Mechanisms of disease: hypertrophic cardiomyopathy

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Abstract | Hypertrophic cardiomyopathy (HCM) is the most-common monogenically inherited form of heart disease, characterized by thickening of the left ventricular wall, contractile dysfunction, and potentially fatal arrhythmias. HCM is also the most-common cause of sudden cardiac death in individuals younger than 35 years of age. Much progress has been made in the elucidation of the genetic basis of HCM, resulting in the identification of more than 900 individual mutations in over 20 genes. Interestingly, most of these genes encode sarcomeric proteins, such as myosin-7 (also known as cardiac muscle β-myosin heavy chain; *MYH7*), cardiac myosin-binding protein C (*MYBPC3*), and cardiac muscle troponin T (*TNNT2*). However, the molecular events that ultimately lead to the clinical phenotype of HCM are still unclear. We discuss several potential pathways, which include altered calcium cycling and sarcomeric calcium sensitivity, increased fibrosis, disturbed biomechanical stress sensing, and impaired cardiac energy homeostasis. An improved understanding of the pathological mechanisms involved will result in greater specificity and success of therapies for patients with HCM.

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most-common form of Mendelian-inherited heart disease, which affects 0.2% of the global population.[1] HCM is also the most-common cause of sudden cardiac death in individuals younger than 35 years of age.[2] Since the discovery of the first HCM-causing gene mutation, in the myosin-7 (also known as cardiac muscle β-myosin heavy chain) gene (*MYH7*),[3] a large number of individual mutations in 23 genes, mostly encoding sarcomeric proteins, have been shown to cause HCM.[4,5]

Characteristic pathological features of HCM include unexplained asymmetric or symmetric cardiac hypertrophy, fibrosis, and cardiomyocyte disarray.[6] The clinical phenotype is highly variable and ranges from lifelong absence of symptoms to rapidly progressive heart failure or early sudden cardiac death, sometimes with little or even no hypertrophy.[7] In the contemporary, causation-targeted classification of cardiomyopathies, HCM is categorized as a primary genetic cardiomyopathy, by contrast with dilated cardiomyopathy (DCM) and restrictive cardiomyopathy, which are classed as mixed cardiomyopathies (genetic and acquired).[5] These diseases can also be viewed as a continuum of phenotypes that share not only typical symptoms of heart failure such as dyspnea, but also morphological and pathophysiological features. For example, during the course of the disease, an HCM phenotype can develop into a DCM-like phenotype. Additionally, the various cardiomyopathies can be caused by mutations within the same genes; mutations of the gene for cardiac muscle troponin T (*TNNT2*) can result in HCM,[7] DCM,[8] restrictive cardiomyopathy,[9] and left ventricular noncompaction cardiomyopathy,[10] which illustrates the complexity of genotype–phenotype correlations.

Despite much progress in unraveling the genetic basis of HCM, a remarkable deficit still exists in our understanding of the molecular events and signaling pathways that lead from a sarcomeric mutation to diverse disease phenotypes. Unsurprisingly, current treatments for HCM focus on the primary and secondary prevention of sudden cardiac death, and relief of left ventricular outflow obstruction by either surgical[11] or interventional[12] septal ablation. Pharmacological treatment options, such as β-adrenergic-receptor blockers or nondihydropyridine calcium-channel antagonists, might provide symptomatic benefit, but do not target HCM-specific pathways and have not been shown to alter the natural history of the disease.[13] The development of novel and targeted therapies will, therefore, depend on an improved understanding of the molecular pathways that translate a mutation of a sarcomere protein into the complex phenotype of HCM.

In this Review, we summarize the current knowledge of the genetic basis of HCM and discuss the pathogenic mechanisms by which HCM-associated mutations might cause the disease phenotype. Furthermore, we provide an outlook on how an improved understanding of the molecular basis of HCM might offer novel diagnostic tools and therapeutic opportunities in the future.

Genetic basis of HCM

HCM was the first cardiomyopathy to be attributed to a genetic cause,[14] and the specific disease-causing gene mutation can be identified in over 50% of HCM cases.[15] A large number of molecular and clinical genetic studies have

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Key points

- Hypertrophic cardiomyopathy (HCM) is the most-common form of monogenic heart disease, affecting up to 0.2% of the population
- The clinical course of HCM is remarkably variable, ranging from lifelong, asymptomatic, mutation-carrier status to early sudden cardiac death in adolescents
- During the past 2 decades, much progress has been made in unraveling the genetic basis of HCM; disease-causing mutations have been identified in over 20 genes, mostly encoding sarcomeric proteins
- The molecular mechanisms of HCM are unclear; potential pathways include altered calcium cycling and sarcomeric calcium sensitivity, increased fibrosis, disturbed biomechanical stress sensing, and impaired cardiac energy homeostasis
- An improved understanding of the pathological mechanisms involved in HCM should increase the specificity and efficacy of therapy for this condition

linked HCM to mutations in 23 sarcomeric or sarcomere-associated proteins (Figure 1).[16,17] However, only 11 of these genes have so far been validated through co-segregation and linkage-analysis studies. Remarkably, alterations in two of these genes—*MYH7* and *MYBPC3* (which encodes cardiac myosin-binding protein C)—explain up to three-quarters of all clinical cases of HCM in which the underlying mutation has been defined. By contrast, mutations in proteins of the thin filament, such as cardiac muscle troponin T, cardiac muscle troponin I, and tropomyosin account for less than 10% of HCM cases. Mutations in the remaining 18 candidate genes of the sarcomeric and calcium-handling proteins that have been reported in clinical and experimental studies are only rarely observed in large cohort studies. Substantial allelic heterogeneity within each disease-linked gene, with more than 900 distinct mutations reported to date, adds to the genetic complexity of HCM. The majority of HCM-causing mutations are unique to a single family ('private mutations').

The early perception of HCM as a "disease of the sarcomere"[18] is, therefore, still valid. Up to 5% of patients carry at least two independent mutations (compound or double heterozygosity),[19] and an incidence of 0.8% has been reported for triple gene mutations in sarcomeric proteins.[20] Studies in small numbers of patients with double and triple mutations suggest that these individuals are especially prone to an early onset and severe course of the disease.[19–21] Likewise, a poor prognosis has also been shown in patients who are homozygous for a mutation.[22] Subsequently, HCM-causing mutations have been identified in several genes encoding Z-disk and non-sarcomeric proteins, including *TCAP* (telethonin), *MYOZ2* (myozenin-2, also known as calsarcin-1), *ANKRD1* (ankyrin repeat and KH domain-containing protein 1), *PLN* (cardiac phospholamban), *JPH2* (junctophilin-2), and *CAV3* (caveolin-3).[23,24]

Mutations in metabolic genes such as *GLA* (α-galactosidase), *LAMP2* (lysosome-associated membrane glycoprotein 2), and *PRKAG2* (5'-AMP-activated protein kinase γ_2), and mitochondrial transfer RNAs cause a phenotype that closely resembles 'sarcomeric HCM' (known as disease phenocopies).[25] The multiple disease-causing gene mutations and the even higher number of allelic variants only partly explain the remarkable variability in the clinical phenotype of HCM. Even within a single family, the same mutation can result in a remarkably variable disease penetrance, age of symptom onset, clinical phenotype, and outcome. These observations indicate that, beyond the specific alteration in structure and function of a mutated protein, other disease modifiers must exist, such as common or intermediate genetic variants across the entire genome, or gene–environment interactions via epigenetic signaling.

The quest to improve the clinical management of patients with HCM has led to genetic testing for both diagnosis and risk assessment.[15] Good reasons for diagnostic genetic testing exist, such as genetic confirmation of the disease in patients with clinical features of HCM, and testing for the presence of a disease-causing mutation in family members of an index patient. Exclusion of carrier status can reduce both costs for the health-care system and the emotional distress of an individual potentially at risk. However, clear limitations to the clinical utility of genetic diagnostics of HCM exist, such as the low negative predictive value of genetic tests because of the analytical limitations of diagnostic methods, and the many causal genes and regulatory DNA sequences that remain unidentified. Consequently, a negative genetic test result in a patient with clinical features of HCM does not necessarily exclude genetic HCM, and a positive result does not predict the manifestation of clinically relevant HCM.

Genetic testing for risk prediction is an even more-controversial issue than its use in diagnostics.[15,16,26,27] Driven by careful analyses of large families, some mutations were identified as being associated with a high risk of sudden cardiac death and progressive heart failure ('malignant mutations') and others were found to be benign.[16] However, in other large cohort and family studies, this genome-based risk stratification was not recapitulated,[27] and many 'benign' mutations were found to be malignant in subjects with other genetic backgrounds, comorbidities, and environmental interactions. Conversely, supposedly malignant mutations were revealed to have a benign clinical course that did not differ from that of most other mutations. Nevertheless, clinical observations and transgenic animal models have established some phenotypic characteristics; for example, *MYH7* mutations cause earlier-onset and more-severe left ventricular hypertrophy than other mutations.[28] However, large investigations or registries to confirm these data are lacking.

Despite these conflicting data, some findings have been confirmed. For example, mutations in the *TNNT2* gene can cause HCM with little hypertrophy, or even normal cardiac morphology, in transgenic animals assessed using ultrasonography,[29] and in human probands.[7] Individuals with these mutations can, nevertheless, carry a high risk of malignant ventricular arrhythmias and sudden cardiac death.[18,29,30] Mutations in *MYBPC* have been associated with incomplete penetrance, and a late onset and benign course of the disease.[31,32] By contrast, in another report, mutations in *MYBPC* were associated with a poor prognosis,[33] again emphasizing that genotype–phenotype correlations are highly variable for most of the known

gene mutations. At present, therefore, genetic testing for a specific mutation will usually not provide incremental risk prediction over mere clinical criteria and will rarely aid in clinical decision-making (for example, whether to prophylactically implant a cardioverter–defibrillator). However, the detection of a disease-causing mutation in a patient with HCM has been linked to a threefold to fourfold increase in the risk of an adverse outcome (cardiovascular death, nonfatal stroke, or progression of heart failure) compared with patients with HCM in whom disease-causing mutations were not identified.[17,21,34] This correlation might, in part, be biased by a higher number of false-positive diagnoses in the group of 'nonmutation' patients with HCM.[21]

Several modifying factors have been proposed to account for the high phenotypic variability of HCM, such as lifestyle,[35] sex,[36] and genetic background.[28] An important role has been attributed to the renin–angiotensin–aldosterone system.[37,38] For example, an association was found between genetic variants of angiotensin-converting enzyme (encoded by *ACE*) and the extent of hypertrophy in patients with HCM.[37] However, the analysis of other

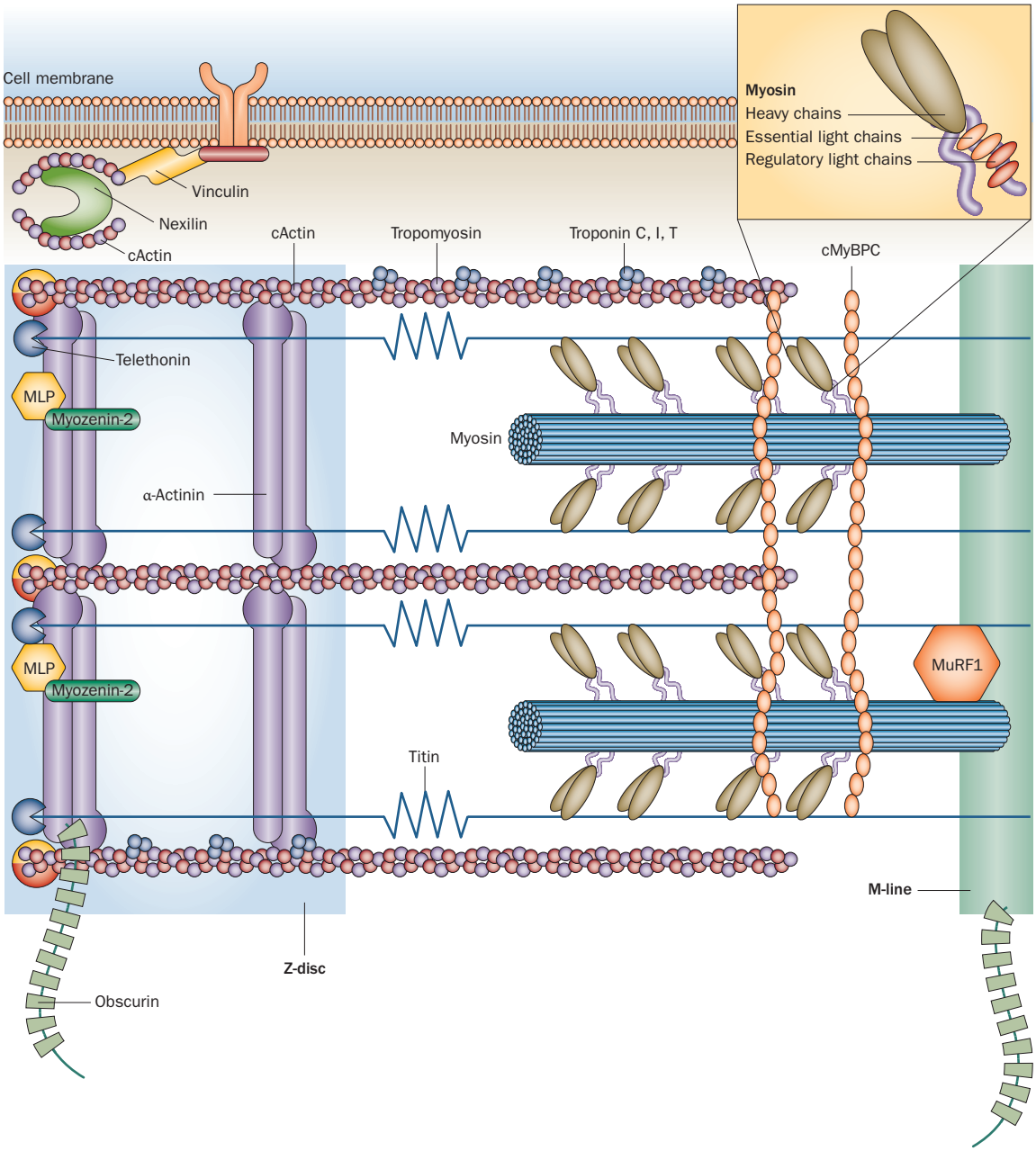

Figure 1 | Proteins in which HCM-causing mutations have been identified. Most of these proteins are components of the sarcomere. Notably, mutations in two genes—*MYH7* and *MYBPC3* (encoding myosin-7 and cMyBPC, respectively)—account for up to three-quarters of all clinical cases of HCM in which the underlying mutation has been defined. Mutations in nonsarcomeric proteins, such as vinculin, can also result in HCM. Abbreviations: cActin, α-cardiac muscle actin 1; cMyBPC, cardiac myosin-binding protein C; HCM, hypertrophic cardiomyopathy; MLP, cysteine and glycine-rich protein 3 (also known as muscle LIM protein); MuRF1, E3 ubiquitin-protein ligase TRIM63 (also known as muscle-specific RING finger protein 1).

components of the renin–angiotensin–aldosterone system has yielded inconclusive results.[28] Nonsense-mediated RNA decay, the ubiquitin–proteasome system, and lysosome-mediated autophagy have been proposed as possible disease pathways that could be causally relevant or involved in modulation of the disease phenotype.[39] The emerging field of microRNAs as post-transcriptional regulators of gene expression adds another layer of complexity.[40]

Molecular pathogenesis of HCM

The pathogenic mechanisms by which HCM-associated mutations cause the disease remain unclear and controversial.[15,41,42] Impaired myofibrillar contractile function was initially suggested to be the most-important mechanism, accounting for 'compensatory' hypertrophy and diastolic dysfunction—two hallmarks of the clinical phenotype.[18] However, the altered contractility caused by various sarcomeric gene mutations are not consistent. For example, on the myofibrillar level, mutations in *MYH7* can result in either reduced,[43] or enhanced,[44] motor activity. Furthermore, mutations in genes encoding thin-filament regulatory proteins, such as the troponins and α-tropomyosin, frequently increase the calcium sensitivity of contractile proteins, consequently augmenting developed force at submaximal calcium concentrations.[45] Several additional molecular mechanisms have been proposed that might explain some, or even all, clinical and pathological manifestations of HCM, including perturbations in calcium cycling and sensitivity, increased myocardial fibrosis, altered sensing of biomechanical stress, impaired energy homeostasis, and microvascular dysfunction (Figure 2). These theories are not mutually exclusive, and are discussed in more detail below.

Impaired calcium cycling and sensitivity

Impaired cardiomyocyte calcium cycling, for example because of altered expression, phosphorylation, or both, of key proteins such as the sarcoplasmic/endoplasmic reticulum calcium ATPase 2 and the ryanodine receptor 2, is central to the pathogenesis of systolic and diastolic heart failure.[46,47] Similarly, several studies have shown that calcium fluxes are perturbed in HCM.[48–50] Conversely, treatment of transgenic mice bearing an HCM-associated mutation in myosin-6 (also known as α-cardiac myosin heavy chain) with a calcium-channel blocker attenuated the pathological HCM phenotype and, particularly, the myocardial hypertrophy.[51] Experimental data from transgenic mice expressing a mutant form of human cardiac muscle troponin T suggest that alterations in calcium cycling and homeostasis might also contribute to ventricular arrhythmias in patients with HCM.[49] Knollmann *et al.* showed that cardiomyocytes from these animals exhibit depressed and prolonged calcium transients compared with wild-type control mice, which might trigger delayed after-depolarizations or spontaneous calcium oscillations.[49] These effects were observed in the absence of hypertrophy, which implies that arrhythmias are not simply a phenomenon secondary to structural perturbations of the myocardium. The same researchers subsequently showed that ventricular tachycardia could be reproduced by calcium-sensitizing agents, suggesting that myofibrillar calcium sensitization was likely to be the underlying molecular mechanism of the arrhythmias in this model of HCM.[51] By contrast, blebbistatin, which decreases calcium sensitivity, rescued the proarrhythmic phenotype of transgenic mice with an I79N mutation in cardiac muscle troponin T, thereby providing a potential cue towards a novel therapeutic approach.[51] Although these and other reports[52] have linked HCM-related mutations to increased myofibrillar calcium sensitivity, the opposite effect—decreased calcium sensitivity—has also been reported.[53]

Increased myocardial fibrosis

Arrhythmias in patients with HCM are commonly attributed to an increase in left ventricular muscle mass,[54] myocyte disarray,[55,56] or fibrosis.[5] Indeed, the degree of myocardial fibrosis correlates with impairment of cardiac relaxation, and increases the propensity for heart failure. By contrast, in transgenic animal models of HCM, no clear correlation between the extent of cardiac fibrosis or myocyte disarray and arrhythmic risk has been shown.[57,58] The molecular trigger for the development of fibrosis in HCM has not been completely elucidated. Fibrosis has been attributed to premature (apoptotic) death of myocytes and subsequent replacement by an expansion of the interstitial matrix,[59] as a result of microvascular ischemia,[60] cardiomyocyte hypertrophy,[59] or both. A role for nonmyocytes (most likely fibroblasts) in HCM-associated fibrosis has been suggested.[61] In this study, Teekakirikul *et al.* proposed that the proliferation rate of fibroblasts, which occurs independently of myocyte proliferation, is increased constantly in the hearts of mice that carry mutations in myosin-7, and patients with HCM.[61] The precise link between sarcomeric mutations and increased nonmyocyte proliferation still needs to be elucidated, but increased expression of profibrotic molecules including collagens, periostin, and elastin seems to be involved in this process.[61] In particular, signaling by transforming growth factor β (TGF-β) seems to be important for activation of fibroblasts in patients with HCM. Transcript levels of Tgf-β have been consistently demonstrated to be increased in the hearts of mice with an HCM-linked mutation.[61] Treatment of myosin-6 transgenic mice with a TGF-β-neutralizing antibody led to a reduction in the proliferation of nonmyocytes, which was associated with reduced cardiac fibrosis.[61] Similarly, the angiotensin-II-receptor antagonist losartan diminished the development of fibrosis, consistent with the known role of angiotensin in promoting TGF-β expression.[62] The antioxidant *N*-acetylcysteine also attenuated fibrosis in a transgenic mouse model of HCM that overexpressed a mutated form of human cardiac troponin T (cTnT-Q92),[63] which suggests that additional mechanisms have a role in the manifestation of fibrosis.

In humans with HCM, the progressive accumulation of collagen during replacement or scarring results in fibrosis that typically appears in a focal or patchy pattern.[64] With the use of gadolinium-based contrast agents, cardiovascular MRI detects these fibrotic areas with high

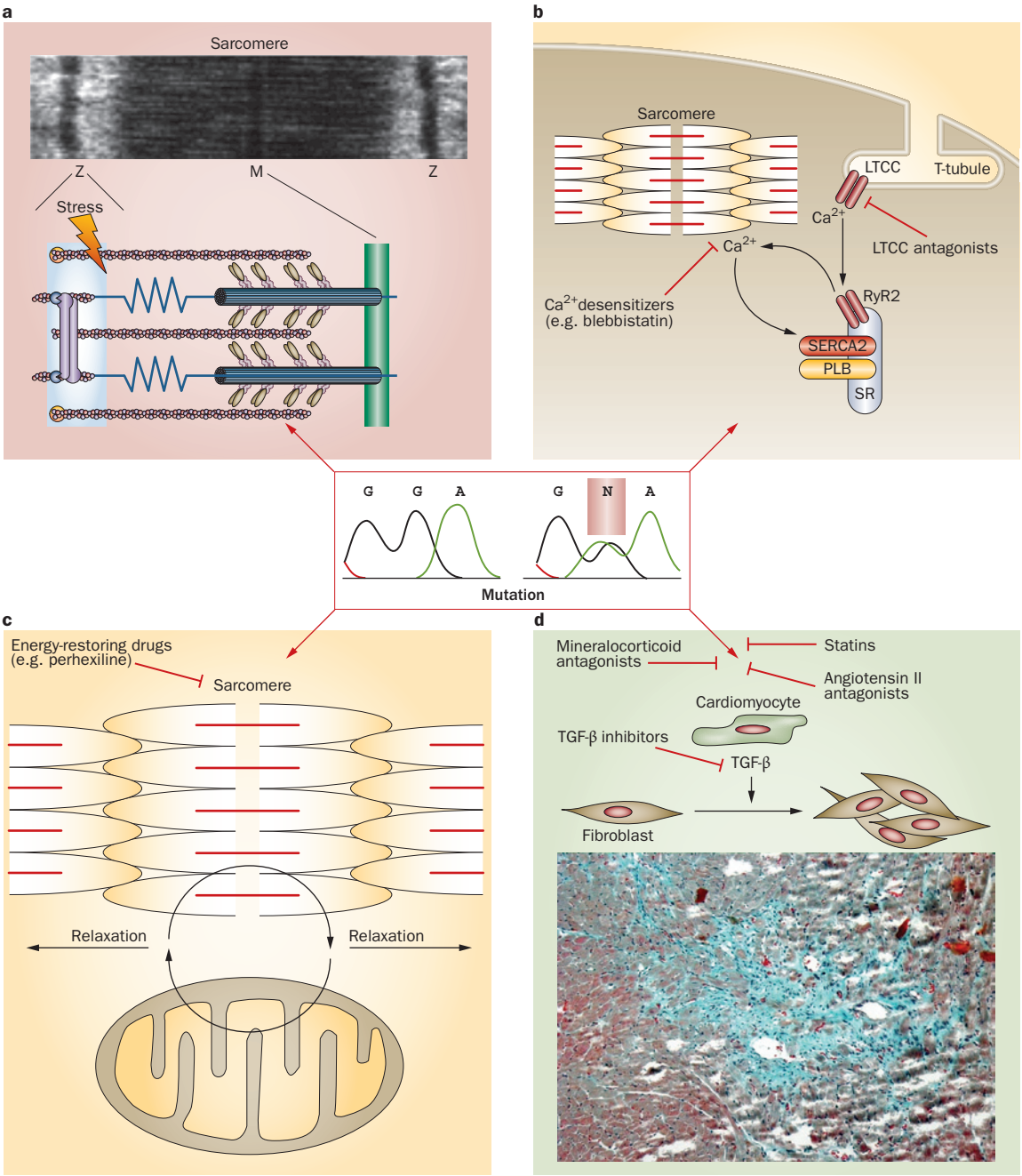

Figure 2 | Disease pathways of hypertrophic cardiomyopathy, and potential therapeutic interventions. Various signaling pathways and disease mechanisms can be activated as the result of a specific gene mutation. **a** | Disturbed biomechanical stress sensing. **b** | Impaired calcium cycling and sensitivity. **c** | Altered energy homeostasis. **d** | Increased fibrosis. These pathways should not be considered in isolation because they can act in concert (for example, metabolic deficits and impaired calcium cycling). Abbreviations: LTCC, voltage-dependent L-type calcium channel; PLB, cardiac phospholamban; RyR2, ryanodine receptor 2; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; SR, sarcoplasmic reticulum; TGF-β, transforming growth factor β; T-tubule, transverse tubule.

spatial resolution.[65] These areas are often detectable in segments of increased wall thickness,[66] which implies a relationship between cardiomyocyte growth and fibrosis in HCM. Cardiac-MRI data from patients with HCM have revealed a close correlation between late gadolinium enhancement (LGE, believed to indicate fibrosis *in vivo*)[64] and outcome—particularly sudden cardiac death.[64,67] These findings suggest that early detection of fibrosis might improve individual risk prediction and identify those patients who might benefit from an implantable cardioverter–defibrillator. Further data indicate that fibrosis is not only a late, secondary phenomenon indicative of cumulative myocardial damage, but might be an inherent feature of HCM that emerges early in the course of the disease. This theory relies on studies in transgenic mouse models of HCM with mutations in myosin-7 that show early profibrotic cardiac remodeling.[61,68] These changes preceded the histopathological changes that are typical of

HCM, including hypertrophy. Accordingly, both a mismatch between extracellular-matrix synthesis and degradation, and an imbalanced collagen turnover might lead to adverse remodeling in HCM.[69,70]

The synthesis of collagen is a complex process. Procollagen molecules are produced within the endoplasmic reticulum of fibroblasts and secreted into the interstitial space where they undergo cleavage of their end-terminal propeptide sequences by procollagen *N*-proteinase and *C*-proteinase to allow formation of mature collagen fibers.[71] The activity of the fibrotic process can be quantified because the amount of cleaved *C*-terminal propeptide from type I procollagen (PICP) correlates with the amount of collagen deposited.[72] The quantity of cleaved propeptides is reflected in their levels in blood serum, meaning that these propeptides have the potential to serve as biomarkers for collagen biosynthesis, which correlates with adverse outcome in patients with either hypertensive heart disease or systolic heart failure.[73,74] Likewise, several reports have also shown increased collagen turnover in overt HCM.[70,75]

The value of these biomarkers for the diagnosis of HCM at an early stage of the disease has been assessed by Ho and colleagues.[69] Participants with known HCM-causing mutations, but without detectable cardiac hypertrophy, were assessed for levels of serum biomarkers of collagen metabolism, such as PICP, and compared with patients with overt HCM and healthy controls. All individuals were examined by echocardiography and cardiac MRI. PICP levels were significantly higher in mutation carriers without left ventricular hypertrophy and in patients with overt HCM than in healthy control individuals.[69] By contrast, the researchers were unable to differentiate between mutation carriers without hypertrophy and healthy controls using LGE-based MRI.[69] Measurement of blood levels of PICP could emerge as an expedient diagnostic tool to detect activated collagen synthesis and, potentially, adverse cardiac remodeling in mutation carriers before phenotypic characteristics of HCM are expressed. However, the serum level of PICP is not only affected by cardiac fibroblasts; it can also be increased by conditions such as increased bone turnover, hyperthyroidism, and diabetic nephropathy.[72] Moreover, advanced MRI techniques, including contrast MRI, strain imaging, and T1 mapping[76] might allow even earlier detection of myocardial fibrosis. Taken together, these novel biomarkers and imaging techniques might serve as diagnostic tools and as surrogates of disease activity and risk in patients with HCM.

Disturbed biomechanical stress sensing

The sarcomere not only generates and transmits contractile force, but is also a critical component of cardiomyocyte signaling pathways (reviewed previously[77–79]). In particular, the sarcomeric M-band[78] and the Z-disc[77,80] have been implicated in sensing and transduction of biomechanical stress. Mutations in critical components of these sarcomeric structures might conceivably lead to impaired stress sensing and an excessive hypertrophic response to mechanical load. Consistent with this notion, mutations in the Z-disc protein and putative stress sensor cysteine and glycine-rich protein 3 (also known as cardiac muscle LIM protein)[81] have been associated with human HCM.[82] Likewise, mutations in Z-disc-associated myozenin-2, a known modulator of the prohypertrophic calcineurin–nuclear factor of activated T-cells pathway,[83] might lead to severe familial HCM.[84] Mutations in another Z-disc protein, telethonin, which interacts with both myozenin-2 and cysteine and glycine-rich protein 3, have also been shown to cause HCM.[85,86] A putative mutation in myomesin-1, an M-band protein, has been linked to human HCM.[87] Finally, titin, a giant sarcomeric protein spanning from the Z-disc to the M-band, is another candidate protein that could be linked with HCM. Titin has been shown to be critical in biomechanical stress sensing;[88] however, the large size of the protein (>1 Mb complementary DNA) has so far precluded systematic screening for mutations in its gene among patients with HCM.

Altered energy homeostasis

Inefficient energy utilization and increased energy demand by the sarcomere have been suggested as key consequences of many, if not all, HCM-associated mutations.[53] According to this premise, inefficient energy usage by the sarcomere compromises the ability of cardiomyocytes to maintain sufficient energy levels for critical homeostatic functions, such as calcium reuptake,[89] especially under conditions of increased energy demand, such as exercise. This impairment might account for diastolic dysfunction and exercise-dependent ventricular arrhythmias. The hypothesis is supported by *in vitro* findings obtained in transgenic models of HCM, including mice with an R403Q mutation in myosin-7 ($\alpha MHC^{403/+}$),[90] mice with an R92Q mutation in cardiac muscle troponin T,[91] and rats with a truncation mutation in cardiac muscle troponin T (DEL-TnT).[29,92] In explanted hearts from these animal models, a decrease in the concentration of phosphocreatine and increased ATP utilization resulted in an impaired ability of the heart to recruit its maximum force-generating capacity.[92] Using *in vivo* 2D ^{31}P-NMR spectroscopy, we demonstrated that cardiac energetics were significantly impaired in transgenic rats expressing a cardiac muscle troponin T deletion mutation, as reflected by a 31% decrease in the phosphocreatine:ATP ratio.[93] A decreased phosphocreatine:ATP ratio of the same order of magnitude (30%) was also observed in patients with HCM harboring mutations in either cardiac muscle troponin T or other sarcomeric proteins.[94] Even mutation carriers who did not display cardiac hypertrophy had an abnormal phosphocreatine:ATP ratio, suggesting that energetic alterations are not simply secondary to hypertrophic growth, but are an early feature in the course of the disease.

The concept of an energy deficit being central in the causation of the HCM phenotype is also supported by the fact that several inherited syndromes in which mitochondrial energy production is impaired can result in asymmetric cardiac hypertrophy that is clinically indistinguishable from HCM (Box 1). These syndromes include abnormalities of mitochondrial function caused by mitochondrial transfer RNA mutations,[25] and Friedreich

ataxia.[95] Likewise, inherited defects in fatty-acid uptake because of CD36 (platelet glycoprotein 4) deficiency,[96] and mitochondrial fatty-acid oxidation secondary to mitochondrial very long-chain specific acyl-CoA dehydrogenase deficiency,[97] also lead to a phenotype that closely resembles HCM.

Evidence to support the 'energy hypothesis'[98] comes from a small, randomized study in which 24 patients with HCM were treated with the metabolic modulator perhexiline, which is believed to shift myocardial substrate utilization from fatty acids to lactate.[99] This therapy markedly increased the myocardial phosphocreatine:ATP ratio, and was associated with improvements in exercise capacity and NYHA functional class.[98]

Microvascular dysfunction

Microvascular dysfunction of the intramyocardial coronary arterioles can be observed in many patients with HCM, and is characterized by intimal hyperplasia and medial hypertrophy that leads to thickening of the vessel wall and, ultimately, reduction of the intraluminal area.[60,100–102] Together with these structural alterations of small vessels, other factors such as a decreased capillary density of the hypertrophied heart and an increased energy demand can lead to cardiac ischemia in the absence of macrovascular coronary heart disease.

Microvascular ischemia is regarded as a predictor of an unfavorable outcome in patients with HCM,[103] because it impairs systolic[104] and diastolic function, and promotes the occurrence of arrhythmias.[100,102] Areas of interstitial fibrosis originating from the replacement of necrotic cardiomyocytes are considered to be a potential morphological marker of microischemia-triggered arrythmias.[64] Novel MRI techniques might, therefore, provide a tool to improve risk stratification of patients with HCM, because they can combine the assessment of microvascular dysfunction via measurement of myocardial blood flow,[102] and the evaluation of fibrosis by quantification of LGE.[64,102,105] However, the available studies that assessed the outcomes of patients with HCM according to LGE imaging included only small numbers of individuals. Moreover, in some of these studies, surrogate (instead of clinical) end points were evaluated, possibly owing to the limited duration of follow-up. Furthermore, because many patients with HCM show LGE to some extent, a critical mass of LGE, which could serve as a threshold for the prediction of an increased risk of sudden cardiac death, is far from being defined. Large-scale studies are necessary before LGE-based MRI can be considered to be a validated method for risk assessment in patients with HCM.

Therapy for HCM

Profound advances have been achieved in the clinical therapy of HCM, in both the management of symptoms and the prevention of life-threatening complications such as end-stage heart failure and sudden cardiac death.[13,106] β-Adrenergic-receptor blockers and calcium-channel antagonists have not only been demonstrated to relieve the left ventricular outflow tract gradient of patients with obstructive HCM during exercise,[106] but might also counteract the microvascular coronary disease that can be observed in many patients.[101] Alcohol septal ablation[12,107] and surgical myectomy[11,108] have both been shown to alleviate HCM-related symptoms. Finally, automated implantable cardioverter–defibrillators have provided a breakthrough in raising the life expectancy of patients at high risk of sudden cardiac death.[109] While modern approaches to treatment help to improve the quality of life and life expectancy of many patients with HCM, the ultimate goal in the treatment of this condition, in our opinion, is a therapy that targets the underlying causative molecular defect. This aim might eventually be feasible, for example via gene therapy with ribozymes,[110] but such an individualized and costly therapy is unlikely to be widely available in the near future. Moreover, whether an established disease process with maladaptive changes would regress upon correction of the pathogenic mutation is unknown.

Box 1 | Hereditary errors of metabolism leading to an HCM-like phenotype[117]

Deficiency of the pyruvate dehydrogenase complex (Leigh disease)

Disorders of oxidative phosphorylation
- Deficiency of Complex I (NDUFV2 protein subunit)
- Deficiency of Complex III
- Deficiency of Complex IV (nuclear COX assembly factors: SURF1, SCO2, .COX10, COX15)
- Deficiency of Complex V (for example, TMEM70)

Combined respiratory-chain deficiencies
- Mutations in mitochondrial transfer RNA (MELAS syndrome, MERRF syndrome)
- Deficiency of mitochondrial elongation factor Ts[118]
- Deletions and duplications of mitochondrial DNA
- Kearns–Sayre syndrome
- Deficiency of mitochondrial 28S ribosomal protein S22[119]
- Barth syndrome (3-methylglutaconic aciduria type II)
- Sengers syndrome

Disorders of fatty-acid metabolism
- Primary carnitine deficiency (lack of organic cation/carnitine transporter 2)
- Muscle carnitine deficiency
- Deficiency of mitochondrial carnitine *O*-palmitoyltransferase 2
- Deficiency of mitochondrial carnitine/acylcarnitine carrier protein
- Deficiency of mitochondrial very long-chain specific acyl-CoA dehydrogenase
- Deficiency of mitochondrial long-chain specific acyl-CoA dehydrogenase
- Deficiency of long chain 3-hydroxyacyl-CoA dehydrogenase
- Deficiency of mitochondrial hydroxyacyl-CoA dehydrogenase
- Deficiency of multiple acyl-CoA dehydrogenases (glutaric acidemia type 2)
- Deficiency of CD36

Deficiency of mitochondrial frataxin (Friedreich ataxia)
- Deficiency of mitochondrial phosphate carrier protein[120]

Abbreviations: CD36, platelet glycoprotein 4; CoA, coenzyme A; COX, cytochrome c oxidase; COX10, mitochondrial protoheme IX farnesyltransferasel; COX15, cytochrome c oxidase assembly protein COX15 homolog; HCM, hypertrophic cardiomyopathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NDUFV2, mitochondrial nicotinamide adenine dinucleotide dehydrogenase [ubiquinone] flavoprotein 2; SCO2, mitochondrial protein SCO2 homolog; SURF1, surfeit locus protein 1; TMEM70, mitochondrial transmembrane protein 70.

Novel therapeutic approaches will, therefore, have to target the most-important clinical manifestations of HCM, particularly malignant arrhythmias and the symptoms of heart failure from systolic and diastolic dysfunction. In this regard, the prevention and treatment of hypertrophy and fibrosis might become important targets for novel therapeutic strategies, such as using angiotensin-II-receptor antagonists,[111] aldosterone antagonists,[112] TGF-β inhibitors,[61] and statins.[113,114] Notably, statins have also been shown to limit the burden of oxidative stress in the heart.[115] Because oxidative stress has been suspected to be increased in HCM, the antioxidative capabilities of these drugs might, at least in part, account for their anti-hypertrophic and antifibrotic properties in patients with HCM.[115] As outlined above, therapeutic modulation of calcium sensitivity, cardiac energy metabolism, or both is a promising strategy to target directly the underlying pathophysiology of HCM.[116] Adequately powered clinical trials are urgently needed to assess the potential of innovative therapies for HCM.

Conclusions

HCM is a common form of inherited heart disease and a frequent cause of sudden cardiac death in the young. The pathogenesis of HCM is complex, corresponding to the high variability of the clinical phenotype. Several hypotheses that might explain the increased susceptibility to arrhythmias and heart failure among patients with HCM have been proposed. However, given the large number of underlying disease-causing mutations in various genes, a single, unifying molecular pathway is unlikely to account for all the facets of HCM. The clinical and experimental data suggest that alterations in cardiac energy homeostasis contribute to the various pathological features of HCM, such as diastolic dysfunction and ventricular arrhythmias. However, other factors (such as altered calcium sensitivity, myocardial fibrosis, and cardiomyocyte hypertrophy) are likely to have an additional role in the pathogenesis of the disease.

Experimental and early clinical evidence demonstrates that targeting these disease pathways might improve conventional treatment of HCM. Although current clinical care of patients with HCM can improve their quality of life and life expectancy, a need for optimized diagnostic and therapeutic strategies still exists. Specifically, improved risk stratification could refine the identification of patients in need of expensive and invasive therapies such as implantable cardioverter–defibrillators. Moreover, only a clear understanding of the genetic basis and molecular pathways involved in HCM will enable further therapeutic advances.

Review criteria

The references in this Review were selected by a MEDLINE search for articles published between 1989 and 2011 using the terms "cardiomyopathy", "hypertrophic cardiomyopathy", and "cardiac hypertrophy". Original research and Review articles were considered, and the reference lists of these publications were searched for additional papers.

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Author contributions

All the authors contributed substantially to researching data for the article, discussion of content, and writing, reviewing, and editing the manuscript before submission.