism. Increased miRNA-146a has been linked with reduced cardiac erbB4 signalling, which is central in regulating glucose metabolism.[93] While inhibition of microRNA-146a may directly improve metabolism of cardiac muscle, energy supply may be improved via modulation of cardiac perfusion. MiRNAs may thus represent targets to improve metabolism and energy supply of the hypertrophied heart. In addition, mitochondrial-derived noncoding RNAs that are likely involved in metabolic processes have recently been found in patients with myocardial infarction and may be useful biomarkers of cardiac diseases and/or prognostic markers.[94]

9. Conclusion

Studies in mice and human have indicated that metabolic changes in development of HCM may represent an attractive therapeutic target. Recent studies in HCM mouse models and human cardiac biopsies emphasized that, although the final clinical HCM phenotype may be independent of genotype, the initial mutation-induced defects in sarcomere function[11,15,16] and subsequent changes in signalling pathways[95] may significantly differ based on the affected gene and even based on the specific mutation. This emphasizes the need to study the early mutation-induced changes in mitochondrial and metabolic pathways, which will aid in the development of patient-tailored (mutation-tailored) preventive therapies.

Conflict of interest: T.T. filed and licensed patents on cardiac noncoding RNAs. T.T. is founder of Cardior Pharmaceuticals. M.M. filed and licensed patents on non-coding RNAs as biomarkers. And all others have none to declare.

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